Late-Stage Fluorination and Perfluoroalkylation

Miriam L. Ó Dúill

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

Merton College

Trinity Term 2015

Author's Declaration

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

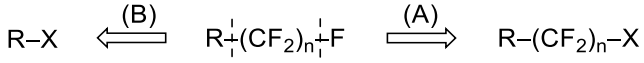
Miriam Ó Dúill

September 2015

Summary

Late-Stage Fluorination and Perfluoroalkylation

In this thesis new synthetic routes towards perfluorinated compounds are described, as well as their radiolabelling with fluorine-18, with the aim of application in pharmaceutically interesting targets.



Part A investigates late-stage fluorination, *i.e.* retrosynthetic C–F bond disconnections.

Chapter 1 gives a general introduction to the effect fluorination has on molecular properties and reactivity, as well as the use of fluorine in medicinal chemistry and postiron emission tomography.

In **Chapter 2** a silver catalysed electrophilic fluorodecarboxylation of fluorinated carboxylic acids for the formation of difluoromethyl-, trifluoromethyl-, and pentafluoroethylarenes is developed and transferred to a radiochemistry setting using [^{18}F]Selectfluor *bis*(triflate).

Part B explores late-stage perfluoroalkylation *via* cross-coupling strategies.

Chapter 3 gives an introduction to transition metal-mediated cross-coupling with perfluoroalkylated reagents, highlighting the challenges of these methodologies.

Chapter 4 investigates the use of visible light-mediated ruthenium catalysis for the radical trifluoromethylation and pentafluoroethylation of vinyl- and alkynylsilanes and alkynes. The silyl group is found to be crucial for high yields and selectivities, but a dependence on trifluoromethylating reagent and solvent is observed as well.

In **Chapter 5** the first generally applicable copper-mediated cross-coupling of Ruppert-Prakash-like aryl(tetrafluoroethyl)trimethylsilanes ($ArCF_2CF_2SiMe_3$) is presented. The use of pyridine as a superior ligand to 1,10-phenanthroline allows for the development of mild reaction conditions.

Chapter 6 gives full experimental procedures and characterisation data for all compounds.

Acknowledgements

I would like to express my gratitude to Prof. Véronique Gouverneur for giving me the opportunity to do my PhD in her group, as well as for all the support and guidance she has offered me over the years.

My thanks also goes to all the people I have worked together with who have made my time at Oxford so much easier, both in the lab and through the fun times we had outside the lab. In particular, I would like to thank Charley Hollingworth for introducing me to the trade; Matthew Tredwell, Keary M. Engle, Jamie Wolstenhume, Emmanuelle Dubost, Sean Preshlock and Michael Schedler for helpful advice and discussions; Keary, Jamie, Emmanuelle, Satoshi Mizuta, Nick Taylor and Stefan Verhoog for help with substrate syntheses; Matthew, Sam Calderwood and Ida Stenhagen for work in the radiolaboratory; Lukas Pfeifer for measuring X-ray crystal structures; Prof. Tim Claridge, Dr. Barbara Odell, Colin Sparrow and all the support staff in the CRL for their help with analysis. Thanks also to the people who proofread my thesis for me, Gregor Cremosnik, Sam, Michael and Lukas.

I am indebted to the BBSRC for providing me with the financial support to undertake my D.Phil.

Many thanks as well to my examiners, Prof. Mimi Hii and Prof. Ed Anderson, who made me think about my chemistry from a completely different angle during our very enjoyable discussion.

Finally, my love goes out to my family, without whose love and support none of this would have been possible.

Abbreviations and Acronyms

18-crown-6	1,4,7,10,13,16-hexaoxacyclo-octadecane
δ	chemical shift (ppm); partial charge
Δ	heat
λ	wavelength
ν	wavenumbers (cm^{-1})
χ	Pauling electronegativity
Å	Angström (10^{-10} m)
$A^{1,3}$	1,3 allylic strain
aq	aqueous
Ar	aryl
ATRA	atom transfer radical addition
BARF	$[B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$
BINAP	(2,2'-bis(diphenyl-phosphino)-1,1'-binaphthyl)
Boc	*tert*-butyloxycarbonyl
bpy	2,2'-bipyridine
Bq	Becquerel
br	broad
BrettPhos	2-(dicyclohexyl-phosphino)-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
ºC	degrees Celcius
cal	calories
cat.	catalytic/catalyst
CHD	cyclohexadiene
CI	chemical ionisation
COD	1,5-cyclooctadiene
cond.	conditions
D	bond dissociation energy
DABCO	1,4-diazabicyclo [2.2.2]octane
DAST	diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DBH	1,3-dibromo-5,5-dimethylhydantoin
DBU	1,8-diazabicycloundec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
$dF(CF_3)$-ppy	(2,4-difluorophenyl)-3-trifluoromethylpyridine
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIH	1,3-diiodo-5,5-dimethylhydantoin
DMAP	4-dimethylaminopyridine
dmb	4,4′-dimethyl-2,2′-bipyridine
dmeda	*N*,*N*'-dimethylethylene-diamine
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMSO	dimethylsulfoxide

dppbz	1,2-*bis*(diphenyl-phosphino)benzene
dppe	1,2-*bis*(diphenyl-phosphino)ethane
dppp	1,3-*bis*(diphenyl-phosphino)propane
dr	diastereomeric ratio
dtb-bpy	4,4′-ditertbutyl-2,2′-biyridine
E^+	electrophile
ee	enantiomeric excess
EF5	etanidazole-f_5
EI	electrospray ionization
EPR	electron paramagnetic resonance
eq	equivalents
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
eV	electron Volt
fac	facial coordination
FDG	2-deoxy-2-fluoro-D-glucose
FI	field ionisation
FITS	(perfluoroalkyl)phenyl-iodonium triflates
Fppy	(2,4-difluorophenyl)pyridine
g	gram(s)
gem-	geminal
GLC	gas-liquid chromatography
GP	General Procedure
h	hour(s)
[H]	reduction
Het	heteroatom
HetAr	heteroaryl
Hex	hexyl; hexane
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	Hertz
hν	light energy
*i*Pr	*iso*-propyl
IPr	1,3-*bis*(2,6-diisopropyl-phenyl)imidazol-2-ylidene
IR	infrared spectroscopy
ISC	intersystem crossing
J	scalar coupling constant
K_{222}	Kryptofix 2.2.2, 4,7,13,16,21,24-hexaoxa-1,10-diaza-bicyclo[8.8.8]-hexacosane
L	ligand; litre(s)
LA	Lewis acid
LAH	lithium aluminium hydride
LED	light-emitting diode
LG	leaving group
M	metal; moles per cubic decimetre (mol dm^{-3})
*m*CPBA	*meta*-chloroperoxy-benzoic acid

Me	methyl
MeCN	acetonitrile
min	minute(s)
mol	mole(s)
Mp	melting point
MS	molecular sieves
n	number of runs
NBS	*N*-bromosuccinimide
*n*Bu	*normal*-butyl
nd	not determined
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
nm	nanometer(s)
NMI	1,3-dimethyl-2-imidazolidinone
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Nu	nucleophile
[O]	oxidant; oxidation
OAc	acetate
ONf	nonaflate, nonafluorobutanesulfonate
OTf	triflate, trifluoromethanesulfonate
PE	polyethylene
PET	positron emission tomography; petroleum ether
Ph	phenyl
phen	1,10-phenanthroline
PIDA	(diacetoxyiodo)benzene
pin	pinacol ester
pK_a	acid dissociation constant
ppm	parts per million
ppy	2-phenylpyridine
py	pyridine
quant	quantitative
R	alkyl group
RCC	radiochemical conversion
RCY	radiochemical yield
RDS	rate-determining step
Red-Al	sodium *bis*(2-methoxyethoxy)aluminumhydride
R_f	perfluorinated group
rt	room temperature
RuPhos	2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
SA	specific activity
salen	*N*,*N*'-ethylene*bis*(salicylimine)
sat.	saturated
SCE	saturated calomel electrode
S_E2'	bimolecular aliphatic electrophilic substitution
SET	single electron transfer
SIPr	1,3-*bis*(2,6-diisopropyl-phenyl)imidazolidene
SM	starting material
S_n	singlet energy state n

S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
$S_{RN}1$	unimolecular radical nucleophilic substitution
TASF	*tris*(dimethylamino) sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
*t*BuXPhos	2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
TEAF	tetraethylammonium fluoride
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
tert-	tertiary
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	3,3,3-trifluoroethanol; tetrafluoroethene
THF	tetrahydrofuran
TIPS	triisopropylsilyl ether
TLC	thin layer chromatography
TMAF	tetramethylammonium fluoride
tmeda	*N*,*N*,*N*',*N*'-tetramethyl-1,2-ethylenediamine
tmp	2,2,6,6-tetramethyl-piperidinato
TMS	tetramethylsilyl
T_n	triplet energy state n
tol	toluene
Tp	trispyrazolylborate
t_R	residence time
TREAT HF	triethylamine trihydrofluoride
TSET	triplet-singlet energy transfer
TTET	triplet-triplet energy transfer
UV/vis	ultraviolet-visible light spectroscopy
V	Volt
v/*v*	volume/volume
W	Watt
X	heteroatom-based functional group
XantPhos	4,5-*bis*(diphenyl-phosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexyl-phosphino-2′,4′,6′-triisopropylbiphenyl
xs	excess
Y	heteroatom-based functional group
Z	heteroatom-based functional group

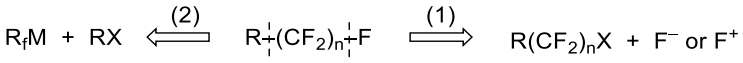
Table of Contents

Preface

The incorporation of fluorine into organic molecules may fundamentally alter their physical, chemical and biological properties.[1] Material sciences benefit from the high thermal and oxidative stability as well as the chemical inertness of fluorinated compounds.[2] Fluorinated pharmaceuticals often show higher efficiency than their non-fluorinated equivalents because of higher metabolic stability and better bioavailability.[3] The radioactive isotope ^{18}F is ideally suited for radioimaging techniques such as positron emission tomography (PET).[4]

Since the importance of fluorine for these fields was recognised, a great amount of research effort has gone into the development of new fluorination methodologies.[5] Lately, perfluoroalkylated targets have become the focus of interest, such as the pentafluoroethylated estrogen receptor antagonist Faslodex® which finds application in advanced breast cancer treatment.[6] So far, however, synthetic strategies for the synthesis of perfluoroalkylated motifs are limited.

There are two retrosynthetic approaches towards a perfluoroalkylated molecule of the form $R(CF_2)_nF$ (Scheme 1): (1) Part A of this thesis will investigate late-stage fluorination of a functionalised perfluoroalkylated molecule $R(CF_2)_nX$ (where X denotes a leaving group); and (2) Part B will explore cross-coupling of an unfluorinated substrate RX with a perfluoroalkylated coupling partner R_fM.



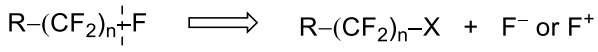
Scheme 1 Retrosynthetic approaches towards perfluoroalkylation: (1) late-stage fluorination; (2) cross-coupling with R_f-reagents

Part A

Late-Stage Fluorination

Part A: Late-Stage Fluorination

Part A of this thesis discusses retrosynthetic C–F disconnections for the synthesis of perfluoroalkylated substrates (Scheme 2).



Scheme 2 Perfluoroalkylation *via* late-stage fluorination

Chapter 1: The Effect of Fluorination on Molecular Properties and Reactivity

1.1 Properties of Fluorinated Compounds

The chemistry of fluorinated organic compounds is governed mainly by two aspects: the high electronegativity and small size of the fluorine atom.

Fluorine is the most electronegative element with a Pauling electronegativity of $\chi_p = 4.0$.[1] This makes the C–F bond very polar, imparting it with significant ionic character. Together with the excellent size and energy match between fluorine's 2s and 2p orbitals with those of carbon,[7] this explains the fact that the C–F bond is the strongest single bond known in organic chemistry with a bond dissociation energy of 105.4 $kcalmol^{-1}$, making it very stable towards chemical and biological processes.[1] Because of its high electronegativity, fluorine 'holds' its electrons close to the nucleus, resulting in low polarizability. Highly fluorinated molecules are thus nonpolar and possess weak intermolecular interactions. This lowers their boiling point relative to their fully hydrogenated equivalents (Table 1). At the same time, weak intermolecular interactions result in high vapour pressures, which means that fluorinated compounds are highly volatile even if they have relatively high boiling points, making careful handling during isolation very important.[7]

	Boiling point [°C]
C_6H_{14}	69
$CF_3(CF_2)_2(CH_2)_3H$	64
C_6F_{14}	57

Table 1 Boiling points of fluorinated alkanes[7]

Furthermore, perfluorination of organic compounds leads to a decrease in lipophilicity and hydrophilicity, causing the formation of a fluorous phase that is insoluble in both water and organic solvents.[7] This property has been exploited in catalysis and fluorous purification methods.[8]

The size of the fluorine atom lies roughly between that of hydrogen and oxygen (Figure 1).[1] Therefore, the replacement of a C–H bond with a C–F bond is common in medicinal chemistry on steric grounds (see section 1.3). This can have a profound effect on the conformation of a small molecule due to stereoelectronic effects and may be exploited for conformational studies.[9] The electronic changes are less pronounced when fluorine replaces oxygen, however this leads to a change in hybridisation (in the case of an sp^2 carbonyl) or the loss of an acidic hydrogen (when a hydroxyl group is replaced). The latter is useful for studies into hydrogen bonding.[1]

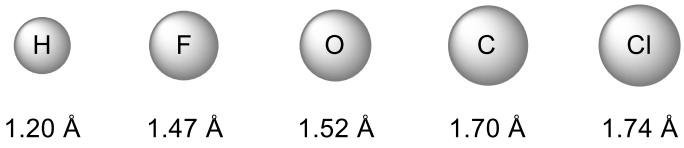


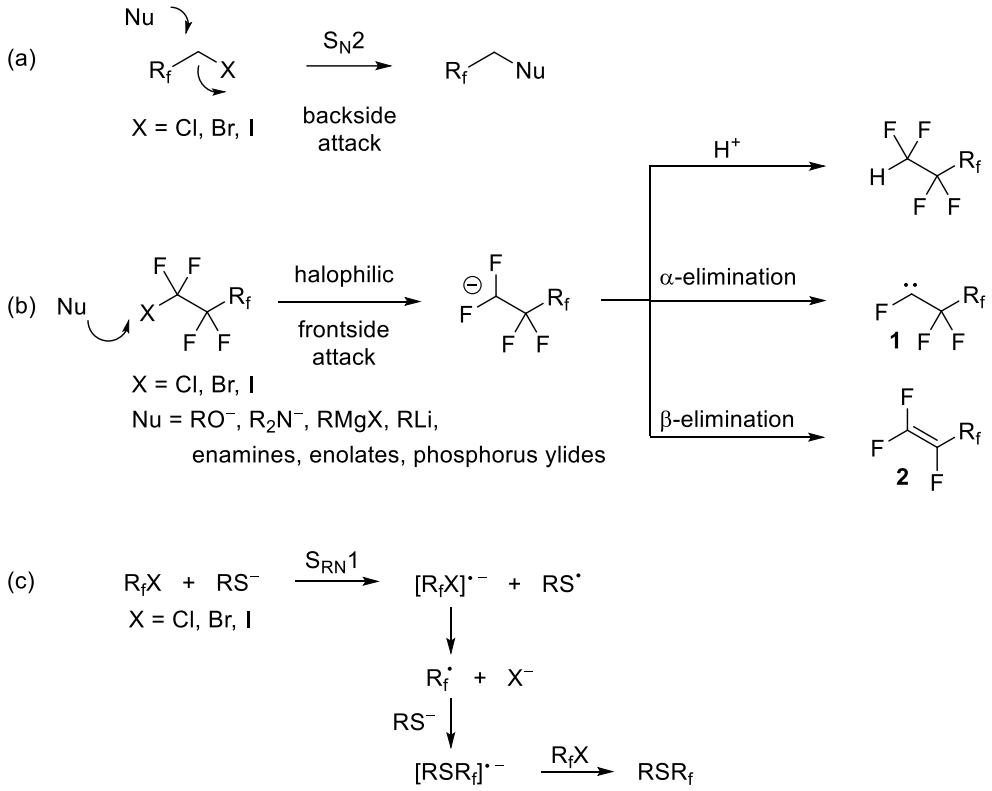
Figure 1 Van-der-Waals radii of common atoms[1]

1.2 Effect of Fluorine Substitution on Reactivity

The high electronegativity of fluorine accounts for the strong electron withdrawing character of trifluoromethyl and perfluoroalkyl groups, while the three electron pairs on fluorine exert a weak mesomerically donating effect.[1] This has important effects on the acidity of adjacent groups, as well as the (de)stabilisation of reaction intermediates. In general, carbocations are mesomerically stabilised by α-fluorine substituents and inductively destabilised by β-fluorines. Similarly, carbanions are thermodynamically inductively stabilised by fluorine substituents. In practice, however, rapid α-elimination to

form carbenes and β-elimination to yield alkenes is observed.[7] These are important side-reactions that need to be taken into account when designing new reactions using fluorinated substrates.

Very importantly, fluorination can have a profound inhibiting effect on the reactivity of organic compounds under substitution conditions (Scheme 3): The electronic and steric repulsion of incoming nucleophiles, together with the electron-withdrawing effect that strengthens the bond with the leaving group and destabilises positively charged transition states and intermediates, leads to the observation that substitution reactions are very difficult on trifluoromethylated and perfluoroalkylated substrates.[7] S_N2 reactivity only becomes possible when the perfluoroalkyl motif is separated from the leaving group by a $(CH_2)_n$ linker ($n \geq 1$) (Scheme 3a).[10] Instead, perfluorinated substrates react *via* halophilic attack or a single-electron $S_{RN}1$ mechanism. The name 'halophilic attack' stems from the fact that the initial step in the reaction sequence is a frontside attack of the nucleophile on a halogen atom which is abstracted to afford a carbanion intermediate (Scheme 3b). This anion may either undergo protonation, or it can eliminate to afford alkene **2** or carbene **1**, which undergoes further reaction. Solvent effects play an important role in determining the final product.[11] In the special case of easily oxidised nucleophiles (*e.g.* sulfur-based nucleophiles), a radical nucleophilic $S_{RN}1$ mechanism is observed. Single-electron transfer occurs from the nucleophile to the perfluoroalkyl halide substrate, giving a radical anion which decomposes into a radical $R_f^{\bullet}$ species *via* scission of the weakest C–X bond. The perfluoroalkyl radical reacts with another molecule of the sulfur nucleophile, forming a $[NuR_f]^{\bullet -}$ radical anion which affords the desired product after single electron transfer (Scheme 3c).[10]



Scheme 3 Reaction of perfluoroalkyl halides with nucleophiles *via* (a) S_N2; (b) halophilic attack; (c) $S_{RN}1$[10]

The inertness of trifluoromethylated and perfluoroalkylated substrates towards nucleophilic substitution makes the synthesis of terminal perfluoroalkylated targets *via* simple nucleophilic fluoride attack virtually impossible. Marchand-Brynaert summarises this hurdle after the unsuccessful radiosynthesis of [^{18}F]EF5 by nucleophilic fluorination of thioesters:

"It appears thus that the creation of the CF_3 motif next to a pre-existing CF_2 motif by [...] nucleophilic exchange is rather difficult."[12]

We have therefore embarked on a research project that aims to furnish these motifs *via* different, more easily realisable strategies. We are particularly interested in methodologies that are transferrable to a radiochemistry setting with fluorine-18 for the synthesis of radiotracers with an application in positron emission tomography (PET).

1.3 Fluorine in Medicinal Chemistry and PET

Although fluorine is the most abundant halogen in the Earth's crust, it forms the lowest number of naturally occurring organohalides.[13] This is mainly due to its existence in the form of insoluble minerals,[9] its extraordinary inertness towards chemical and biological processes, and the toxicity of most small fluorinated molecules for bioorganisms. Only one fluorinase enzyme is known to date that catalyses C–F bond formation in the bacterium *Streptomyces cattleya*.[14] Despite, or perhaps as a consequence of, the rarity of organofluorine compounds in nature, they have found widespread application as drugs and pharmaceutical tracers (Figure 2).[15-17] Thus, about 20% of marketed drugs contain one or more fluorine atoms.[15, 17]

The introduction of fluorine into pharmaceutically active compounds is often achieved by exchange of a hydrogen, hydroxy or methoxy substituent.[9] Beside the stereoelectronic and conformational changes that are associated with such an exchange, fluorination may have other effects which can be exploited in medicinal chemistry. First, labile positions can be protected by fluorination which may improve the metabolic stability of a drug. This is due both to the strength of the carbon-fluorine bond, and the fact that fluorinated compounds are rarely recognised as substrates by enzymes, most importantly cytochrome P450 monooxygenases which are responsible for enzymatic oxidation.[9] Second, fluorinated drugs often show better bioavailability (defined as the percentage of administered dose reaching the circulatory system) than their non-fluorinated counterparts.[3]

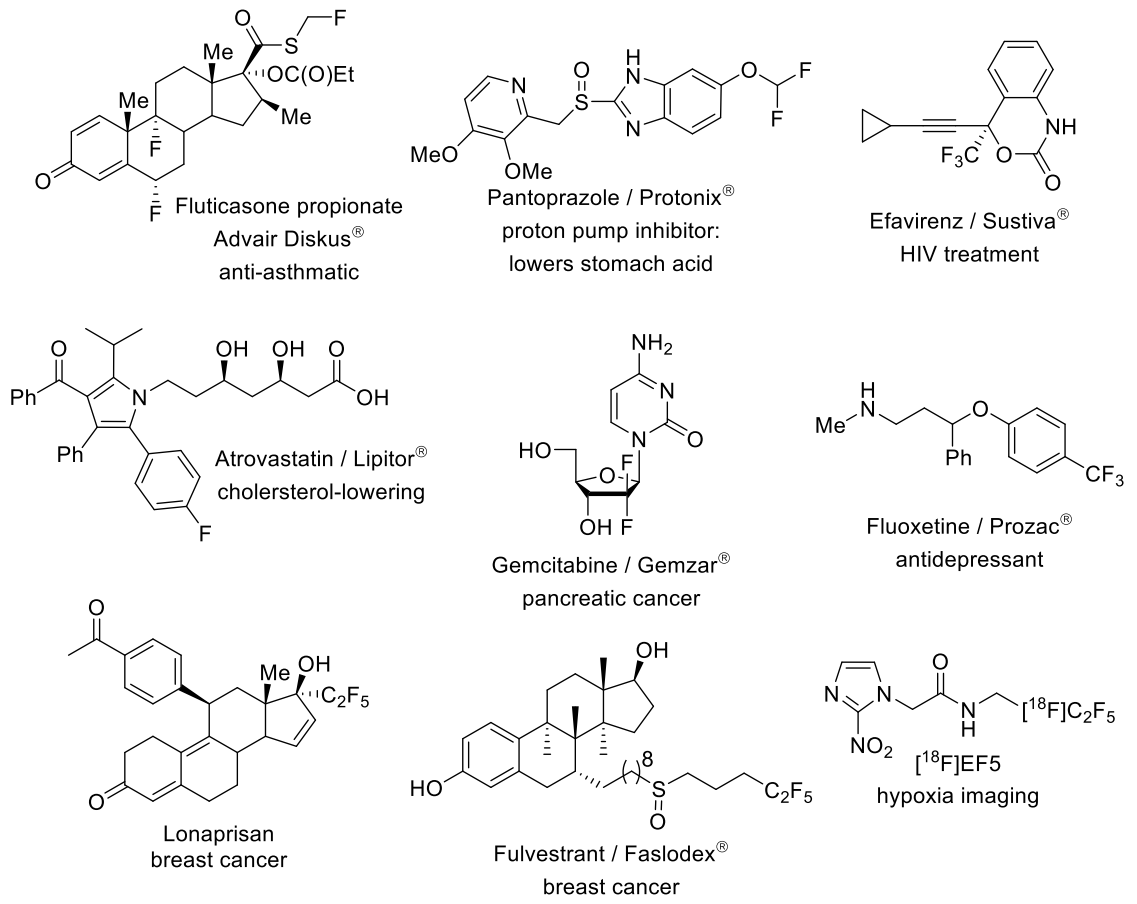


Figure 2 Fluorinated pharmaceuticals and radiotracers

However, the applications of fluorine in medicinal chemistry are not only limited to treatment; it also plays an important role in diagnosis and drug development. Positron emission tomography (PET) is a sensitive, non-invasive imaging technique that uses positron-emitting radiotracers to observe biological systems *in vivo*.[18] It is used both as a diagnostic tool in oncology, neurology and cardiology, as well as for drug development by giving quantitative information about biodistribution, drug occupancy and metabolites of drug targets in the early stages of clinical development.[15] Radioactive isotopes in the tracer undergo β^+ decay, emitting a neutrino and a positron. When the positron encounters an electron, an annihilation reaction takes place, producing two γ photons which are emitted at almost 180 degrees to each other (Figure 3a). The PET scanner generates a three-dimensional image of the radio source of interest by detecting the photons generated during

these annihilation events.[19] Of the isotopes commonly used for PET, ^{18}F is particularly advantageous. Its relatively long half-life of 109.8 minutes enables off-site production and good radiochemical yields, while a clean decay profile (97% β^+ emission) and low positron energy (0.635 MeV) result in high resolution even at low tracer concentrations.[4, 20] Furthermore, ^{18}F decays into ^{18}O which is non-toxic and non-radioactive and is hence safely excreted from the body.[15] The most commonly used radiotracer in PET is 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG), a fluorinated glucose analogue (Figure 3b). Due to the fluorine atom in the 2-position, [^{18}F]FDG is not recognised as a substrate for glycolysis by the relevant enzymes, trapping it in cancer cells with increased glucose metabolism. This allows for early diagnosis of tumorous tissue, as well as treatment planning for cancer patients.[15]

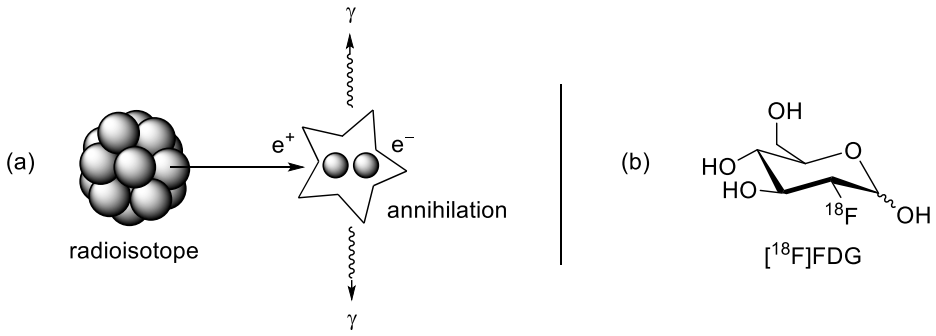


Figure 3 Positron Emission Tomography: (a) β^+ Decay; (b) [^{18}F]FDG

1.4 Strategies for the ^{18}F-Labelling of Perfluoroalkyl Groups

While [^{18}F]FDG is an extremely powerful diagnostic tool, it is not omnipotent. The nitroimidazole EF5 (Figure 2), for example, may be used for the selective imaging of hypoxic tumours which have been shown to be resistant to most radio- and chemotherapy.[21, 22] Furthermore, the radiolabelling of drugs used for the treatment of cancer would offer a powerful tool for personalised medicine.[23] Initial PET scans could

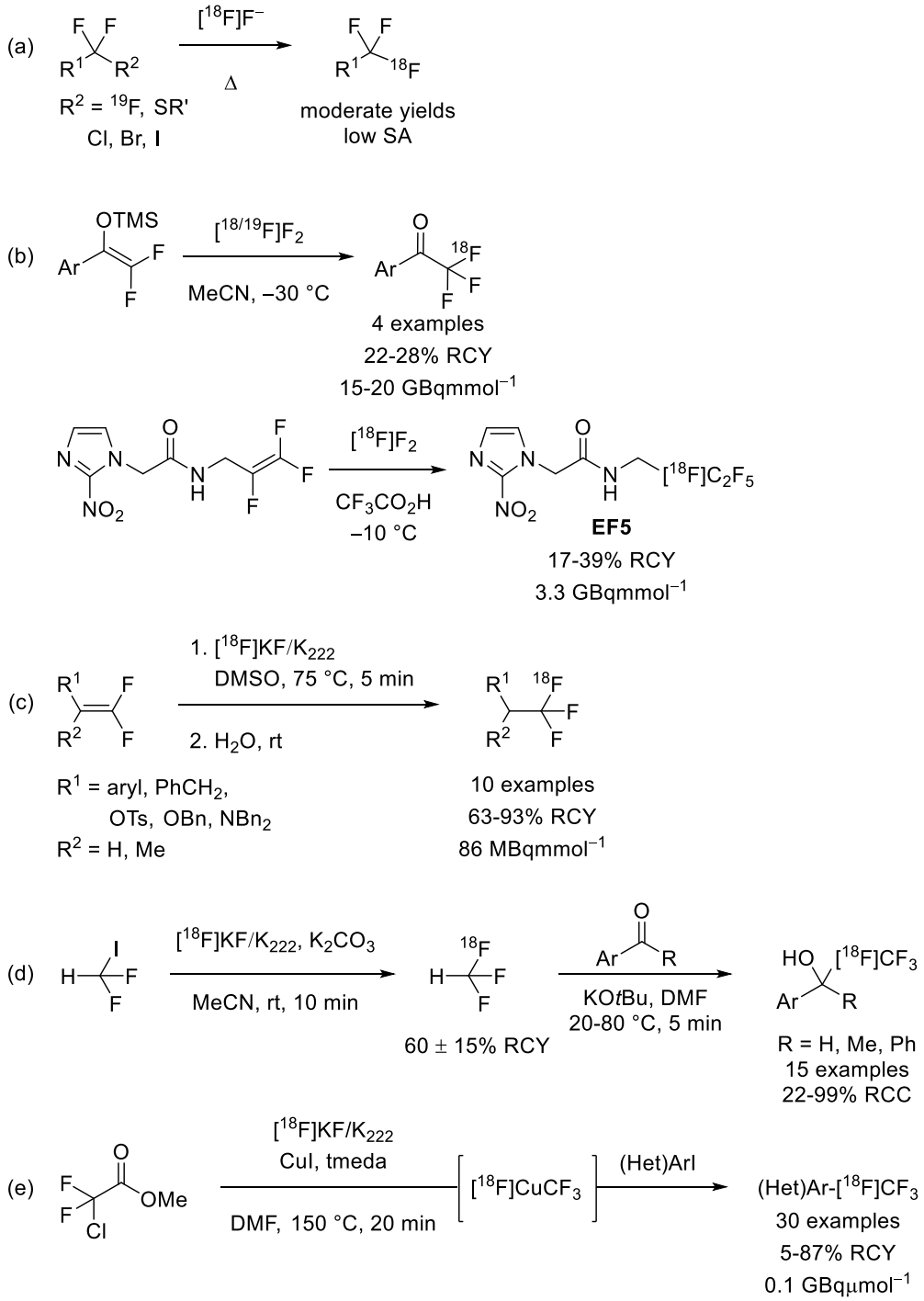
indicate how well a patient responds to specific treatment, enabling doctors to make decisions on individual therapy or dosage. For these reasons, it is important to have a toolkit of different radiolabelling strategies to hand. While a lot of research has been done on radiofluorination[24, 25] and ^{18}F-trifluoromethylation,[26] few methods exist for the synthesis of [^{18}F]-radiolabelled perfluoroalkyl motifs.

The first examples of [^{18}F]-radiolabelled perfluoroalkyl groups relied on halogen exchange (halex) reactions (Scheme 4a). This approach required high reaction temperatures, limiting the substrate scope, and generally gave only moderate radiochemical yields (RCY) and low specific activities (SA).[26] One of the reasons for the low specific activities observed in these cases is isotopic dilution, *i.e.* the scrambling of ^{18}F and ^{19}F substituents at the desired position.[27] There are two possible pathways by which this may occur: radiofluorination of the precursor would liberate $^{19}F^-$ as the leaving group which could in turn afford ^{19}F fluorinated product; alternatively, degradation of a reaction component other than the starting material under the reaction conditions may act as a source of 'cold' fluoride.

Addition of [^{18}F]F_2 across double bonds affords fluorine-18 labelled trifluoromethylated and pentafluoroethylated targets (Scheme 4b).[22, 28] However, as ^{18}F-fluoride is available in much higher specific activities than [^{18}F]F_2,[29],[i] nucleophilic methods are often preferred (Scheme 4c).[30]

More recent strategies have moved away from late-stage fluorination and focus instead on the introduction of pre-labelled building blocks. The first examples used small molecules that were attached to the target of interest *via* nucleophilic substitution, such as 3,3,3-[^{18}F]trifluoropropylamine or 2,2,2-[^{18}F]trifluoroethyl triflate.[27, 31]

[i] Theoretical maximum SA of [^{18}F]F^-: *ca.* 63.3 x 10^3 GBqμmol^{-1}; highest measured SA of [^{18}F]F_2: *ca.* 55 GBqμmol^{-1}.[29]

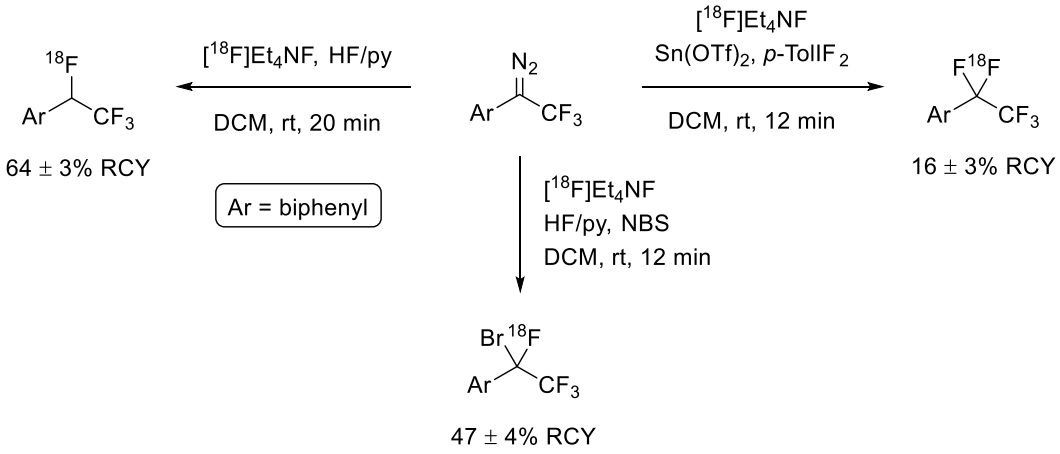


Scheme 4 Radiofluorination strategies for the synthesis of [^{18}F]-labelled perfluoroalkyl groups: (a) halogen exchange reactions; (b) addition of [^{18}F]F_2 across double bonds; (c) addition of [^{18}F]HF across double bonds; (d) building-block strategies; (e) cross-coupling strategies

Vugts and co-worker elegantly synthesised [^{18}F]trifluoromethane from difluoroiodomethane and cryptand Kryptofix 2.2.2./[^{18}F]fluoride in good radiochemical yields, which was then used to trifluoromethylate aldehydes and ketones under basic

conditions (Scheme 4d).[32] While radiochemical conversions (RCC) were good, the use of gaseous radiofluorinating reagents requires careful handling and has certain safety implications. This issue was addressed by Passchier and Gouverneur with the *in situ* formation of [^{18}F]$CuCF_3$ from methyl chlorodifluoroacetate and [^{18}F]KF in the presence of CuI and tmeda at 150 °C (Scheme 4e).[33] They demonstrated the first generally applicable radio-trifluoromethylation of (hetero)aryl iodides with this reagent, affording moderate to good radiochemical yields on a wide scope of substrates. The Vugts group were able to improve the specific activity reported by Gouverneur and Passchier to 22–32 GBqμmol^{-1} by using their radiolabelled fluoroform in the presence of CuBr, KO*t*Bu and triethylamine trihydrofluoride (TREAT-HF) (which was added to stabilise the [^{18}F]$CuCF_3$ intermediate) for the radiotrifluoromethylation of aryl iodides (at 130 °C) and arylboronic acids (at ambient conditions).[34] Jubault *et al.* showed that the sulfonium salt $HCF_2S(Ph)(Mes)^+$ $[B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$ ($BARF^-$) could also be used as a difluorocarbene precursor.[35]

While these methodologies have been seminal in progressing the field of radio-trifluoromethylation and -perfluoroalkylation, the final goal in radiochemistry is ideally that of *late-stage* functionalisation under ambient conditions, due to the relatively short half-life of the radionuclides involved.[25] Very recently, the Gouverneur group published a diversity-oriented late-stage functionalisation strategy towards ^{18}F-labelled perfluoroalkyl motifs *via* direct ^{18}F-fluorination of trifluoromethylated diazo precursors with [^{18}F]Et_4NF in DCM at room temperature (Scheme 5).[36] By varying the co-reagent, the reaction could be fine-tuned to yield radiolabelled products of hydrofluorination, *gem*-difluorination and bromo-fluorination. Due to the limited substrate scope caused by the synthesis of the diazo starting materials and their explosive properties, we set out to develop a more widely applicable late-stage protocol for the synthesis of perfluoroalkylated substrates.

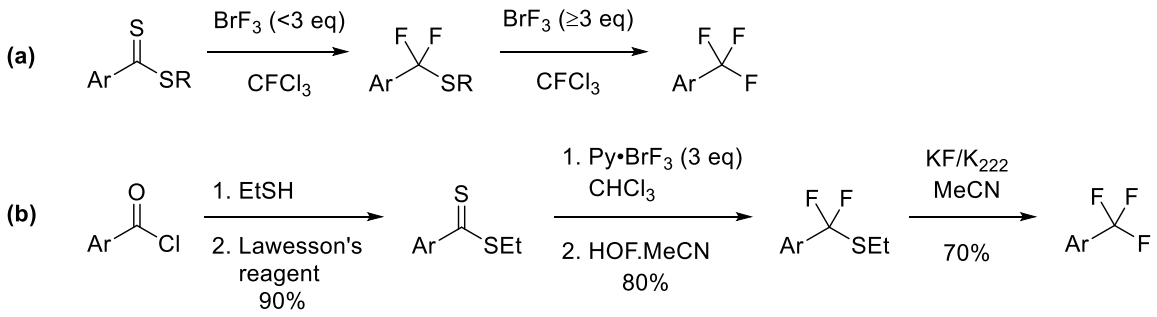


Scheme 5 Late-stage radiofluorination for the synthesis of ^{18}F-labelled perfluoroalkanes[36]

Chapter 2: Electrophilic Fluorodecarboxylation

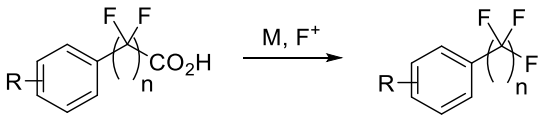
2.1 Introduction: Decarboxylative Fluorination

A widely used CF_2–F bond disconnection for trifluoromethylation is the oxidative desulfurisation-fluorination strategy with BrF_3 developed by Rozen *et al*.[37] This reaction relies on a stepwise, electrophilic *gem*-difluorination of aromatic carbodithionates to the difluorinated thioether $ArCF_2SR$ which, in the presence of an excess of BrF_3, is transformed to the desired aryl-CF_3 compound (Scheme 6a). It was later shown that complexation of BrF_3 with pyridine was able to afford higher yields and avoid the formation of halogenated by-products, suppressing both chlorination (from the reaction of BrF_3 with the solvent $CFCl_3$) and bromination (as BrF_3 may also act as an electrophilic bromine source). Furthermore, 'taming' the reactivity of bromine trifluoride enabled the development of a protocol amenable to radiolabelling conditions (Scheme 6b), though the reaction was never carried out with ^{18}F-fluoride.[38] Nevertheless, BrF_3 is a highly corrosive oxidant and dangerous to handle. Hiyama *et al.* showed that a combination of $[n\text{Bu}_4\text{N}]H_2F_3$ as the fluoride source and DBH as the oxidant similarly gave trifluoromethylated products in moderate to good yields, while NBS and NIS furnished the *gem*-difluorinated products $ArCF_2SR$.[39]



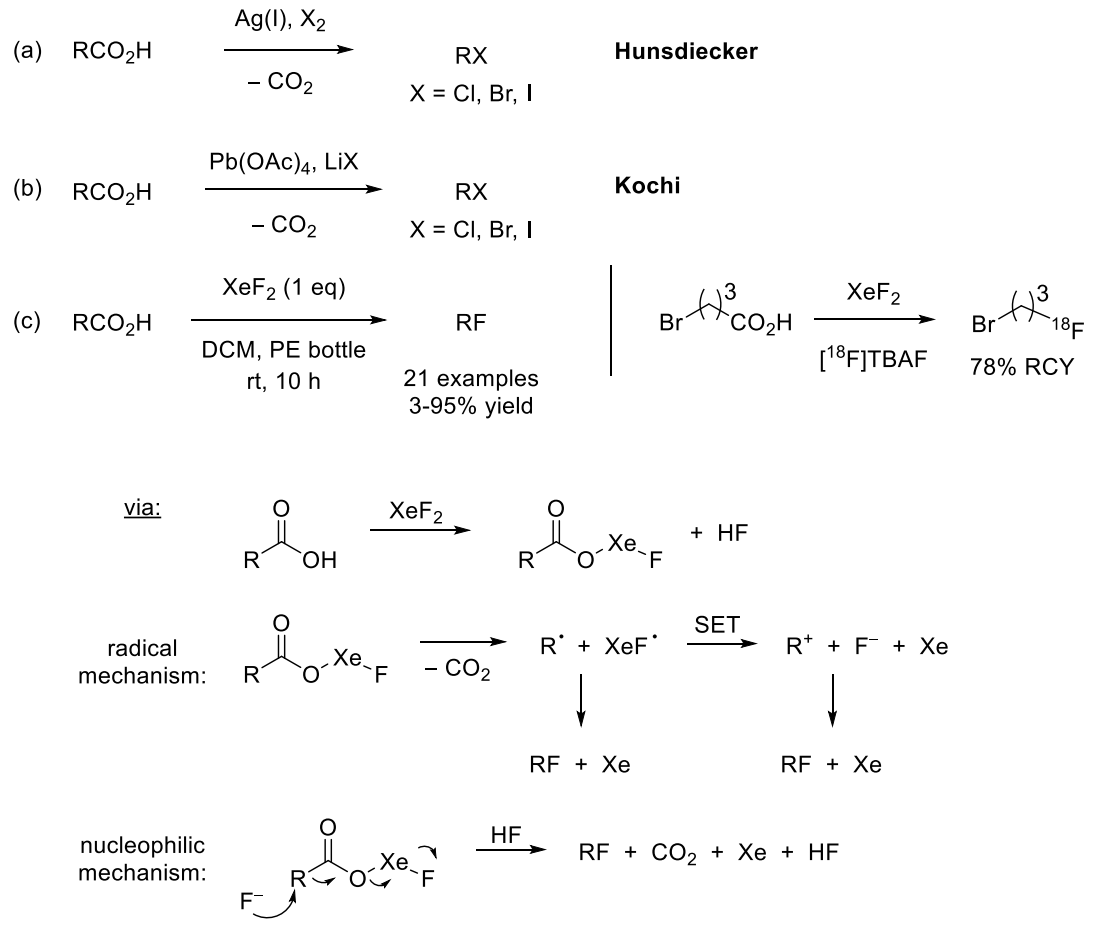
Scheme 6 Aromatic trifluoromethylation with BrF_3[37, 38]

We sought to employ the principles of this transformation using a more convenient fluorinating reagent and avoiding the need for sulfur chemistry. The parent carboxylic acid compounds seem an ideal choice of substrate, as they are odourless crystalline solids that are easily synthesised from commercially available aryl iodides in high yields (*vide infra*). We hence envisaged the decarboxylative fluorination of α,α-difluoroaryl carboxylic acids in the presence of a metal catalyst and an electrophilic fluorinating agent for the formation of trifluoromethyl arenes. Extension of the perfluoroalkyl unit should yield perfluoroalkylated aromatics (Scheme 7).



Scheme 7 CF_2–F disconnection strategy for the synthesis of perfluoroalkylated aromatics

In 1983, the most useful methodologies for the formation of alkyl halides were the Hunsdiecker and Kochi halodecarboxylation reactions (Scheme 8a,b). The substrate scope was, however, limited to chlorides, bromides and iodides, since fluorine could not be used as the halogen of choice in these transformations. Timothy Patrick addressed this problem by showing that aliphatic carboxylic acids reacted with xenon difluoride to form alkyl fluorides with loss of carbon dioxide (Scheme 8c).[40-42] In his initial findings, Patrick bubbled gaseous hydrogen fluoride though his reaction mixture,[40] but he later reported identical yields in the absence of a fluoride source.[41] HF is well-known to catalyse reactions with xenon difluoride due to hydrogen bonding between the HF proton and one of the XeF_2 fluorines, which polarises the remaining Xe–F bond, rendering it more electrophilic.[43] Since the fluorodecarboxylation reaction produces HF *in situ* ($RCO_2H + XeF_2 \rightarrow RF + CO_2 + HF + Xe$), the addition of an external fluoride source is unnecessary.

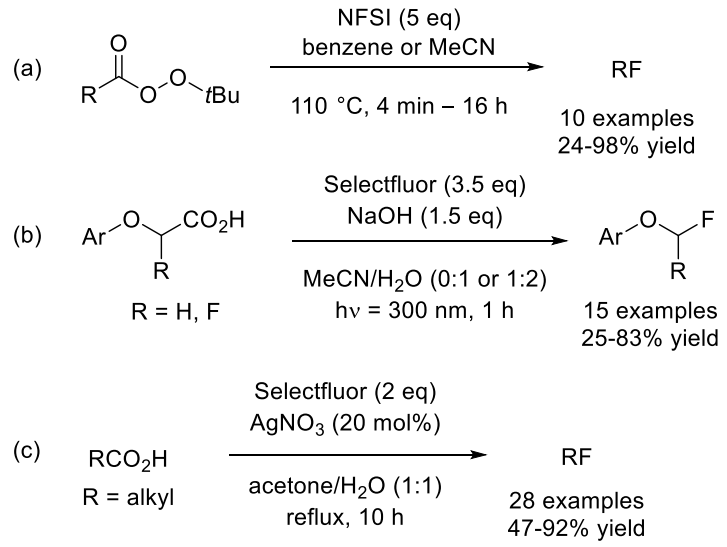


Scheme 8 Halodecarboxylation[40-42]

Primary and tertiary carboxylic acids were found to give high yields, while secondary carboxylic acids showed very low reactivity and substrates bearing protic functional groups were unreactive towards fluorodecarboxylation under these conditions.[41] The authors postulated that the carboxylic acids react with xenon difluoride to form a xenon ester. This species was first isolated by DesMarteau *et al.* from the reaction of xenon difluoride with strong oxy acids at low temperatures, and was shown to rapidly decarboxylate upon warming to room temperature.[44] Formation of the xenon ester has been shown to be inhibited by the presence of protic or nucleophilic functional groups.[42] Patrick and co-workers suggested that fluorination of the decarboxylated xenon ester occurred *via* a free radical mechanism, based on radical clock experiments and EPR spin-trapping.[42] In a radiochemical variant of the reaction using xenon difluoride and [^{18}F]TBAF, a nucleophilic

mechanism was proposed, since no exchange of fluoride-18 with xenon difluoride was observed, implying that incorporation of the radionuclide occurred from nucleophilic attack of $^{18}F^-$ from the TBAF reagent.[41]

In recent years, the focus of fluorodecarboxylation reactions has shifted away from xenon difluoride towards fluorinating reagents that are less dangerous and easier to handle. Sammis and co-workers demonstrated that NFSI and Selectfluor are viable alternatives under thermal and photocatalytic conditions respectively (Scheme 9a,b)[45, 46] in the same year as Li published a silver-catalysed fluorodecarboxylation with Selectfluor (Scheme 9c).[47]



Scheme 9 Fluorodecarboxylation with NFSI and Selectfluor[45-47]

Sammis postulated that due to the low homolytic N–F bond dissociation energies calculated for Selectfluor and NFSI (Table 2) these reagents should be good radical fluorine transfer agents. As proof of principle, the group showed that alkyl radicals, formed by the thermal decarboxylation of peresters, efficiently abstracted fluorine from NFSI affording the desired alkyl fluorides in low to excellent yields (Scheme 9a). Substrate reactivity mirrored radical stability, and the scope included primary, secondary, tertiary and benzylic, as well

as α-heteroatom stabilised substrates.[45] Similarly, 2-aryloxyacetic acids reacted with Selectfluor under irradiation with 300 nm light to afford fluorodecarboxylated monofluoro- and difluoromethyl ethers (Scheme 9b). The authors suggest that after excitation of the substrate, single-electron transfer to Selectfluor occurs followed by decarboxylation and subsequent radical or anionic fluorination. The reaction is limited to 2-aryloxy carboxylic acids as these have the correct UV/vis absorption profile to enable the first excitation step; alkyl carboxylic acids are completely unreactive.[46]

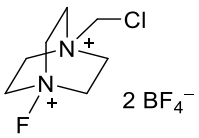
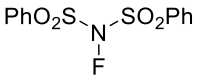
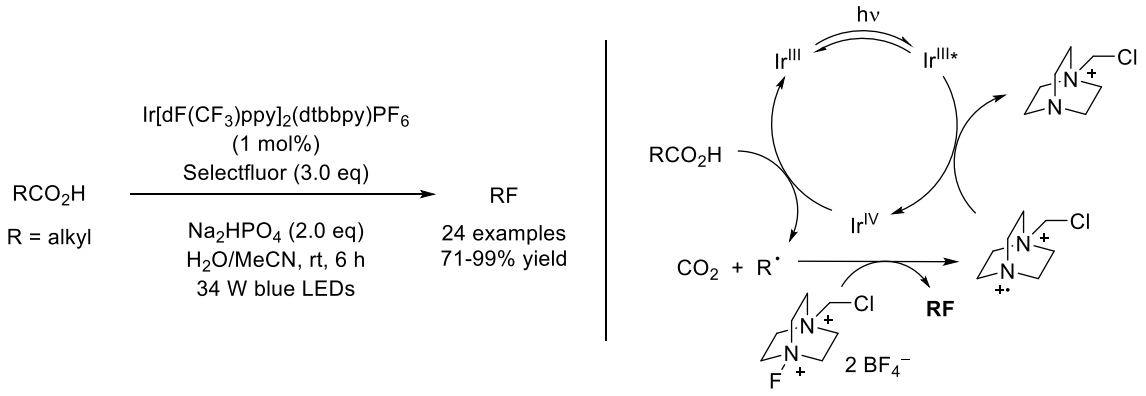
	 Selectfluor®	 NFSI
Solvent	D_{NF} (kcalmol^{-1})	D_{NF} (kcalmol^{-1})
Hexane	61.0	63.4
THF	61.7	63.3
MeCN	60.9	63.1
H_2O	62.2	63.5

Table 2 DFT-calculated N–F bond dissociation energies for electrophilic fluorinating reagents[45]

The reaction was later shown to proceed under visible light catalysis as well: in this case, the single electron-transfer to Selectfluor occurs form photoexcited $Ru(bpy)_3Cl_2$ under irradiation with a 500 W lamp which affords fluorination of aryloxy carboxylic acids after NaOH mediated decarboxylation in a mixed H_2O/MeCN solvent system after 1 hour at room temperature.[48] (For an introduction to photocatalysis, see section 3.6.1) Both methods show good yields for electroneutral and electron-poor substrates, however electron-rich aryloxy carboxylic acids suffer from fluorination on the aromatic ring. The authors realised the photocatalytic fluorodecarboxylation of electron-rich precursors by using NFSI as the fluorine source in the presence of 2,6-di-*tert*-butylpyridine in acetone under irradiation with 350 nm light at room temperature for 3 hours. 2,6-Di-*tert*-

butylpyridine acts both as a photosensitiser which supports single electron transfer from the aryloxy carboxylic acid to NFSI, and as a base to mediate decarboxylation.[49]

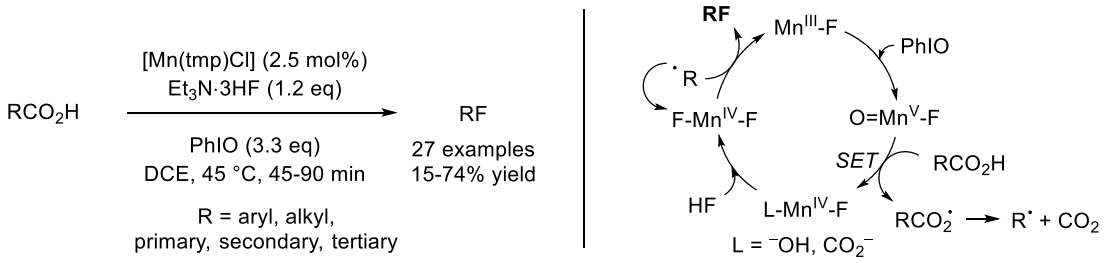
The MacMillan group considerably broadened the scope of this transformation with the development of a visible light-mediated, iridium catalysed decarboxylative fluorination of unactivated aliphatic carboxylic acids with Selectfluor (Scheme 10).[50] The reduced photocatalyst undergoes single electron transfer with the carboxylic acid substrate, causing decarboxylation. The resulting radical abstracts a fluorine from Selectfluor, affording the fluorodecarboxylated product as well as a Selectfluor radical cation which is reduced to chloromethylated 1,4-diazabicyclo[2.2.2]octane (DABCO) by the excited photocatalyst, forming the reduced catalyst necessary for the first reaction step described above. The method afforded a wide range of primary, secondary and tertiary aliphatic fluorides in high yields.



Scheme 10 Fluorodecarboxylation under iridium photocatalysis[50]

Recently, Groves and co-workers reported a nucleophilic fluorodecarboxylation protocol with HF (Scheme 11).[51] In previous work on oxidative C–H fluorination,[52] the group showed that a manganese porphyrin catalyst forms a manganese(V)-fluoride complex when heated gently in DCE in the presence of F^- and an oxidant. This complex oxidises the carboxylic acid substrate, initiating decarboxylation, and also serves as a fluorine source

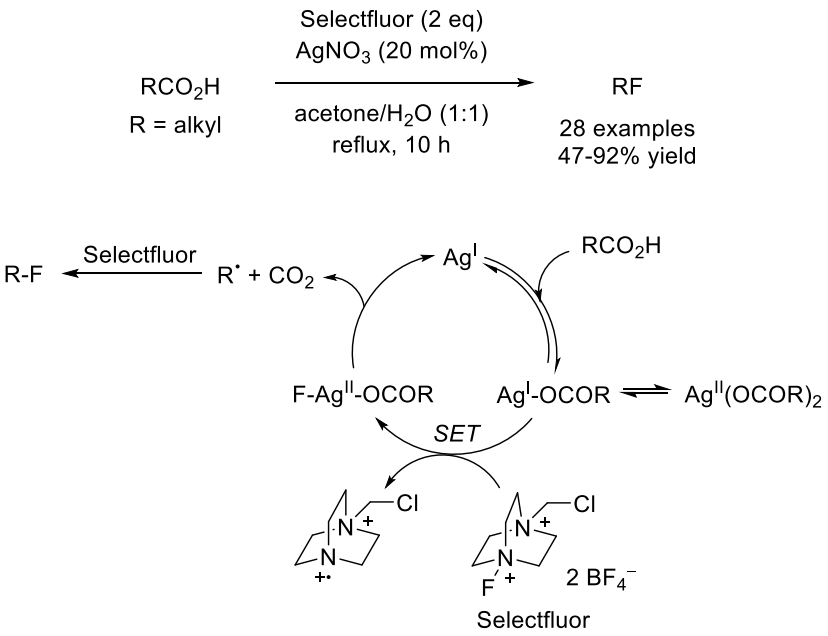
after being reduced to manganese(IV). The substrate scope of this transformation is extensive, and a radiolabelling protocol with [^{18}F]KF was developed as well, by Carroll and co-workers, yielding ^{18}F-labelled fluorides in 20–50% RCY with specific activities around 65.9 GBqμmol^{-1}.[53]



Scheme 11 Fluorodecarboxylation under manganese catalysis[51]

Based on Sammis' pioneering work, Li *et al.* developed a radical fluorodecarboxylation of aliphatic carboxylic acids with Selectfluor under silver(I) catalysis in acetone/water at 55 °C (Scheme 12).[47] Water was found to be essential to solubilise Selectfluor and the silver catalyst. Substrate reactivity increases with radical stability: primary < secondary < tertiary; aromatic carboxylic acids were completely unreactive under the reaction conditions. The original paper supplied little mechanistic evidence, but Patel and Flowers later carried out spectroscopic and kinetic studies to understand the reaction mechanism at work.[54] The silver(I) salt rapidly forms a carboxylate complex with the substrate which can be detected by infrared spectroscopy. This may either coordinate a second carboxylate, thus inhibiting the reaction (which is apparent from an observed rate-order of –1.5 for the substrate), or undergo rate-determining oxidation by Selectfluor to a silver(II) complex. Formation of a defluorinated DABCO radical cation during this step was observed by loss of the N–F signal when following the reaction of silver nitrate with Selectfluor by ^{19}F NMR. Formation of a silver(III) intermediate, which is postulated in the original paper, was ruled out since it usually requires the presence of specific ligands as well as basic conditions. The silver(II) intermediate causes oxidative decarboxylation of the substrate generating an alkyl

radical which abstracts fluorine from a second equivalent of Selectfluor. Addition of sodium persulfate, which is known to oxidise silver(I) to silver(II), was shown to increase the efficiency of the transformation, decreasing the reaction time to 15 minutes. Furthermore, in the presence of $Na_2S_2O_8$ the reaction was also feasible with NFSI which is not a strong enough oxidant on its own to form the silver(II) intermediate.



Scheme 12 Silver catalysed electrophilic fluorodecarboxylation of aliphatic carboxylic acids[47, 54]

In their conclusion, Patel and Flowers point out that this mild and efficient process would be well suited for the development of an ^{18}F-radiolabelling protocol.

2.2 Results and Discussion

The Gouverneur group has developed and validated an ^{18}F variant of Selectfluor, [^{18}F]Selectfluor *bis*(triflate).[55, 56] With this reagent in hand, we sought to expand Li's silver-catalysed fluorodecarboxylation methodology to the radiosynthesis of trifluoromethylarenes, as this reaction profits from mild conditions, short reaction times

and a wide substrate scope. We were interested whether α,α-difluoroaryl acetic acids would allow us to access the desired trifluoromethylarenes when subjected to Li's reaction conditions, and whether we could further extend the scope to perfluoroalkylated products. As mentioned above, Li *et al.* observed that substrate reactivity mirrored radical stability.[47] Dolbier has done extensive work on the properties of fluorinated radicals: Fluorine acts as a strong inductively electron-withdrawing substituent through the σ-bond network. It may also act as a strong π electron-donor, due to the good size and energy match of its lone pair 2p orbitals with those of carbon. In the proposed near-planar α,α-difluoroaryl radical formed from the decarboxylation of α,α-difluoroaryl acetic acids this effect dominates, creating radicals stabilised both through benzylic conjugation into the aromatic ring, as well as conjugation with the fluorine lone-pair p orbitals (Figure 4).[57]

Pittman *et al.* have studied the α,α-difluorobenzyl radical by EPR and found that it exhibits a small hyperfine coupling constant of the unpaired electron with the α-fluorine nuclei of 51.4 G which is indicative of a planar structure.[58] Calculations by Platonov later suggested the structure to be only near-planar, with a slight pyramidal distortion.[59] By corollary, we assume our α,α-difluoroaryl radicals to be near-planar as well.

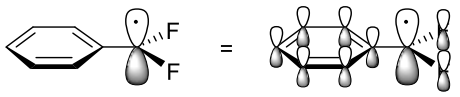
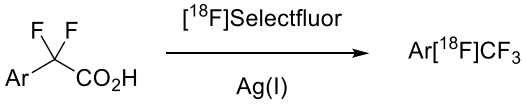


Figure 4 Stabilisation of α,α-difluoroaryl radical *via* π-conjugation

α,α-Difluoroaryl acetic acids hence seem like promising substrates for our endeavour to create trifluoromethylarenes *via* decarboxylative fluorination. We propose the following model reaction for investigation (Scheme 13):

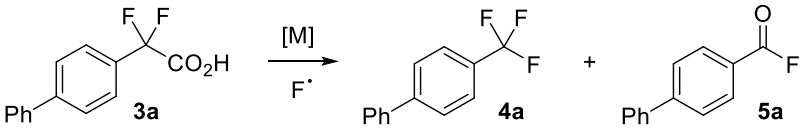


Scheme 13 Proposed radiofluorodecarboxylation for the formation of Ar[^{18}F]CF$_3$

2.2.1 Reaction Development

Initial validation studies were carried out on biphenyl-4-yl(difluoro)acetic acid **3a** which was chosen as a model substrate due to its relative electroneutrality and the formation of a non-volatile trifluoromethylated product **4a** (Table 3). Product **4a** shows a diagnostic downfield shift in the ^{19}F NMR to −62.4 ppm compared to the less deshielded starting material **3a** at −102.37 ppm.

We were pleased to find that refluxing **3a** with 2.0 eq of Selectfluor in the presence of a catalytic amount of $AgNO_3$ afforded fluorodecarboxylated product **4a** in quantitative yield after just one hour (Table 3, Entry 1). A solvent screen revealed that water was essential for the success of the reaction, and no product formation was observed in MeCN, DCM or THF (Entries 2–6). These results corroborate those of Li who suggested that water is necessary for the solvation of the silver catalyst and the fluorinating agent.[47] Selectfluor *bis*(triflate) showed comparable reactivity to the commercial Selectfluor *bis*(tetrafluoroborate) (Entry 7), suggesting that the fluorine atom incorporated into the final product originates from the Selectfluor DABCO motif and not the BF_4^- counterion which confirms an electrophilic fluorination pathway. Furthermore, this result made us optimistic that transfer of the reaction to a radiochemical setting with [^{18}F]Selectfluor *bis*(triflate) would be viable. A control reaction without silver gave none of the desired product and neither did an attempt to use Au(I) catalysis, verifying that this reaction is indeed catalysed by Ag(I) (Entries 8–9). An attempt to combine the sources of silver and fluorine by using nucleophilic AgF together with sodium persulfate as an external oxidising agent was unsuccessful, leading to decomposition of the starting material (Entry 10). The reaction could not be extended to other electrophilic sources of fluorine which either showed no reactivity under the standard conditions (NFSI), or gave substantial amounts of acyl fluoride formation (XeF_2) (Entries 11–14).

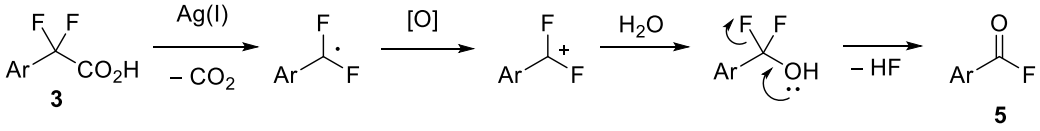


Entry	F Source	Catalyst	Solvent, T, t	Yield **4a** [%][a]	Yield **5a** [%][a]
1	Selectfluor (2.0 eq)	$AgNO_3$ (20 mol%)	acetone/H_2O (1:1), 55 °C, 1 h	>95	0
2	Selectfluor (2.0 eq)	$AgNO_3$ (20 mol%)	acetone, 55 °C, 1 h	0	0
3	Selectfluor (2.0 eq)	$AgNO_3$ (20 mol%)	MeCN, 55 °C, 1 h	0	0
4	Selectfluor (2.0 eq)	$AgNO_3$ (20 mol%)	MeCN/H_2O (1:1), 55 °C, 1 h	0	0
5	Selectfluor (2.0 eq)	$AgNO_3$ (20 mol%)	DCM, 40 °C, 1 h	0	0
6	Selectfluor (2.0 eq)	$AgNO_3$ (20 mol%)	THF, 55 °C, 1 h	0	0
7	Selectfluor *bis*(triflate) (2.0 eq)	$AgNO_3$ (20 mol%)	acetone/H_2O (1:1), 55 °C, 1 h	>95	0
8	Selectfluor (2.0 eq)	-	acetone/H_2O (1:1), 55 °C, 1 h	0	0
9	Selectfluor (2.0 eq)	AuCl (20 mol%)	acetone/H_2O (1:1), 55 °C, 1 h	0	0
9	Selectfluor (2.0 eq)	AuCl (20 mol%)	acetone/H_2O (1:1), 55 °C, 1 h	0	0
10	AgF (1.0 eq)	$Na_2S_2O_8$ (2.0 eq)	acetone/H_2O (1:1), 55 °C, 1 h	0[b]	<5
11	NFSI (2.0 eq)	$AgNO_3$ (20 mol%)	acetone/H_2O (1:1), 55 °C, 1 h	0	0
12	NFSI (2.0 eq)	$AgNO_3$ (20 mol%)	acetone/H_2O (9:1), 70 °C, 1 h	0	0
13	NFSI (5.0 eq)	$AgNO_3$ (20 mol%)	MeCN, 100 °C, 1 h	5	31
14	XeF_2 (1.0 eq)	-	DCM, rt, 1 h	26[b]	29

Conditions: 1.0 eq **3a** (0.2 mmol), fluorine source, metal catalyst, solvent, T, t. [a] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq 1-fluoro-3-nitrobenzene. Remaining mass balance: unreacted starting material unless stated otherwise. [b] Trace starting material only. Mainly decomposition.

Table 3 Screening conditions for the fluorodecarboxylation of 3a

The formation of an acyl fluoride by-product was also observed by Patrick in the reaction of benzoic acid with xenon difluoride, which afforded 20% benzoyl fluoride.[41] Presumably the α,α-difluoroaryl radical formed upon decarboxylation of substrate **3a** is oxidised by xenon difluoride to the carbocation which is then captured by the aqueous solvent. Elimination of HF finally affords acyl fluoride **5a** (Scheme 14). Due to the presence of the strongly electron-withdrawing α-carbonyl, by-product **5a** has a distinctive ^{19}F NMR shift of +17.78 ppm.

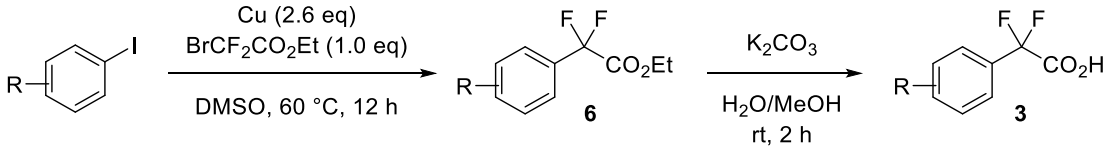


Scheme 14 Proposed mechanism for formation of by-product 5

Under our optimal conditions, 1.0 eq α,α-difluoroaryl acetic acid **3a** was reacted with 2.0 eq Selectfluor and 20 mol% $AgNO_3$ in a 1:1 (*v*/*v*) mixture of water and acetone at 55 °C for 1 h to afford quantitative yields of fluorodecarboxylated product **4a** (Table 3, Entry 1). We thus continued to use these conditions, developed previously by Li *et al.*,[47] to probe the substrate scope of this transformation.

2.2.1.1 Trifluoromethylarenes

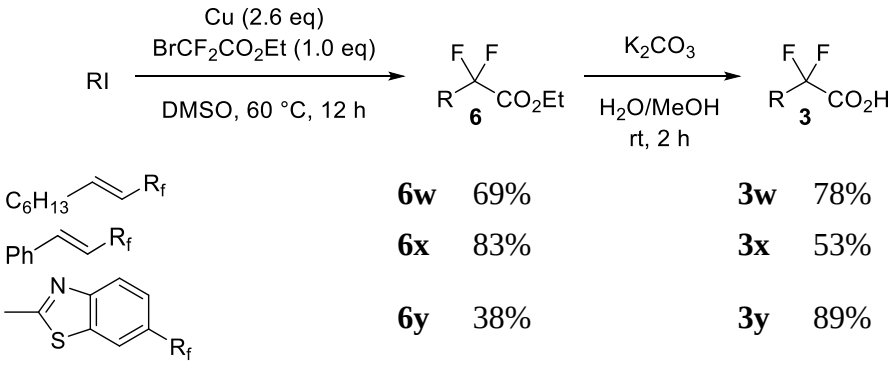
Further substrates were readily prepared from the corresponding aryl iodides by a copper catalysed Ullmann coupling with ethyl bromodifluoroacetate and subsequent hydrolysis of the resulting ethyl ester (Scheme 15, Scheme 16).[60]



R =					
	4-Ph	**6a**	79%	**3a**	85%
	4-OMe	**6b**	37%	**3b**[a]	79%
	3-OMe	**6c**	78%	**3c**[a]	55%
	2-OMe	**6d**	66%	**3d**	98%
	3,4-*bis*OMe	**6e**	63%	**3e**[a]	80%
	4-OH	**6f**	38%	**3f**[a]	0%[b]
	4'-bromobiphenyl	**6g**	54%	**3g**[a]	68%
	4-*t*Bu	**6i**	47%	**3i**	66%
	4-*i*Pr	**6j**	44%	**3j**[a]	75%
	Mes	**6k**	65%	**3k**[a]	40%
	4-acetamide	**6l**	86%	**3l**	48%
	Naphthyl	**6m**	34%	**3m**	68%
	4-Br	**6n**	31%	**3n**[a]	76%
	3-Br	**6o**	49%	**3o**[a]	54%
	4-CN	**6p**	71%	**3p**	86%
	3-CN	**6q**	67%	**3q**	46%
	4-COMe	**6r**	92%	**3r**	53%
	4-NO_2	**6s**	66%	**3s**	87%
	4-CO_2H	**6t**	98%	**3t**	74%
	4-CH_2CO_2Me	**6u**	37%	**3u**	43%
	4-CF_2CO_2Me	**6v**	44%	**3v**	94%

Yields are of isolated compounds. [a] Substrate synthesised by Dr. J. Wolstenhulme. [b] Unstable towards fluoride elimination.

Scheme 15 Synthesis of aromatic α,α-difluoroaryl acetic acids



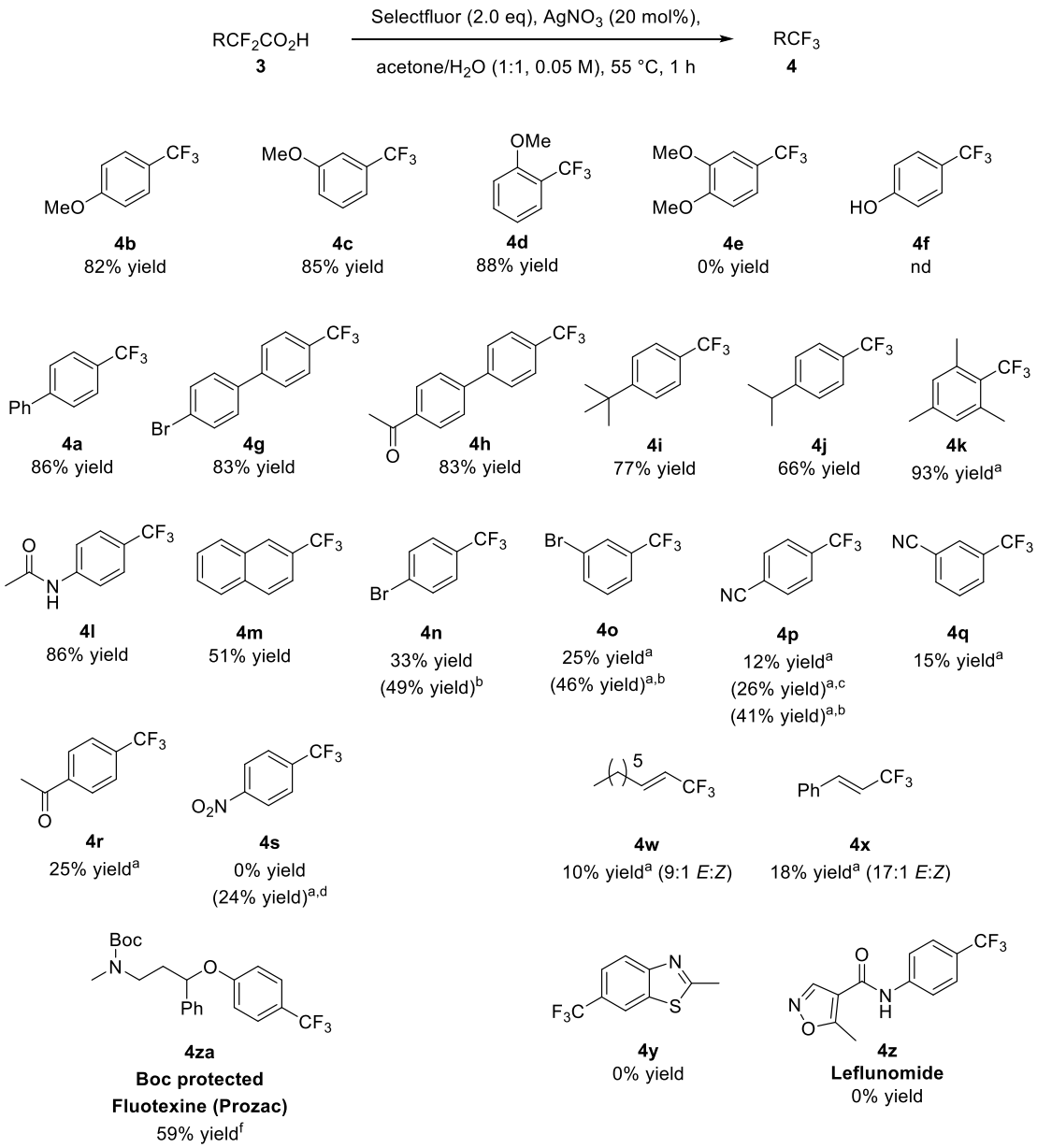
	6w	69%	**3w** 78%
	6x	83%	**3x** 53%
	6y	38%	**3y** 89%

Scheme 16 Synthesis of aliphatic and heteroaromatic α,α-difluoroaryl acetic acids

When substrates **3a–y** were subjected to the fluorodecarboxylation conditions, a clear correlation between electronics and reactivity became apparent (Scheme 17). Electron-rich compounds (**3b**–**3d**) reacted very cleanly to afford the corresponding trifluoromethylated products in excellent yields. Since Selectfluor is known to fluorinate electron-rich aromatic

rings, it came as no surprise that *bis*methoxylated substrate **3e** did not form the desired fluorodecarboxylation product **4e**, but underwent multiple aromatic fluorination instead. *para*-Hydroxy substrate **3f** was unstable towards fluoride elimination and decomposed within minutes of formation. Electroneutral substrates (**3a**, **3g**–**3m**) also underwent facile decarboxylative fluorination in very good yields. Slightly lower isolated yields in this series (**4i**, **4j**) reflect the volatility of the trifluoromethylated products. The efficiency of the transformation decreased dramatically for electron-poor substrates (**3n**–**3r**). In this case, increasing the reaction time did not lead to an appreciable enhancement in yields (**4p**), however doubling the amount of Selectfluor to 4.0 eq and changing the solvent ratio to acetone/H_2O 4:1 afforded a marked improvement (**4n**–**4p**). *para*-Nitro substrate **3s** stands out in the series of electron-poor substrates as it gives no conversion to product whatsoever. We postulate that this is due to the nitro group acting as a radical quencher, since a test reaction with biphenyl-4-yl(difluoro)acetic acid **3a** showed that in the presence of 1.0 eq 3-fluoro-1-nitrobenzene the reaction shut down completely, leading to full recovery of starting material with no trifluoromethylated product being formed. Work by Dr. I. Stenhagen established that the fluorodecarboxylation of substrate **3s** could be implemented with F_2, albeit in low yields.[61] For electron-rich and -neutral substrates, however, Selectfluor was far superior to F_2.

Unfortunately, the reaction could not be extended to vinylic (**3w**–**3x**) or heteroaromatic substrates (**3y**–**3z**), the latter suffering from heteroatom oxidation and subsequent rupture of the ring structure. This limits the application of our methodology to the synthesis of natural products and drug targets; however, work by Dr. S. Mizuta showed that more complex, non-heteroaromatic targets are readily accessible; *e.g.* Fluoxetine, marketed as the antidepressant Prozac, which was synthesised in 59% yield as its Boc protected precursor (**4za**). Deprotection with TFA afforded Fluoxetine triflate in quantitative yield.

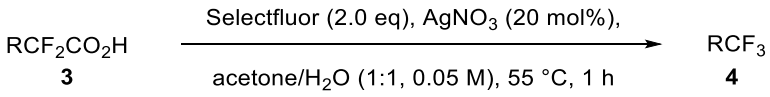


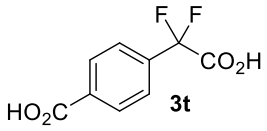
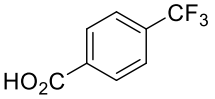
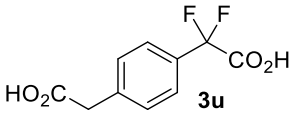
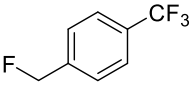
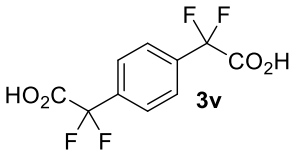
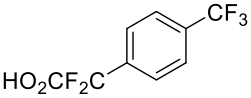
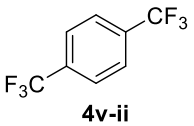
Conditions: 1.0 eq **3** (0.2 mmol), 2.0 eq Selectfluor, 20 mol% $AgNO_3$, acetone/H_2O (1:1), 55 °C, 1 h. [a] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq 1-fluoro-3-nitrobenzene. [b] Yield in parenthesis is for the reaction performed with 4.0 eq of Selectfluor in acetone/H_2O 4:1. [c] Yield in parenthesis is for a reaction time of 5 h. [d] Yield in parenthesis is for the reaction performed by Dr. I. Stenhagen with 3.0 eq F_2, 20 mol% $AgNO_3$, MeCN, –10 °C. [e] Yield in parenthesis is for the reaction performed with 4.0 eq of Selectfluor and 40 mol% $AgNO_3$. [f] Synthesised by Dr. S. Mizuta.

Scheme 17 Substrate scope trifluoromethylated products

Next, the chemoselectivity of the reaction was probed (Table 4). 4-[Carboxy(difluoro)methyl]benzoic acid **3t** selectively afforded 4-(trifluoromethyl)benzoic acid **4t**, confirming that aryl carboxylic acids are unreactive under the presented conditions, as previously observed by Li and co-workers[47] (Entry 1).

[4-(Carboxymethyl)phenyl](difluoro)acetic acid **3u** preferentially formed the *bis*-fluorinated product **4u-i** under the standard reaction conditions, with some trifluoromethylated product **4u-ii** and trace amounts of benzylic fluoride **4u-iii** (Scheme 18). In addition, a large amount of unreacted starting material was recovered, highlighting the fact that this transformation requires an excess of fluorinating reagent for high conversions to product.[ii] (As shown in the mechanism proposed by Patel and Flowers in Scheme 12,[54] one equivalent of Selectfluor acts as an oxidant, while another is required for fluorination.) Increasing the amount of Selectfluor to 4.0 eq and the $AgNO_3$ catalyst loading to 40 mol% pushed the reaction to form exclusively product **4u-i**. The *bis*(difluoroacetic acid) **3v** formed a mixture of *mono*- and *bis*-fluorodecarboxylated products, favouring the *mono*-CF_3 product **4v-i** (Entry 3).

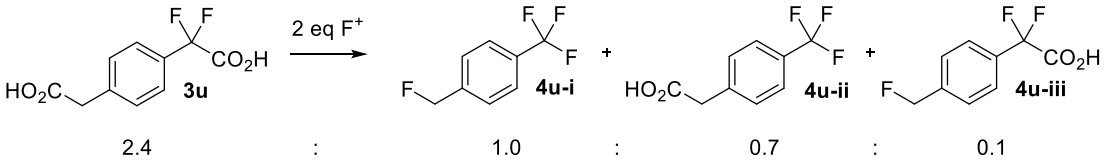


Entry	Substrate	Product	Yield **4** [%][a]
1	 **3t**	 **4t**	49
2	 **3u**	 **4u-i**	16[b] (100)[c]
3	 **3v**	 **4v-i**	62 (73)[c]
		 **4v-ii**	2 (26)[c]

Conditions: 1.0 eq **3** (0.2 mmol), 2.0 eq Selectfluor, 20 mol% $AgNO_3$, acetone/H_2O (1:1), 55 °C, 1 h. [a] ^{19}F NMR yield, determined by integration of the product peak(s) relative to 1.0 eq 1-fluoro-3-nitrobenzene. [b] The reaction also afforded 11% **4u-ii**, 2% **4u-iii** and 38% unreacted **3u** (see Scheme 18). [c] Yield in parenthesis for the reaction performed with 4.0 eq of Selectfluor and 40 mol% $AgNO_3$.

Table 4 Chemoselectivity of fluorodecarboxylation

[ii] This was also observed when substrate **3d** was reacted with a substoichiometric amount of Selectfluor (0.5 eq), which afforded only 38% of **4d** relative to the amount of F^+ used (cf. 88% yield with 2.0 eq Selectfluor).



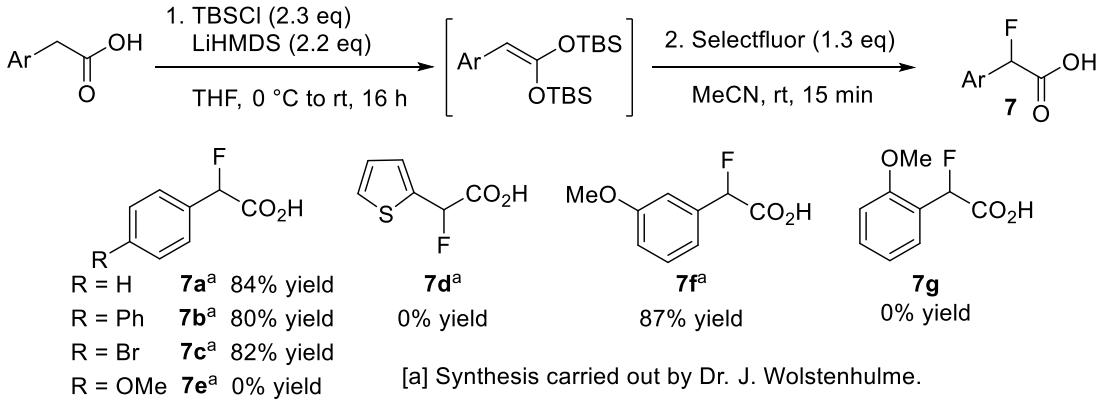
(^{19}F NMR ratios)

Scheme 18 Fluorination of 3u with stoichiometric amounts of Selectfluor

These results show that α-fluorinated benzylic carboxylic acids are of similar reactivity under our fluorodecarboxylation conditions as non-fluorinated benzylic carboxylic acids (Table 4, Entry 3 and Scheme 18), while aryl carboxylic acids are completely unreactive (Table 4, Entry 1). The general reactivity trend can thus be summarised as: Ar–CF_2–CO_2H ≈ Ar–CH_2–CO_2H >> Ar–CO_2H. Electron-rich substrates are more reactive than electron-poor substrates, possibly as a result of radical stabilisation. Therefore, *bis*-functionalised substrates such as **3v** preferentially undergo *mono*-fluorodecarboxylation, due to the electron-withdrawing nature of the trifluoromethyl substituent formed during the first decarboxylative fluorination step which decreases the product's reactivity relative to its precursor.

2.2.1.2 Difluoromethylarenes

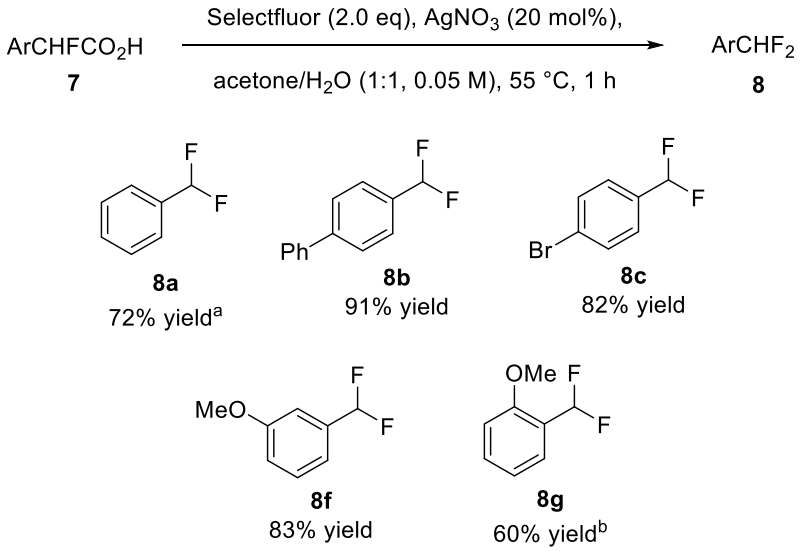
We envisaged it would also be possible to access a difluoromethyl functionality by this methodology, starting from the corresponding monofluorinated carboxylic acids. *In situ* formation of *bis*(silyl)ketene acetals and subsequent electrophilic fluorination with Selectfluor furnished the necessary substrates in good yields (Scheme 19). Electron-rich substrates (**7d**, **7e**, **7g**) were unstable towards fluoride elimination.



Scheme 19 Synthesis of α-fluoroaryl acetic acids 7

The monofluorinated substrates readily underwent fluorodecarboxylation under the conditions presented above to give difluoromethylated arenes **8a**–**8g** with a reactivity profile corresponding to that observed for the trifluoromethylated products (Scheme 20). Methoxylated substrates **7e** and **7g**, as well as thiophene substrate **7d** were unstable towards fluoride elimination; **7d** and **7e** decomposed within minutes of workup so their reactivity could not be probed, whereas the marginally slower decomposition of **7g** enabled us to submit it to the fluorodecarboxylation conditions immediately after its synthesis and obtain **8g** in a moderate yield.

Traditionally, difluoromethyl groups have been accessed through the reaction of aldehydes with diethylaminosulfur trifluoride (DAST).[62] Whilst very fast and efficient, this transformation suffers from a limited substrate scope due to the high reactivity of DAST towards alcohol and carbonyl functional groups. The milder decarboxylative fluorination offers a complementary route towards difluoromethyl groups.



Conditions: 1.0 eq **7** (0.2 mmol), 2.0 eq Selectfluor, 20 mol% $AgNO_3$, acetone/H_2O (1:1), 55°C, 1 h. [a] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq 1-fluoro-3-nitrobenzene. [b] Low yield due to instability of starting material towards fluoride elimination.

Scheme 20 Substrate scope difluoromethylated products

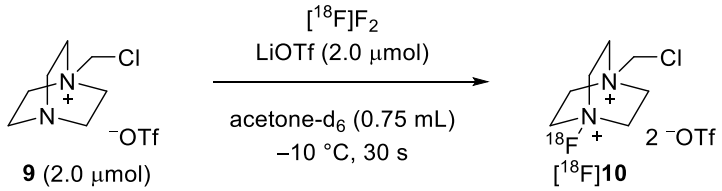
2.2.2 Radiolabelling of Trifluoro- and Difluoromethylarenes[iii]

We were interested in translating our decarboxylative fluorination strategy to a radiochemistry setting with a view to expanding the chemical space available for ^{18}F-radiolabelling. Previously, the group has established [^{18}F]Selectfluor *bis*(triflate) as a valuable electrophilic radiofluorinating reagent.[56] With this expertise at hand, we investigated a radiolabelling protocol for the fluorodecarboxylation of α,α-difluoroaryl acetic acids and α-fluoroaryl acetic acids using this reagent.

[^{18}F]F_2 was produced by the 'post-target' synthesis developed by Bergman and Solin:[29] Irradiation of oxygen-18 enriched water to achieve an $^{18}O(p,n)^{18}F$ nuclear reaction afforded [^{18}F]fluoride which was reacted with iodomethane, yielding gaseous [^{18}F]CH_3F. [^{18}F]F_2 was generated from this intermediate in an electrical discharge chamber with addition of

[iii] All radiochemical work was carried out by Dr. I. Stenhagen in the Turku PET Centre under supervision of Prof. O. Solin.

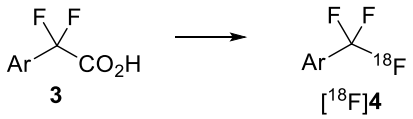
carrier [^{19}F]F_2. This was then bubbled through a vial containing the non-fluorinated Selectfluor-precursor 1-methyl-4-aza-1-azoniabicyclo[2,2,2]-octane triflate **9** and lithium triflate in acetone-d_6 at –10 °C for the radiosynthesis of [^{18}F]Selectfluor *bis*(triflate) [^{18}F]**10** (Scheme 21). All radiolabelling experiments were carried out with aliquots taken from this crude stock solution.



Scheme 21 Radiosynthesis of [^{18}F]Selectfluor bis(triflate)

Model substrate **3a** was used for the optimisation of the radiolabelling conditions (Table 5). Addition of [^{18}F]Selectfluor *bis*(triflate) **10** to a vial containing substrate **3a** and 20 mol% $AgNO_3$ in water and stirring at 55 °C for 30 min afforded none of the desired radiofluorinated product (Table 5, Entry 1). As is the norm for radiochemical reactions, substrate **3a** was present in great excess compared to the fluorine-18 source. In the 'cold' reaction, however, it was observed that 2.0 eq Selectfluor were required to obtain good yields and a substoichiometric amount of the reagent resulted in a dramatic decrease in yield. In order to better mirror 'cold' stoichiometry, a stock solution of 0.1 µmol **3a** and 20 mol% $AgNO_3$ in H_2O (0.01 M) was prepared. 210 µL [^{18}F]Selectfluor *bis*(triflate) **10** was added to a 10 µL aliquot of this stock solution. The mixture was concentrated to about 15 µL and stirred at 55 °C for 30 min (Entry 2). Again, no radiolabelled product was observed. We postulated that the amount of water in this protocol was not sufficient to solubilise the silver catalyst, so a 10-fold more dilute stock solution of **3a** and $AgNO_3$ was produced which allowed for larger aliquots to be taken (Entry 3: 100 µL water, compared to 10 µL in Entry 2). Pleasingly, this resulted in the formation of ^{18}F-labelled **4a** in 9.1 ± 2.4% radiochemical yield. A control reaction showed that no

radiofluorodecarboxylated product was formed when $[^{18}F]F_2$ was bubbled through a solution of **3g** and $AgNO_3$ in acetonitrile at room temperature for 30 seconds (Entry 4). A complex group of radioactive peaks was observed in the radio-HPLC at the expected retention time of the starting material, suggesting unselective $[^{18}F]$ fluorination on the aromatic rings.[61]



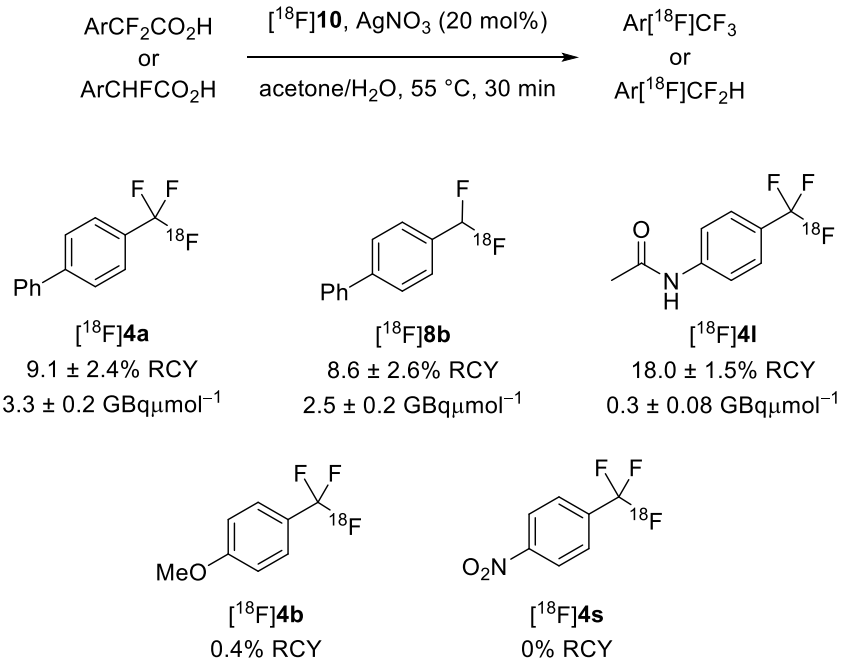
Entry	Substrate (eq)	$^{18}F^+$ source	$AgNO_3$ (eq)	Conditions	Yield $[^{18}F]$**4** [%][a]
1	**3a** (20 µmol)	$[^{18}F]$**10** (100 µL)	20 mol%	H_2O (100 µL) 55 °C, 30 min	0
2	**3a** (0.1 µmol stock solution)[b]	$[^{18}F]$**10** (210 µL)	20 mol%	H_2O (10 µL) 55 °C, 30 min	0
3	**3a** (0.1 µmol stock solution)[c]	$[^{18}F]$**10** (210 µL)	20 mol%	H_2O (100 µL) 55 °C, 30 min	9.1 ± 2.4
4	**3g** (0.5 µmol)	$[^{18}F]F_2$	20 mol%	MeCN (500 µL) 30 s, rt	0

[a] Radiochemical yields determined by radio-TLC and radio-HPLC, n=3. Work done by Dr. I. Stenhagen.[61] [b] 10 µL aliquot. [c] 100 µL aliquot.

Table 5 Optimisation of radiolabelling conditions

With these optimised conditions in hand, the protocol was extended to further substrates (Scheme 22). ^{18}F-labelled 4-(trifluoromethyl)biphenyl $[^{18}F]$**4a** was synthesised in 9.1 ± 2.4% radiochemical yield with a specific activity of 3.3 ± 0.2 GBqµmol^{-1}; its difluoromethyl analogue $[^{18}F]$**8b** was obtained in 8.6 ± 2.6 % RCY with a specific activity of 2.5 ± 0.2 GBqµmol^{-1}. Similarly, the electron-poor *para*-acetamide **4l** afforded good radiochemical yields (18.0 ± 1.5%) but a rather low specific activity of 0.2 ± 0.08 GBqµmol^{-1}. This was presumably due to ineffective $[^{18}F]F_2$ synthesis which lead to a marked decrease in specific activity of the $[^{18}F]$Selectfluor *bis*(triflate) used that day. Surprisingly, the electron-rich *p*-methoxy substrate **3b** which is fluorodecarboxylated in very good yields under 'cold' conditions only afforded 0.4% $[^{18}F]$**4b** in the reaction with

[^{18}F]Selectfluor *bis*(triflate). As expected, *para*-nitro substrate **3s** was unreactive, which corroborates the observations made under 'cold' conditions.

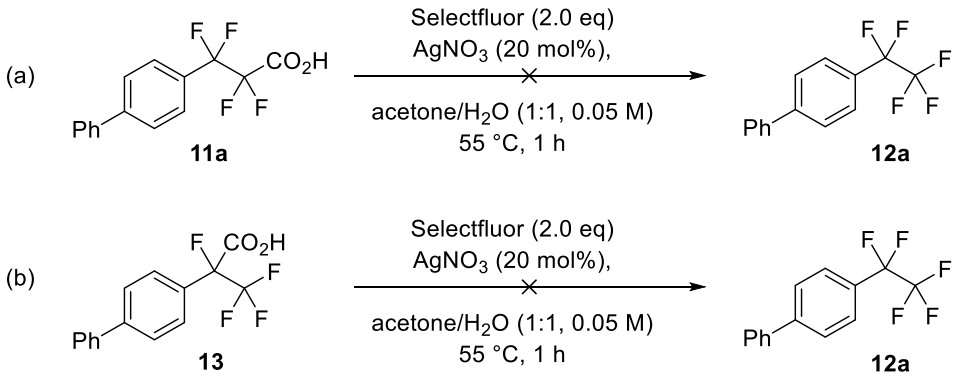


Scheme 22 Radiosynthesis of fluorine-18 labelled trifluoromethyl- and difluoromethylarenes (n=3); work done by Dr. I. Stenhagen[61]

We have thus developed a mild, late-stage radiofluorination protocol for the synthesis of ^{18}F-labelled trifluoromethyl- and difluoromethylarenes with [^{18}F]Selectfluor *bis*(triflate) and silver nitrate. To the best of our knowledge, this is the first radiosynthesis of ^{18}F-difluoromethylarenes, which expands the chemical space of radiolabelled compounds available for PET imaging. Reaction with [^{18}F]F_2 affords only unselective fluorination of the aromatic moiety, showcasing the importance of having a variety of electrophilic fluorinating reagents with complementary reactivity on hand.

2.2.3 Fluorodecarboxylation for the Synthesis of Pentafluoroethyl Motifs

Due to the successful fluorodecarboxylation for the formation of difluoromethyl- and trifluoromethylarenes, we decided to investigate the feasibility of a decarboxylative strategy towards higher perfluoroalkylated substrates.

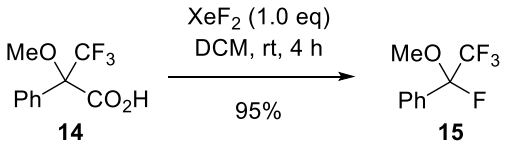


Scheme 23 Unsuccessful fluorodecarboxylation for the formation of 12a

When 3-(biphenyl-4-yl)-2,2,3,3-tetrafluoropropanoic acid **11a** was submitted to Li's fluorodecarboxylation conditions, none of the desired pentafluoroethylated product **10a** was observed (Scheme 23a). Instead, only unreacted starting material was recovered. We postulated that the formation of the pentafluoroethyl radical intermediate presumed in this reaction was prohibited by the destabilising effect of the fluorine substituents *beta* to the radical centre. Due to the stabilising effect of the aromatic π-system observed in the α,α-difluoroaryl radicals above, we synthesised 2-(biphenyl-4-yl)-2,3,3,3-tetrafluoropropanoic acid **13**. However, upon reaction with Selectfluor and catalytic $AgNO_3$ in acetone/water at 55 °C, no fluorodecarboxylation was observed, with full recovery of starting material (Scheme 23b). It seems that the benzylic stabilisation of the radical intermediate is not strong enough to offset the destabilising effect of the β-fluorines.

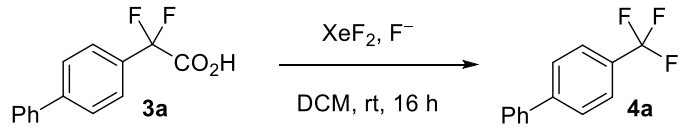
In Patrick's seminal work on xenon difluoride mediated fluorodecarboxylation, one of the substrates investigated was α-trifluoromethyl aryl acetic acid **14** (Scheme 24). In the

presence of the stabilising methoxy substituent, the *beta* fluorines did not seem to exude a detrimental effect on the reaction, as the corresponding fluorinated compound **15** was obtained in 95% yield after reaction with XeF_2 at room temperature for 4 hours.[40, 41]



Scheme 24 XeF_2 mediated fluorodecarboxylation of perfluorinated substrate 14[40, 41]

Encouraged by this result, we decided to investigate the reactivity of xenon difluoride with other perfluorinated carboxylic acids (Table 6, Table 7). Pleasingly, biphenyl-4-yl(difluoro)acetic acid **3a** reacted with 2.0 equivalents XeF_2 in DCM at room temperature to afford 48% of the desired fluorodecarboxylated product **4a** after 16 hours (Table 6, Entry 1). ^{19}F NMR also showed a significant amount (ca. 44%) of other trifluoromethylated by-products, suggesting unselective fluorination on the aromatic ring, as well as trace aldehyde formation. Addition of TBAF trihydrate to the reaction suppressed ring-fluorination and aldehyde formation but yields of the desired product were still low (34%) (Entry 2). When HF/pyridine was used instead of TBAF the reaction proceeded cleanly to afford 90% (74% isolated) **4a** without any by-product formation (Entry 3). A control reaction with HF/pyridine in the absence of xenon difluoride yielded only unreacted starting material, confirming that XeF_2 is necessary for decarboxylation (Entry 4).

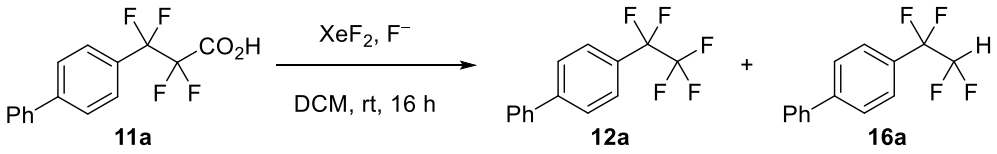


Entry	XeF_2 (eq)	F^- Source (eq)	Yield **4a** [%][a]
1[b]	2.0	-	48 (57)[c]
2[b]	2.0	TBAF[d] (2.0)	34 (35)
3[e]	2.0	HF/py (1.0)	90 (74)
4[e]	-	HF/py (1.0)	0

Conditions: 1.0 eq **3a** (0.2 mmol), XeF_2, DCM, rt, 16 h. [a] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq 3-fluoro-1-nitrobenzene. Yields in parentheses are of the isolated products. [b] 0.13 M. [c] 44% other trifluoromethylated products detected by ^{19}F NMR. [d] $TBAF{\cdot}3H_2O$. [e] 0.07 M.

Table 6 Fluorodecarboxylation of 3a with XeF_2

Perfluorinated 3-(biphenyl-4-yl)-2,2,3,3-tetrafluoropropanoic acid **11a** forms a less stable radical upon decarboxylation. Reaction of **11a** with 1.0 eq xenon difluoride and 1.0 eq HF/pyridine thus afforded only 37% of the desired fluorodecarboxylated product **12a**, together with a significant amount (33%) of protodecarboxylated by-product **16a** as well as some trifluoromethylated compound **4a** and traces of aldehyde (Table 7, Entry 1). Increasing the amount of XeF_2 and HF/py to 2.0 eq each eliminated most of the by-product formation except protodecarboxylation (28%), furnishing **12a** in 70% yield by ^{19}F NMR (Entry 2). Our optimised conditions for the decarboxylative synthesis of perfluorinated substrates were hence determined as: 1.0 eq **11a**, 2.0 eq XeF_2, 2.0 eq HF/pyridine in DCM at room temperature for 16 hours (Entry 2).

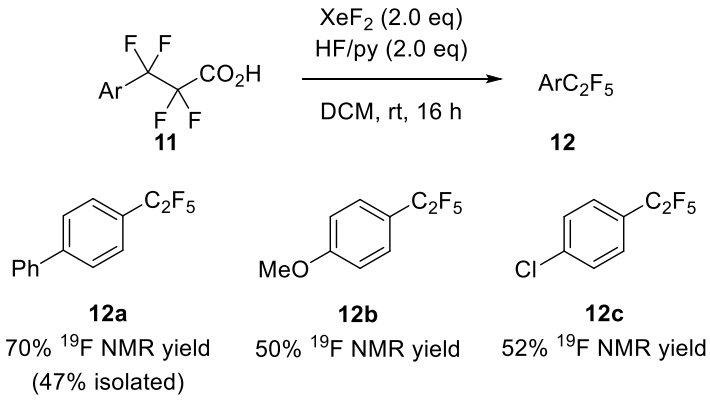


Entry	XeF_2 (eq)	F^- Source (eq)	Yield **12a** [%][a]	Yield **16a** [%][a]
1	1.0	HF/py (1.0)	37	33
2	2.0	HF/py (2.0)	70 (47)	28 (19)

Conditions: 1.0 eq **11a** (0.2 mmol), XeF_2, HF/pyridine, DCM (0.07 M), rt, 16 h. [a] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq 3-fluoro-1-nitrobenzene. Yields in parentheses are of the isolated products.

Table 7 Fluorodecarboxylation of 11a with XeF_2

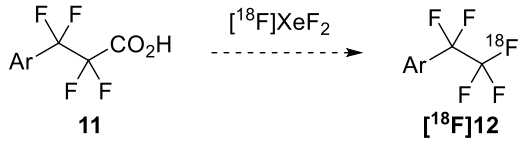
Yields of isolated products for this methodology are low, as the products co-elute with the protodecarboxylated by-products during silica flash column chromatography. However, we were able to show that 4-(pentafluoroethyl)biphenyl **12a** can be synthesised in good yields (70% ^{19}F NMR yield) by this method, while electron-rich 1-methoxy-4-(pentafluoroethyl)benzene **12b** (50%) and electron-poor 1-chloro-4-(pentafluoroethyl)benzene **12c** (52%) are afforded in moderate yields (Scheme 25).



Conditions: 1.0 eq **11** (0.5 mmol), 2.0 eq XeF_2, 2.0 eq HF/py, DCM, rt, 16 h. ^{19}F NMR yields determined by integration of the product peak(s) relative to 1.0 eq α,α,α-trifluorotoluene

Scheme 25 Fluorodecarboxylation for the formation of pentafluoroethylarenes

A fluorodecarboxylation strategy for the synthesis of trifluoromethylarenes from aryl-2,2,3,3-tetrafluoropropanoic acids in the presence of XeF_2 and HF/pyridine has been developed. The radiolabelling of xenon difluoride by Lu and Pike[63] offers the possibility of late-stage electrophilic ^{18}F-labelling of pentafluoroethylarenes *via* the disclosed fluorodecarboxylation protocol (Scheme 26).



Scheme 26 Suggested decarboxylative radiofluorination of pentafluoroethylarenes

2.3 Conclusion

Our aim was the synthesis of perfluoroalkylated substrates *via* a late-stage fluorination strategy suitable for fluorine-18 labelling with a view towards applications in PET.

A decarboxylative fluorination methodology was presented with catalytic silver nitrate and Selectfluor as the fluorine source. α-Fluoroaryl acetic acids and α,α-difluoroaryl acetic acids were converted to the corresponding di- and trifluoromethylarenes in good to

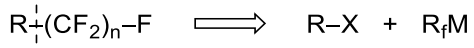
excellent yields. The methodology benefits from milder reaction conditions and thus a larger substrate scope than traditional routes to access these motifs. A radiolabelling protocol based on this methodology was developed, which allowed for the preparation of [^{18}F]labelled di- and trifluoromethylarenes using [^{18}F]Selectfluor *bis*(triflate). This constitutes the first known radiosynthesis of difluoromethylarenes, extending the scope of motifs available for PET imaging. Radiolabelling with [^{18}F]F_2 was unsuccessful, showcasing the need for a variety of different labelling reagents. Pentafluoroethylarenes were accessed *via* a decarboxylative fluorination strategy employing xenon difluoride and HF/pyridine, paving the way for the radiolabelling of this motif with [^{18}F]XeF_2. New mechanistic insight[54] suggests the addition of $Na_2S_2O_8$ could increase the efficiency of the silver-mediated fluorodecarboxylation with Selectfluor, possibly enabling an extension of this methodology to perfluorinated carboxylic acids as well.

Part B

Cross-Coupling Strategies

Part B: Cross-Coupling Strategies

In Part A, a fluorination approach for the formation of perfluoroalkyl motifs was presented. It was discussed that this approach is usually fraught with difficulties, as perfluoroalkylated substrates are very unreactive towards substitution, which also became quickly apparent in our own work. Due to these challenges, it is useful to consider the use of pre-formed labelling reagents. Part B will therefore focus on late-stage trifluoromethylation and perfluoroalkylation *via* metal-mediated cross-coupling with perfluoroalkylated reagents (Scheme 27).

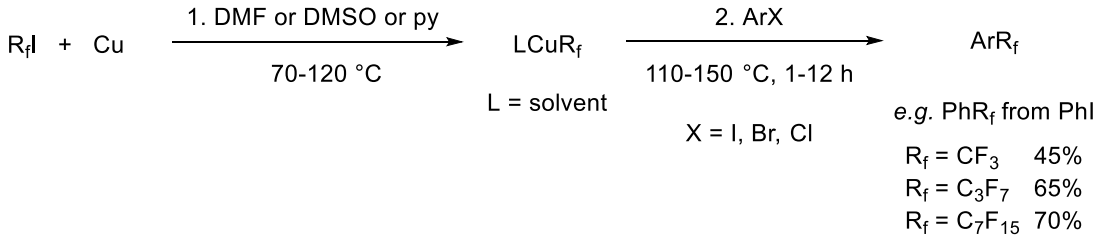


Scheme 27 Perfluoroalkylation *via* cross-coupling

Chapter 3: Transition Metal-Mediated Cross-Coupling with Perfluoroalkylated Reagents

Due to the challenges associated with late-stage fluorination of perfluoroalkylated substrates, a wide variety of cross-coupling strategies with perfluoroalkylated reagents have been developed which will be reviewed in the following section. Most methodologies focus on trifluoromethylation, with occasional examples of higher perfluoroalkylation products mentioned as well.

After forays into perfluoroalkyl mercury[64] and cadmium[65] complexes, which are extremely toxic, the first widely applicable metal-mediated perfluoroalkylation was demonstrated by McLoughlin and Thrower.[66] In their ground-breaking work of 1969 they described the formation of perfluoroalkylcopper species from the reaction of perfluoroalkyl iodides and copper metal in polar aprotic solvents at 100–130 °C. These were used to perfluoroalkylate aryl halides in moderate to good yields (Scheme 28).



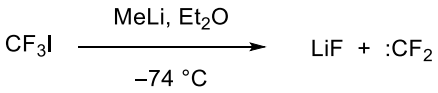
Scheme 28 Perfluoroalkylation with CuR_f[66]

The reaction proceeded both as a stepwise process with isolation of the organocopper species and a one-pot procedure. Use of coordinating solvents was postulated to be of importance for the stabilisation of the perfluoroalkylcopper reagents and the reactivity of the aryl halide coupling partners followed the order I > Br >> Cl. This discovery paved the way for the entire field of transition metal-mediated perfluoroalkylation. This section will

provide an introduction to cross-coupling methodologies with copper, palladium, nickel and silver, as well as photocatalytic approaches employing ruthenium and iridium.

3.1 General Considerations on Perfluoroalkyl-Metal Complexes

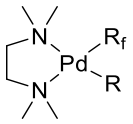
While perfluoroalkyl complexes with alkali and alkaline earth metals are unstable towards disproportionation into metal fluorides and carbenes (Scheme 29),[67, 68] complexes with transition metals have been found to be more thermodynamically stable and less reactive than their hydrocarbon equivalents.[69] (The expression 'perfluoroalkyl-metal complexes' and all its variations will be used herein to describe transition metal complexes unless stated otherwise.)



Scheme 29 Disproportionation of $LiCF_3$[70]

The nature of perfluoroalkyl groups, and specifically CF_3, as ligands has caused some debate. Vivic argues that they act as hard, electron-withdrawing ligands, based on the Pauling electronegativity of χ_p (CF_3) = 3.5.[71] To support this theory he presents electrochemical data that shows the oxidation potential of selected two-coordinate copper complexes increasing with the electron-withdrawing power of the ligands: [(SIPr)Cu(CH_3)] < [(SIPr)Cu(Cl)] < [(SIPr)Cu(CF_3)] (SIPr = 1,3-*bis*(2,6-diisopropyl-phenyl)imidazolidene).[72] Grushin, on the other hand, makes the claim that while a trifluoromethyl group *globally* decreases the electron-density on a molecule, it *locally* increases electron density on the metal centre it is attached to.[69] He refers to calculations made by Pople and Gordon that suggest fluorine substituents cause inductive effects of alternating charge along a carbon chain: $F(\delta^-)–C(\delta^+)–C(\delta\delta^-)–C(\delta\delta^+)$.[73]

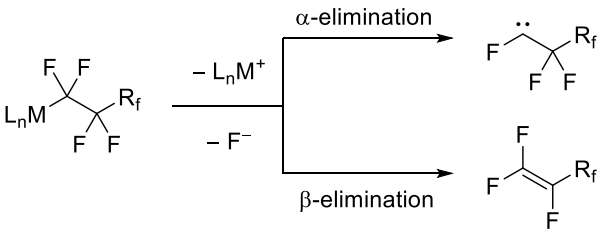
Experimentally, two main observations have been made in square planar [(tmeda)Pd(R_f)(R)] complexes (R_f = CF_3, C_2F_5; R = Me, Ph) (Table 8).[74] First, the palladium–carbon bond lengths follow the order Pd–Me (2.171 Å) > Pd–CF_2CF_3 (2.019 Å) > Pd–CF_3 (1.993 Å) > Pd–Ph (1.990 Å).[74] *I.e.* the metal–carbon bond lengths for perfluoroalkylated ligands are longer and weaker than for phenyl which benefits from π-backbonding to the metal, but shorter and stronger than for alkyl ligands. It has been argued that the s character of the carbon hybrid orbital directed towards Pd increases in the presence of electron-withdrawing perfluoroalkyl substituents according to Bent's rule, resulting in shorter, stronger bonds.[74] (Bent's rule states that "In a molecule, smaller bond angles are formed between electronegative ligands since the central atom, to which the ligands are attached, tends to direct bonding hybrid orbitals of greater p character towards its more electronegative substituents."[75]) This increase in s character is less pronounced with C_2F_5, where one of the fluorine atoms (χ_F = 4.0) is replaced with a less electronegative CF_3 group (χ_{CF3} = 3.5), leading to a lengthening and weakening of the M–CF_2 bond.[74] However, the *trans* influence of CF_3 and C_2F_5 was found to be indistinguishable within experimental error, as indicated by the Pd–N bond lengths *trans* to both ligands being almost identical (Table 8).[74] This suggests that the character of the bonding orbitals is very similar in both cases.



	R_f = C_2F_5 R = Ph	R_f = CF_3 R = Ph	R_f = C_2F_5 R = Me
Pd–C(R_f)	2.019	1.993	2.034
Pd–C(R)	1.990	1.996	2.171
Pd–N (*trans* to R_f)	2.166	2.169	2.180
Pd–N (*trans* to R)	2.213	2.198	2.221

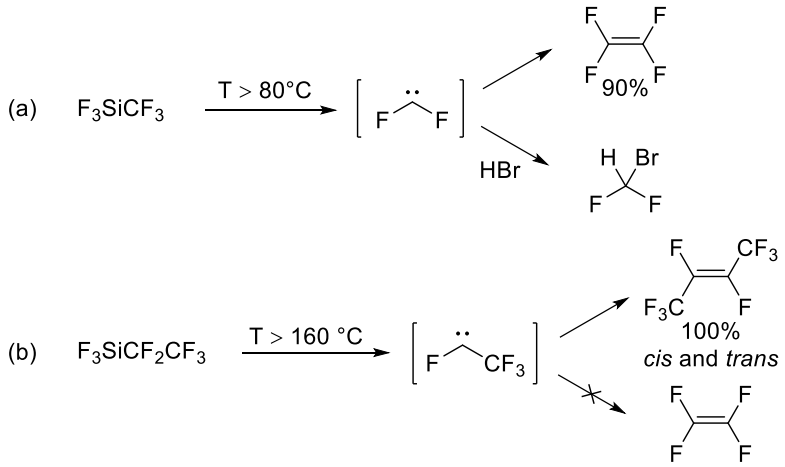
Table 8 Bond lengths [Å] in [(tmeda)Pd(R_f)(R)][74]

Despite the higher stability of perfluoroalkyl metal complexes, the optimisation of many metal-mediated perfluoroalkylation conditions involves minimising the formation of perfluoroalkylated decomposition by-products. Decomposition of perfluoroalkyl-metal complexes may occur *via* one of two mechanisms: (1) α-elimination to form a carbene which then undergoes further reactions, or (2) β-elimination to form an alkene (Scheme 30). Which of these two pathways occurs depends on the nature of the perfluoroalkyl-metal complex and the conditions it is subjected to.



Scheme 30 Decomposition of perfluoroalkyl-metal complexes *via* α or β elimination

Thermolysis of neat F_3SiCF_3 occurs above 80 °C *via* a difluorocarbene to form mainly tetrafluoroethene (TFE), with some traces of C_8F_6 (Scheme 31a). In the presence of HBr, the difluorocarbene is trapped, affording bromodifluoromethane.[76] $F_3SiC_2F_5$ is more thermally stable than its trifluoromethylated equivalent, with no significant decomposition below 160 °C. A mixture of *cis* and *trans* 1,1,1,2,3,4,4,4-octafluorobut-2-ene is formed *via* fluoro(trifluoromethyl)carbene CF_3CF: (Scheme 31b), which may also be trapped in the presence of HBr to form CF_3CFHBr. Interestingly, no evidence of *beta* elimination to afford tetrafluoroethene was observed in the gas phase.[76]



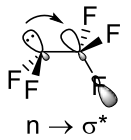
Scheme 31 Thermolysis of F_3SiR_f (R_f = CF_3, C_2F_5)[76]

Gas-phase acidities calculated for CF_3H and CF_3CF_2H show that the latter is more acidic (Table 9).[77, 78] It has been argued that this may be due to 'negative hyperconjugation', *i.e.* anion stabilisation by donation of electron density from the carbanion lone pair electrons into the antibonding σ_{C-F}* orbital of the adjacent CF_3 group (Scheme 32).[79] A similar effect may be stabilising the carbene formed during the thermolysis of $F_3SiC_2F_5$. In solution, however, rapid β-elimination of the carbanion is observed.[7]

	ΔH [kcalmol^{-1}][a]	pK_a[b]
CF_3H	380.5[77]	27 (calc)[78] 32 (exp)[80]
CF_3CF_2H	372.0[79]	-

[a] Gas-phase acidities, calculated by G2(MP2) method. [b] pK_a values: aqueous pK_a calculated from pKa = 0.4453 ΔG^0_{gas} – 135.99 (calc),[78] and determined experimentally in DMSO (exp)[80]

Table 9 Acidities of CF_3H and C_2F_5H

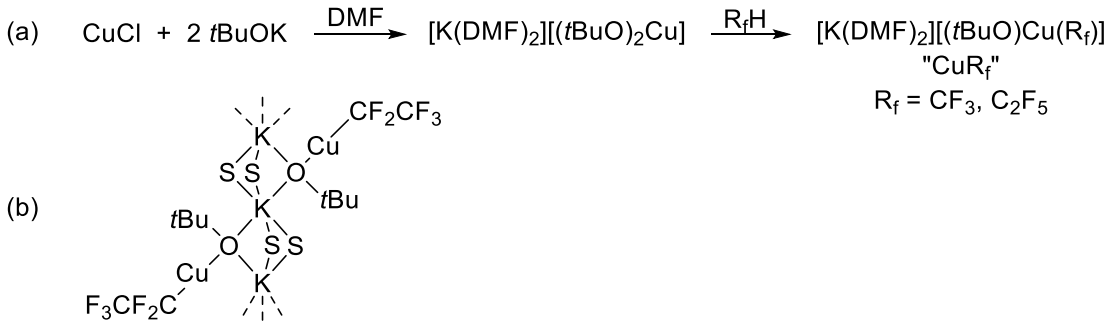


Scheme 32 Negative hyperconjugation in gas-phase $CF_3CF_2^-$ [81]

When bound to a metal surface, a similar trend was observed as in the gas phase: α-elimination for the formation of carbenes was greatly favoured over β-elimination, both

for CF_3 and C_2F_5. Similarly as with unbound perfluoroalkanes, thermal activation of Cu(100) bound Cu–CF_3CF_2 occurred at higher temperatures (42 °C) and slower rates than that of Cu–CF_3 (–113 °C).[82]

Recently, Grushin and co-workers synthesised and analysed the perfluoroalkylcopper complexes [K(DMF)$_2$][(*t*BuO)Cu(R_f)] (R_f = CF_3, C_2F_5) by direct cupration of the corresponding perfluoroalkanes R_fH (Scheme 33a).[74, 83] As predicted by the data presented above, CuC_2F_5 showed enhanced stability towards thermal decomposition and oxidation by air compared to $CuCF_3$. It was also less reactive towards aryl iodides under standard perfluoroalkylation conditions. While the trifluoromethylcopper complex could not be isolated, its pentafluoroethyl variant formed stable white crystals that were amenable to single X-ray diffraction analysis. The complex was found to exist as a polymeric structure in the solid state with Cu–CF_2 bond lengths of 1.983 Å (Scheme 33b).[74]



Scheme 33 (a) Synthesis of "CuR_f"; (b) Structure of "CuC_2F_5"[74]

Higher perfluoroalkylated CuR_f complexes could not be accessed from the corresponding perfluoroalkanes $CF_3(CF_2)_nH$ (n>1), as these preferentially underwent HF elimination over cupration. The reason for this change in reactivity is not yet understood.[74]

To summarise, the main challenges faced in the development of transition metal catalysed perfluoroalkylation reactions are (1) suppression of α/β-fluoride elimination and formation of the resulting by-products, and (2) C–R_f bond formation *via* reductive elimination, which

is difficult due to the strength of the M–R_f bond. Comparison of CF_3 and C_2F_5 as ligands has shown that pentafluoroethyl metal complexes are more thermodynamically stable and less reactive than their trifluoromethyl or alkyl equivalents. The higher stability of MC_2F_5 complexes should make the practical handling of metal-mediated pentafluoroethylation reactions easier. For instance, while the trifluoromethylation of aryl bromides with fluoroform-derived $CuCF_3$ is carried out in a glovebox,[84] only a slight erosion of yield (from >99% to 97%) is observed when the pentafluoroethylation of 2-bromonaphthalene with CuC_2F_5 is carried out outside the glovebox.[74] On the other hand, the lower reactivity of M–C_2F_5 complexes introduces the challenge of developing mild reaction conditions that will afford the desired perfluoroalkylated products while suppressing competing side-reactions. For example, while Me_3SiCF_3 has been used extensively in copper catalysed trifluoromethylation reactions (see below), no successful conditions for the copper-mediated cross-coupling of 1,4-bis(trimethylsilyl)octafluorobutane have been found so far due to competing protodesilylation.[85]

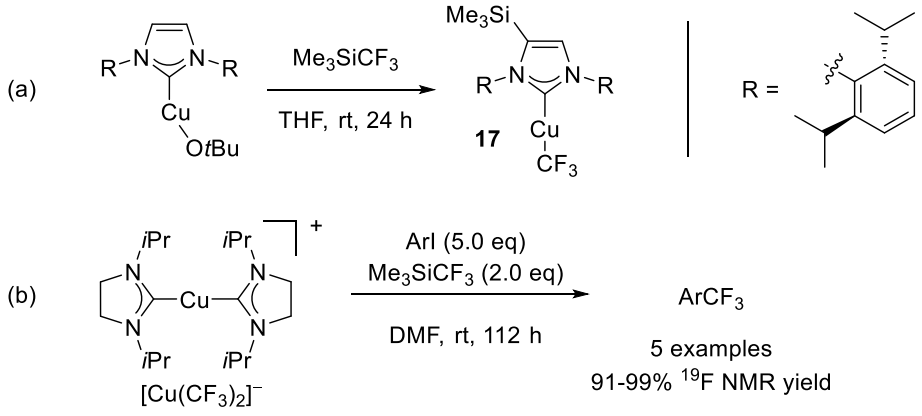
The following section will show how some of these challenges have been overcome, while others still remain.

3.2 Copper

3.2.1 Stoichiometric Trifluoromethylation of Aryl Halides with Copper

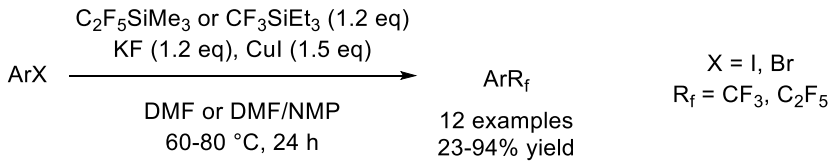
Since the seminal work by McLoughlin and Thrower, by far the most research into metal-mediated perfluoroalkylation has been done with copper.[86] The first spectroscopic evidence of a trifluoromethyl-copper complex was obtained in 1986 by Burton and Wiemers who observed the formation of a $CuCF_3$ species by ^{19}F NMR with a chemical

shift of −28.8 ppm (relative to $CFCl_3$) during the transmetallation of $XCdCF_3$ (X = Cl, Br) with CuBr in DMF at –50 °C, which decomposed upon heating to room temperature to two other organocopper species until only $CuCF_2CF_3$ remained after 11 hours. Addition of HMPA was shown to stabilise the organocuprate, supressing this decomposition.[87] Kolomeitsev *et al.* recently carried out a similar NMR study in which they reacted CuBr with Me_3SiCF_3 and KF in DMF at 0 °C with DMI added for stabilisation.[88] They tentatively assigned the $CuCF_3$ species observed by Burton and Wiemers as $[CuCF_3]KBr$ (−28.8 ppm), and its decomposition products as $[Cu(CF_3)_2]K$ (−32.4 ppm) and $[Cu(CF_3)_4]K$ (−35.7 ppm). It was not until 2008 that the first well-defined $Cu(I)CF_3$ complexes were isolated by Vicic *et al.* (Scheme 34a).[89] Reaction of [(IPr)Cu(O*t*Bu)] with Me_3SiCF_3 in THF at room temperature afforded complex **17** as the major product (IPr = 1,3-*bis*(2,6-diisopropyl-phenyl)imidazol-2-ylidene). Analysis by X-ray diffraction confirmed the incorporation of the TMS group on the aromatic moiety as well as the trifluoromethyl group on the metal centre. To avoid silylation, copper complexes with saturated *N*-heterocyclic carbene (NHC) ligands were developed. These [(NHC)Cu(CF_3)] species existed in dimeric form in the solid state, but afforded efficient trifluoromethylation of aryl halides in the presence of Me_3SiCF_3 which was shown to liberate the monomeric copper complex (Scheme 34b).



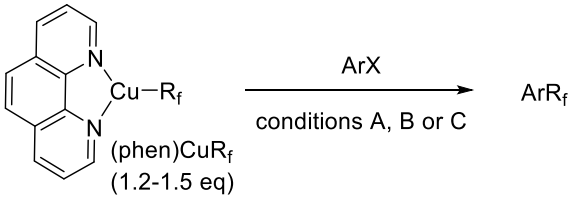
Scheme 34 Synthesis and reactivity of Vicic's well-defined $Cu(I)CF_3$ reagents[89]

Until then, most copper-mediated cross-coupling reactions were realised with stoichiometric amounts of CuI, Me_3SiCF_3 and KF (Scheme 35).[90] Other commonly used trifluoromethyl sources included CF_3X (X = I, Br, H), CF_3CO_2R (R = Na, Me), XCF_2CO_2Me (X = Cl, Br, I), ICF_2SO_2F, $CF_3N(NO)SO_2CF_3$ – an extensive review on this topic was published by Grushin in 2011.[69] The important ligand effects discovered by the Vicic group paved the way towards catalytic transformations, though examples of these are still relatively rare.



Scheme 35 Perfluoroalkylation of aryl halides[90]

Further insight was provided by Hartwig *et al.* with their investigation of the perfluoroalkylation properties of a (phen)CuR_f complex synthesised from $[CuOtBu]_4$, 1,10-phenanthroline and Me_3SiR_f in benzene at room temperature (Table 10).[91-93] This complex was isolated and shown to perfluoroalkylate (hetero)aryl halides (Entries 1–2, 4)[91, 93] and aryl boronate esters (Entry 3)[92] in moderate to good yields. For the trifluoromethylation of aryl iodides it was also shown that similar results could be obtained by generating the copper complex *in situ* from copper(I) chloride, potassium *tert*-butoxide, 1,10-phenanthroline and Me_3SiCF_3 in DMF at room temperature, circumventing the need for a glove-box.[91] The copper-mediated difluoromethylation of aryl and vinyl iodides with Me_3SiCF_2H, CuI and CsF in NMP at 120 °C has also been described by the same group.[94]



Entry	ArX	Conditions[a]	R_f	Results
1	ArI	A	CF_3 C_3F_7	15 examples, 69–99% yield 4 examples, 88–99% yield
2	ArBr	A	CF_3	3 examples, 50–81% yield
3	ArBpin	B	CF_3 C_2F_5 C_3F_7	16 examples, 34–75% yield 3 examples, 31–51% yield 6 examples, 39–64% yield
4	HetArBr	C	CF_3 C_2F_5	44 examples, 32–99% yield 24 examples, 56–99% yield

[a] Conditions A: 1.0–5.0 eq ArI, 1.0–1.5 eq (phen)CuR_f, 2.0 eq KF, DMF or NMP, rt to 50 °C, 18 h; Conditions B: 1.0 eq ArBpin, 1.2 eq (phen)CuR_f, 1.0 eq KF, DMF, 50 °C, 18 h; Conditions C: 1.0 eq HetArBr, 1.2 eq (phen)CuR_f, DMF, 80–100 °C, 8 h.

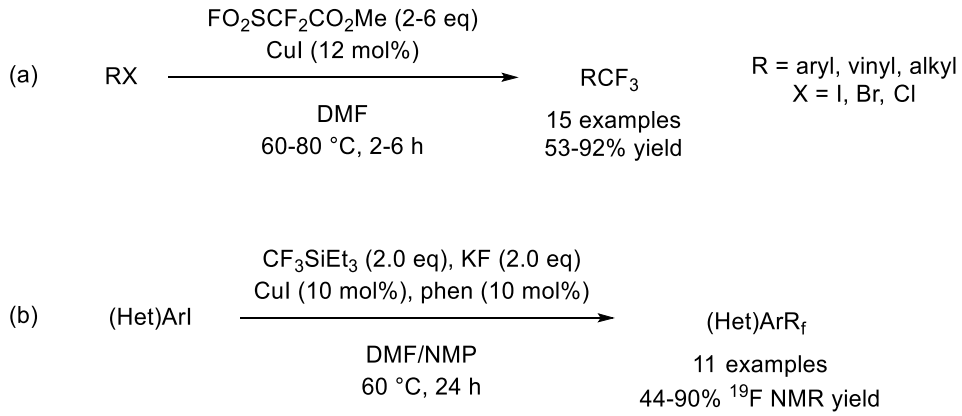
Table 10 Perfluoroalkylation with (phen)CuR_f[91-93]

3.2.2 Catalytic Trifluoromethylation with Copper

3.2.2.1 Copper-Catalysed Trifluoromethylation of Organohalides

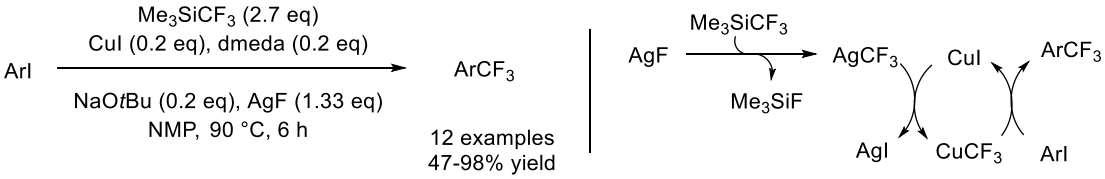
The first copper-catalysed trifluoromethylation was reported by Chen and Wu as early as 1989. Methyl fluorosulfonyldifluoroacetate underwent decarboxylation and desulfonylation in the presence of 12 mol% CuI to afford a difluoromethyl carbene which combined with fluoride and copper to afford the active $CuCF_3$ species *in situ*. Reaction with aryl halides gave the corresponding trifluoromethyl arenes in moderate to good yields (Scheme 36a).[95] This strategy was later adapted to the formation of radiolabelled [^{18}F]$CuCF_3$ by Gouverneur *et al.* (see Chapter 1.4).[33] Recently, a catalytic version of the standard copper-mediated perfluoroalkylation conditions for aryl halides (Scheme 35) was developed by Amii and co-workers, affording a more general substrate scope (Scheme 36b).[96] Aryl and heteroaryl iodides were trifluoromethylated with Et_3SiCF_3 (2.0 eq) in 44–90% ^{19}F NMR yield in the presence of 10 mol% CuI and 10 mol% 1,10-phenanthroline

in DMF/NMP at 60 °C in 24 hours. The phenanthroline ligand was postulated to stabilise the $CuCF_3$ species as well as accelerating Ar–CF_3 reductive elimination by increasing electron-density on the metal centre.



Scheme 36 Copper-catalysed trifluoromethylation[90, 95]

Weng *et al.* discovered a cooperative effect of silver in copper-catalysed trifluoromethylation of aryl iodides.[97] First, AgF is thought to react with Me_3SiCF_3 and dmeda to form a silver–CF_3 complex, inhibiting decomposition of Me_3SiCF_3 to Me_3SiF and a difluorocarbene. Transmetallation with CuI then forms the active $CuCF_3$ trifluoromethylating species which efficiently trifluoromethylates both electron-rich and electron-poor aryl iodides (Scheme 37).

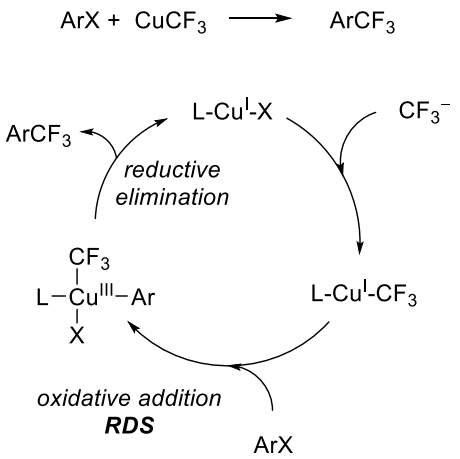


Scheme 37 Cooperative effect of Ag in Cu-catalysed trifluoromethylation of ArI[97]

Alternative reagents to Me_3SiCF_3 have recently been developed for copper-catalysed cross-coupling; notably Gooßen's reagent $(MeO)_3B(CF_3)^-K^+$ (synthesised from Me_3SiCF_3 and $B(OMe)_3$ in the presence of KF),[98] hemiaminals of trifluoroacetaldehyde,[99]

trifluoroacetates such as CF_3CO_2Na,[100] fluoroform CF_3H,[101] and electrophilic iodine and chalcogen salts derived from Me_3SiCF_3 (Umemoto's and Togni's reagents).[102-104]

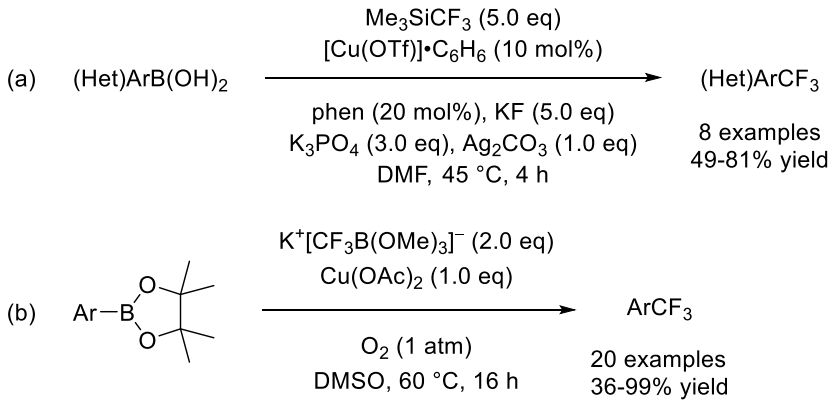
The combining characteristics of the methods summarised above are high temperatures, long reaction times and coordinating (polar, aprotic) solvents, as well as an order of reactivity that follows the trend ArI > ArBr >> ArCl. Combining experimental and computational results, Grushin proposed the following reaction mechanism (Scheme 38):[105] In the absence of other ligands, the solvent (in this case DMF) acts as a stabilising ligand for the $CuCF_3$ complex (which was derived from the cupration of fluoroform for this study). Addition of extra ligands with high affinity to Cu(I) inhibits the cross-coupling reaction. Reaction kinetics were determined by ^{19}F NMR and shown to be overall second order, *i.e.* first order in both ArX and $CuCF_3$. This suggests that oxidative addition of the aryl halide to $CuCF_3$ is rate-determining, followed by rapid reductive C–C elimination to furnish the trifluoromethylated products. A radical mechanism was ruled out by radical clock experiments and DFT calculations. Computational ΔG^0 values also disfavour an SET mechanism. Hammett plot analysis of the reaction indicated a significant –M effect on the oxidative addition step, *i.e.* an accelerated rate for mesomerically electron withdrawing para-substituents on the aromatic substrate. DFT calculations were able to accurately reproduce the experimental Hammett data.



Scheme 38 Mechanism for $CuCF_3$ cross-coupling with aryl halides (L = DMF)[105]

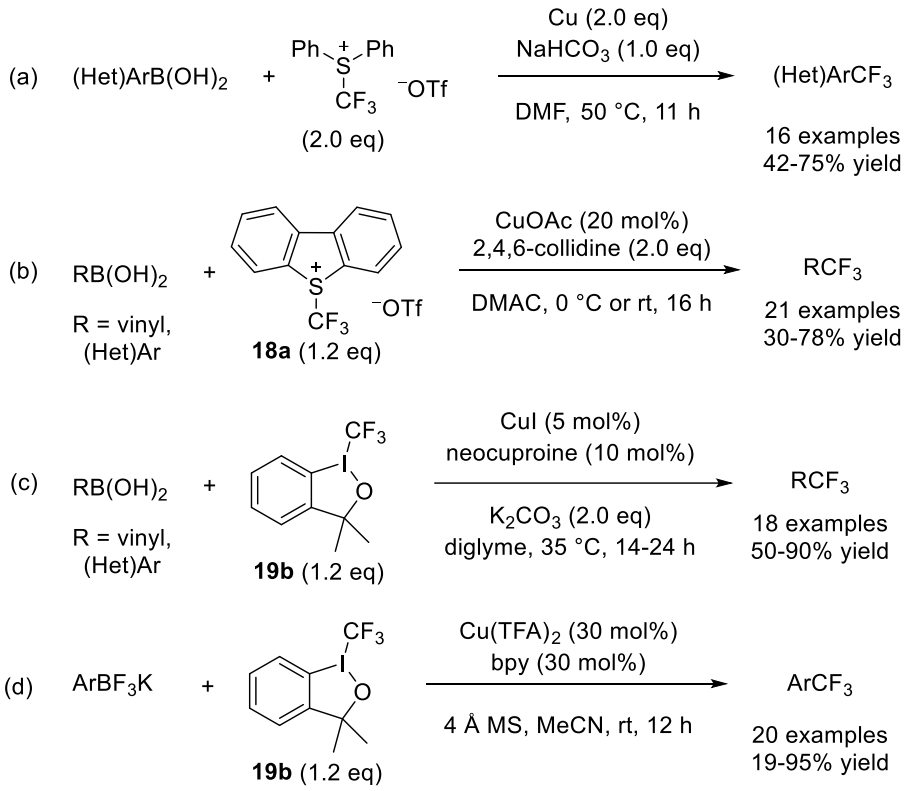
3.2.2.2 Copper-Mediated Trifluoromethylation of Organoboronates

Beside (hetero)aryl halides, boronic acids and esters as well as trifluoroborate salts undergo efficient trifluoromethylation under copper catalysis. Qing and co-workers developed the first catalytic oxidative Chan-Lam like trifluoromethylation of aryl and vinyl boronic acids with $[Cu(OTf)]\cdot C_6H_6$ in 2010 (Scheme 39a). Similar to the reaction mechanism described by Grushin for aryl iodides, a $CuCF_3$ reagent formed *in situ* from copper triflate and Me_3SiCF_3 is thought to transmetallate with the boronic acid substrate in the presence of an oxidant to afford an Ar–Cu(III)–CF_3 species from which the desired trifluoromethylated products reductively eliminate. Initial catalyst loadings of 60 mol%[106] could be dropped to 10 mol% when Me_3SiCF_3 was added slowly to the reaction *via* a syringe pump to avoid fast formation and decomposition of the $CuCF_3$ intermediate.[107] A large excess of Me_3SiCF_3 (5.0 equivalents) is necessary for the reaction to proceed in moderate to good yields. The Gooßen group was able to improve on known protocols by using pinacol boronic esters which reduce the introduction of water and other proton sources into the reaction (Scheme 39b).[108] The formation of protodeborylated side-products was thus reduced without the need for addition of bases or molecular sieves to the reaction.



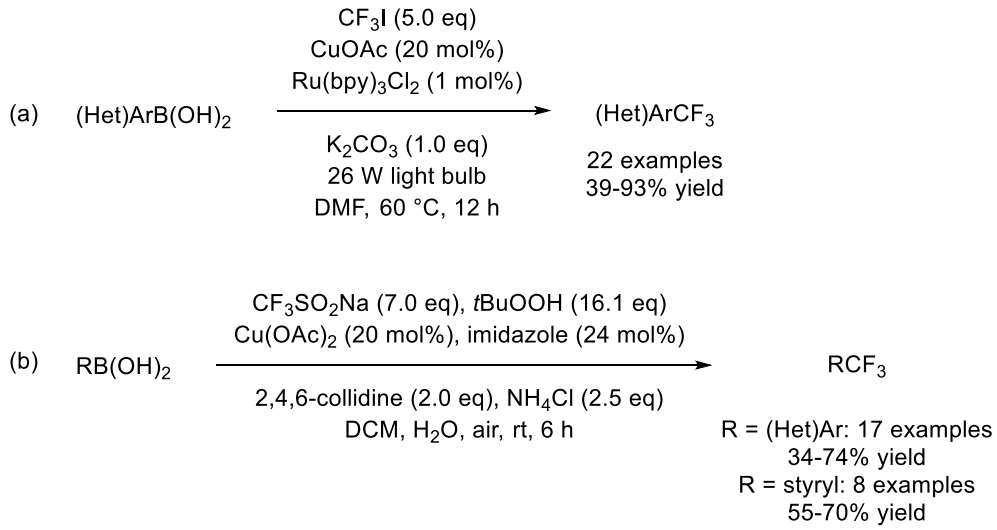
Scheme 39 Nucleophilic copper-mediated trifluoromethylation of boronic acids and esters[107, 108]

Electrophilic strategies have been developed which do not require the addition of an oxidant. Xiao demonstrated the stoichiometric trifluoromethylation of (hetero)aryl boronic acids with a trifluoromethyl sulfonium salt and copper(0) in moderate yields (Scheme 40a).[109] The groups of Liu and Shen developed copper(I)-catalysed trifluoromethylation reactions of aryl and vinyl boronic acids under mild conditions using similar electrophilic CF_3 sources (Scheme 40b,c).[110] The authors postulate that, unlike the reactions discussed so far, no Cu(I)CF_3 intermediate is formed. Instead, the boronic acid substrates react with the copper catalyst to give a Cu(I)Ar species which is transformed into Ar–Cu(III)–CF_3 in the presence of an electrophilic trifluoromethyl source. The trifluoromethylated products are liberated by reductive elimination. Similar reactivity is observed for potassium trifluoroborate salts in the presence of a Cu(II) catalyst (Scheme 40d).[111]



Scheme 40 Electrophilic copper-mediated trifluoromethylation of boronic acids and esters[109-111]

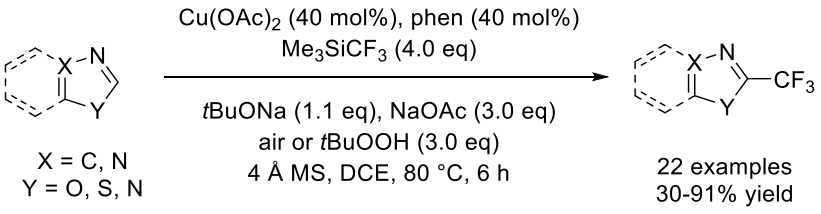
Sanford has combined copper and light-mediated ruthenium catalysis for the radical trifluoromethylation of (hetero)aryl boronic acids (Scheme 41a; for more detail see section 3.6.2.2). The formation of higher perfluoroalkylated aryls (4-Ph-C_6H_4-R_f, R_f = C_4F_9, $C_{10}F_{21}$) with the corresponding perfluoroalkyl iodides was also successful. The Beller group recently developed a similar protocol, in which the perfluoroalkyl radicals were not formed *via* photocatalysis, but by peroxide radical initiators (Scheme 41b).[112] While sodium trifluoromethanesulfonate is cheaper and easier to handle than iodotrifluoromethane, a large excess of the radical $CF_3^{\bullet}$ source is still required.



Scheme 41 Radical copper-catalysed trifluoromethylation of boronic acids[112, 113]

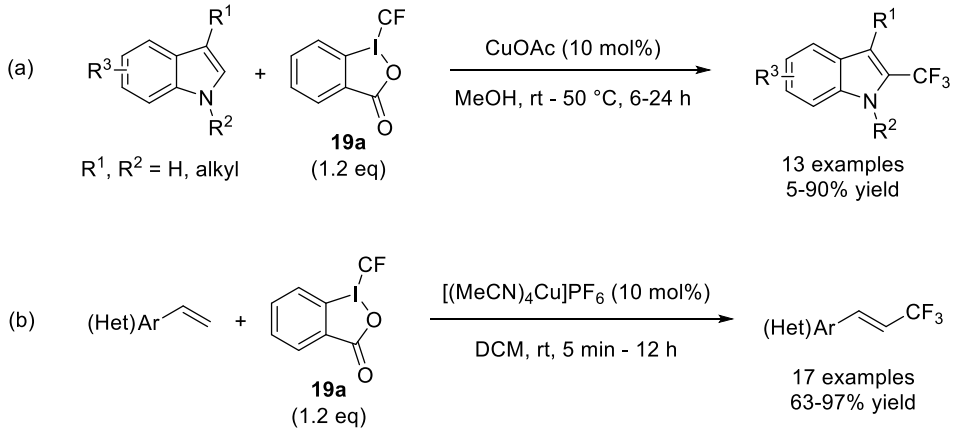
3.2.2.3 Copper-Catalysed Trifluoromethylation *via* C–H Activation

C–H trifluoromethylation with nucleophilic CF_3 reagents has been realised *via* copper(II) catalysis: Chu and Qing demonstrated stoichiometric oxidative trifluoromethylation of terminal alkynes with CuI, 1,10-phenanthroline and Me_3SiCF_3 in the presence of KF and air in moderate to good yields.[114] This strategy was extended to the catalytic trifluoromethylation of highly activated heteroaromatics with 40 mol% $Cu(OAc)_2$ and air or peroxides acting as the oxidant (Scheme 42).[115] The authors proposed that the Cu(II) pre-catalyst is transformed into a Cu(I) species under the reaction conditions, which forms $CuCF_3$ in the presence of Me_3SiCF_3. Ligand exchange with the aromatic substrate affords an Ar–Cu(II)–CF_3 complex which is oxidised to copper(III) from which reductive elimination of the product occurs.



Scheme 42 Nucleophilic copper-catalysed C–H trifluoromethylation[115]

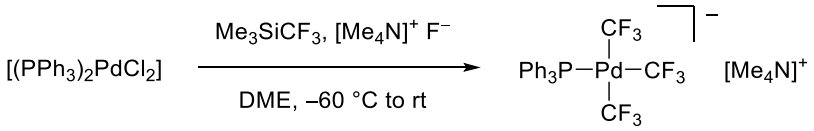
The use of electrophilic and radical CF_3 sources for catalytic C–H trifluoromethylation is more common than that of nucleophilic reagents. Togni's benziodoxolone **19**, in particular, has found widespread application. Sodeoka *et al.* developed the trifluoromethylation of indoles with Togni's reagent **19a** under ligandless Cu(I) catalysis (Scheme 43a).[116] Later, similar conditions were also shown to trifluoromethylate electron-rich terminal alkenes *via* a formal oxitrifluoromethylation-elimination process (Scheme 43b).[117] Similar procedures have been developed for pivanilides,[118] hydrazones,[119] and quinones,[120] however as of yet no C–H trifluoromethylation of unactivated substrates has been achieved.



Scheme 43 Electrophilic copper-catalysed C–H trifluoromethylation[116, 117]

3.3 Palladium

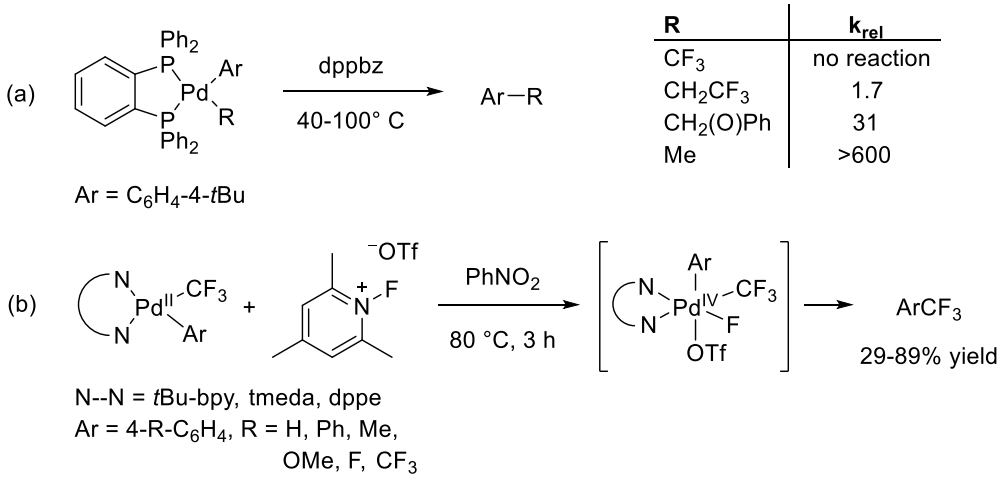
Perfluoroalkyl palladium complexes have been known since the 1960s. The first examples were synthesised by oxidative addition of perfluoroalkyl iodides to palladium; *e.g.* the reaction of iodotrifluoromethane with tetrakis(triphenylphosphine)palladium afforded $[(PPh_3)_2Pd(CF_3)(I)]$.[121] Later, it was also shown that CF_3^- could displace halogen and monodentate phosphine ligands on palladium centres (Scheme 44).[122] Tightly binding bidentate phosphine and amino ligands are inert towards this displacement, allowing for the synthesis of a wide selection of perfluoroalkylated palladium complexes.[69]



Scheme 44 Synthesis of perfluoroalkyl palladium(II) complexes[122]

3.3.1 Pd(II/IV)-Catalysed Trifluoromethylation

For a long time, however, it was unclear whether C–CF_3 reductive elimination from palladium(II) was possible, due to the great strength and inertness of bonds between late transition metals and perfluoroalkyl groups.[69] Hartwig *et al.* demonstrated that in Ar−Pd(II)−X systems the fastest reductive elimination occurs for the most nucleophilic, electron-donating heteroatoms, while electronegative heteroatoms impart ionic character to the M–X bond, increasing the bond strength and hence decreasing its reactivity. [(dppbz)Pd(CF_3)(Ph)], for example, is inert to reductive elimination at elevated temperatures, while [(dppbz)Pd(Me)(Ph)] rapidly forms Ph–Me at 15–40 °C (Scheme 45a).[123]

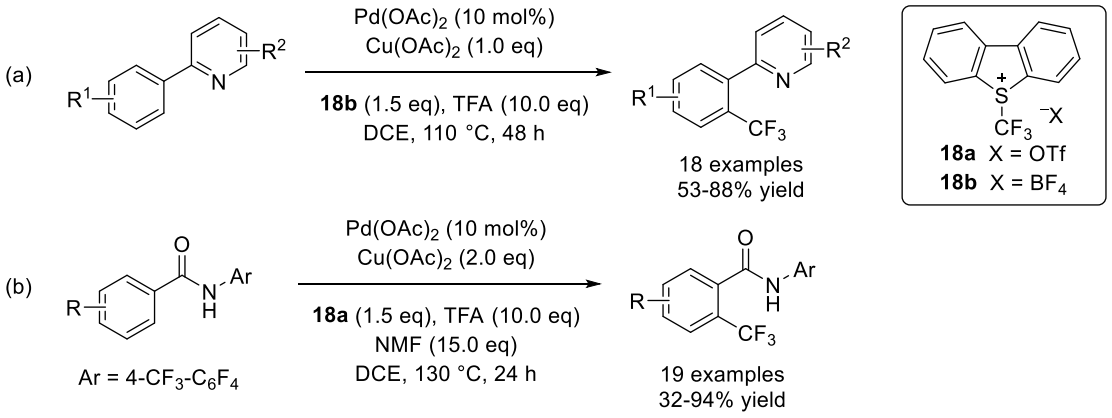


R	k_{rel}
CF_3	no reaction
CH_2CF_3	1.7
$CH_2(O)Ph$	31
Me	>600

Scheme 45 Reductive elimination (a) from Pd(II); (b) from Pd(IV)[123, 124]

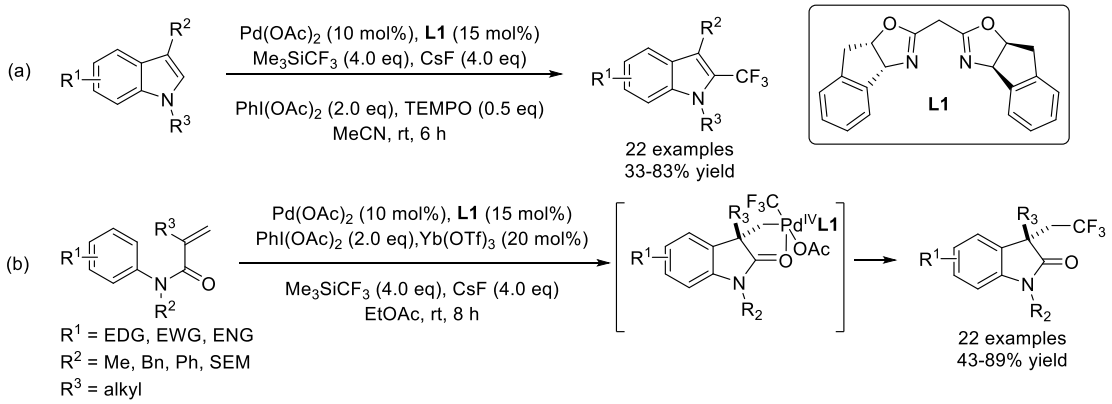
Reductive elimination is generally believed to occur faster from electron-poor transition metals, as electron density on the metal centre increases during the process. Oxidation of

the metal can often induce reductive elimination in more sluggish systems.[125] For example, reductive elimination is known to occur more readily from Pd(IV) than from Pd(II) complexes.[126] It was thus demonstrated by Sanford and co-workers that in the presence of an N–F reagent which was able to oxidise Pd(II) to Pd(IV), complexes of the form $[L_2Pd(Ar)(CF_3)]$ (where L_2 is a bidentate nitrogen-based ligand) underwent efficient aryl−CF_3 reductive elimination at just 80 °C (Scheme 45b).[124] This led to the first Pd(II/IV) catalysed C–H trifluoromethylation of electron-rich and electroneutral arenes bearing a variety of nitrogen-heterocyclic *ortho*-directing groups (Scheme 46a).[127] The Yu group showed that in the presence of catalytic $Pd(OAc)_2$, Umemoto's reagent **18b** as the CF_3 source and oxidant, $Cu(OAc)_2$ and trifluoroacetic acid, the desired trifluoromethylated arenes were obtained in 53–88% yield. Functional groups that can act as ligands to palladium, *e.g.* hydroxyl and carbonyl groups, were not tolerated. This issue was overcome when NMF was added as an acidic amide auxiliary with high binding affinity towards palladium (Scheme 46b).[128] A very similar transformation of acetanilides was developed by Shi and co-workers, using pivalic acid instead of TFA and without addition of NMF.[129] The mechanism of these reactions, in particular the role of the copper and acid additives, still requires elucidation.



Scheme 46 Pd(II/IV)-catalysed electrophilic C–H trifluoromethylation[127, 129]

Liu *et al.* demonstrated a Pd(II/IV) C–H trifluoromethylation with a nucleophilic source of CF_3 (Scheme 47a).[130] The use of PIDA as oxidant and TEMPO to suppress radical side-reactions allowed them to employ Me_3SiCF_3 as a nucleophilic trifluoromethyl source for the trifluoromethylation of indoles at room temperature in low to good yields. The group later followed a similar strategy to develop a tandem cyclisation–trifluoromethylation of activated alkenes (Scheme 47b).[131] $Pd(OAc)_2$ mediated cyclisation of a vicinal aromatic ring onto the alkene is thought to afford a Pd(II) intermediate stabilised by a β-carbonyl. Oxidative addition of CF_3^- in the presence of PIDA yields a Pd(IV) intermediate from which facile C–CF_3 reductive elimination occurs. Addition of the Lewis Acid $Yb(OTf)_3$ in catalytic amounts accelerated the reaction by activating the substrates.

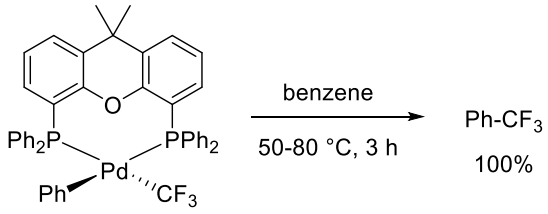


Scheme 47 Pd(II/IV)-catalysed nucleophilic C–H trifluoromethylation[130, 131]

3.3.2 Pd(II/0)-Catalysed Trifluoromethylation

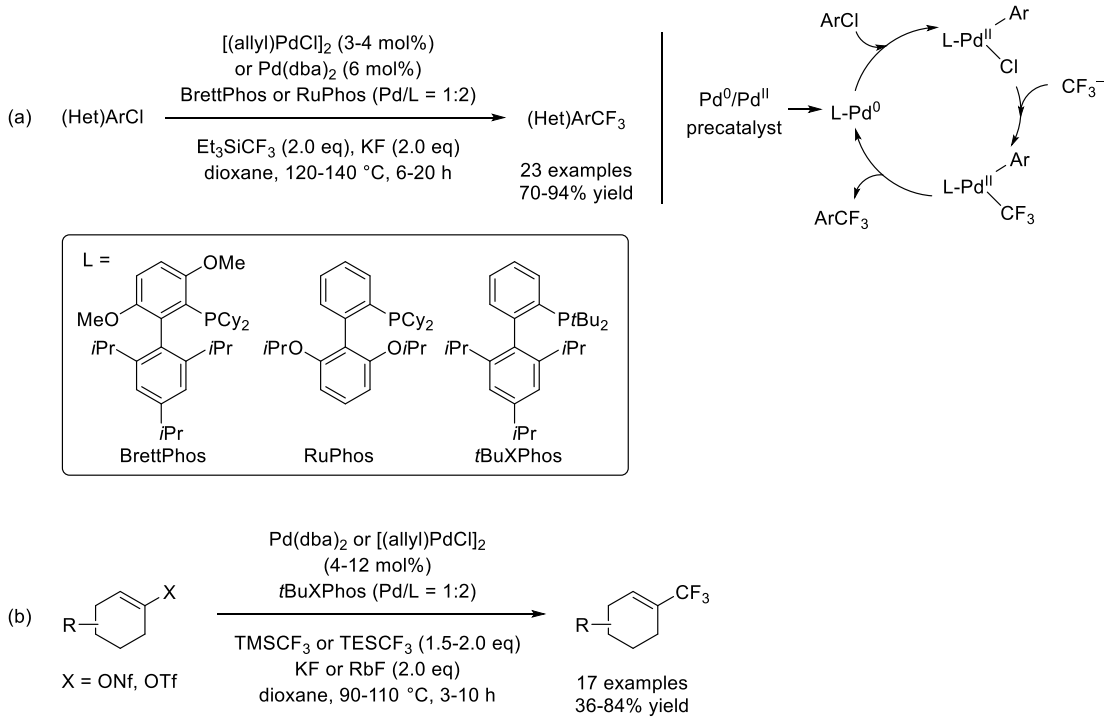
When Grushin *et al.* further investigated C–CF_3 reductive elimination from Pd(II), they found that palladium complexes with rigid, *cis*-chelating bidentate ligands (*e.g.* dppe, dppp, dppbz, tmeda) or monodentate phosphine ligands (*e.g.* PPh_3) preferentially underwent competing C–P or C–N reductive elimination. However, clean aryl–CF_3 reductive elimination was observed from [(XantPhos)Pd(Ph)(CF_3)] (Scheme 48). The authors

postulate that this is due to the flexibility of XantPhos, a *trans*-chelating ligand with a wide bite angle.[132]



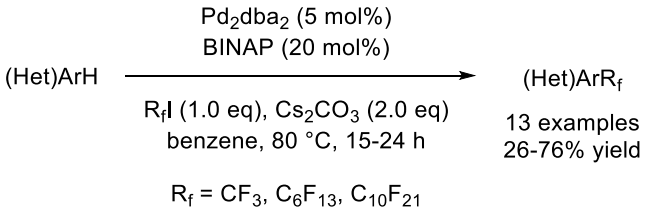
Scheme 48 C–CF_3 reductive elimination from (XantPhos)Pd(II)[132]

This paved the way for the first oxidant-free Pd(II/0) trifluoromethylation, developed by Buchwald *et al.* in 2010 (Scheme 49a).[133] The advantage of palladium over copper is that less activated aryl chlorides can be used as substrates which are significantly cheaper than aryl iodides. Oxidative addition of ArCl to a palladium(0) catalyst affords an Ar–Pd(II)–Cl complex which undergoes ligand exchange with CF_3^-. The resulting Ar–Pd(II)–CF_3 reductively eliminates at 120–140 °C in dioxane, affording electron-rich and electron-poor trifluoromethylated arenes and heteroarenes in good to excellent yields. Bulky BrettPhos successfully enabled reductive elimination for most substrates, however *ortho*-substituted aryl chlorides gave better yields with the slightly less bulky RuPhos. The reaction was later extended to cyclic vinyl triflates and nonaflates to afford trifluoromethylated cyclohexenes (Scheme 49b).[134]



Scheme 49 Palladium(II/0)-catalysed trifluoromethylation[133, 134]

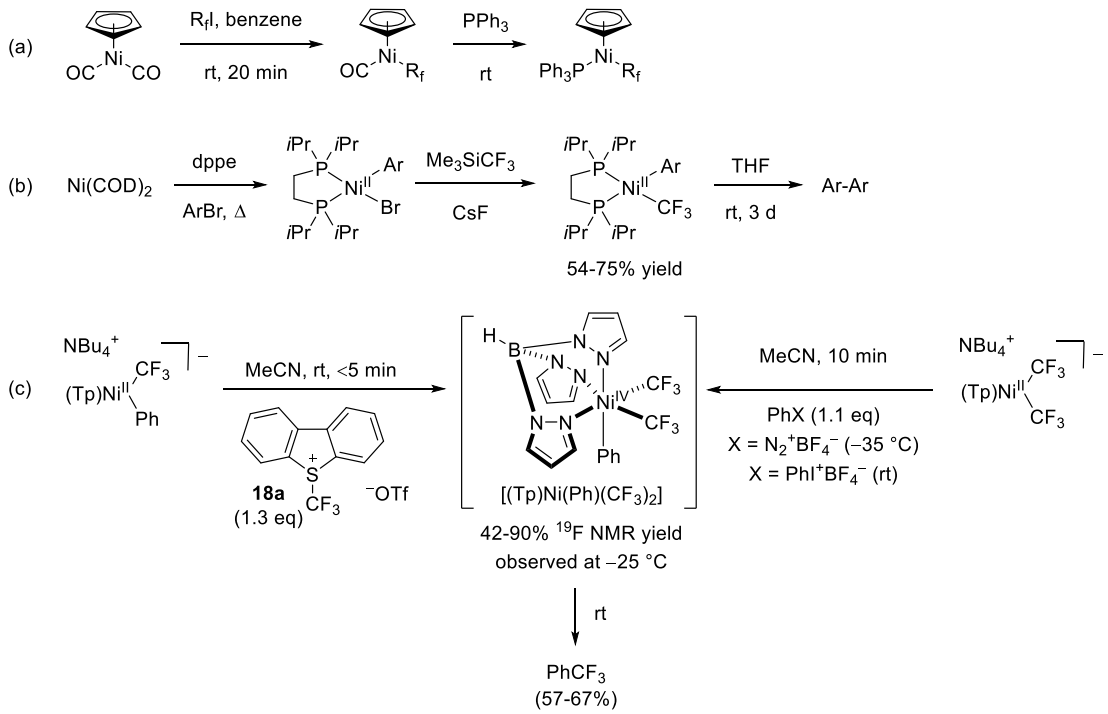
The Sanford group later developed a C–H perfluoroalkylation with perfluoroalkyl iodides (Scheme 50).[135] The authors postulate that oxidative addition of R_fI to Pd(0) afforded a R_f–Pd(II)–I complex. Reaction with the arene *via* C–H activation gives R_f–Pd(II)–Ar from which reductive elimination of the product occurs. Since addition of radical scavengers did not affect the yields of the reaction, a free radical mechanism is excluded, though a "caged", palladium-associated $R_f^{\bullet}$ radical may be involved.



Scheme 50 Palladium(II/0)-catalysed perfluoroalkylation[135]

3.4 Nickel

The first well-defined perfluoroalkyl nickel(II) complexes were synthesised in the 1960s *via* oxidative addition of perfluoroalkyl iodides to nickel carbonyl complexes (Scheme 51a).[136] The resulting structures were air-stable solids that were amenable to X-ray crystallographic analysis.[137] However, the chemistry of these complexes received little attention in the literature until the Vicic group began to explore their use in cross-coupling reactions in 2007.[138] Since nickel has a range of easily accessible oxidation states (from −1 to +4), they postulated that Ar–CF_3 reductive elimination from nickel(II) could be oxidatively induced. To this end, a series of [(dppe)Ni(Ar)(CF_3)] complexes were prepared from $Ni(COD)_2$, however thermal decomposition afforded Ar–Ar reductive elimination, and addition of oxidants – such as PhZnBr, $ZnBr_2$ or H_2O – only gave trace formation of the Ar–CF_3 cross-coupling product (Scheme 51b).[139]

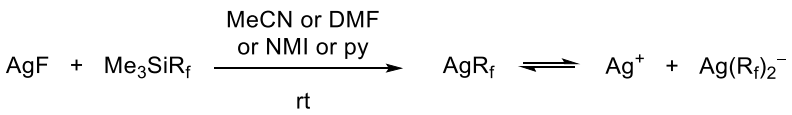


Scheme 51 Perfluoroalkyl nickel complexes: (a) Original synthesis;[136] (b) First attempts at Ar–CF_3 reductive elimination from Ni(II);[138] (c) Successful Ph–CF_3 reductive elimination from Ni(IV) [140]

Earlier this year, Sanford reported that Umemoto's reagent **18a**, as well as aryl diazonium and diaryliodonium reagents, were strong enough oxidants to realise a Ni(II) to Ni(IV) oxidation. The resulting [(L)Ni^{IV}(Ph)$(CF_3)_2$] complexes underwent facile C–CF_3 reductive elimination at room temperature, affording the Ph–CF_3 cross-coupling product in 57–67% yield (Scheme 51c).[140] This finding paves the way towards the development of a variety of nickel-catalysed perfluoroalkylation reactions.

3.5 Silver

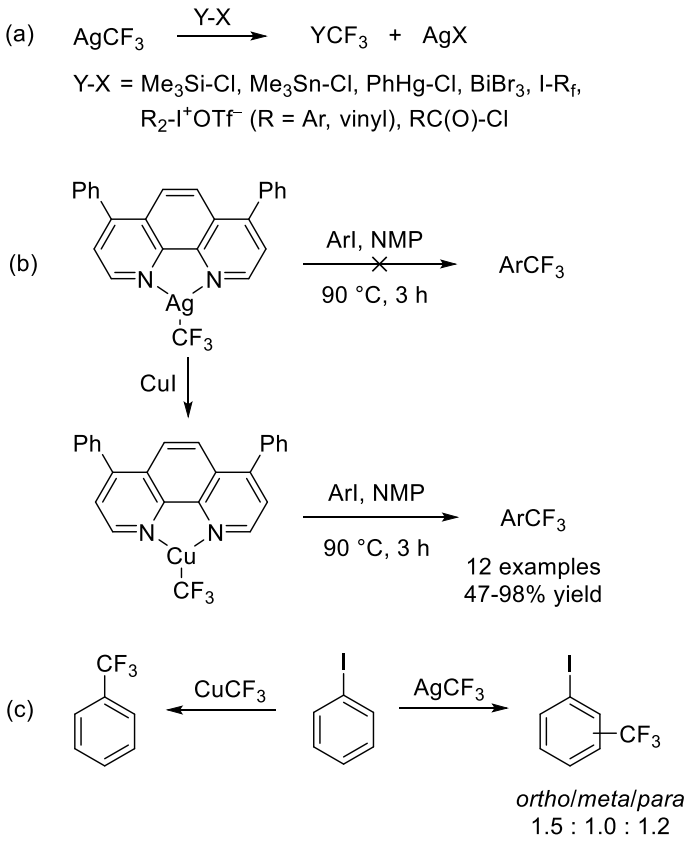
Originally, perfluoroalkyl silver(I) species were accessed *via* transmetallation of the corresponding organocadmium or -bismuth complexes. These methods suffered from disproportionation of the resulting AgR_f, catalysed by the metal ions remaining from the original complex.[141] More recently, these species have been synthesised from the reaction of AgF with perfluoroalkyl trimethylsilanes in polar, aprotic solvents at room temperature, which affords the desired AgR_f complexes in almost quantitative yields (Scheme 52).[141] A dynamic equilibrium exists between the neutral and ionic forms of these complexes. In stabilising solvents, perfluoroalkylated silver(I) salts are more stable towards thermal and light-induced decomposition than their non-fluorinated equivalents.[142]



Scheme 52 Synthesis of perfluoroalkyl silver species[141]

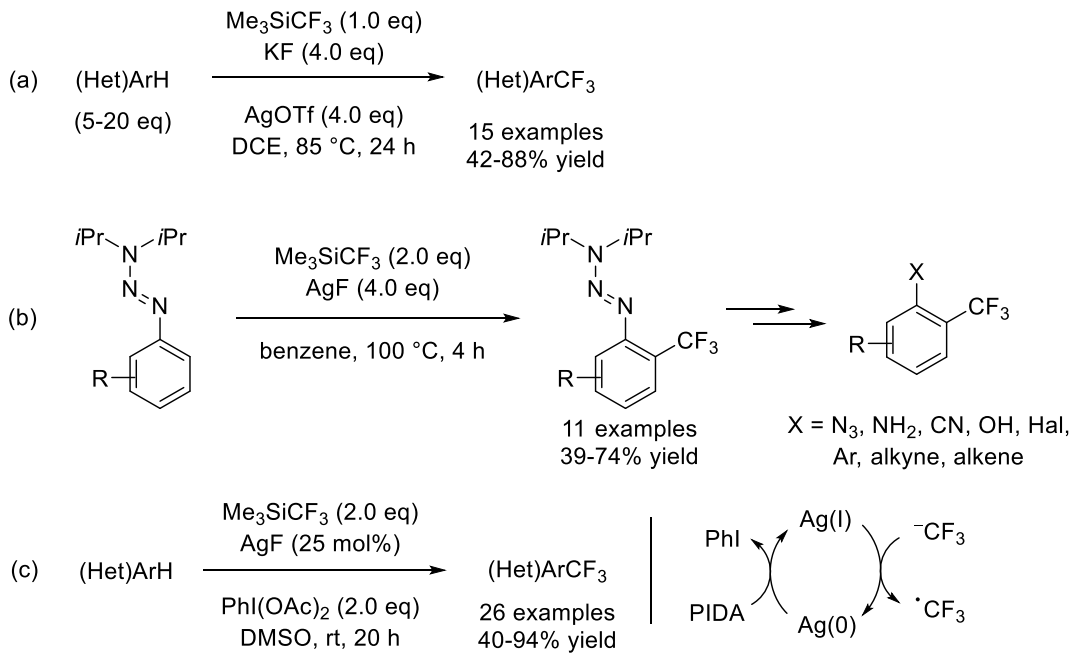
At the beginning of this decade, a cooperative effect of silver in copper-catalysed trifluoromethylation of aryl iodides was observed by the Huang group (see section 3.2.2.1).[97] They found that (bathophenanthroline)$AgCF_3$ was inert to cross-coupling with

aryl iodides in NMP at 90 °C, while the corresponding copper complex afforded the desired trifluoromethylarenes in good yields (Scheme 53b), suggesting that $AgCF_3$ is acting as a transmetallating reagent. Until then, the use of perfluoroalkyl silver reagents, specifically $AgCF_3$, was limited to nucleophilic substitution reactions (Scheme 53a).[143-145] With Huang's discovery, however, the interest in cross-coupling reactions with $AgCF_3$ was piqued. The first trifluoromethylation of aryl halides was disclosed by Sanford and co-workers in 2011.[146] They found that the reaction of iodobenzene with ligandless $AgCF_3$ did not give the cross-coupling product expected from the reaction of this substrate with $CuCF_3$; instead a mixture of C–H trifluoromethylated products was obtained with an isomeric ratio hinting at a radical reaction mechanism (Scheme 53c).[146, 147]



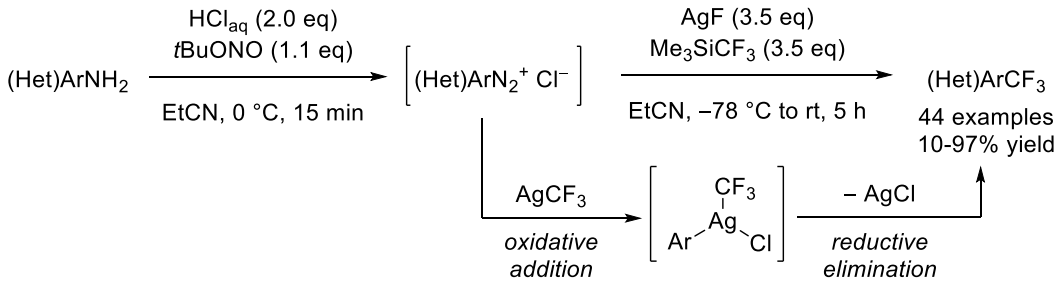
Scheme 53 (a) Nucleophilic substitution with Ag;[143] (b) Failed cross-coupling with Ag(I)CF_3;[97] (c) Complementary reactivity of $AgCF_3$ and $CuCF_3$ [146, 147]

Based on this result, a radical trifluoromethylation of arenes was developed, affording electron-rich and electron-poor trifluoromethyl(hetero)arenes in good and moderate yields respectively (Scheme 54a).[146] The authors proposed a reaction mechanism in which a trifluoromethyl radical is liberated from $AgCF_3$ under the reaction conditions. This theory is corroborated by a silver(0) mirror forming during the course of the reaction. However, trapping experiments with TEMPO and nitrobenzene were inconclusive (TEMPO dramatically reduced the yield of the reaction while nitrobenzene had almost no effect at all), suggesting the $CF_3^{\bullet}$ intermediated may not be a free radical. The reaction was extended to perfluoroalkylation with $Me_3SiC_3F_7$. Importantly, this methodology proved to be orthogonal to known transition metal-mediated trifluoromethylations. However, a large excess of starting material is necessary for high yields and most substrates suffer from low site-selectivity, forming a mixture of regioisomers which are difficult to separate. The Bräse group addressed this limitation by applying this reaction to aromatic triazenes, in which the triazene moiety acted as an *ortho*-directing group and a handle for further chemical modification (Scheme 54b).[148] Perfluoroalkylation and difluoromethylacetylation were also demonstrated.[149] Greaney and co-workers hypothesised that addition of an oxidant would recover the active silver(I) species after oxidation of CF_3^- to $CF_3^{\bullet}$, thus making these transformations catalytic. Indeed, in the presence of PIDA the catalyst loading of AgF could be dropped to 25 mol% to afford trifluoromethylated (hetero)arenes in comparable yields to those obtained under Sanford's conditions (Scheme 54c).[150] Recently, the less expensive trifluoromethyl sources CF_3CO_2H and CF_3CO_2Na have also been shown to efficiently trifluoromethylate (hetero)arenes under silver catalysis.[151]



Scheme 54 Radical trifluoromethylation of arenes with $AgCF_3$[146, 148, 150]

The first example of 'classical' cross-coupling chemistry with $AgCF_3$ was published by Wang and co-workers in 2014, when they demonstrated a Sandmeyer-type trifluoromethylation of (hetero)aryl diazonium salts (Scheme 55).[152] The corresponding trifluoromethylarenes were afforded in good to excellent yields for aromatic substrates, and low to medium yields for heteroaromatics.



Scheme 55 Sandmeyer-type silver-mediated trifluoromethylation of aryl diazonium salts[152]

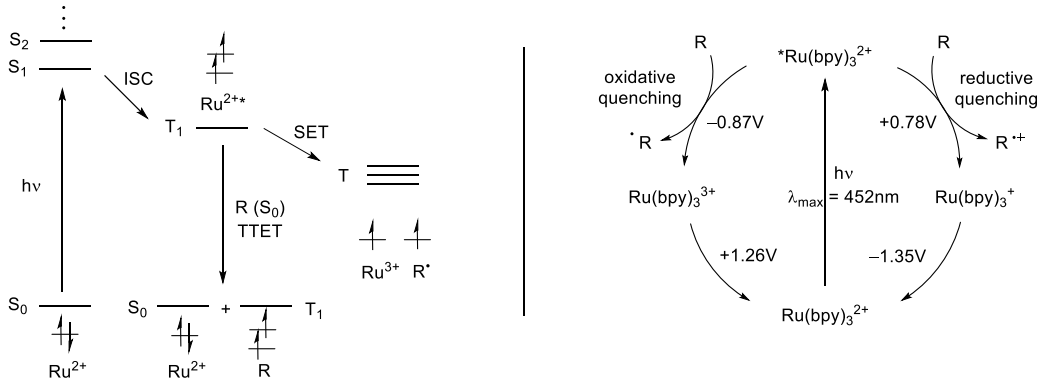
Compared to copper and palladium, perfluoroalkyl silver chemistry is still in its infancy. Since the beginning of this decade, however, great strides have been made to expand the reactivity accessible by these species with complementary selectivity to other metals.

3.6 Ruthenium and Iridium Photoredox Catalysis

3.6.1 General Principles of Photoredox Catalysis

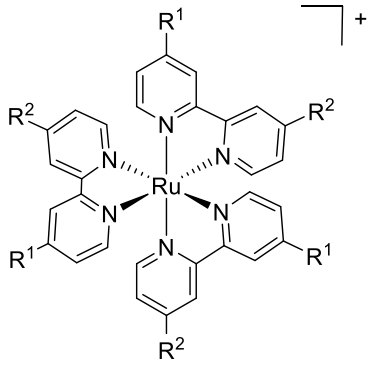
Photoredox catalysis relies on the excitation of a metal or organocatalyst by visible light and subsequent exploitation of the excited complex's redox potential to catalyse organic reactions.[153] Since most organic molecules do not absorb the low energy photons used for this process (λ_{max} = 452 nm), a plethora of different reactions is accessible via this method, including reduction, C–C bond formation and radical addition to π-bonds – also known as atom transfer radical addition (ATRA).[153, 154]

Taking $Ru(bpy)_3Cl_2$ as an example, the principles of photoredox catalysis shall be discussed in more detail (Scheme 56):[153] Initially, the photocatalyst [$Ru(bpy)_3^{2+}$] absorbs a photon to generate a high energy excited state [$Ru(bpy)_3^{2+}$]*. Ru^{2+} has a relatively broad absorption band, forming numerous excited singlet states S_n, however these undergo rapid intersystem crossing (ISC) to a long lived excited triplet state T_1. It is this triplet state T_1 which acts as the photocatalytic species by one of two possible pathways: single electron transfer (SET) or, less frequently, triplet-triplet or triplet-singlet energy transfer (TTET/TSET) to an organic molecule. Single electron transfer may cause either oxidation or reduction of the photocatalyst: In an oxidative quenching cycle, SET to an organic molecule R oxidises the catalyst to [$Ru(bpy)_3^{3+}$] while reducing the organic species to $R^{\bullet}$. The photocatalyst [$Ru(bpy)_3^{2+}$] is recovered after a second SET step. Similarly, in a reductive quenching cycle, the excited catalyst is reduced to [$Ru(bpy)_3^{+}$] *via* single electron transfer from an organic molecule R to afford a radical cation $R^{+\bullet}$. A second SET recovers the catalytic species [$Ru(bpy)_3^{2+}$].



Scheme 56 Photoredox catalysis exemplified by $Ru(bpy)_3Cl_2$[153]

These single electron transfer reactions are only efficient if the redox potential of the ruthenium species matches that of the organic molecule it is reacting with. The correct design of photocatalysts specifically for the reaction of interest is thus of great importance. A catalyst's ground state reduction potential depends on the identity of the metal and the electronics of the ligands: the more electron density resides on the metal, the more negative its reduction potential, *i.e.* the more difficult it is to reduce (Figure 5). This allows for fine-tuning of the catalyst's redox potential for each new reaction. DFT calculations have been shown to be powerful tools for predicting redox potentials that are not currently available in the literature.[155]



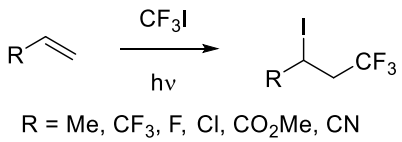
$R^1 = R^2 = Me$	$Ru(dmb)_3$	$E_{red} = -1.45V$
$R^1 = R^2 = H$	$Ru(bpy)_3$	$E_{red} = -1.35V$
$R^1 = H, R^2 = NO_2$	$Ru(4\text{-}NO_2\text{-}bpy)_3$	$E_{red} = -0.63V$

Figure 5 Tuning of Ru^+ ground-state redox potential[153]

Another important parameter to consider in photochemistry is the light source. Since the M → M* excitation of the photocatalyst is rate-determing for the subsequent chemical process, it is crucial to chose a lamp with the correct wavelength and wattage for optimal energy transfer.

3.6.2 Photocatalytic Trifluoromethylation

One of the first examples of photocatalytic trifluoromethylation was reported by Haszeldine and Steele in 1953.[156] They observed that when alkenes were reacted with trifluoroiodomethane under visible light catalysis (λ_{max} > 300 nm) in the gas phase, the trifluoromethyl radical added selectively to the unsubstituted end of the double bond, affording 1,1,1-trifluoro-3-iodobutane *via* a stabilised secondary alkyl radical intermediate (Scheme 57).

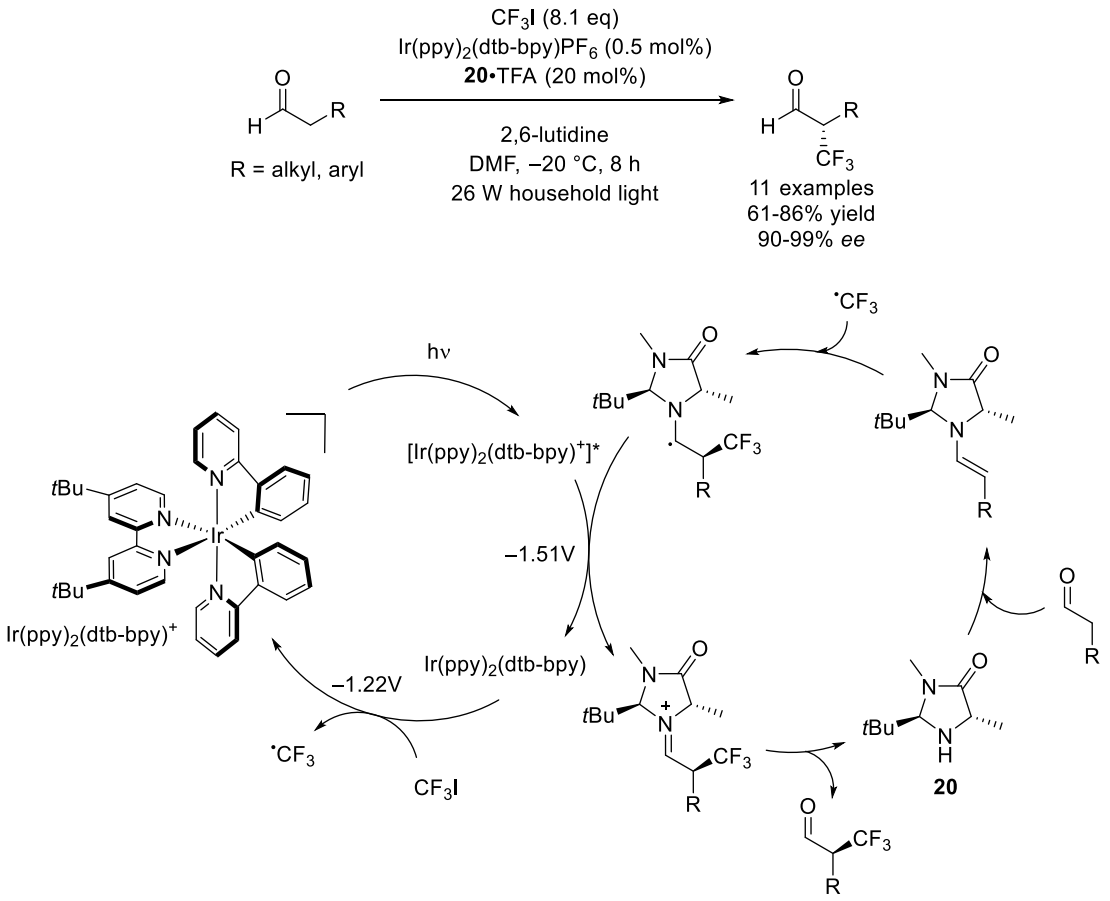


Scheme 57 Early examples of photocatalytic trifluoromethylation[156]

3.6.2.1 α-Trifluoromethylation of Carbonyls

The field underwent a revival in 2009, when the MacMillan group elegantly combined photoredox catalysis with organocatalysis to afford the enantioselective α-trifluoromethylation of aldehydes in good yields and excellent enantioselectivities (Scheme 58).[157] Aldehyde substrates were desymmetrised by addition to chiral amine catalyst **20**, which directs addition of a $CF_3^{\bullet}$ radical formed from trifluoroiodomethane to the *si*-face of the chiral enamine. The resulting α-amino radical is easily oxidised to an imine by the excited photocatalyst $[Ir(ppy)_2(dtb\text{-}bpy)^+]^*$ and finally expels the enantioenriched

trifluoromethylated aldehyde products, recovering organocatalyst **20**. The reduced photocatalyst $Ir(ppy)_2(dtb\text{-}bpy)$ has the optimal reduction potential to reduce trifluoroiodomethane to $CF_3^{\bullet}$, whilst being oxidised back to its $Ir(ppy)_2(dtb\text{-}bpy)^+$ ground state. The reaction could also be extended to perfluoroalkylation. The photocatalytic reaction of silyl enol ethers with CF_3I to afford trifluoromethylated ketones, esters and amides, albeit not enantioselectively, was later developed by the same group, using $Ru(bpy)_3Cl_2$ as the photocatalyst and Hüning's base ($EtNiPr_2$) as an electron donor.[158]



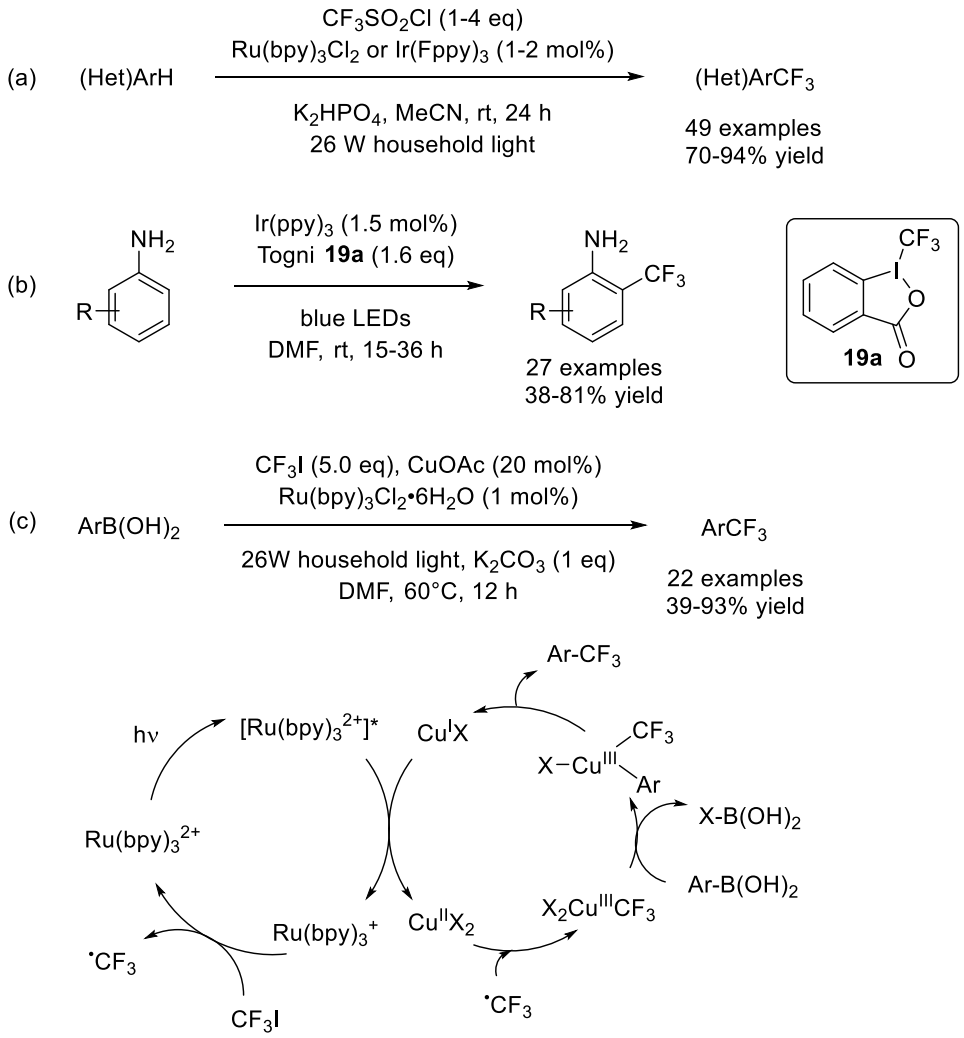
Scheme 58 Photocatalytic/organocatalytic enantioselective α-trifluoromethylation of aldehydes[159]

3.6.2.2 Trifluoromethylation of (Hetero)Arenes

Following a similar principle, MacMillan and co-workers developed a direct C–H trifluoromethylation of arenes and heteroarenes in 2011 that afforded the corresponding

trifluoromethyl(hetero)arenes in good to excellent yields (Scheme 59a).[160] Trifluoromethanesulfonyl chloride was used as the radical $CF_3^{\bullet}$ source, both to avoid radical iodination and because it is easier to handle than gaseous CF_3I. Both $Ru(bpy)_3Cl_2$ and $Ir(Fppy)_3$ were efficient photocatalysts. The iridium catalyst afforded higher yields, which the authors postulated may be due to a longer lived excited state, while the ruthenium catalyst gave higher levels of regiocontrol, which was attributed to reduction potentials. Regioselectivity was generally good, though some substrates suffered from a certain amount of trifluoromethylation on competing positions on the aromatic ring and concomitant purification problems (*e.g.* 1-methoxy-2-(trifluoromethyl)benzene was formed in a 2:1 mixture with its 3-(trifluoromethyl) isomer). At the same time, the Cho group developed a similar methodology for the photocatalytic trifluoromethylation of heteroarenes, using CF_3I as the source of electrophilic $CF_3^{\bullet}$ radicals, the photocatalyst $Ru(bpy)_3Cl_2$ and tmeda as an electron donor (Scheme 60a).[161] Yields are comparable to those obtained by the MacMillan group, and a range of new heteroaromatics were exemplified. As with MacMillan's method, the reaction's regioselectivity is very substrate-dependent and neither of these two reports included unprotected anilines in their substrate scope. This shortcoming was addressed by Ma and Zhu who developed an iridium-catalysed, light-mediated trifluoromethylation of free anilines with Togni's reagent **19a** (Scheme 59b).[162] Trifluoromethylation generally occurred on the 2-position, however – as with previous methods – complete regioselectivity could not be achieved. While C–H activation is, of course, the pinnacle of reaction development, the regioselectivity issue may be addressed by pre-functionalisation of the desired labelling position. To this end, the Sanford group reported a light-mediated ruthenium/copper-catalysed trifluoromethylation of arylboronic acids with trifluoroiodomethane (Scheme 59c).[113] In this reaction, the cross-coupling of arylboronic acids and photocatalytically formed $CF_3^{\bullet}$ radicals is realised

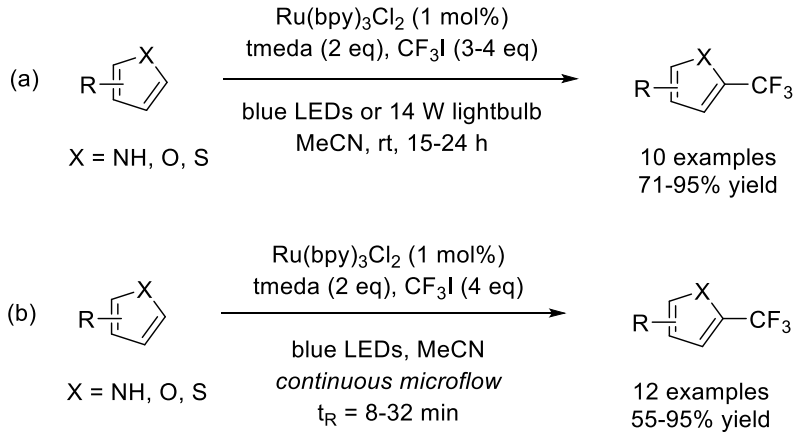
by means of a copper(I) catalyst. Yields were generally lower than for MacMillan's C–H activation method, but the reaction afforded a single regioisomer of the desired product.



Scheme 59 Photocatalytic trifluoromethylation of (hetero)arenes[113, 160, 162]

One major disadvantage of batch photocatalysis is that reaction efficiency decreases markedly at larger scale, due to inefficient light transmission into the bulk of the reaction, according to the Beer-Lambert Law, especially when the reaction mixture is not homogeneous. A solution to this problem has been the development of continuous flow photoreactors. For example, Noël *et al.* adapted Cho's photocatalytic trifluoromethylation of heteroarenes to a continuous flow microreactor (Scheme 60b).[163] The advantages of this strategy over batch methodologies include a substantial decrease in reaction time from

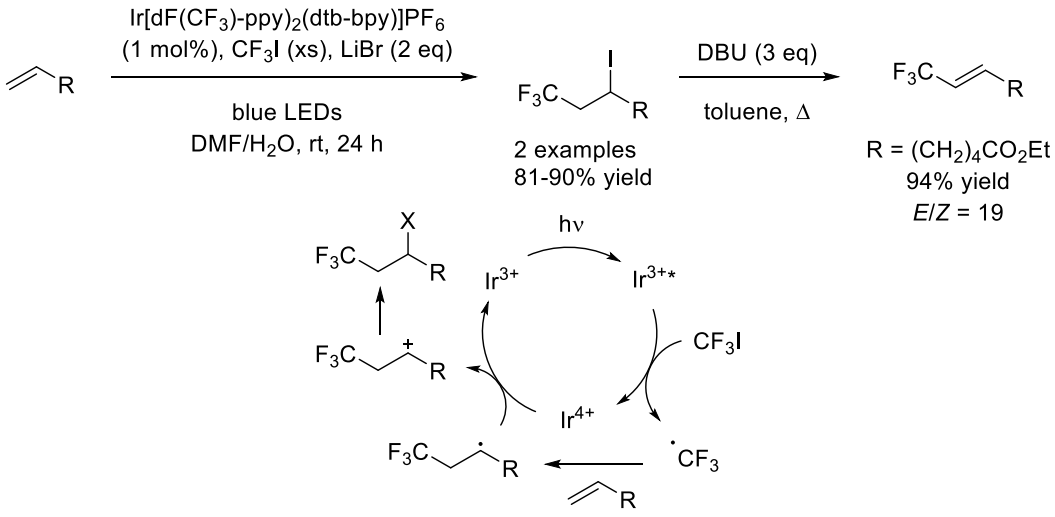
15–24 hours to a residence time t_R of 8–32 minutes (*i.e.* the time the substrate spends in the microflow reactor, defined as reactor volume / flow rate), scalability (almost 2g of 3-methyl-2-(trifluoromethyl)-1*H*-indole were synthesised in 95% yield), and a decrease in catalyst loading (0.05 mol% $Ru(bpy)_3Cl_2$ afforded 75% 3-methyl-2-(trifluoromethyl)-1*H*-indole after 32 minutes, compared to 95% after 8 minutes with 1 mol% catalyst). This solution to the scalability problem was crucial in establishing photocatalysis not only as an interesting research field, but also as a valuable tool for the chemical industry.



Scheme 60 Batch *vs.* flow photocatalytic trifluoromethylation of heteroarenes[162, 163]

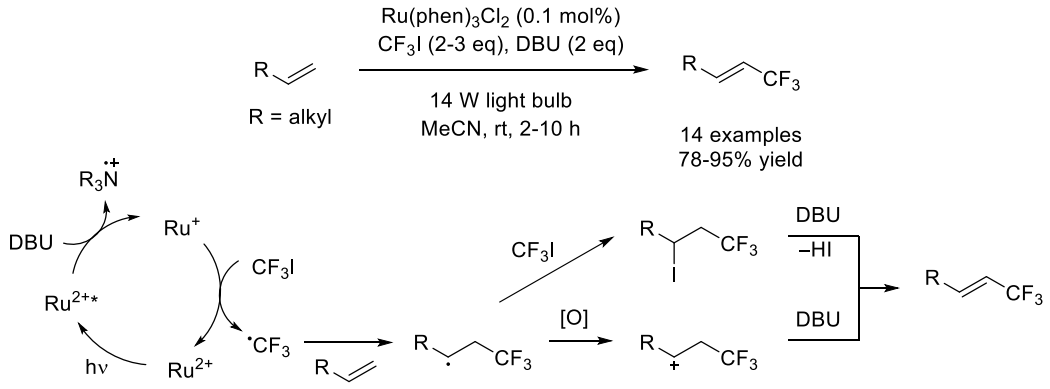
3.6.2.3 Trifluoromethylation of Alkenes

While not strictly a cross-coupling reaction, direct C–H trifluoromethylation of alkenes occurs *via* addition-elimination pathways. Stephenson *et al.* exemplified this in their paper on the photocatalytic iodotrifluoromethylation of alkenes, when they showed that the iodotrifluoromethylated products they obtained underwent HI elimination in the presence of DBU to afford trifluoromethylated alkenyl products (Scheme 61).[154]



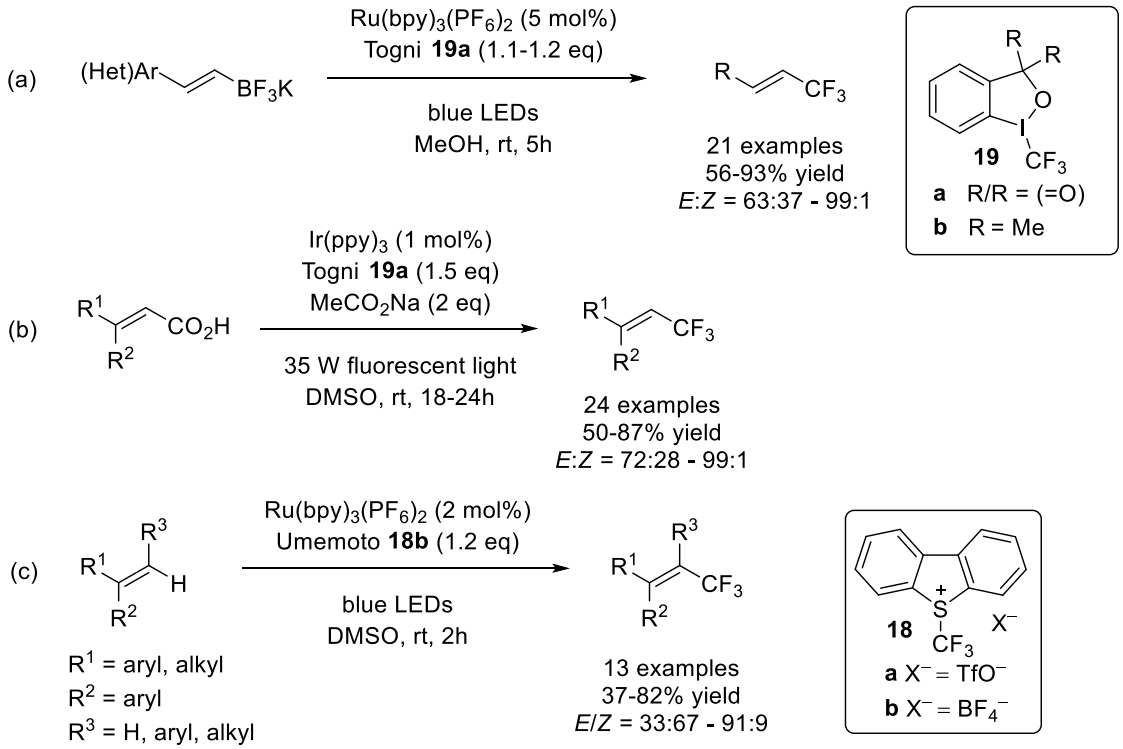
Scheme 61 Radical photocatalytic addition of CF_3–I across alkenes[154]

The Cho group developed a one-pot procedure for the synthesis of these products (Scheme 62).[164] Alkenes reacted with $CF_3^{\bullet}$ radicals generated *via* an oxidative photocatalytic quenching cycle from CF_3I. The radical intermediates are either iodinated by trifluoroiodomethane in a radical propagation step, or oxidised to the corresponding carbocations. Both intermediates undergo elimination to furnish the desired trifluoromethylated alkenyl products in good to excellent yields. DBU acts both as a base and an electron source for the reduction of the photocatalyst. The reaction shows remarkable *E*-selectivity for terminal alkenes, which made the authors favour the iodination-elimination mechanism over the oxidation-elimination mechanism, while internal alkenes gave a mixture of *E* and *Z* products. Furthermore, good alkenyl-CF_3 over allyl-CF_3 selectivity was observed for terminal alkenes, unless conjugation with an aromatic π-system was possible in the allylic product. Styrenes and other aromatic systems were completely unreactive under these conditions.



Scheme 62 Photocatalytic C–H trifluoromethylation of terminal alkenes[164]

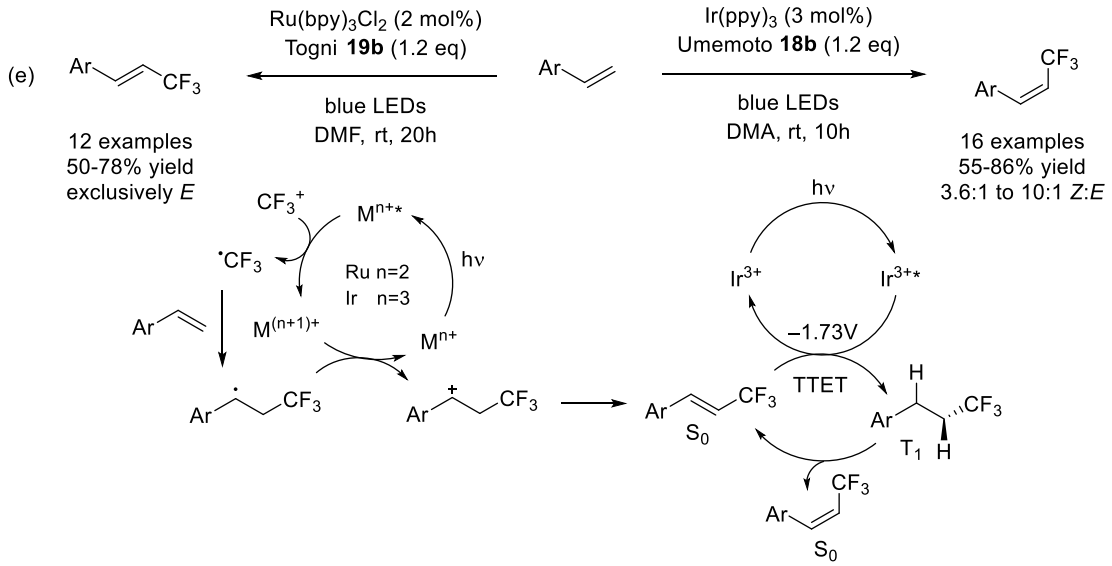
This limitation was addressed by Akita and Koike who developed two different protocols for the synthesis of trifluoromethylated (hetero)aromatic alkenes using Togni's and Umemoto's reagents. They demonstrated that a wide range of electron-deficient potassium vinyltrifluoroborates reacted with Togni's reagent **19a** in the presence of $Ru(bpy)_3(PF_6)_2$ in methanol to afford trifluoromethylated alkenes with high *E*-selectivity (Scheme 63a).[165] To circumvent the two-step synthesis of potassium vinyltrifluoroborates, Zhu described a decarboxylative trifluoromethylation of commercial α,β-unsaturated carboxylic acids (Scheme 63b).[166] However, Akita and Koike soon developed a direct C–H trifluoromethylation, using Umemoto's reagent **18b**, precluding the need for prefunctionalisation (Scheme 63c).[167] Yields were generally slightly lower, but even sterically hindered triphenylethenes were amenable to this transformation, affording tetrasubstituted trifluoromethylated alkenes. Terminal double bonds afforded germinal bis(trifluoromethyl)alkenes in up to 80% yield when 4 equivalents of Umemoto's reagent were used.



Scheme 63 Photocatalytic synthesis of trifluoromethylated alkenes[165-167]

While the above methods afford trifluoromethylated alkenes with high *E*-selectivity due to the E2 elimination pathway furnishing the final products, Qing *et al.* developed a trifluoromethylation of styrenes that allows for fine-tuning to give either the *E* or the *Z* isomer starting from the same substrate, depending on the photocatalyst used (Scheme 64).[168] With Togni's reagent **19b** and $Ru(bpy)_2Cl_2$, the expected *E* products were formed, following the general mechanism discussed previously. When $Ir(ppy)_3$ was used as the photocatalyst together with Umemoto's reagent **18b**, the corresponding *Z*-products were isolated. The authors postulate that this is due to a photocatalytic triplet-triplet energy transfer process which converts the thermodynamic *E* product into its kinetic *Z* isomer: Energy transfer from the excited triplet state of $Ir(ppy)_3$* to the *E* alkene in its singlet ground state S_0 affords the lowest-energy excited triplet state of the alkene T_1, which possesses two unpaired electrons instead of a double bond and can thus freely rotate, affording a mixture of *E* and *Z* alkenes. Since the *E* isomer acts as an energy sink for the

$Ir(ppy)_3$* triplet state, this leads to a gradual enrichment of the *Z* product. The protocol was also extended to pentafluoroethylation.



Scheme 64 Stereoselective photocatalytic trifluoromethylation of alkenes[168]

Beside ruthenium and iridium catalysis, examples of photocatalytic trifluoromethylation with cobalt,[169] copper (Cu^{II}dmeda),[170] platinum (Pt^{II}ppy)[171] and organocatalysts[172] have recently emerged. A growing number of methods for trifluoromethylthiolation[173] and trifluoromethyloxylation[174] have been developed as well, however these will not be covered in this thesis.

3.7 Summary: Challenges in Transition Metal-Mediated Perfluoroalkylation

The two main difficulties of transition metal catalysed trifluoromethylation, $C–CF_3$ reductive elimination and suppression of fluoride elimination, have been addressed in the literature by the development of a plethora of methodologies, employing Cu, Pd, Ni, Ag, Ru and Ir catalysts. However, several challenges remain, of which two will be addressed in this thesis:

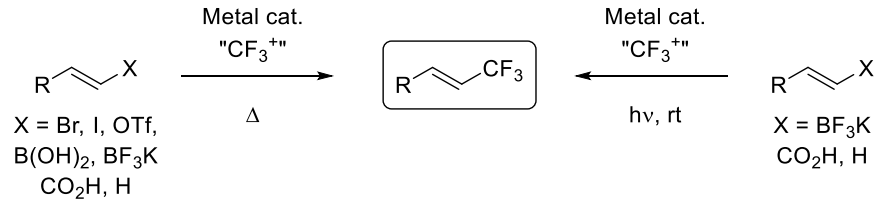
(1) Most copper and palladium catalysed reactions require high temperatures and long reaction times, limiting the substrate scope accessible by these methodologies. Photocatalysis with ruthenium and iridium occurs under very mild reaction conditions, offering an attractive alternative. The application of this strategy to the trifluoromethylation and pentafluoroethylation of organosilanes is developed in Chapter 4.

(2) While the suppression of by-product formation has been mostly successful for transition metal catalysed trifluoromethylation reactions, the less reactive $M(CF_2)_nR$ (n>1) complexes have received less attention, often only mentioned as one lone entry in a trifluoromethylation substrate scope. Organometallic MR_f complexes with $R_f = (CF_2)_nCF_3$ (n>1), in particular, have been found to be unstable towards *beta*-elimination and other side-reactions.[74] In Chapter 5, the copper-mediated cross-coupling of aryl(tetrafluoroethyl)trimethylsilane reagents, $Ar(CF_2)_2SiMe_3$, is presented. Protodesilylation and subsequent *beta*-fluoride elimination are minimised through judicious ligand choice. We believe that the results from this project may help with the development of other challenging cross-coupling chemistry.

Chapter 4: Photocatalytic Perfluoroalkylation

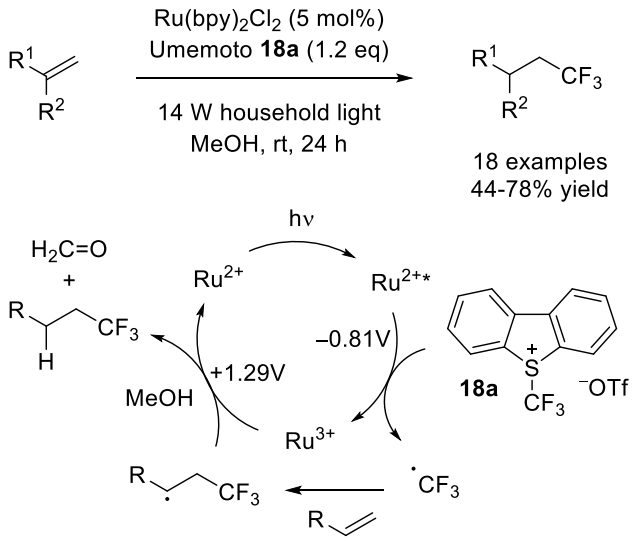
4.1 Introduction

As demonstrated above, many methodologies have been developed for the trifluoromethylation of aliphatic and aromatic substrates, however lately the focus has shifted towards unsaturated substrates.[175] Transition metal catalysis under high reaction temperatures and harsh conditions has been shown to furnish trifluoromethylated alkenes (Scheme 65).[175] A milder route towards these products recently emerged in the form of photoredox catalysis (Scheme 65).[162, 164, 165]



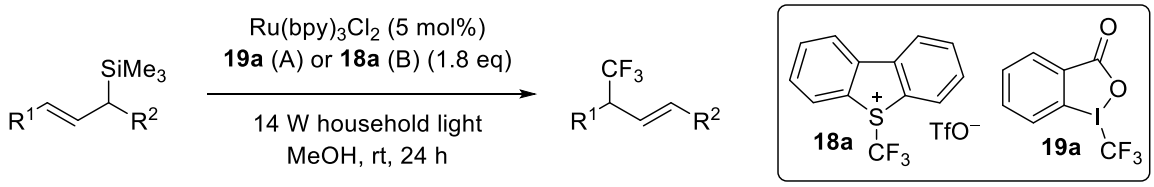
Scheme 65 Strategies for the synthesis of trifluoromethylated alkenes[175]

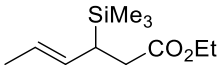
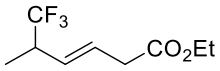
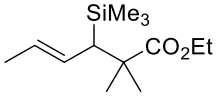
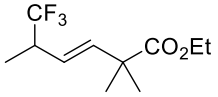
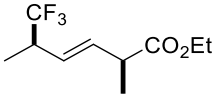
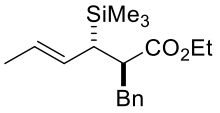
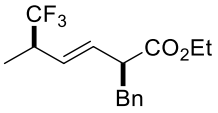
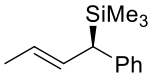
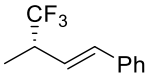
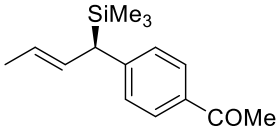
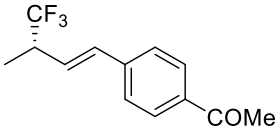
Previously, our group reported the first photocatlytic hydrotrifluoromethylation of unactivated alkenes, using methanol as the proton source (Scheme 66).[176] We propose that $Ru(bpy)_2^{2+}$ is excited by visible light to give $Ru(bpy)_2^{2+}$*. This species reacts with Umemoto's reagent **18a** to liberate CF_3 radicals *via* an oxidative quenching pathway, which add to the olefin substrate. Subsequent single-electron oxidation of methanol to formaldehyde by $Ru(bpy)_2^{3+}$ provides a proton to quench the radical alkyl intermediate which affords the desired hydrotrifluoromethylated products in moderate to good yields. The hydrotrifluoromethylation of alkynes for the synthesis of trifluoromethylated alkenes was also successful in comparable yields.



Scheme 66 Photocatalytic hydrotrifluoromethylation of alkenes[176]

We also developed an alternative route towards trifluoromethylated alkenes by adapting the methodology to allylsilanes. These substrates reacted with Togni's or Umemoto's reagent under $Ru(bpy)_3Cl_2$ catalysis in methanol under visible light irradiation to afford branched allylic products not accessible under copper(I) catalysis (Table 11).[177] The silicon group was found to be important for the stereo- and regioselectivity of the reaction, directing addition of the trifluoromethyl group *beta* to itself, with high *E* selectivity (Entries 1–2). Experiments with diastereomerically pure substrates showed that addition of CF_3 occurred *anti* to the silicon group (Entries 3–4). Encouraged by the clean stereocontrol observed for these reactions, the efficiency of chirality transfer was studied with enantioenriched allylsilanes (Entries 5–6). Pleasingly, it was found that the corresponding trifluoromethylated products were formed with only minor erosion of *ee*.



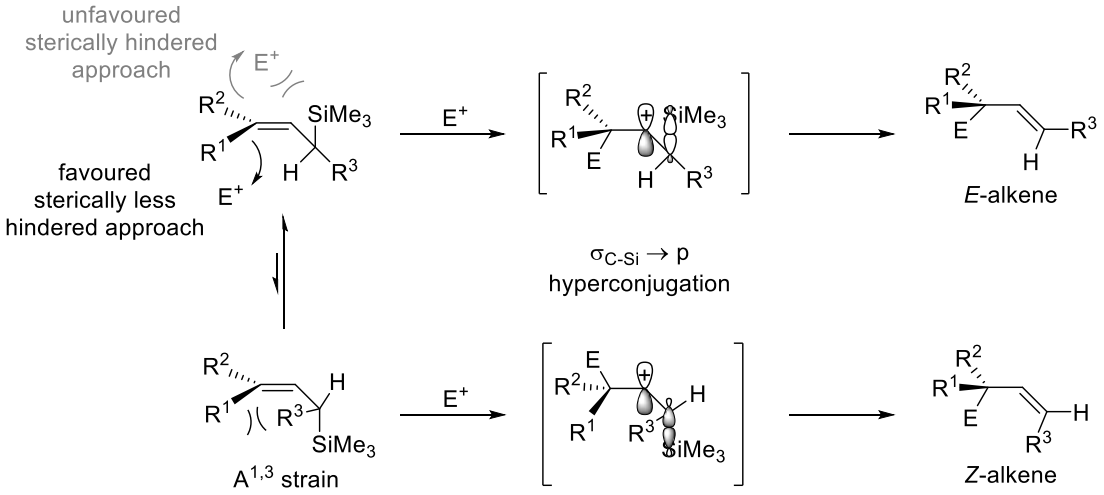
Entry	Substrate	Product	Cond.[a]	Yield [%][b]	*E*/*Z*[c] (*syn*/*anti*)
1			A B	55 38	1.7 3.4
2			A	69	>20
3			A B	65 33	15 (7) >20 (6.1)
4			A B	83 24	15 (10) >20 (8.6)
5	 er = 97:3	 er (*E*) = 85:15	A	56	5
6	 er > 99:1	 er (*E*) = 88:12 er (*Z*) = 98:2	A	68	7

[a] Condition A: 5 mol% $Ru(bpy)_2Cl_2 \cdot 6H_2O$, 1.8 eq **19a**, 1.0 eq substrate, MeOH, rt, 24 h, 14 W light bulb. Condition B: As A, but using 1.8 eq **18a** as the trifluoromethyl scource. [b] Yields of isolated products. [c] Determined by ^{19}F NMR (*syn*/*anti* ratio of the *E* isomer in parentheses).

Table 11 Selected examples of photocatalytic trifluoromethylation of allylsilanes[177]

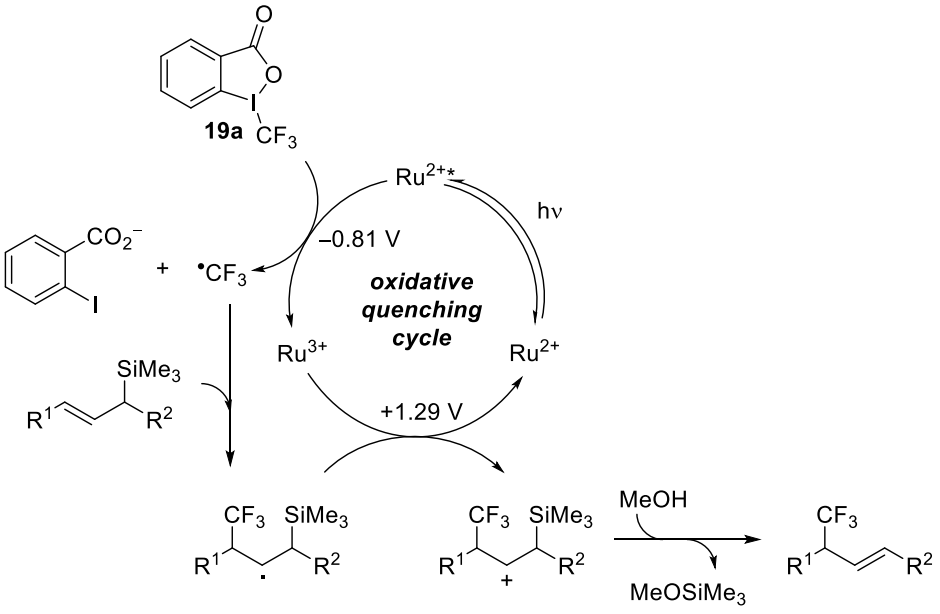
The high selectivity can be explained by an aliphatic electrophilic S_E2' substitution pathway, a well-established reactivity-mode of allylsilanes with electrophiles (Scheme 67).[178-180] Assuming the silyl group is the bulkiest substituent in the allylsilane substrate, sterics will direct attack of the incoming electrophile E^+ mainly onto the opposite face of the double-bond, *i.e. anti* to silicon. The resulting carbocation is stabilised by hyperconjugation with the σ_{C-Si} bonding orbital, which requires the C–Si bond to be periplanar with the empty p-orbital. (Hyperconjugation between the filled σ_{C-Si} bonding orbital and the empty p orbital on the carbocation affords a stabilising effect of *ca.*

39−48 kcalmol^{-1} for primary carbocations and *ca.* 28 kcalmol^{-1} for secondary carbocations compared to the non-silylated equivalent.[181]) The intermediate will adopt the configuration in which $A^{1,3}$ strain is minimised, causing a stereoselective elimination to yield the *E*-alkene. In our case some *Z*-alkene formation is observed, owing to the fact that $A^{1,3}$ strain is reduced in 1,2-disubstituted allylsilanes (Scheme 67: R^1 = H). Furthermore, *anti* selectivity is not perfect (Entries 3–6).



Scheme 67 Stereocontrol in the reaction of allylsilanes with electrophiles[178]

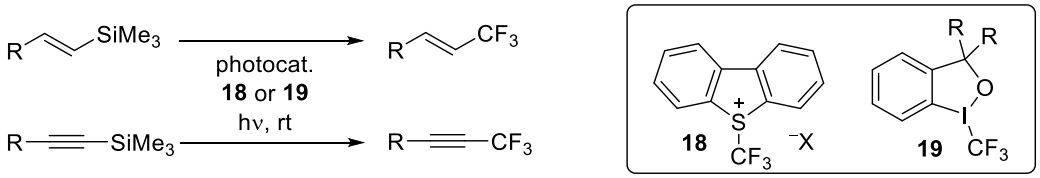
The proposed mechanism for this transformation is thus shown in Scheme 68. Cyclic voltammetry measurements confirmed that the reaction proceeds *via* an oxidative photocatalytic quenching cycle. This would suggest that the trifluoromethyl reagent is reduced to a $CF_3^{\bullet}$ radical by the excited photocatalyst $Ru(bpy)_3^{2+}$*. It is plausible that the $CF_3^{\bullet}$ radical then attacks the allylsilane substrate in an *anti*-S_E2' manner, forming a β-silicon stabilised radical intermediate which undergoes oxidation to the corresponding carbocation by Ru^{3+}. Finally, methanol-aided elimination of the trimethylsilyl group affords the desired trifluoromethylated products. It was found that the nature of the CF_3 source influenced both reactivity and stereoselectivity of the reaction: Umemoto's reagent **18a** gave lower yields than Togni's reagent **19a**, but higher *E* selectivity.



Scheme 68 Proposed mechanism for the photocatalytic trifluoromethylation of allylsilanes[176]

This mechanism is supported by the following observations:[177] Radical clock experiments with trimethyl[2-(*trans*-2-phenylcyclopropyl)allyl]silane showed the formation of two ring-opened allylic CF_3 products under the standard conditions, indicating a radical mechanism. In the presence of TEMPO none of the expected trifluoromethylated products were observed; instead, 19% of the TEMPO–CF_3 adduct was detected by ^{19}F NMR, suggesting that a trifluoromethyl radical is involved in the reaction mechanism. Cyclic voltammetry measurements show that the reduction potentials of both Togni's reagent **19a** (–1.10 V *vs.* SCE in MeCN) and Umemoto's reagent **18a** (–0.63 V *vs.* SCE in MeCN) are compatible with an oxidative quenching pathway in which the trifluoromethylating reagent is reduced by single electron transfer from the excited $Ru(bpy)^{2+}$* photocatalyst (–0.81 V *vs.* SCE in MeCN).[182]

We postulated that this approach would also be beneficial for the synthesis of trifluoromethylated alkenes and alkynes, starting form vinyl- and alkynylsilanes (Scheme 69). We therefore set out to investigate the reactivity of these substrates with electrophilic trifluoromethylating reagents under photocatalytic conditions.



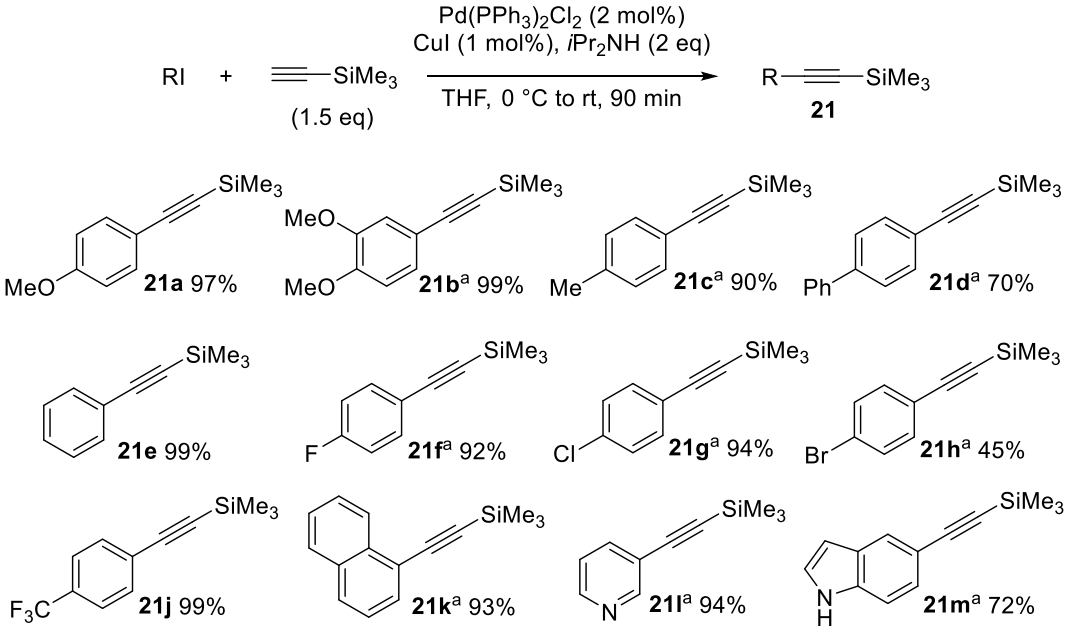
Scheme 69 Proposed photocatalytic trifluoromethylation of vinyl- and alkynylsilanes

4.2 Results and Discussion

4.2.1 Substrate Synthesis

A substrate library was synthesised in order to probe the scope and selectivity of the proposed photocatalytic trifluoromethylation of vinyl- and alkynylsilanes. Specifically, we were interested in investigating the reactivity of *E vs. Z* vinylsilanes, stereoselectivity, functional group tolerance and tolerance towards steric convolution (*i.e.* reactivity of di- *vs.* trisubstituted substrates).

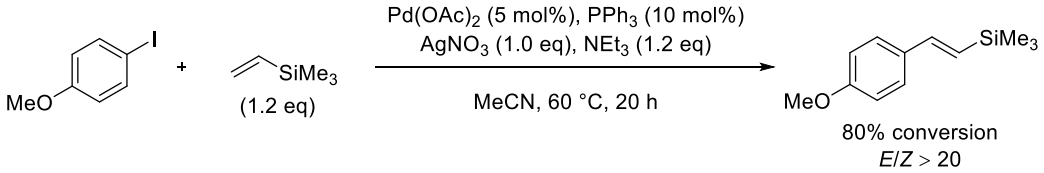
Aromatic alkynylsilanes **21** were prepared by Sonogashira coupling of aryl iodides with ethynyltrimethylsilane (Scheme 70).[183] Good yields were obtained for electron-rich and electron-poor aromatics, as well as for heteroaromatics.



[a] Substrate was synthesised by Dr. K. M. Engle.

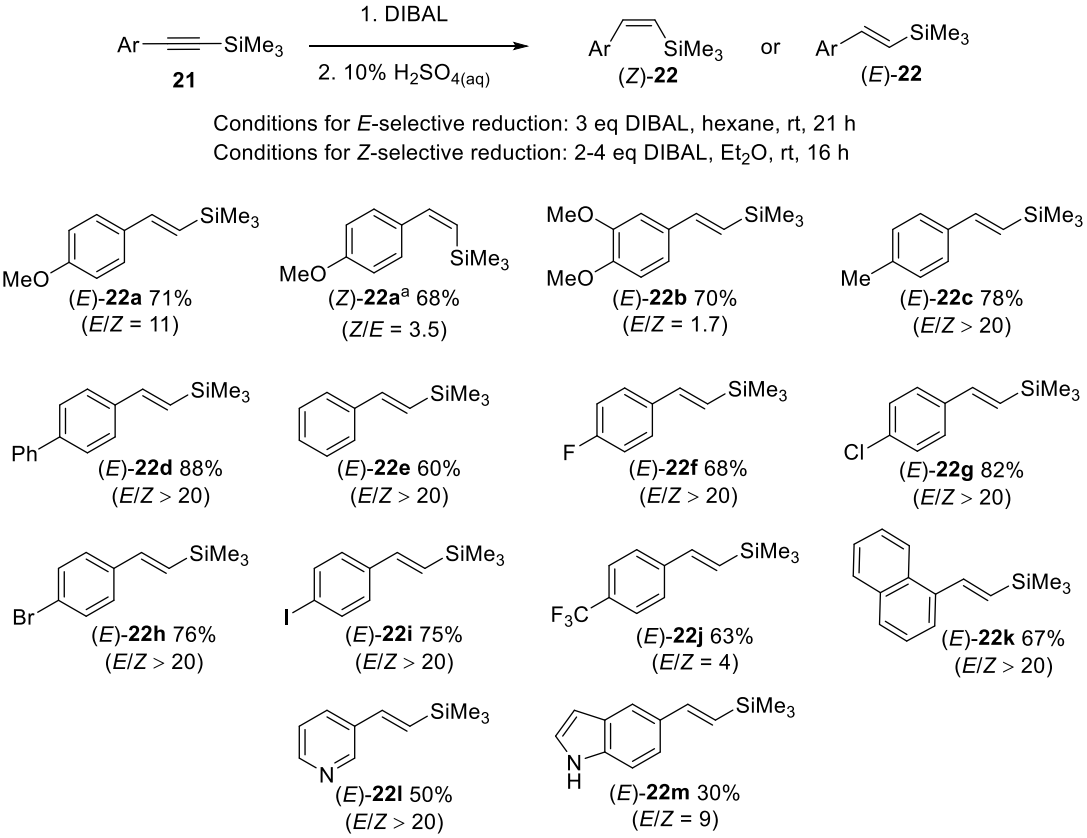
Scheme 70 Synthesis of aromatic alkynylsilanes *via* Sonogashira coupling[183]

The synthesis of vinylsilanes *via* palladium-mediated Heck coupling of aryl iodides with vinyltrimethylsilane gave good conversions, but separation of the desired products from the iodide starting material proved to be very difficult (Scheme 71). We thus decided to employ a different synthetic strategy.



Scheme 71 Synthesis of vinylsilanes *via* Heck coupling

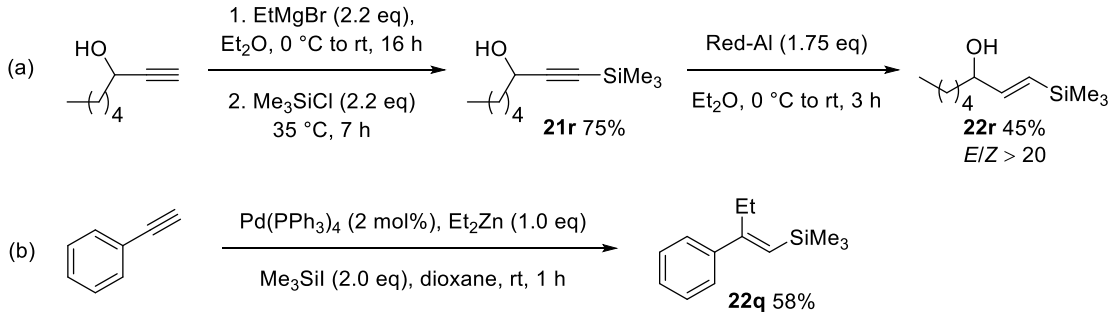
DIBAL reduction of alkynylsilanes in ether and hexane afforded *Z* and *E* alkenylsilanes **22** respectively with high selectivity – clearly distinguishable by their $^{3}J_{HH}$ coupling constants of 15.0 Hz and 19.0 Hz –and allowed for easier purification by silica gel column chromatography (Scheme 72).[184, 185]



[a] Substrate was synthesised by Dr. K. M. Engle.

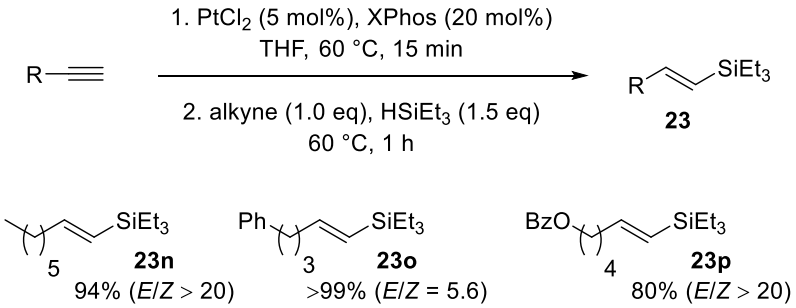
Scheme 72 Selective DIBAL reduction of alkynylsilanes to *E* and *Z* alkenylsilanes[184]

Aliphatic vinylsilanes were not tolerated under these conditions, as they underwent over-reduction to the alkane. Therefore, aliphatic hydroxyvinylsilane **22r** was synthesised by directed Red-Al reduction of hydroxyalkynylsilane **21r** (Scheme 73a).[186] Trisubstituted alkene **22q** was afforded by palladium-catalysed coupling of ethynylbenzene with diethylzinc and iodotrimethylsilane (Scheme 73b).[187]



Scheme 73 (a) Synthesis of hydroxyvinylsilanes by directed reduction; (b) Synthesis of trisubstituted vinylsilanes

Further aliphatic vinylsilanes **23** were accessed *via* hydrosilylation of terminal alkynes under platinum catalysis (Scheme 74).[188] The compounds afforded by this strategy were synthesised with triethylsilane substituents since trimethylsilane was not as easily commercially obtainable.

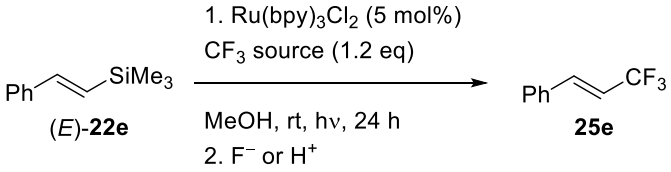


Scheme 74 Hydrosilylation of terminal alkynes[188]

4.2.2 Reaction Development

4.2.2.1 Optimisation

Vinylsilanes were found to be more reactive under our conditions than alkynylsilanes; hence it was decided to carry out optimisation studies on (*E*)-2-(phenylethenyl)trimethylsilane (*E*)-**22e** (*E*/*Z* > 20) (Scheme 75).

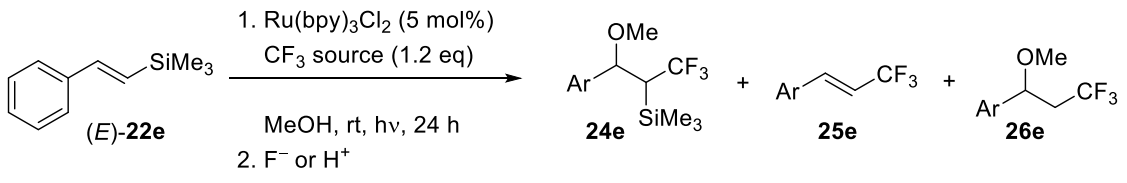


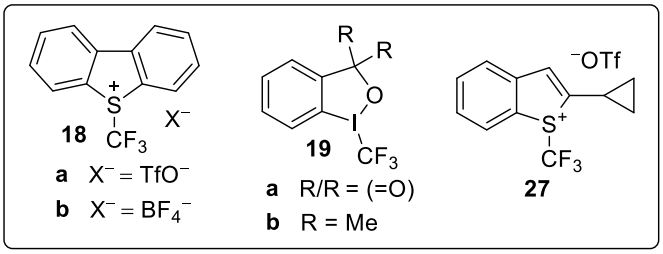
Scheme 75 Photocatalytic trifluoromethylation of (*E*)-22e

This compound was chosen as a test-substrate since it is an electronically neutral system that selectively forms a known trifluoromethylated product with a diagnostic doublet of doublets in the ^{19}F NMR at −63.76 ppm (dd, $^{3}J_{HF}$ = 7.0 Hz, $^{4}J_{HF}$ = 2.0 Hz) and a set of two doublets of quartets in the ^{1}H NMR at 6.12 (dq, $^{2}J_{HH}$ = 16.0 Hz, $^{3}J_{HF}$ = 7.0 Hz) and 7.19

(dq, $^3J_{HH}$ = 16.0 Hz, $^4J_{HF}$ = 2.0 Hz) for the alkene protons.[189] The fluorine-splitting in the ^{1}H NMR of trifluoromethylated product **25e** makes it easily distinguishable from the starting vinylsilane which shows two doublets for the alkene protons at 6.57 (d, $^3J_{HH}$ = 19.0 Hz) and 6.97 (d, $^3J_{HH}$ = 19.0 Hz).[190]

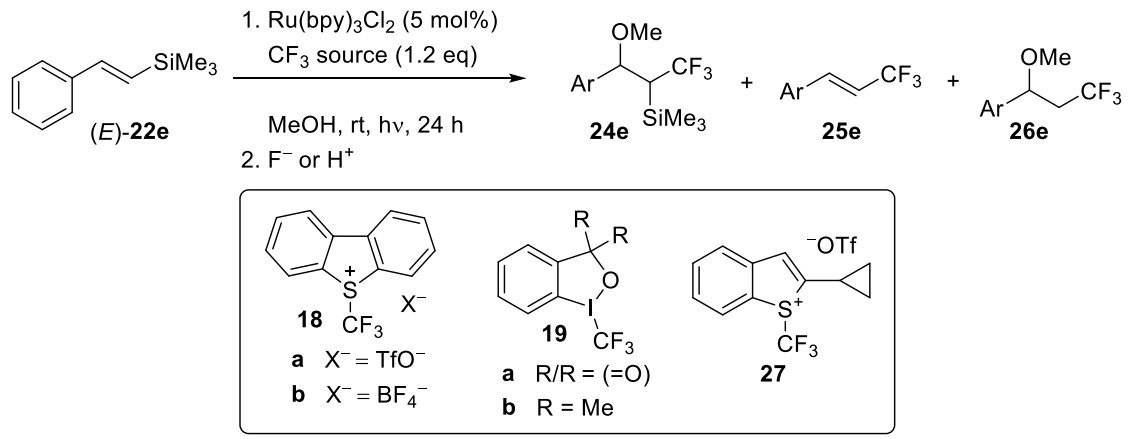
Pleasingly, when (*E*)-**22e** was reacted with 1.2 eq Togni's reagent **19a** in the presence of 5 mol% $Ru(bpy)_3Cl_2 \cdot 6H_2O$ in methanol at room temperature for 24 hours under irradiation with a 14 W household lightbulb, 34% of the desired trifluoromethylated product **25e** was formed exclusively as the *E*-isomer, as determined by ^{19}F NMR (Table 12, Entry 1). Control reactions showed that no product was formed without the photocatalyst or under exclusion of light, confirming the photocatalytic concept (Entries 2–3). Furthermore, the results obtained by our photocatalytic methodology were superior to those observed under copper(I) catalysis which yielded only trace amounts of the product (Entry 4). A lower catalyst loading afforded a significantly lower yield of 12% **25e** (Entry 5). Conversely, increasing the amount of trifluoromethylating reagent **19a** to 2.0 eq (Entries 6–7) and the catalyst loading to 10 mol% afforded an increase in yield to 57% **25e** (Entry 8); increasing the catalyst loading to 15 mol% did not have a beneficial effect (Entry 9). An increased reaction time of 48 hours made no change to the yield of **25e** (Entry 10). MacMillan employed $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ as a photocatalyst in his photocatalytic/organocatalytic trifluoromethylation of aldehydes with CF_3I.[157] In our case, this catalyst gave a similar conversion to $Ru(bpy)_3Cl_2$; however while ruthenium catalysis gave 45% of biphenyl product **25e** exclusively as the *E* isomer (Entry 11), the iridium catalyst afforded 38% of a 5:1 *E*:*Z* mixture (Entry 12). This may be due to triplet-triplet energy transfer reactions (TTET) which have previously been observed to afford *Z* alkenes under iridium photocatalysis (see Section 3.6.2.3).[168] Activation of the ruthenium catalyst by 3W Blue LEDs (λ = 465 nm) did not show any improvement over the standard conditions (Entry 13).





Entry	CF_3 Source	Conditions[a]	Conversion (%)[b,c]	Yield **24e** [%][c]	Yield **25e** [%][c]	Yield **26e** [%][c]
1	**19a**	-	62	0	34	1
2	**19a**	no catalyst	<1	0	<1	0
3	**19a**	no light	<1	0	<1	0
4	**19a**	CuCl, 70°C[d]	57	3	14	0
5	**19a**	2 mol% Ru	50	0	12	<1
6	**19a** (1.8 eq)	-	59	0	23	<1
7	**19a** (2.0 eq)	-	95	10	46	0
8	**19a** (2.0 eq)	10 mol% Ru	94	7	57	0
9	**19a** (2.0 eq)	15 mol% Ru	99	11	49	0
10	**19a**	48 h	90	8	35	0
11[e]	**19a** (2.0 eq)	-	65	8	45	0
12[e]	**19a** (2.0 eq)	5% $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	90	16	38 (5:1 *E*:*Z*)	0
13[e]	**19a** (2.0 eq)	3 W Blue LED (465 nm)	>99	11	41	7
14	**19b**	-	15	0	2	0
15	**18a** (2.0 eq)	-	>99	0	50	5
16	**18b** (2.0 eq)	-	>99	0	37	3
17	**27**	-	87	0	34	0

[a] General conditions: (i) 1.0 eq (*E*)-**22e** (0.25 mmol), 1.2 eq CF_3 source, 5 mol% $Ru(bpy)_3Cl_2 \cdot 6H_2O$ in MeOH at rt for 24 h under irradiation with a 14 W household light bulb. Workup by extraction and evaporation *in vacuo*. (ii) 1.0 eq TBAF (1 M in THF), THF, rt for 10 min. [b] Conversion is defined as 100 – x %, where x is the percentage of starting material detected by ^{19}F NMR. [c] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq α,α,α-trifluorotoluene. [d] Conditions: 1.0 eq (*E*)-**22e**, 1.2 eq **19a**, 20 mol% CuCl in MeOH at 70 °C for 2 h. [e] Reaction was run with 1.0 eq [(*E*)-2-(biphenyl-4-yl)ethenyl](trimethyl)silane (*E*)-**22a** instead of (*E*)-**22e**.



Entry	CF_3 Source	Conditions[a]	Conversion (%)[b,c]	Yield **24e** [%][c]	Yield **25e** [%][c]	Yield **26e** [%][c]
18	CF_3I (10 eq)	-	<1	0	0	0
19	CF_3I (10 eq)	*i*Pr_2NEt (2 eq)	<10	0	2	0
20	CF_3SO_2Cl	-	<10	0	2	0
21	**19a** (2.0 eq)	10 mol% Ru MeCN	<10	0	9	0
22	**19a** (2.0 eq)	10 mol% Ru HMPA	60	0	17	0
23	**19a** (2.0 eq)	10 mol% Ru TFE	>99	0	62	0
24	**19a** (2.0 eq)	10 mol% Ru HFIP	>99	0	13	0
25	**19a**	DCM	71	0	24	0
26	**19a**	DMF, 48 h	71	0	30	0
27	**19a**	EtOH	77	6	28	0
28	**19a**	H^+ workup[f]	74	5	22	0
29	**18a** (2.0 eq)	H^+ workup[f]	>99	5	42	0
30	**18a**	no workup before TBAF	96	8	37	8

[a] General conditions: (i) 1.0 eq (*E*)-**22e** (0.25 mmol), 1.2 eq CF_3 source, 5 mol% $Ru(bpy)_3Cl_2 \cdot 6H_2O$ in MeOH at rt for 24 h under irradiation with a 14 W household light bulb. Workup by extraction and evaporation *in vacuo*. (ii) 1.0 eq TBAF (1 M in THF), THF, rt for 10 min. [b] Conversion is defined as 100 – x %, where x is the percentage of starting material detected by ^{19}F NMR. [c] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq α,α,α-trifluorotoluene. [d] Conditions: 1.0 eq (*E*)-**22e**, 1.2 eq **19a**, 20 mol% CuCl in MeOH at 70 °C for 2 h. [e] Reaction was run with 1.0 eq [(*E*)-2-(biphenyl-4-yl)ethenyl](trimethyl)silane (*E*)-**22a** instead of (*E*)-**22e**. [f] (ii) 1 M HCl at rt for 1 h.

Table 12 Optimisation table for the photocatalytic trifluoromethylation of vinylsilanes

As observed for allylic trifluoromethylation, Togni's reagent **19a** and Umemoto's reagents **18a** and **18b** were the most promising CF_3 sources (Entries 8, 14–20). Although Umemoto's reagent **18a** afforded slightly higher yields than Togni's reagent **19a** (Entries 8

vs. 15), an unidentified insoluble by-product was formed during the course of the reaction with **18a**, making further stirring very difficult unless a vigorous rate was maintained. Methanol was identified as the optimal reaction solvent (Entries 21–27), although in some cases trifluoroethanol proved to be superior (Entry 23; see section 4.3.3.3 below). By-product **24e**, which shows a distinct upfield shift of the ^{19}F NMR signal to −52.29 ppm (d, $^{3}J_{HF}$ = 12.0 Hz) due to its electropositive α-silicon substituent, was converted into vinyl-CF_3 product **25e** after work-up and solvent exchange from MeOH to THF by attack of fluoride on silicon to initiate E2 elimination of the silyl and methoxy groups. Efforts to initiate elimination with an acid workup showed moderate results (Entries 28–29). Attempts to develop a one-pot procedure by adding TBAF directly to the reaction mixture without prior work-up led to a significant amount of by-product **24e** remaining in the final product mixture, suggesting that the fluoride ion is too strongly solvated to act as a nucleophile (Entry 30).

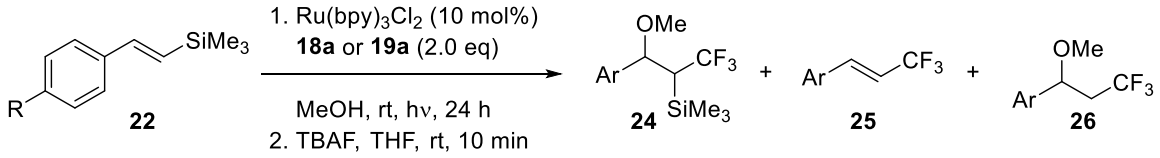
The optimal conditions for photocatalytic trifluoromethylation of alkenylsilanes are thus: 1.0 equivalent vinylsilane, 2.0 equivalents Togni's reagent **19a** (Conditions A, Entry 8) or Umemoto's reagent **18a** (Conditions B, Entry 15) and 10 mol% $Ru(bpy)_3Cl_2 \cdot 6H_2O$ in methanol at room temperature for 24 hours under irradiation with a 14 W household light bulb. After extraction and evaporation of the reaction mixture and a solvent exchange to THF, reaction with 1.0 equivalents TBAF at rt for 10 minutes afforded alkenyl-CF_3 product **25e** in 57% (Entry 8, Conditions A) or 50% (Entry 15, Conditions B) by ^{19}F NMR.

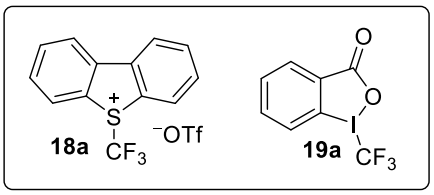
The mass balance in these reactions is not sufficiently explained by the by-products observed in the crude reaction mixture. It is plausible to assume that vinylsilanes **22** are unstable towards protodesilylation (see Scheme 76b) and the resulting styrenes undergo photocatalytic polymerisation in the presence of a $CF_3^{\bullet}$ radical initiator.[191] This would

explain the insoluble by-product formed in some of these reactions, the black colour of the crude reaction mixture and the incorrect mass balance.

4.2.2.2 Effect of the Trifluoromethylating Reagent

A preliminary substrate screen with reagents **18a** and **19a** showed a correlation between electronics and reactivity, with more electron-rich substrates generally showing higher conversions to products **25** and **26** (Table 13).





Entry	R	σ[a]	CF_3 source	Conversion [%][b]	Yield **24** [%][c]	Yield **25** [%][c]	Yield **26** [%][c]
1	OMe	–0.29	**19a**	>99	10	40	0
			18a	>99	0	7	77
2	H	0	**19a**	>99	10	46	0
			18a	>99	0	47	5
3	Cl	0.22	**19a**	58	0	32	0
			18a	>99	0	51	3
4	CF_3	0.53	**19a**	69	0	16	0
			18a	>99	0	47	0

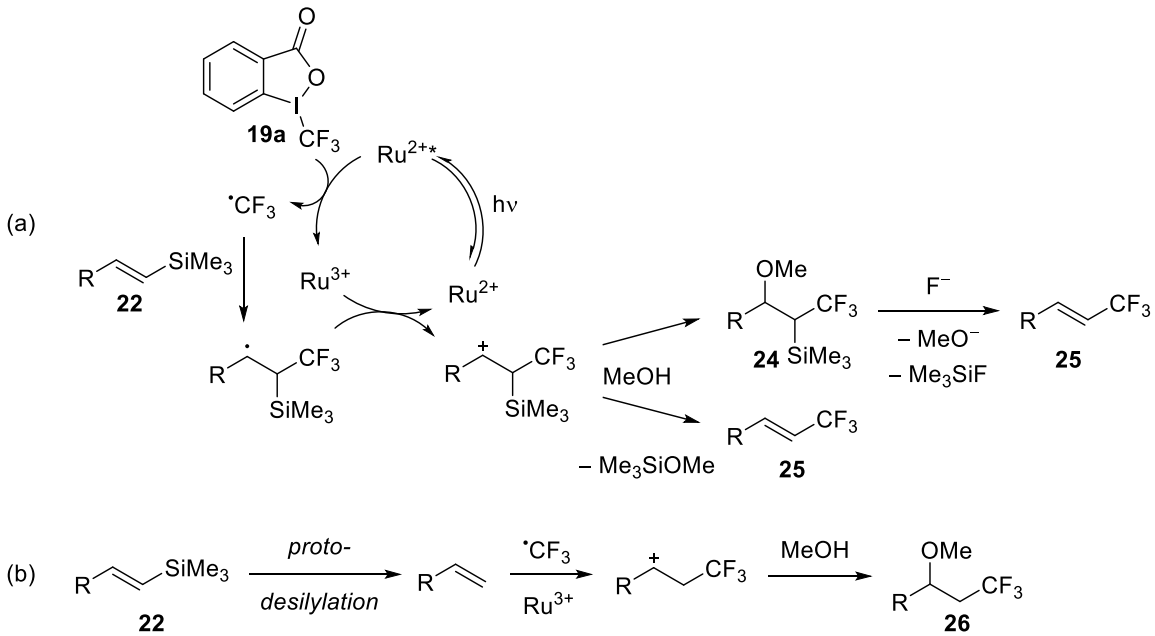
Conditions: (i) 1.0 eq (*E*)-**22** (0.25 mmol), 2.0 eq **18a** or **19a**, 5 mol% $Ru(bpy)_3Cl_2 \cdot 6H_2O$, MeOH, rt, 14 W light bulb, 24 h. (ii) 1.0 eq TBAF, THF, rt, 10 min. [a] Hammett sigma parameter: $\sigma_x = pK_a(C_6H_5CO_2H) - pK_a(X\text{-}C_6H_5CO_2H)$. Negative σ denote electron donating groups, positive σ denote electron withdrawing groups.[192] [b] Conversion is defined as 100 – x %, where x is the percentage of starting material detected by ^{1}H NMR, relative to the trifluoromethylated product peak(s). [c] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 equivalent α,α,α-trifluorotoluene.

Table 13 Hammett correlation of substrate reactivity and electronics

As mentioned above, the reaction mechanism seems to include formation of by-product **24** which is consistent with silicon-directed radical $CF_3^{\bullet}$ addition α to the TMS group and

subsequent methanol capture of the carbocationic intermediate (Scheme 76a). Fluoride-mediated E2 elimination of the trimethylsilyl and methoxy groups could then selectively form the trifluoromethylated *E*-alkene. The Me_3SiF liberated as a result of this elimination can be seen in the crude ^{19}F NMR of these reactions as an apparent octet with a chemical shift of −157.7 ppm and a $^3J_{FH}$ coupling constant of 7.0 Hz. Alternatively, product **25** may also be accessed by direct elimination of the TMS group from the carbocationic intermediate.

Vinylsilanes are known to undergo protodesilylation in the presence of acid or metal catalysts,[193] and substrates **22** were unstable towards decomposition when stored on the bench. It is thus reasonable to assume that by-products **26** are formed by radical trifluoromethylation of protodesilylated starting material (Scheme 76b). Qing *et al.* observed formation of the same by-product in their copper-catalysed radical *bis*-trifluoromethylation of electron-rich styrenes with Togni's reagent.[194]



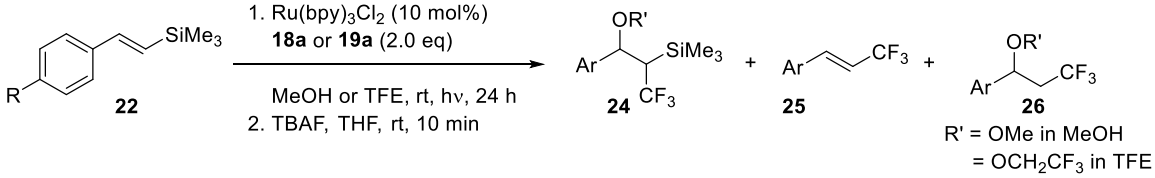
Scheme 76 Proposed reaction mechanism

We thus propose the following catalytic cycle for our trifluoromethylation of vinylsilanes with Togni's reagent **19a** (Scheme 76a): Togni's reagent **19a** is reduced to a trifluoromethyl radical and 2-iodobenzoate by the excited photocatalyst $Ru(bpy)_3^{2+}$*. The $CF_3^{\bullet}$ radical attacks the vinylsilane substrate α to the silyl group, forming a β-silicon stabilised radical intermediate which undergoes oxidation to the corresponding carbocation by Ru^{3+}. The alcoholic solvent may either act as a base, eliminating Me_3SiOMe from the carbocationic intermediate to give the desired trifluoromethylated products **25**, or as a nucleophile, affording by-product **24** which can be converted to **25** in a fluoride-mediated elimination step. This mechanism is supported by the observations made previously in the group with allylsilane substrates under the same conditions (see above).[177]

The mechanism seems to depend on the trifluoromethylation reagent used. Togni's reagent **19a** shows better results for electron-rich substrates (Table 13, Entry 1), giving lower conversions for electron-poor substrates (Entries 3–4). Conversely, Umemoto's reagent **18a** favours electron-poor substrates, owing to the fact that electron-rich substrate predominantly form by-product **26** (Entries 1 *vs.* 3–4). In the mechanism shown in Scheme 76a, a trifluoromethyl radical is proposed to add to vinylsilane **22**. If the species involved in the reaction was truly a free radical, we would expect to see the same results in terms of reactivity and selectivity regardless of the trifluoromethyl source used. As this is not the case, we propose that it is not a free radical that is involved in the reaction mechanism. It is conceivable that a charge-transfer complex is formed with the chalcogen or iodonium moiety of **18a** or **19a** respectively. Alternatively, the decomposition products of **18a** (4a,9b-dihydrodibenzo[*b*,*d*]thiophene) and **19a** (2-iodobenzoate) may have different effects on the lifetime of the radical reaction intermediates, thus influencing the reactions outcome.

4.2.2.3 Solvent Effect

A more detailed investigation into the role of the solvent (Table 14) showed that in reactions with Togni's reagent **19a**, methanol gives slightly better results for electron-rich substrates (Entry 2) while trifluoroethanol (TFE) increases the reactivity of electron-poor substrates (Entry 3). Fluorinated alcohol solvents are ideally suited for the stabilisation of radical cations as they are strong hydrogen bond donors, highly polar and ionising, but only weakly nucleophilic.[195] The beneficial effect of TFE on the reaction of electron-poor substrates may be explained by the fact that solvent stabilisation is more important for these substrates than for electron-rich ones. With Umemoto's reagent **18a**, none of the desired product **25** was formed in TFE, affording predominantly alkoxylated by-product **26** (R' = OCH_2CF_3, Entry 4). Since photocatalytic $CF_3^{\bullet}$ radical formation from Umemoto's reagent **18a** produces triflic acid as a by-product we hypothesise that in combination with the acidic solvent TFE (pK_a = 12.5), acid-mediated protodesilylation becomes facile under these conditions, favouring the formation of **26**.



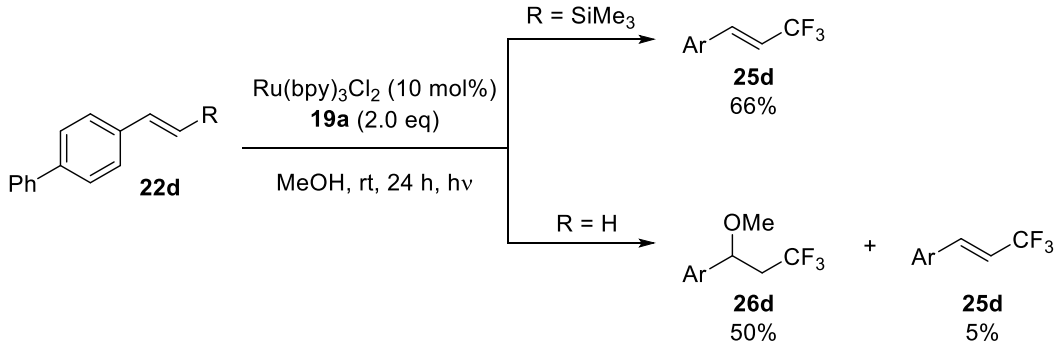
Entry	R	σ[a]	CF_3 source	Solvent	Conversion [%][b]	Yield **24** [%][c]	Yield **25** [%][c]	Yield **26** [%][c]
1	H	0	**19a**	MeOH	94	13	57	0
				TFE	>99	0	62	0
2	Ph	0.01	**19a**	MeOH	>99	7	65	0
				TFE	98	0	53	0
3	Cl	0.22	**19a**	MeOH	53	0	45	0
				TFE	94	0	73	0
4	Cl	0.22	**18a**	MeOH	>99	0	52	3
				TFE	>99	0	0	45

Conditions: (i) 1.0 eq (*E*)-**22** (0.25 mmol), 2.0 eq **18a** or **19a**, 10 mol% $Ru(bpy)_3Cl_2 \cdot 6H_2O$, MeOH or TFE, rt, 14 W light bulb, 24 h. (ii) 1.0 eq TBAF, THF, rt, 10 min. [a] Hammett sigma parameter: $\sigma_x = pK_a(C_6H_5CO_2H) - pK_a(X\text{-}C_6H_5CO_2H)$.[192] [b] Conversion is defined as 100 – x %, where x is the percentage of starting material detected by ^1H NMR, relative to the trifluoromethylated product peak(s). [c] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 equivalents α,α,α-trifluorotoluene.

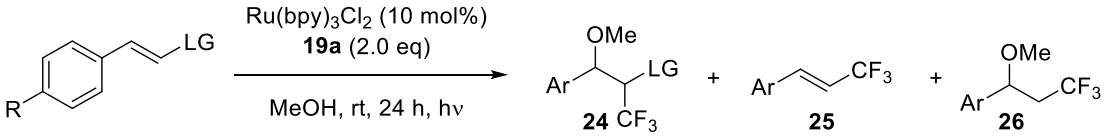
Table 14 Solvent effects

4.2.2.4 Leaving Group Effect

As discussed above, both the trimethylsilyl group and the substituent on the other side of the double bond direct attack of the $CF_3^{\bullet}$ radical α to silicon, affording a radical intermediate that is stabilised by hyperconjugation with the C–Si bonding orbital as well as by the *beta*-substituent *via* π-conjugation or σ-induction effects (Scheme 76). The silyl group, however, is crucial for the selective formation of trifluoromethylated alkene products **25** by E2 elimination. In the absence of this stabilising group, the reactive intermediates are captured by the solvent to afford mainly oxytrifluoromethylated alkane **26** together with only traces of the desired product **25** (Scheme 77). The size of the silyl group seems to be of some importance, with bulkier substituents such as $SiEt_3$ decreasing the yield of product **25** markedly compared to $SiMe_3$, presumably by hindering the approach of the trifluoromethylating reagent (Table 15, Entries 1–3).



Scheme 77 Effect of the silicon group on product outcome



Entry	LG	R	Conversion (%)[a]	Yield **24** (%)[b]	Yield **25** (%)[b]	Yield **26** (%)[b]
1	$SiMe_3$ (**22d**)	Ph	>99	11	65	0
2	$SiEt_3$ (**23d**)	Ph	>90	39	23	0
3	$SiMe_2Ph$ (**28d**)	Ph	70	4	40	0
4	$SiMe_3$ (**22e**)	H	94	7	57 (*E* only)	0
5	$GeMe_3$ (**29e**)	H	90	0	53 (*E*/*Z* = 6)	3
6	$SnBu_3$ (**30e**)	H	>99	0	45 (*E*/*Z* = 17)	17

Conditions: 1.0 eq (*E*)-**22**–**23** or (*E*)-**28**–**29** (0.25 mmol), 2.0 eq **19a**, 5 mol% $Ru(bpy)_3Cl_2 \cdot 6H_2O$, MeOH, rt, 14 W light bulb, 24 h. No TBAF workup.

Table 15 Leaving group effect on product outcome

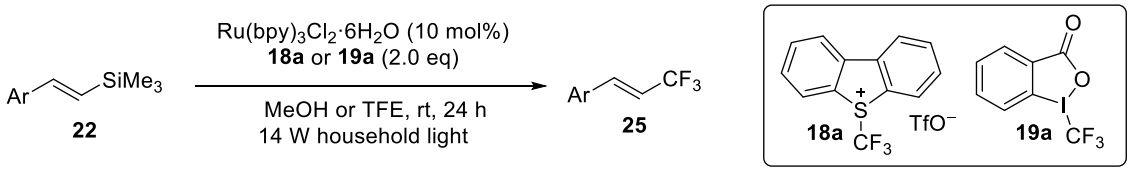
Due to larger orbital size, the β-effect of germanium is slightly larger than for silicon and that of tin is dramatically stronger than for both its congeners.[196] We were thus interested to see what effect the introduction of germanium and tin leaving groups would have on the reactivity of vinylic substrates under our reaction conditions (Table 15, Entries 4–5). Interestingly, allylgermane **29e** and allylstannane **30e** afforded slightly lower yields of trifluoromethylated product **25e** than allylsilane **22e**, as well as an erosion of stereocontrol. The lower yields may be explained by the steric bulk of these groups hindering attack of the trifluoromethylating reagent, similar to the bulkier silyl groups in substrates **23d** and **28d**. The erosion of stereocontrol, on the other hand, is surprising and requires further mechanistic work for a satisfactory explanation.

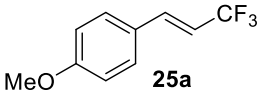
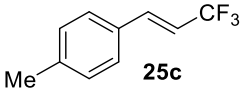
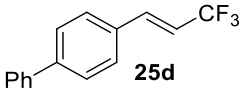
4.2.3 Substrate Scope

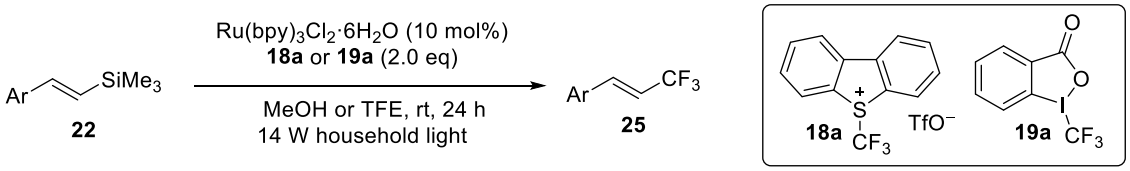
With optimised conditions in hand, the substrate scope for the trifluoromethylation of alkenylsilanes was investigated (Table 16). All yields quoted in Table 16 are ^{19}F NMR yields; yields of the isolated products – when given (Entries 3, 8–9) – are generally low, reflecting the difficulty in separating products **25** from the by-products formed during the

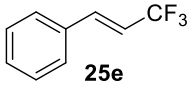
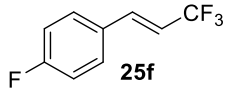
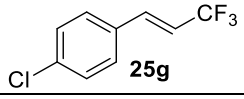
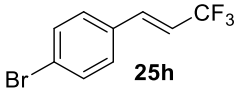
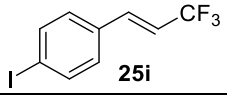
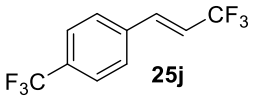
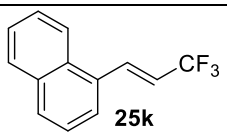
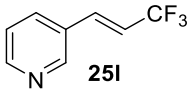
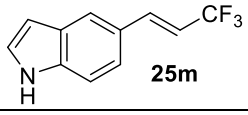
reaction as well as unreacted starting material by silica flash column chromatography or preparative TLC, due to the low polarity of all species in the reaction mixture. Products **25** are identified by a clear doublet of doublets in the ^{19}F NMR at −63.7 ppm ($^{3}J_{HF}$ = 7.0 Hz, $^{4}J_{HF}$ = 2.0 Hz). The corresponding protons resonate at 6.12 ppm and 7.19 ppm in the ^{1}H NMR for electroneutral **25e**. Both proton signals are split into doublets of quartets due to coupling to the second alkene proton and the CF_3 group. The $^{3}J_{HH}$ coupling constant of 16.0 Hz are diagnostic of *E*-alkenes.

Electron-poor and electron-rich aromatic vinylsilanes were trifluoromethylated in moderate yields as the *E* isomer exclusively (Entries 1–9). For electron-rich substrates, Togni's reagent **19a** was used (Entries 1–2), while electron-poor substrates gave better results with Umemoto's reagent **18a** (Entries 5–9). Electroneutral substrates **22d** and **22e** gave comparable results with both trifluoromethylating reagents (Entries 3–4). Trimethyl[(*E*)-2-(naphthalen-1-yl)ethenyl]silane **22k** and heteroaromatic alkenylsilanes **22l** and **22m** only afforded the corresponding trifluoromethylated products in low yields (Entries 10–12). *Z*-Vinylsilane (*Z*)-**22** afforded the same yield as its *E*-isomer (Entry 1) and also gave product **25** exclusively as the *E* isomer.



Entry	Product	Yield **25** [%][a] Cond. A (**19a**, MeOH)	Yield **25** [%][a] Cond. B (**18a**, MeOH)	Yield **25** [%][a] Cond. C (**19a**, TFE)
1	 **25a**	40 39[b,c]	7	-
2	 **25c**	39	24	28
3	 **25d**	65 (50)	63	53



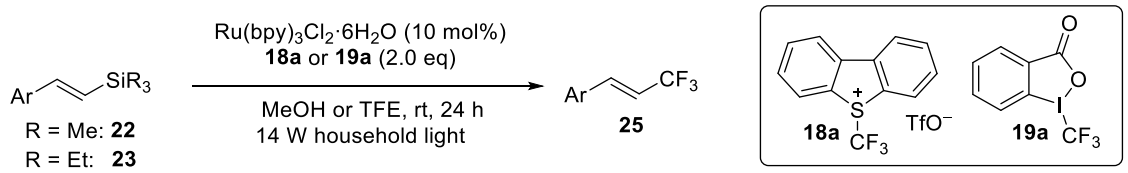
Entry	Product	Yield **25** [%][a] Cond. A (**19a**, MeOH)	Yield **25** [%][a] Cond. B (**18a**, MeOH)	Yield **25** [%][a] Cond. C (**19a**, TFE)
4	 **25e**	57	50	62
5	 **25f**	-	40[b]	-
6	 **25g**	45	52	73
7	 **25h**	40	-	-
8	 **25i**	-	58 (44)	-
9	 **25j**	30	57 (33)	55
10	 **25k**	20	25	10
11	 **25l**	-	22[b]	-
12	 **25m**	9[b]	-	-

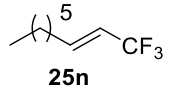
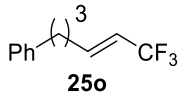
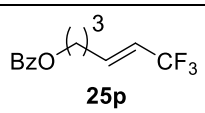
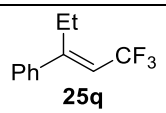
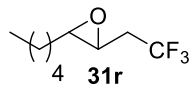
[a] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq α,α,α-trifluorotoluene. (Yields in parentheses are of isolated products). All products were afforded exclusively as the *E* isomer. A dash in the table entry means this reaction was not run. **Conditions A**: (i) 1.0 eq (*E*)-**22** (0.25 mmol), 2.0 eq **19a**, 10 mol% $Ru(bpy)_3Cl_2·6H_2O$, MeOH, 14 W household light bulb, rt, 24 h. (ii) 1.0 eq TBAF, THF, rt, 10 min. **Conditions B**: As A, but using 2.0 eq **18a** as the trifluoromethyl source. **Conditions C**: As A, but using TFE as the solvent. [b] 5 mol% $Ru(bpy)_3Cl_2·6H_2O$. [c] Starting from 1.0 eq (*Z*)-**22**.

Table 16 Substrate scope for the photocatalytic trifluoromethylation of aromatic vinylsilanes

Linear aliphatic vinylsilanes gave low yields of trifluoromethylated products **25** with low stereoselectivity (Table 17, Entries 1–3). Branched aliphatic substrate **22q**, in which the radical intermediate profits from extra inductive stabilisation from the alkyl group, afforded product **25q** in 41% yield (Entry 4). When the vinylsilane contains an internal nucleophile,

as is the case for (1*E*)-1-(trimethylsilyl)oct-1-en-3-ol **22r**, the reactive intermediate is captured by the internal nucleophile, affording trifluoromethylated epoxide **31r** in 19% yield (Entry 5). An interesting effect of the trifluoromethylating reagent on the stereoselectivity was observed with aliphatic substrates: Umemoto's reagent **18a** afforded the expected *E* isomer in slight excess, while Togni's reagent **19a** marginally favoured the formation of the *Z* isomer (Entries 15–17).



Entry	Product	Yield **25** [%][a] Cond. A (**19a**, MeOH)	Yield **25** [%][a] Cond. C (**19a**, TFE)	Yield **25** [%][a] Cond. B (**18a**, MeOH)
1[b]	 **25n**	13 (1:1.5 *E*:*Z*)	-	8 (3:1 *E*:*Z*)
2[b]	 **25o**	15 (1:1.2 *E*:*Z*)	-	-
3[b]	 **25p**	9 (1:1.4 *E*:*Z*)	6 (2:1 *E*:*Z*)	-
4	 **25q**	47 (17)	13	-
5	 **31r**	19	-	-

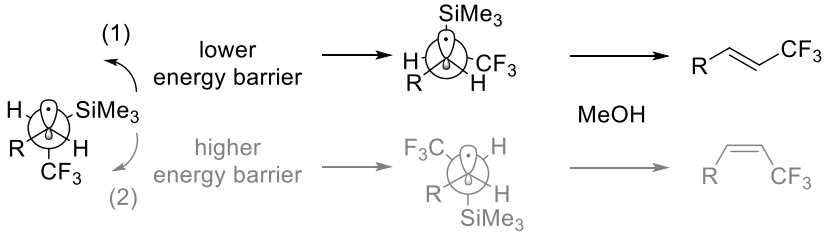
[a] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq α,α,α-trifluorotoluene. (Yields in parentheses are of isolated products). All products were afforded exclusively as the *E* isomer unless stated otherwise. A dash in the table entry means this reaction was not run. **Conditions A**: (i) 1.0 eq (*E*)-**22** (0.25 mmol), 2.0 eq **19a**, 10 mol% $Ru(bpy)_3Cl_2·6H_2O$, MeOH, 14 W household light bulb, rt, 24 h. (ii) 1.0 eq TBAF, THF, rt, 10 min. **Conditions B**: As A, but using 2.0 eq **18a** as the trifluoromethyl source. **Conditions C**: As A, but using TFE as the solvent. [b] From triethylsilane (*E*)-**23**.

Table 17 Substrate scope for the photocatalytic trifluoromethylation of aliphatic vinylsilanes

The stereochemistry is determined during addition of the $CF_3^{\bullet}$ radical to the vinylsilane (Scheme 78). In order to stabilise the resulting alkyl radical by hyperconjugation, the silicon group must rotate so that the σ_{C-Si} bonding orbital is periplanar with the radical hybrid

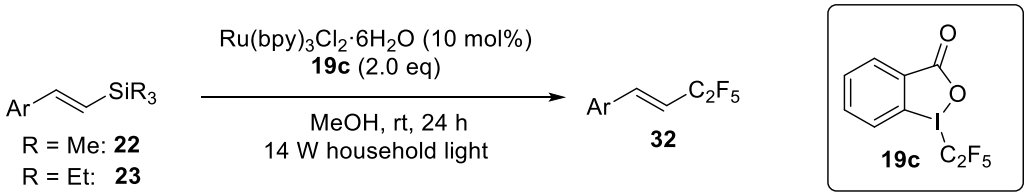
orbital.[179] It may do so *via* two possible ways: (1) An upward rotation proceeds through a low energy barrier, resulting directly in a stable conformation with the σ_{C-Si} bonding orbital parallel to the radical hybrid orbital, while (2) the downward rotation has a high energy barrier, as it passes through a conformation in which the σ_{C-Si} and radical hybrid orbitals are orthogonal and the intermediate does not profit from any stabilising effects. The upward rotation (1) is thus favoured, giving the *E* alkene after elimination of the silyl group.

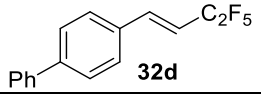
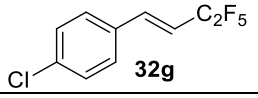
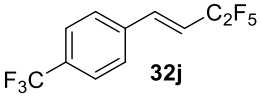
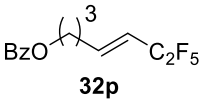
Conjugation with the aromatic ring in substrates **22a–m** generates a more stable radical with a higher energy SOMO. Therefore, the SOMO presumably has more sp^3 character, while the radicals obtained from aliphatic vinylsilanes **23n–p** have SOMOs with stronger sp^2 character. Since sp^2 hybrid orbitals are perpendicular to the central C–C bond, orbital overlap between the radical SOMO and the σ_{C-Si} bonding orbital is better than for sp^3 orbitals which are at an angle of 109.5° to the C–C bond. The energy difference between rotation (1) and rotation (2) is thus smaller for aliphatic radicals (generated from substrates **23n–p**) than for benzylic radicals (generated from substrates **22a–m**), because the preference to maintain orbital overlap with the C–Si bond is not as strong. This may explain the erosion of stereocontrol in the case of aliphatic vinylsilanes **23n–p**, as both rotations become energetically feasible. However, a direct comparison between aromatic and aliphatic substrates is difficult, since aliphatic substrates **23n–p** were synthesised containing the triethylsilyl group which was shown above (Table 15) to be substantially less reactive than the trimethylsilyl group.



Scheme 78 Torquoselectivity determines stereochemical outcome

Pleasingly, pentafluoroethylation with a variant of Togni's reagent, **19c**, was highly efficient under these conditions, affording the corresponding pentafluoroethylated alkenes in yields superior to their trifluoromethylated analogues (Table 18). Electron-rich, electroneutral and electron-poor aromatic vinylsilanes **22a**, **22g** and **22j** furnished perfluorinated products **32** in 63–90% yields (Entries 1–3). Aliphatic vinylsilane **23p** afforded a lower yield of 33% **32p** (Entry 4).

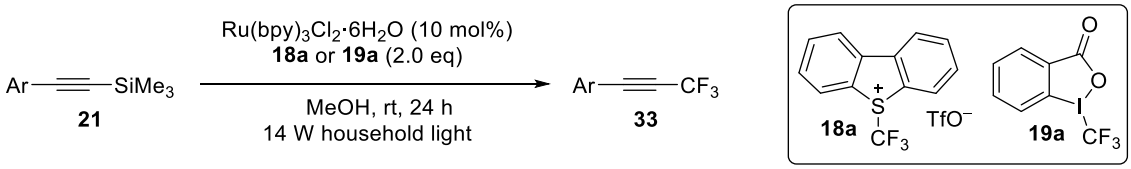


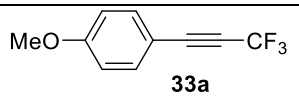
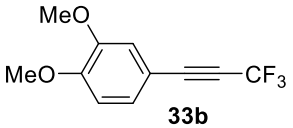
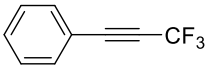
Entry	Product	Yield **32** [%][a]
1	 **32d**	90 (40)
2	 **32g**	81
3	 **32j**	63
4[b]	 **32p**	33 (*E*/*Z* = 2.3)

[a] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq α,α,α-trifluorotoluene. (Yields in parentheses are of isolated products). Conditions: (i) 1.0 eq (*E*)-**22** (0.25 mmol), 2.0 eq **19c**, 10 mol% $Ru(bpy)_3Cl_2·6H_2O$, MeOH, 14 W household light bulb, rt, 24 h. (ii) 1.0 eq TBAF, THF, rt, 10 min. [b] From triethylsilane (*E*)-**23**.

Table 18 Substrate scope for the photocatalytic pentafluoroethylation of vinylsilanes

Alkynylsilanes are less reactive under our trifluoromethylating conditions than alkenylsilanes, furnishing trifluoromethylated alkynes **33** in 4–40% yield (Table 19).



Entry	Product	Yield **33** [%][a] Cond. A (**19a**, MeOH)	Yield **33** [%][a] Cond. B (**18a**, MeOH)
1	 **33a**	40	-
2	 **33b**	22	-
3	 **33e**	4	8

[a] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq α,α,α-trifluorotoluene. A dash in the table entry means this reaction was not run. **Conditions A**: (i) 1.0 eq **21** (0.25 mmol), 2.0 eq **19a**, 10 mol% $Ru(bpy)_3Cl_2·6H_2O$, MeOH, 14 W household light bulb, rt, 24 h. (ii) 1.0 eq TBAF, THF, rt, 10 min. **Conditions B**: As A, but with 2.0 eq **18a** as the trifluoromethylating reagent.

Table 19 Selected examples of the photocatalytic trifluoromethylation of alkynylsilanes

We postulate that this is due to the lower stability of sp^2 centred radicals compared to sp^3 radicals. Radical stability is usually quantified in terms of the C–H bond dissociation energy necessary to form the radical.[197] In a review collecting bond dissociation energies determined by kinetic methods, J. A. Kerr recorded that the C–H bond dissociation energy of ethane is 98.0 kcalmol^{-1}, while that of ethene is 105.0 kcalmol^{-1} (Table 20).[198] By corollary, this indicates that the sp^3 ethane radical is *ca.* 7.0 kcalmol^{-1} more stable than the sp^2 ethene radical. Calculations by Zhang showed that fluorinated hydrocarbons follow a similar trend: The β-trifluoromethylated sp^3 ethane radical is *ca.* 10.5 kcalmol^{-1} more stable than its corresponding sp^2 ethene radical (Table 20).[199]

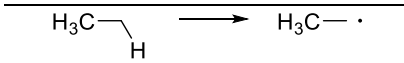
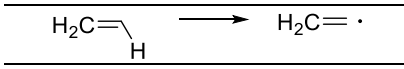
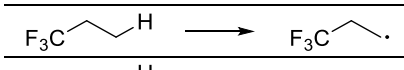
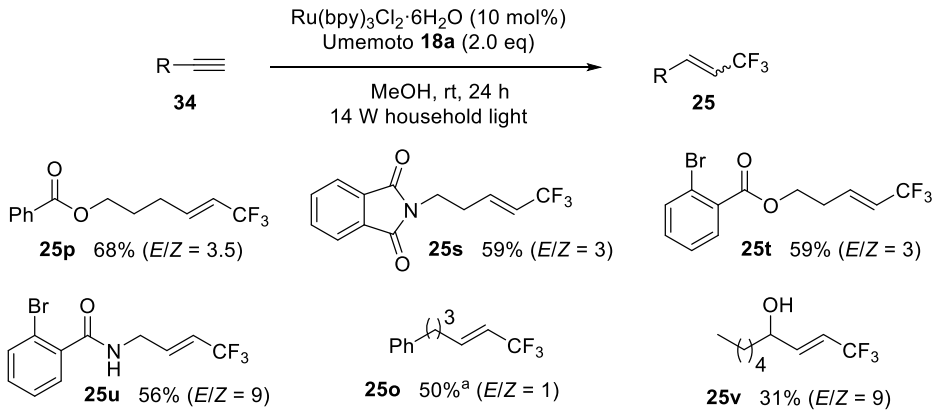
	$D_{C–H}$ [kcalmol^{-1}]
	98.0
	105.0
	102.8
	113.3

Table 20 C–H bond dissociation energies of hydrocarbons at 298 K[198, 199]

In the absence of the silyl group, terminal alkynes underwent an interesting hydrotrifluoromethylation reaction (Scheme 79): Trifluoromethylated alkenes **25** were afforded in moderate to good yields.[176]



Conditions: 1.0 eq **34** (0.25 mmol), 2.0 eq **18a**, 10 mol% Ru(bpy)$_3$Cl$_2$·6H$_2$O, MeOH, 14 W household light bulb, rt, 24 h. Yields are of isolated products. [a] ^{19}F NMR yield, determined by integration of the product peak(s) relative to 1.0 eq α,α,α-trifluorotoluene.

Scheme 79 Photocatalytic hydrotrifluoromethylation of terminal alkynes[176]

4.3 Conclusion

We have developed the first photocatalytic trifluoromethylation of vinyl- and alkynylsilanes to afford trifluoromethylated alkenes and alkynes in moderate yields. Extension to pentafluoroethylation was highly successful.

This transformation demonstrates the value of radical photoredox processes to extend the scope of stereoselective trifluoromethylation to non-aromatic substrates not activated by traditional carbonyl-based functional groups. The silyl group is vital for the high regio- and

stereoselectivity observed in this reaction. Furthermore, the trifluoromethylating reagent and solvent were shown to have important effects on reactivity and selectivity. More in-depth studies are necessary to fully understand the nature of the radical species involved in the reaction mechanism.

The methodology presumably suffers from a competing protodesilylation/polymerisation side-reaction. Suppression of this undesired process may be achieved by the addition of inhibitors (such as 4-*tert*-butylcatechol or 4-methoxyphenol), however a careful screen of additives would have to be carried out to avoid inhibition of the desired reaction.

Chapter 5: Copper-Mediated Cross-Coupling of Aryl(tetrafluoroethyl)trimethylsilanes

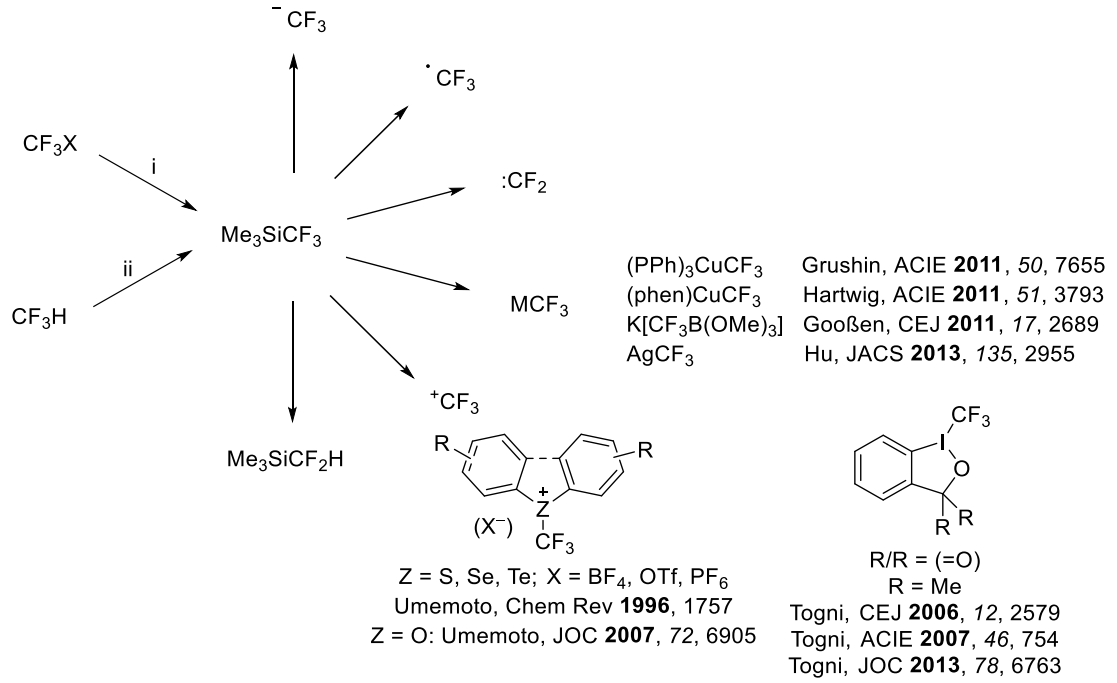
5.1 Introduction: The Ruppert-Prakash Reagent and its Perfluorinated Variants

The Ruppert-Prakash reagent, Me_3SiCF_3, is a powerful and extremely useful reagent for trifluoromethylation. It is commercially available, easy to handle and stable when stored at low temperatures. Moreover, this reagent allows for the formation of CF_3^- anions (*via* nucleophilic activation with catalytic fluoride or Lewis acids),[200] CF_3^+ cations (*via* trifluoromethyl transfer to form chalcogen[102, 201] and hypervalent iodine[103] salts), $CF_3^\bullet$ radicals (*via* oxidation of CF_3^+) and $:CF_2$ difluorocarbenes (*via* α-elimination of fluoride from CF_3^-), giving rise to a wide reactivity profile (Scheme 80). In comparison, its perfluoroalkylated derivatives (R_fSiMe_3, $R_f = (CF_2)_nR$, R = F, alkyl, aryl) have been studied less comprehensively.[202] In particular, cross-coupling chemistry with reagents of the form $R(CF_2)_nSiMe_3$ (R = F, alkyl, aryl) is plagued by competing side-reactions. We sought to address this challenge by developing a copper-mediated cross-coupling strategy for aryl(tetrafluoroethyl)trimethylsilanes, $Ar(CF_2)_2SiMe_3$. We hope that the insights gained from this project will be beneficial for the development of other challenging cross-coupling methodologies.

5.1.1 Synthesis

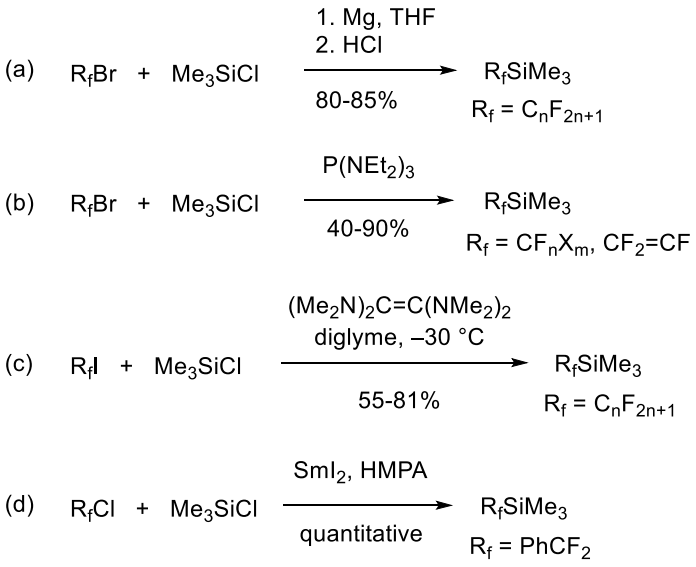
Nucleophilic trifluoromethylation reactions are challenging on account of the great instability of the CF_3^- anion towards dissociation into F^- and a difluorocarbene.[67] The organometallic species trifluoromethyl lithium and magnesium, for example, are too

unstable to be used as nucleophilic trifluoromethylating reagents due to their rapid disproportionation into the corresponding metal fluoride (LiF or MgF_2) and a difluorocarbene.[68] This problem was overcome with the development of the Ruppert-Prakash reagent Me_3SiCF_3 by Ruppert in 1984 (Scheme 80).[203] $P(NEt_2)_3$ was reacted with CF_3Br to form a $[(NEt_2)_3PBr]^+$ CF_3^- complex which was able to transfer CF_3^- to Me_3SiCl to afford the desired (trifluoromethyl)trimethylsilane in 95% yield. The original synthesis has since been optimised to access Me_3SiCF_3 from other trifluoromethyl halogens after the ban of trifluoromethyl bromide by the Montreal protocol. Recently, Prakash published a new procedure that allows the synthesis of Me_3SiCF_3 from fluoroform (CF_3H), a waste product in the industrial production of fluorous materials (Teflon, refrigerants, fire extinguishing agents, *etc.*).[204] CF_3H is deprotonated by KHMDS in toluene at –78 °C and the resulting trifluoromethide anion is trapped by Me_3SiCl, forming Me_3SiCF_3 in 80% yield (Scheme 80).



Scheme 80 Synthesis and Reactivity Modes of the Ruppert-Prakash Reagent[91, 98, 102, 103, 144, 203-206]

While many CF_3-organometallics are unstable towards disproportionation, perfluoroalkylated organosilicon compounds are easily accessible *via* an organometallic route in good yields (Scheme 81a).[202] Alternatively, these reagents may also be accessed *via* Ruppert's methodology, in which $P(NEt_2)_3$ attacks a perfluoroalkylbromide to afford a phosphonium salt from which R_f^- is transferred to Me_3SiCl (Scheme 81b). Yields are moderate for partially fluorinated and perfluorinated alkenes,[207] but high for the mixed trihalomethyl compounds ($R_f = CF_nX_m$, n = 1–3, m = 1–2, X = Cl, Br, I, H).[208] Similarly, tetrakis(dimethylamino)ethylene forms a charge-transfer complex with perfluoroalkyliodides which can transfer R_f^- to Me_3SiCl (Scheme 81c).[209] Finally, it has also been shown that reduction of chlorodifluoromethylbenzene with samarium iodide in the presence of Me_3SiCl affords phenyldifluoromethylbenzene in quantitative yield (Scheme 81d).[210]

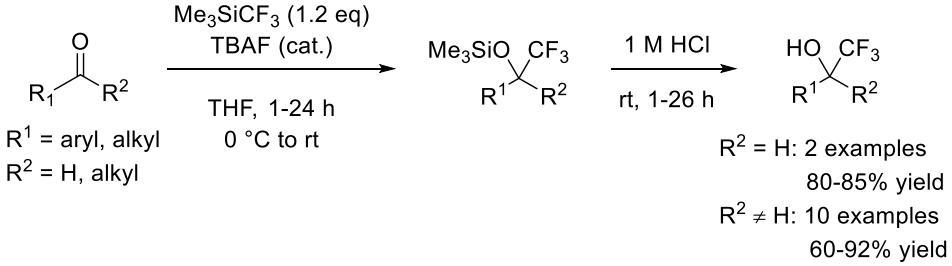


Scheme 81 Synthesis of perfluoroalkylated organosilicon compounds[202, 207-210]

5.1.2 Reactivity

5.1.2.1 Nucleophilic Addition

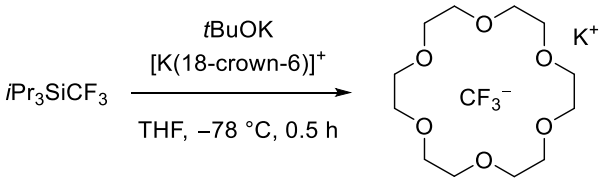
Shortly after their re-discovery of Me_3SiCF_3, Prakash *et al.* published the first nucleophilic trifluoromethylation of aldehydes and ketones with this reagent (Scheme 82).[211] Nucleophilic trifluoromethylation with Me_3SiCF_3 was hypothesised to occur *via* liberation of a CF_3^- anion. A nucleophilic initiator – usually catalytic fluoride, although other examples include metal alkoxides, as well as Lewis acids and bases[200] – attacks the silicon centre forming a negatively charged trigonal pyramidal intermediate from which CF_3^- is expelled to react with the electrophile of choice.[211] In the case of carbonyls, the products of this reaction are trifluoromethylated silyl ethers, which are usually deprotected to yield trifluoromethylated alcohols with aqueous HCl. Since the first examples published by Prakash, nucleophilic trifluoromethylation with Me_3SiCF_3 has progressed rapidly with the development of enantioselective methodologies employing cinchona alkaloids and phase-transfer catalysts.[68]



Scheme 82 Trifluoromethylation of aldehydes and ketones with Me_3SiCF_3[211]

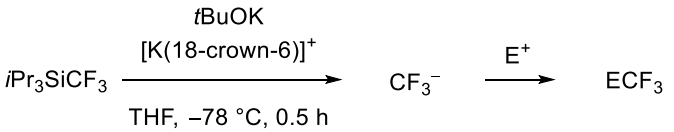
The trifluoromethanide anion has long only been theoretically postulated as a short-lived intermediate without any experimental evidence of its formation. Recently, however, Prakash and co-workers were able to generate and characterise the CF_3^- $[K(18\text{-crown-6})]^+$ complex in THF at –78 °C from iPr_3SiCF_3 (Scheme 83).[212] This more sterically hindered variant of the Ruppert-Prakash reagent was used to avoid the formation of pentavalent

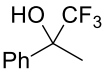
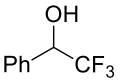
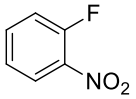
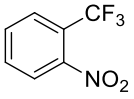
silicon by-products of the form $R_3Si(X)CF_3$. The resulting trifluoromethide anion was reported to be stable for several days at –78 °C, but decomposition occured between −50 °C and −35 °C. The relative stability at low temperatures allowed the authors to obtain low-temperature ^{19}F and ^{13}C NMR spectra of the CF_3^- anion. The ^{19}F NMR spectrum at −78 °C showed a sharp singlet at −18.7 ppm, while ^{13}C NMR at −56 °C revealed a quartet at 175.0 ppm with a carbon-fluorine coupling of $^1J_{CF}$ = 432.5 Hz.



Scheme 83 Formation of CF_3^- at –78 °C[212]

Trapping experiments with various electrophiles showed the formation of the expected trifluoromethylated products (Table 21).

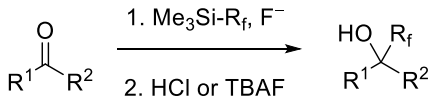


Entry	E^+ (eq)	ECF_3	NMR Yield [%][a]
1	PhSSPh (2.2)	$PhSCF_3$	70
2	I_2 (2.2)	CF_3I	48
3	MeI (11.0)	$MeCF_3$	21
4	$(PhSO_2)_2NF$ (2.2)	$PhSO_2CF_3$	41
5	 (11.0)		22
6	 (2.2)		68
7	CO_2 (xs)	CF_3CO_2K	76
8	 (11.0)		7
9	CuI (11.0)	$CuCF_3$	66

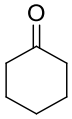
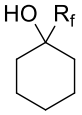
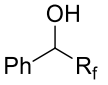
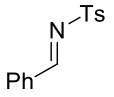
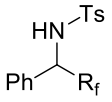
[a] Determined by ^{19}F NMR relative to $PhCF_3$ as an internal standard.

Table 21 Trapping of pre-formed CF_3^- with common electrophiles[212]

Similarly, addition of (perfluoroalkyl)trimethylsilanes to carbonyls affords perfluoroalkylated silyl ethers, the deprotection of which is usually also realised with HCl (Table 22).[213-215]



$R_f = C_nF_{2n+1}$

Entry	Substrate	Product	Yield [%][a]	Reference
1			74 ($R_f = CF_3$) 81 ($R_f = C_2F_5$) 78 ($R_f = C_3F_7$) 0 ($R_f = CF_2H$)	[213]
2			77 ($R_f = CF_3$) 82 ($R_f = C_2F_5$) 81 ($R_f = C_3F_7$)	[213]
3			85 ($R_f = CF_3$) 86 ($R_f = C_2F_5$) 66 ($R_f = C_3F_7$)	[213]
4			93 ($R_f = CF_3$) 91 ($R_f = C_2F_5$) 87 ($R_f = C_3F_7$) 85 ($R_f = CF_2CO_2Et$) 82 ($R_f = CF_2$-(4-CF_3)C_6H_4)	[215]

Conditions: Entry 1–3: Carbonyl (1.0 eq), Me_3SiR_f (1.2 eq), TBAF or TASF (cat.), THF, 0 °C to rt; then: $HCl_{(aq)}$. Entry 4: Imine (1.0 eq), Me_3SiR_f (1.4 eq), AcOLi (10 mol%), DMF, –20 °C, 16 h; then: $NH_4Cl_{(aq)}$. [a] Yields of isolated products.

Table 22 Reaction of (perfluoroalkyl)trifluoromethylsilanes with carbonyls[213-215]

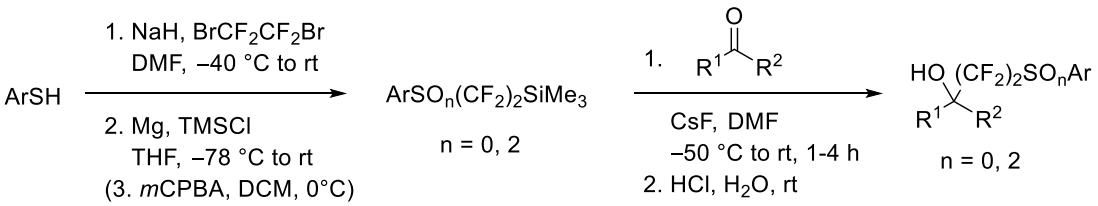
The reaction outcome seems to depend on the inherent stability of the R_f^- anion: Yields for addition of R_f^- ($R_f = C_nF_{2n+1}$) to aldehydes, ketones and imines vary only slightly depending on the length of the perfluoroalkyl chain, although yields for pentafluoroethylation are marginally higher than for trifluoromethylation on the same substrate. For example, addition of (pentafluoroethyl)trimethysilane to acetophenone gave 81% of the desired perfluorinated alcohol, while (trifluoromethyl)trimethylsilane afforded 74% product (Table 22, Entry 1).[213] As discussed in Chapter 1, *alpha*-fluorination is known to destabilise

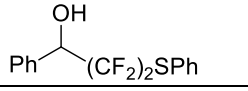
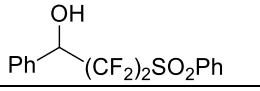
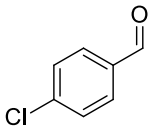
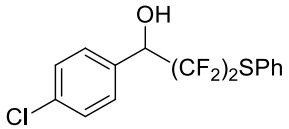
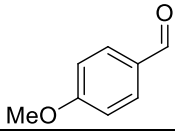
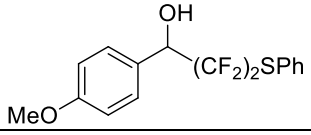
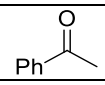
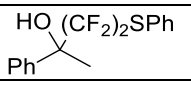
anions due to electronic repulsion between the fluorine lone pairs and the negative charge centred on the carbon atom. *Beta*-fluorination, on the other hand, stabilises anions by negative hyperconjugation of electron density from the anion's p-orbital into the antibonding σ*-orbital of the neighbouring C–F bond, as well as – to a much smaller degree – through the inductive electron-withdrawing effect of the highly electronegative fluorine substituent (Figure 6).[7] Thus, the pentafluoroethide anion is stabilised more than its trifluoromethyl analogue. However, the difference between the two is only small, much like the difference in pK_a of their parent perfluoroalkanes. Similarly, addition of ethyl difluoro(trimethylsilyl)acetate and {difluoro[4-(trifluoromethyl)phenyl]methyl}-(trimethyl) silane to tosyl-protected benzimine gives 85% and 82% of the perfluorinated product respectively (Entry 4). This suggests that the anions formed from (perfluoroalkyl)trimethylsilanes of the form Me_3SiR_f ($R_f = (CF_2)_nR$) are stable enough to act as nucleophilic perfluoroalkylating agents under fluoride catalysed conditions. (Difluoromethyl)trimethylsilane, however, did not yield any of the desired difluoromethylated alcohol (Entry 1). Upon reaction of Me_3SiCF_2H with acetophenone in the presence of catalytic TASF, no 1,1-difluoro-2-phenylpropan-2-ol was detected. The authors suggest this may be due to the instability of the difluoromethanide anion which makes it act as a base instead of a nucleophile under these conditions, leading to the formation of silyl enol ethers. (No silyl enol ether formation is observed with the other Me_3SiR_f reagents under the same conditions.) Use of sterically bulky groups on the silicon centre ($SiPhMe_2CF_2H$) or the use of *bis*(trimethylsilyl)difluoromethane ($Si(CF_3)_2CF_2H$) as a source of CF_2H^- allow this problem to be circumvented and enable difluoromethylation of carbonyls.[202]

	CF_3H	$CF_3(CF_2)_5CF_2H$	$(CF_3)_2CFH$	$(CF_3)_3CH$	CHF_2CO_2Et
pK_a	30.5	30	20	11	25

Figure 6 Destabilising α-effect and stabilising β-effect of fluorine substituents on carbanions[7]

In 2007, Toulgoat *et al.* described the synthesis of various trimethyl(1,1,2,2-tetrafluoroarylsulfanylethyl)silanes, $ArS(CF_2)_2SiMe_3$, and trimethyl(1,1,2,2-tetrafluoroarylsulfonylethyl)silanes, $ArSO_2(CF_2)_2SiMe_3$, from the nucleophilic attack of thiols on 1,2-dibromotetrafluoroethane, followed by magnesium-mediated silylation.[216] The Beier group recently demonstrated the addition of these reagents to ketones and aldehydes in moderate and good yields respectively (Table 23).[217, 218] This suggests that the $Ar(CF_2)_2SiMe_3$ reagents we envisage may show similar reactivity, enabling the formation of tetrafluoroethylated alcohols.



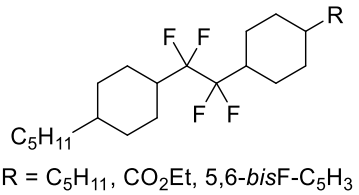
Entry	Carbonyl	Product	Yield [%][a]
1			91
2			72
3			93
4			86
5			36

[a] Yields of isolated products.

Table 23 Addition of trimethyl(tetrafluoroarylsulfanyl/sulfonylethyl)silanes to carbonyls[216, 217]

5.1.2.2 Cross-Coupling for the Synthesis of Internal Tetrafluoroethyl Bridges

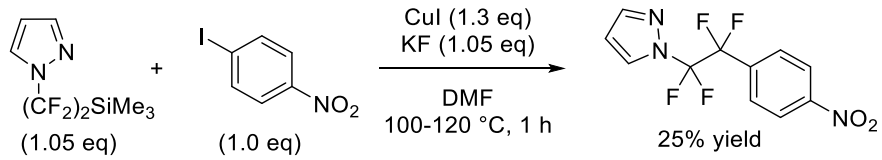
The cross-coupling chemistry of perfluoroalkylsilanes was covered in Chapter 3. Cross-coupling with Ruppert-Prakash type reagents of the form $R(CF_2)_nSiMe_3$ would offer a mild and efficient strategy for the introduction of internal perfluorinated bridges flanked by two different R groups into organic molecules. This motif is of great interest in material sciences, particularly for liquid crystals.[219, 220] The $(CF_2)_2$ linker in the liquid crystals shown in Figure 7, *e.g.*, is structurally more rigid than a $(CH_2)_2$ linker, favouring a linear, rod-like conformation and hence stabilising the liquid crystal phase. Traditional syntheses of $(CF_2)_2$ bridges rely on building block strategies or the use of harsh reaction conditions – mainly the addition of F_2 gas across triple bonds or the nucleophilic fluorination of dicarbonyls.[221]



R = C_5H_{11}, CO_2Et, 5,6-*bis*F-C_5H_3

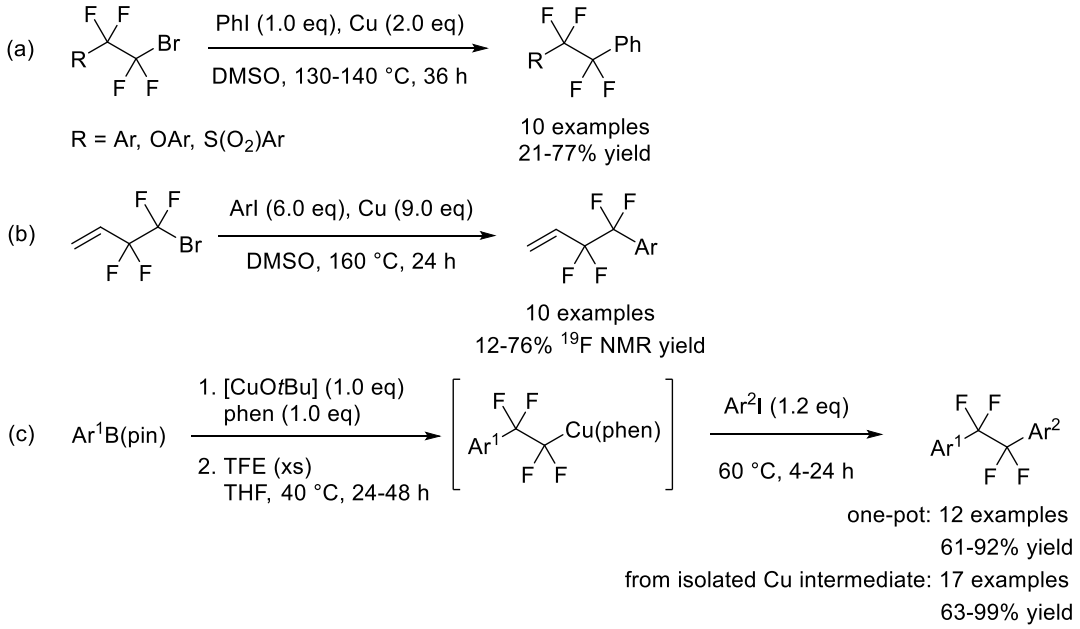
Figure 7 Examples of fluorinated liquid crystals[219, 220]

For many years, cross-coupling of $R(CF_2)_nSiMe_3$ type reagents was limited to ethyl difluoro(trimethylsilyl)acetate,[222, 223] as any other type of perfluoroalkyl silanes suffered from competing protodesilylation.[85] To the best of our knowledge, there is only one example of a copper-mediated cross-coupling of [2-pyrazole-1,1,2,2-tetrafluoroethyl](trimethyl)silane with 1-iodo-4-nitrobenzene, however the low yield afforded for this reaction implies it lacks wider applicability (Scheme 84).[224]



Scheme 84 Copper-mediated cross-coupling of HetAr$(CF_2)_2SiMe_3$ with 1-iodo-4-nitrobenzene[224]

To circumvent the protodesilylation problem, cross-coupling reactions with coupling partners bearing functional groups other than silanes were developed. Earlier this year, the groups of Hu and Konno reported two copper-mediated cross-coupling reactions with 2-bromo-1,1,2,2-tetrafluoroethyl compounds (Scheme 85a,b).[225] In both cases an excess of Cu(0), high temperatures and long reaction times are required to furnish the desired tetrafluoroethylated products in low to good yields. Ogoshi *et al.* isolated the 2-aryl-1,1,2,2-tetrafluoroethylcopper intermediate $R(CF_2)_2Cu$ postulated for these reactions in an elegant method, reacting aryl boronic esters with copper *tert*-butoxide and 1,10-phenanthroline, after which an excess of tetrafluoroethene (TFE) was added to afford the desired copper complex stabilised by a 1,10-phenanthroline ligand. This isolated compound – or a complex formed *in situ* in a one-pot reaction – could then be used for cross-coupling with aryl iodides in good yields (Scheme 85c). While the reaction temperature was significantly lower compared to previous methods, long reaction times are still required, as well as the use of explosive, gaseous TFE and highly air-sensitive [CuO*t*Bu].[226]

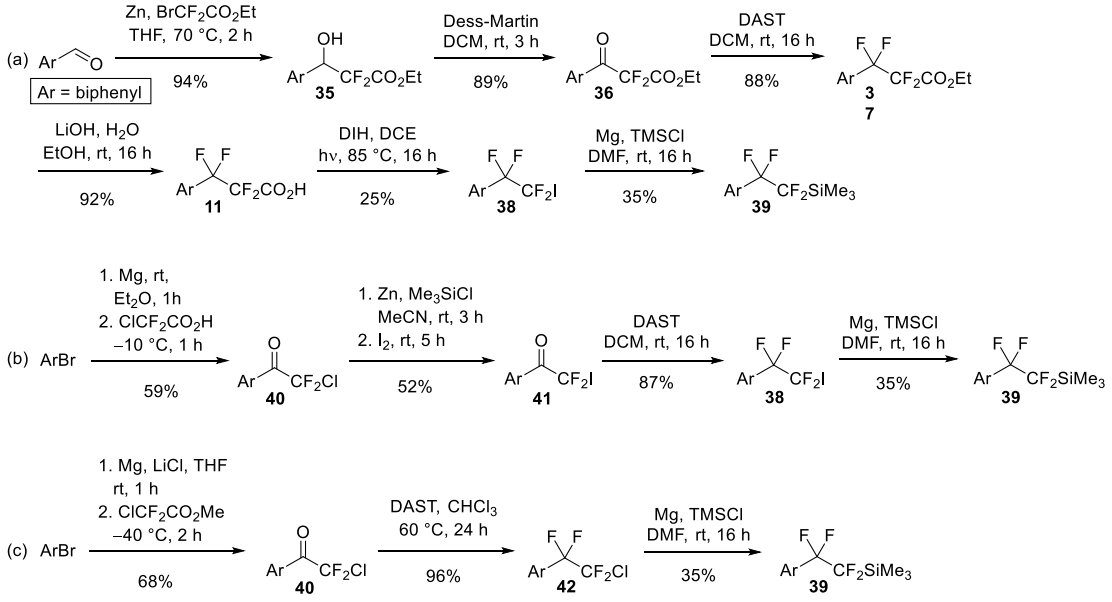


Scheme 85 Copper-mediated cross-coupling approaches towards tetrafluoroethyl bridges[225, 226]

5.2 Results and Discussion

5.2.1 Synthesis of [2-Aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes

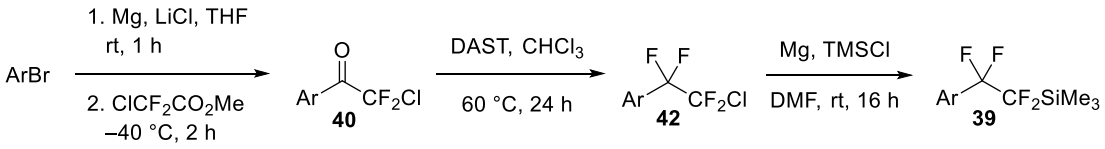
We set out to synthesise a series of [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes, $Ar(CF_2)_2SiMe_3$, with the aim of developing a mild, simple cross-coupling strategy towards 1,1,2,2-tetrafluoro-1,2-arylethanes $Ar(CF_2)_2Ar'$.



Scheme 86 Synthesis optimisation for [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silane 39a

Originally, a six-step procedure was developed for the synthesis of [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes (Ar = 4-Ph-C_6H_4) (Scheme 86a). Reformatsky coupling of benzylic aldehydes with ethyl bromodifluoroacetate, followed by oxidation of the resulting alcohol, difluorination with DAST and hydrolysis afforded tetrafluorinated carboxylic acid **11a** in 68% yield after four steps. Decarboxylative iodination was perfomed with diiodohydantoin[227] under photocatalytic conditions to afford [2-aryl-1,1,2,2-tetrafluoroethyl]iodides **38** which were silylated by a magnesium-mediated reaction with Me_3SiCl. Overall yields only reached around 13%, indicating a need for optimisation. The synthetic route was shortened by two steps (Scheme 86b) by inverse addition of the

Grignard reagent derived from aryl bromides to ClF_2CO_2H to give 1-aryl-2-chloro-2,2-difluoroethanones **40**. Halogen exchange with I_2 *via* the zinc enolate followed by fluorination with DAST afforded [2-aryl-1,1,2,2-tetrafluoroethyl]iodides **38**. These intermediates and their precursors **41** are extremely sensitive to light, temperature and purification on silica gel, due to fast decomposition by protodeiodination. It was thus desirable to avoid their formation, accessing the trimethylsilylated products **39** directly from the chlorinated 1-aryl-2-chloro-2,2-difluoroethanone precursors **40**. Fluorination of these compounds under the standard conditions, using 1.2 eq DAST in DCM at room temperature for 16 hours, afforded only unreacted starting material. Increasing the reaction temperature to 60 °C with 2.0 eq DAST in higher-boiling chloroform, however, yielded up to 96% of the fluorinated products. Further optimisation of the first step by addition of the Schlosser Grignard salt to ClF_2CO_2Me at –40 °C significantly reduced the formation of self-condensation by-product Ar–Ar. The final substrate synthesis thus consisted of a three-step procedure (Scheme 86c): Schlosser Grignard reaction of ArMgBr.LiCl with methyl chlorodifluoroacetate, followed by fluorination with DAST and magnesium-mediated silylation with Me_3SiCl. Unfortunately, the scope of reagents accessible by this route is limited, due to the orthogonal electronic requirements for the different steps (Table 24): the first Grignard reaction is not amenable to strongly electron deficient substrates (Entry 6), bulky substituents (Entries 8–9) or heteroaromatics (Entries 10–11). The following DAST reaction works best for electron-rich carbonyls (Entry 7 *vs* Entry 5), while the magnesium-mediated silylation does not support electron-rich substrates (Entry 5). Overall, only electroneutral substrates **39** have been synthesised successfully (Entries 1–4). In the case of **39e** and **39f**, lithium-halogen exchange with *n*-butyllithium was superior to Grignard formation for the silylation step (Entries 3–4). Overall yields are still low, but the process is easily scalable, delivering more than two grams of **39a**.



Entry	Ar	Yield **40** [%][a]	Yield **42** [%][a]	Yield **39** [%][a]
1	C_6H_5 (**d**)	89	59	39
2	4-Ph-C_6H_4 (**a**)	68	96	35 (19)[b]
3	2-naphthyl (**e**)	56	85	34 (72)[b]
4	4-C_5H_{11}-C_6H_4 (**f**)	61	95	3[c] (80)[b]
5	4-OMe-C_6H_4 (**b**)	42	82	0 (0)[b]
6	4-NO_2-C_6H_4	0 (0)[d]	-	-
7	4-CF_3-C_6H_4 (**g**)	54	0	-
8	2,4,5-tri(*i*Pr)-C_6H_4	0	-	-
9	2-Ph-C_6H_4	0	-	-
10	2-pyridine	0	-	-
11	2-quinoline	0	-	-

[a] Yields of isolated products. [b] *n*BuLi, Me_3SiCl, THF, –78 °C to rt, 16 h. [c] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq α,α,α-trifluorotoluene. [d] Reaction run at 60 °C.

Table 24 Substrate Scope for the formation of 39

Depending on the substituents on the aromatic ring, these reagents ranged from volatile colourless oils (**39d**) to white crystalline solids with a melting point of 52–53 °C (**39a**). They are bench-stable over several months when kept dry and under argon. The TMS group's singlet at 0.36 ppm in the ^1H NMR and the two singlets at −106.79 ppm and −125.02 ppm in the ^{19}F NMR were useful for quick analysis of **39a** by NMR. Of particular diagnostic value for this compound was the splitting pattern of the quaternary fluorinated carbons observed at 119.4 ppm and 122.6 ppm in the ^{13}C NMR. Due to coupling to two sets of two fluorine atoms, they each presented as a triplet of triplets with $^1J_{CF}$ coupling constants of 245 Hz and 271 Hz and and $^2J_{CF}$ coupling constants of 21 Hz and 52 Hz respectively. The solid-state structure of [2-(biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl](trimethyl)silane **39a** was verified by X-ray crystallographic analysis (Figure 8a), showing the biphenyl and trimethylsilane substituents in *anti*-conformation to each other. Interestingly, the singlets observed in the ^{19}F NMR spectrum indicate that there is no – or very little – through-bond coupling between the fluorine substituents, suggesting

a staggered solution conformation in which all fluorine substituents are *gauche* to each other (Figure 8b). This in agreement with the general observation that perfluorinated compounds favour *gauche* conformations to maximise $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ (and, in this case $\sigma_{C-Si} \rightarrow \sigma^*_{C-F}$) hyperconjugation.[1]

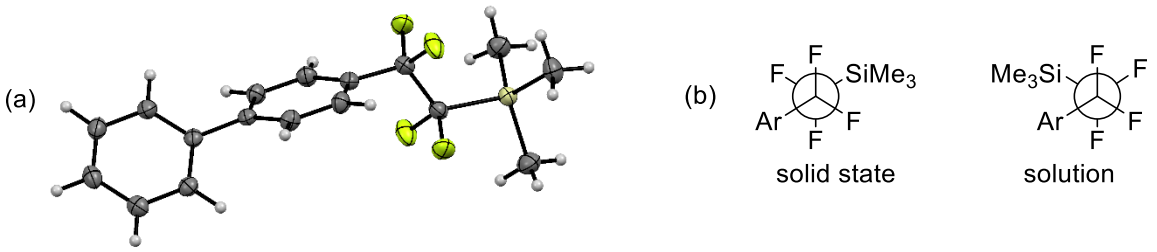
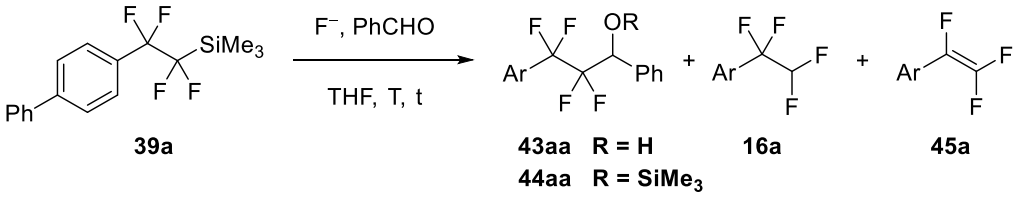


Figure 8 (a) X-ray crystal structure of 39a, (b) Conformation of 39a in the solid state and in solution

5.2.2 Addition of [2-Aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes to Aldehydes

With these substrates in hand, we decided to validate their reactivity with a benchmark nucleophilic addition to aldehydes (Table 25). 1.2 eq [2-(biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl](trimethyl)silane **39a** was reacted with 1.0 eq benzaldehyde in the presence of 2 mol% TBAF in THF at room temperature for 2 hours to afford 32% combined yield of the protonated and silicon-protected alcohols **43aa** and **44aa**, together with small amounts of by-products due to protodesilylation and elimination of reagent **39a** (Entry 1). Increasing the reaction time to 3.5 h doubled the yield of addition products to 64% (Entry 2). Decreasing the temperature or running the reaction over crushed 4Å molecular sieves did not suppress by-product formation (Entries 3–5). Using DMF as the solvent instead of THF did not have any beneficial effects either (Entry 6). The use of stoichiometric amounts of fluoride initiator led predominantly to protodesilylation of the starting material (Entry 7). When caesium fluoride was used instead of TBAF, higher conversion of starting material was observed, as well as decreased by-product formation

(Entry 8). This is presumably due to the lower solubility of caesium fluoride which causes a lower concentration of the reactive tetrafluoroethide anion to be in solution, favouring its addition to benzaldehyde over decomposition to products **16a** and **45a**. Finally, deprotection of the silyl ether was more efficient with TBAF than with HCl (Entries 9–10). Our optimised conditions of reacting 1.2 eq **39a** with 1.0 eq benzaldehyde in 1 M THF at room temperature in the presence of 10 mol% CsF for 1 hour, followed by deprotection with TBAF at rt for 30 minutes, afforded the desired alcohol **43aa** in 91% yield.



39a **43aa R = H** **16a** **45a**
44aa R = $SiMe_3$

Entry	F^- source	T, t	Yield **39a** [%][a]	Yield **43aa** [%][a]	Yield **44aa** [%][a]	Yield **16a** [%][a]	Yield **45a** [%][a]
1	TBAF (0.02 eq)	rt, 2 h	50	9	23	16	2
2	TBAF (0.02 eq)	rt, 3.5 h	8	4	60	24	5
3	TBAF (0.02 eq)	0 °C to rt, 3.5 h	44	7	37	19	3
4	TBAF (0.02 eq)	–78 °C to –50 °C, 3.5 h	78	8	2	12	-
5[b]	TBAF (0.02 eq)	0 °C to rt, 3.5 h	15	2	66	13	5
6[c]	TBAF (0.02 eq)	0 °C to rt, 3.5 h	0	6	56	14	5
7	TBAF (1.0 eq)	0 °C to rt, 3.5 h	0	0	44	56	0
8	CsF (0.1 eq)	rt, 3.5 h	0	12	80	8	<1
9[d]	TBAF (0.02 eq)	rt, 1 h	37	25	16	19	3
10[e]	CsF (0.1 eq)	rt, 1 h	0	91	5	2	3

Conditions: 1.2 eq **39a** (0.24 mmol), 1.0 eq benzaldehyde (0.2 mmol), THF (1 M), Schlenck conditions. [a] Determined by ^{19}F NMR by integration of the product peak(s) with respect to $PhCF_3$ (1.0 eq as an internal standard). [b] Reaction was run over crushed 4 Å molecular sieves. [c] DMF was used as the solvent. [d] After reaction time, 5 M HCl was added and the reaction was stirred for a further 2.5 h to hydrolyse the TMS protecting group (**44aa** → **43aa**). [e] After reaction time, 1.2 eq TBAF (1 M in THF) was added and the reaction was stirred for a further 30 min to hydrolyse the TMS protecting group (**44aa** → **43aa**).

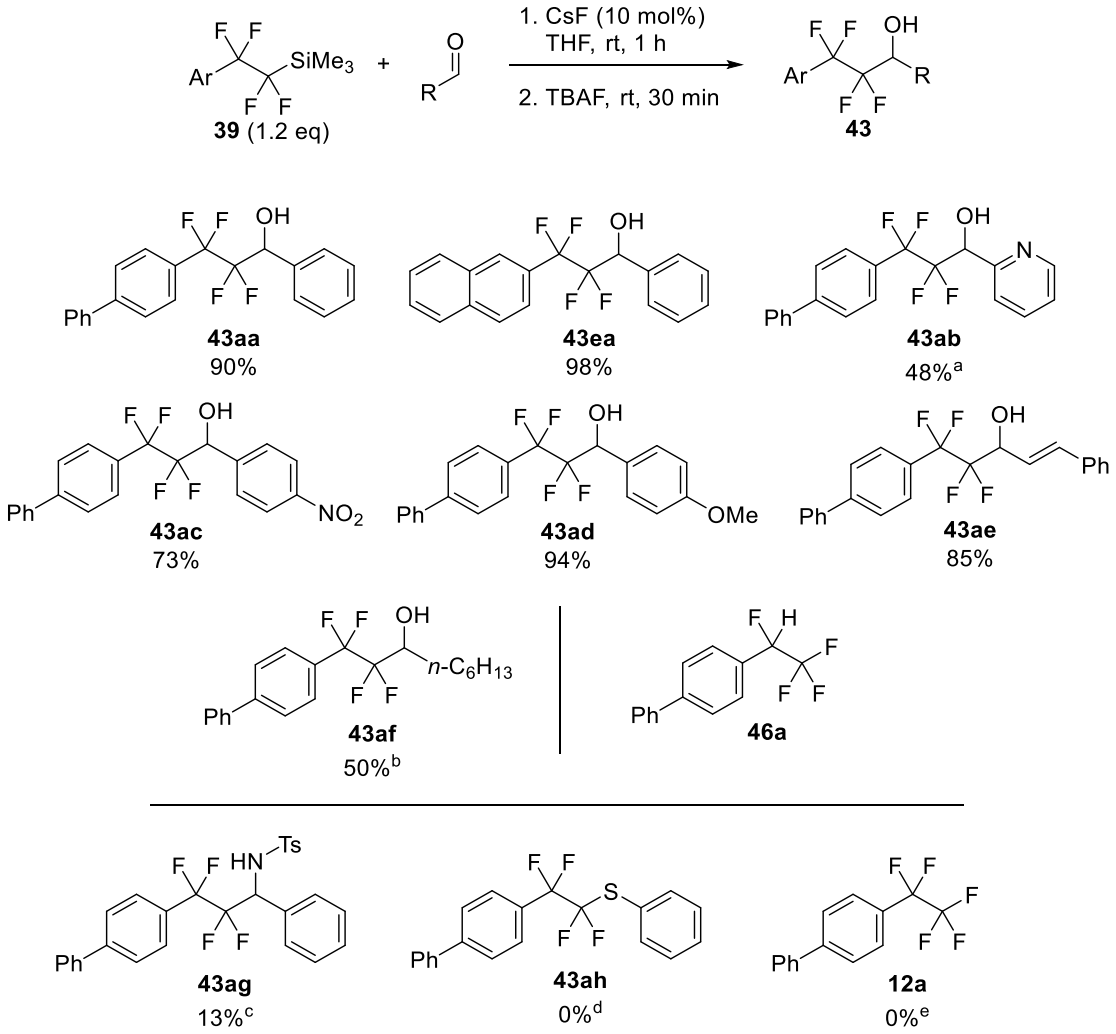
Table 25 Optimisation for the fluoride-catalysed addition of 39a to benzaldehyde

All four fluorines in **43aa** and **44aa** are diastereotopic, resulting in very distinctive NMR spectra. The benzylic fluorine substituents in **43aa** form two doublets of triplets at −108.76 ppm and −109.53 ppm ($^2J_{FF}$ = 266.5 Hz, $^3J_{FH}$ = 3.0 Hz), that appear like an AB quartet with extremely strong roofing. The fluorine substituents *alpha* to the hydroxyl group form a more regular AX set of two doublets of doublets of triplets at −117.52 ppm and −126.45 ppm ($^2J_{FF}$ = 275.5 Hz, $^3J_{FH}$ = 7.0 Hz and 17.0 Hz respectively, $^3J_{FF}$ = 3.0 Hz). As in **39a**, the small $^3J_{FF}$ coupling in **43aa** indicates a conformation in which the *vicinal* fluorine substituents are at *ca.* 90° to each other, minimising orbital overlap.

The quaternary fluorinated carbon centres are split into a doublet of triplets at 117.5 ppm for the benzylic carbon ($^1J_{CF}$ = 253 Hz, $^2J_{CF}$ = 34 Hz) and a doublet of doublets of triplets at 115.6 ($^1J_{CF}$ = 160 Hz, 154 Hz, $^2J_{CF}$ = 36 Hz). The most diagnostic peak in the ^{1}H NMR is the proton geminal to the hydroxy group which couples to the two fluorine atoms ($^3J_{HF}$ = 17.0 Hz, 7.0 Hz) and the −O*H* proton ($^3J_{HH}$ = 4.5 Hz) and thus presents as a doublet of doublets of doublets at 5.23 ppm. **44aa** has very similar spectra to **43aa**, though this proton loses its coupling to the hydroxy group, turning into a doublet of doublets, and a new TMS signal arises at 0.00 ppm.

The reaction tolerates electron-poor and electron-rich benzaldehydes, as well as unsaturated cinnamaldehyde, giving the desired alcohols **43ac**, **43ad** and **43ae** in 73%, 94% and 85% yields respectively (Scheme 87). [2-(Naphthalene-2-yl)-1,1,2,2-tetrafluoroethyl](trimethyl)silane **39e** gave similar results to its biphenyl equivalent. Pyridine 2-carboxaldehyde and hexanal proved less reactive, affording **43ab** and **43af** in 48% and 50% respectively. The major by-product in these cases was protodesilylated starting material **16a**, though when using hexanal a substantial amount of 4-(1,2,2,2-tetrafluoroethyl)-biphenyl **46a** was formed as well. Tosyl-protected benzamine was an exceptionally poor electrophile under these conditions, affording only 13% **43ag**. Non-

carbon electrophiles, such as PhSSPh and XeF_2,[224] were not tolerated, giving mainly unreacted starting material **39a** with traces of protodesilylation.



Conditions: (i) 1.2 eq **39** (0.24 mmol), 1.0 eq aldehyde (0.2 mmol), 10 mol% CsF, THF, rt, 1 h. (ii) TBAF (1 M in THF), rt, 30 min. Yields are of isolated products. [a] 40% **16a**. [b] 30% **16a,** 20% **46**. [c] 87% **16a**. [d] 1.2 eq **39a**, 1.0 eq PhSSPh, 0.1 eq CsF, THF, rt, 1 h: only unreacted **51a**. [e] 1.0 eq **39a**, 1.1 eq XeF_2, DCM, –30 °C to rt, 16 h: mainly unreacted **39a**, traces of **16a**.

Scheme 87 Substrate scope: Additions of [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes to carbonyls and other electrophiles

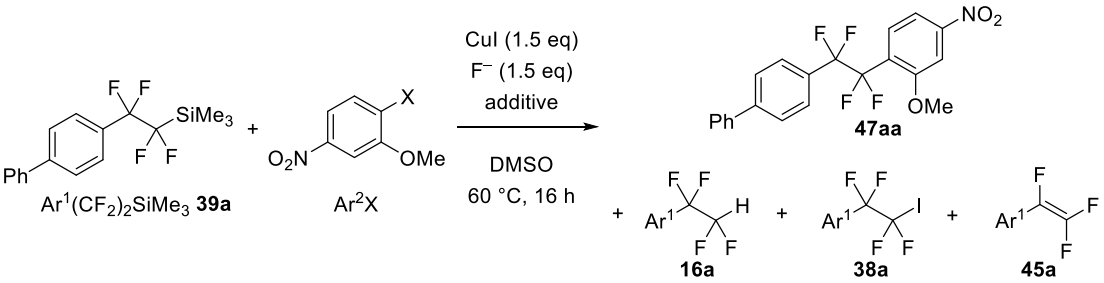
5.2.3 Cross-Coupling Chemistry of [2-Aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes

5.2.3.1 Optimisation Studies

We focused next on the copper-mediated cross-coupling of [2-(biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl](trimethyl)silane **39a** with 1-iodo-2-methoxy-4-nitrobenzene. This aryl iodide was chosen as it had previously been shown to give good yields in copper-mediated cross-coupling reactions with $Me_3SiC_2F_5$ and $Me_3SiCF_2CO_2Et$ by Hafner and Bräse.[228] With the conditions reported in this paper, reacting 1.2 eq **39a** with 1.0 eq 1-iodo-2-methoxy-4-nitrobenzene in the presence of 1.5 eq CuI and 1.5 eq KF in 0.25 M DMF at 60 °C for 16 hours, 26% of the desired coupling product **47aa** was observed by ^{19}F NMR (Table 26, Entry 1). The three major side-reactions were identified as protodesilylation or elimination of reagent **39a** to afford by-products **16a** and **45a** in 35% and 8% yield respectively, as well as competing C–I reductive elimination to form 31% **38a**. The product outcome was similar in NMP (Entry 2), but formation of **47aa** was increased to 31% in DMSO (Entry 3). KF, CsF, TBAF and AgF were screened as fluoride activators (Entries 3–6), with AgF giving superior results. Weng *et al.* previously observed a cooperative effect of silver in their copper-catalysed cross-coupling of aryl iodides with Me_3SiCF_3.[97] We then screened CuCl, CuBr and $CuOTf(MeCN)_4$ as alternative sources of Cu(I), but these were not found to be beneficial (Entries 7–9). Next, a selection of additives was investigated. Lewis acids, especially $B(OMe)_3$, have been shown to reduce protodesilylation of Me_3SiCF_3 in copper-mediated cross-coupling reactions by stabilising the CF_3^- anion.[229] However, addition of trimethyl borate to our reaction did not suppress the formation of protodesilylated by-product **16a** (Entry 10). Of the bidentate nitrogen-ligands tested, tmeda led predominantly to protodesilylation (Entry 11), while 2,2'-bipyridine and 1,10-phenanthroline did not increase the formation of **47aa** relative to the ligandless reaction (Entries 12–13). The more electron-rich 4,4'-di-*tert*-butyl-2,2'-

bipyridine and monodentate pyridine afforded an increase in product formation from 53% to 64% and 63% respectively (Entries 14–15). Due to cost considerations,[iv] further optimisation was carried out using pyridine as the ligand. The use of pyridine instead of 1,10-phenanthroline for copper-mediated cross-coupling chemistry with fluorinated trimethylsilanes is uncommon, but there is some precedent for its use in flow-chemistry.[230] 5.0 equivalent of pyridine were found to be optimal for the suppression of side reactions (Entry 16); however, higher amounts did not lead to a decrease in yield of **47aa** (Entry 17), and pyridine could also be used as the reaction solvent (Entry 18). Following the reaction by ^{19}F NMR showed that the starting material was fully consumed after 6 hours (Entry 19). Our optimised conditions thus consisted of 1.2 eq **39a** reacted with 1.0 eq 1-iodo-2-methoxy-4-nitrobenzene in the presence of 1.5 eq CuI and 1.5 eq AgF in 0.25 M DMSO at 60 °C for 6 hours (Entry 19); this afforded product **47aa** in 76% ^{19}F NMR yield (78% yield upon isolation). Pleasingly, similar results were obtained at room temperature, with yields of **47aa** reaching 63% (Entry 20). Catalytic amounts of CuI (20 mol%) also showed promising results, furnishing **47aa** in 60% yield (Entry 21). Control reactions in the absence of copper iodide and pyridine and without AgF showed that all three reagents were necessary for successful cross-coupling. In the absence of copper and ligands, decomposition to black tar due to carbene formation and polymerisation was observed (Entry 24). Conversely, without a source of activating fluoride, mainly unreacted starting material was recovered (Entry 25).

[iv] Sigma Aldrich, May 2015: anhydrous pyridine = 0.30 GBP/g; 4,4'-di-*tert*-butyl-2,2'-bipyridine = 10.96 GBP/g.



Entry	X	F⁻ Source (1.5 eq)	Conditions[a]	Yield **47aa** [%][b]	Yield **16a** [%][b]	Yield **38a** [%][b]	Yield **45a** [%][b]
1	I	KF	DMF	26	35	31	8
2	I	KF	NMP	16	33	28	22
3	I	KF	-	31	38	18	13
4	I	CsF	-	36	38	15	11
5	I	TBAF	-	0	100	0	0
6	I	AgF	-	53	18	19	10
7	I	AgF	CuCl (1.5 eq)	9	56	21	14
8	I	AgF	CuBr (1.5 eq)	48	16	26	11
9	I	AgF	CuOTf $(MeCN)_4$ (1.5 eq)	27	55	11	6
10	I	AgF	$B(OMe)_3$ (1.5 eq)	37	25	25	12
11	I	AgF	tmeda (1.5 eq)	2	92	4	2
12	I	AgF	bpy (1.5 eq)	47	10	30	13
13	I	AgF	phen (1.5 eq)	50	26	12	13
14	I	AgF	dtb-bpy (1.5 eq)	64	14	5	16
15	I	AgF	py (1.5 eq)	63	11	21	3
16	I	AgF	py (5.0 eq)	76	5	13	5
17	I	AgF	py (10.0 eq)	70	6	21	4
18[c]	I	AgF	py (0.25 M)	74	7	14	5
19	I	AgF	py (5.0 eq), 6 h	76	5	13	5
20	I	AgF	py (5.0 eq) rt, 6h	63	6	27	4
21	I	AgF	py (5.0 eq) 20 mol% CuI	60	20	18	2
22	Br	AgF	-	59	24	0	17
23	OTf	AgF	-	0	63	4	33
24[d]	I	AgF	no copper	21	9	0	0
25[e]	I	-	py (5.0 eq)	1	3	0	10

[a] Standard conditions: 1.0 eq ArI (0.1 mmol), 1.2 eq **39a** (0.12 mmol), 1.5 eq fluoride source, 1.5 eq CuI, 0.25 M DMSO, 60 °C, 16 h. [b] Determined by ^{19}F NMR by integration of the product peak(s) relative to $PhCF_3$ (1.0 eq) as an internal standard. [c] Pyridine was the reaction solvent. [d] Decomposition to black tar. [e] 72% unreacted starting material remaining.

Table 26 Optimisation for the cross-coupling of 39a with 1-iodo-2-methoxy-4-nitrobenzene

The reaction could be extended to aryl bromides (Entry 22), but aryl triflates were unreactive, affording mainly products of protodeslilylation and elimination after workup (Entry 23).

Coupling products **47a** are bench stable white solids with melting points around 125 °C (value for **47aa**). The ^{19}F and ^{13}C NMR spectra are of diagnostic value for analysis of these compounds. The ^{19}F NMR shows two singlets at *ca.* −109.25 ppm and −111.40 ppm. (In the case of some electron poor coupling partners – *e.g.* **47ab**, **47ag**, **47ao** – the fluorine signals may also present as two triplets due to long-range coupling ($^4J_{FH}$ = 5–6 Hz) with the aromatic *ortho*-protons.) The two fluorinated quaternary carbons form two distinct triplets of triplets at 116.5 ppm ($^1J_{CF}$ = 256 Hz, $^2J_{CF}$ = 38 Hz) and 116.9 ($^1J_{CF}$ = 154 Hz, $^2J_{CF}$ = 35 Hz). The diagnostic nucleus in **16a** is the terminal hydrogen which couples to the two geminal fluorines as well as the vicinal ones, giving a triplet of triplets at 5.86 ppm ($^2J_{HF}$ = 54.0 Hz, $^3J_{HF}$ = 2.5 Hz) in the ^{1}H NMR spectrum. This coupling is also visible in the ^{19}F NMR spectrum, where the geminal fluorines are detected as a doublet of triplets ($^2J_{HF}$ = 54.0 Hz, $^3J_{FF}$ = 2.5 Hz) and the vicinal fluorines as an apparent quartet ($^3J_{HF}$ = $^3J_{FF}$ = 2.5 Hz). **38a** was identified by its ^{19}F NMR signals at −58.57 ppm (t, $^3J_{FF}$ = 7.0 Hz) and −104.17 ppm (t, $^3J_{FF}$ = 7.0 Hz). This constitutes a downfield shift from its brominated (**48**: −64.75 ppm (t, $^3J_{FF}$ = 5.0 Hz), −107.83 ppm (t, $^3J_{FF}$ = 5.0 Hz)) and chlorinated (**42a**: −70.31 ppm (s), −110.04 ppm (s)) equivalents, owing to the lower electronegativity of iodine compared to Br and Cl. Since the chemical shifts of these compounds lie so close together, however, the identity of **38a** in the reaction mixture was confirmed by ^{19}F NMR spiking experiments and high resolution mass spectrometry (*m*/*z* = 379.9691). In alkene **45a** all fluorine atoms couple to each other, giving rise to three doublets of doublets at −99.47 ppm ($^3J_{FF}$ = 70.5 Hz and 32.0 Hz), −114.31 ppm ($^2J_{FF}$ = 109.0 Hz, $^3J_{FF}$ = 70.5 Hz) and −176.92 ppm ($^2J_{FF}$ = 109.0 Hz , $^3J_{FF}$ = 32.5 Hz) in the ^{19}F NMR.

As with compounds **39** and **43**, the ^{19}F NMR spectra of compounds **47** have interesting implications for their conformation in solution. Since the two fluorine environments do not couple to each other, this suggests the molecule assumes a double *gauche* conformation, maximising $\sigma_{C–H} \rightarrow \sigma^*_{C–F}$ hyperconjugation (Figure 9).

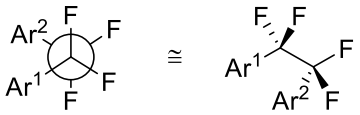
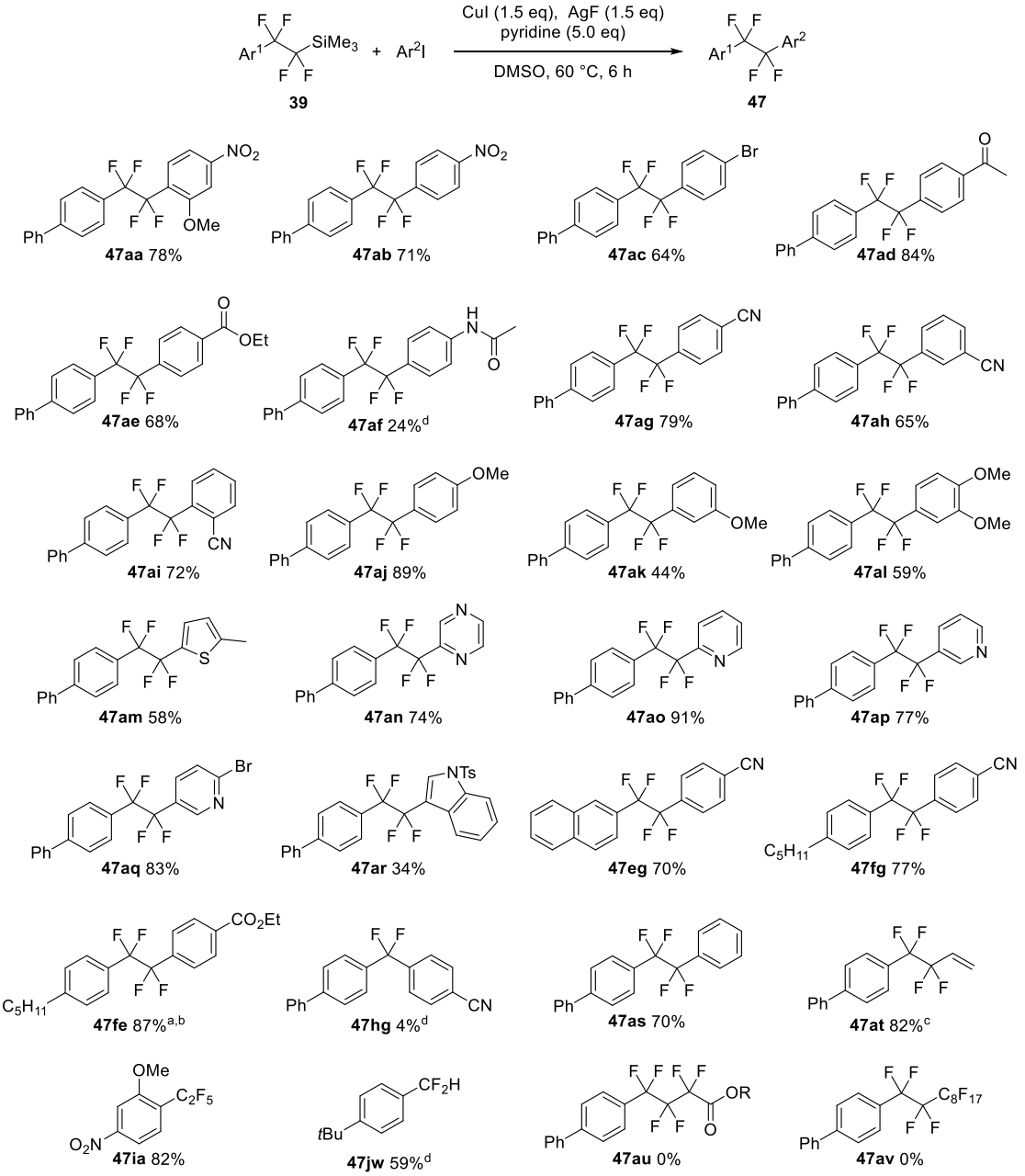


Figure 9 Solution conformation of compounds 47

5.2.3.2 Copper-Mediated Cross-Coupling of [2-Aryl-1,1,2,2-tetrafluoroethyl] (trimethyl)silanes with Aryl Iodides

With our optimised reaction conditions in hand, we were poised to investigate the substrate scope of this reaction (Scheme 88). The reaction did not seem to be greatly influenced by the electronics of the aryl iodide, with both electron-rich and electron-poor substrates affording good yields. 2-Iodobenzonitrile gave similar results to 4-iodobenzonitrile, however *meta*-substitution led to a significant decrease in yield (**47ai**, **47ah**, **47ak**). Different (trimethyl)silane coupling partners were supported (**47eg**, **47fg**, **47fh**), as were simple perfluoroalkyl(trimethyl)silanes like $Me_3SiCF_2CF_3$ (**47ia**) and Me_3SiCF_2H (**47jw**). However, when the fluorinated chain in the silane coupling partner was decreased from $(CF_2)_2$ to CF_2 only traces of the cross-coupled product **47hg** were observed.

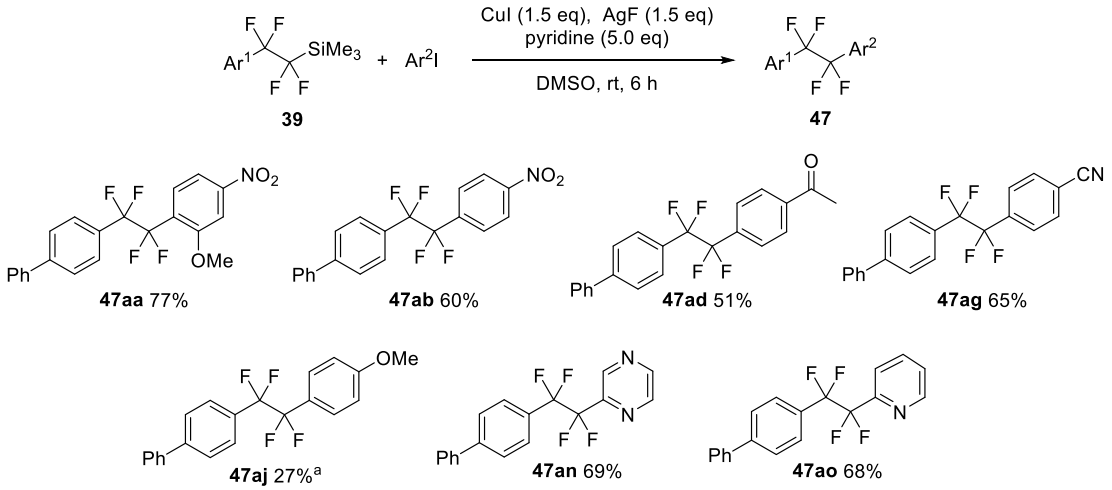


Conditions: 1.2 eq **39** (0.24 mmol), 1.0 eq ArI (0.2 mmol), 1.5 eq CuI, 1.5 eq AgF, 5.0 eq pyridine, DMSO, 60 °C, 6 h. Yields are of isolated products unless stated otherwise. [a] 0.5 mmol scale. [b] Chemical purity 90%. [c] Chemical purity 91%. [d] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq α,α,α-trifluorotoluene.

Scheme 88 Cross-coupling of [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes with aryl iodides

It was possible to run the reaction at room temperature, though yields were generally lower (Scheme 89). This constitutes a marked improvement over known copper-mediated cross-coupling reactions for the synthesis of tetrafluoroethyl motifs, which require reaction temperatures over 130 °C and extended reaction times. With the development of a mild

methodology which is effective at 60 °C or even room temperature in just 6 hours the substrate scope for these transformations can be extended to more sensitive substrates which would not survive the harsh conditions used to date.



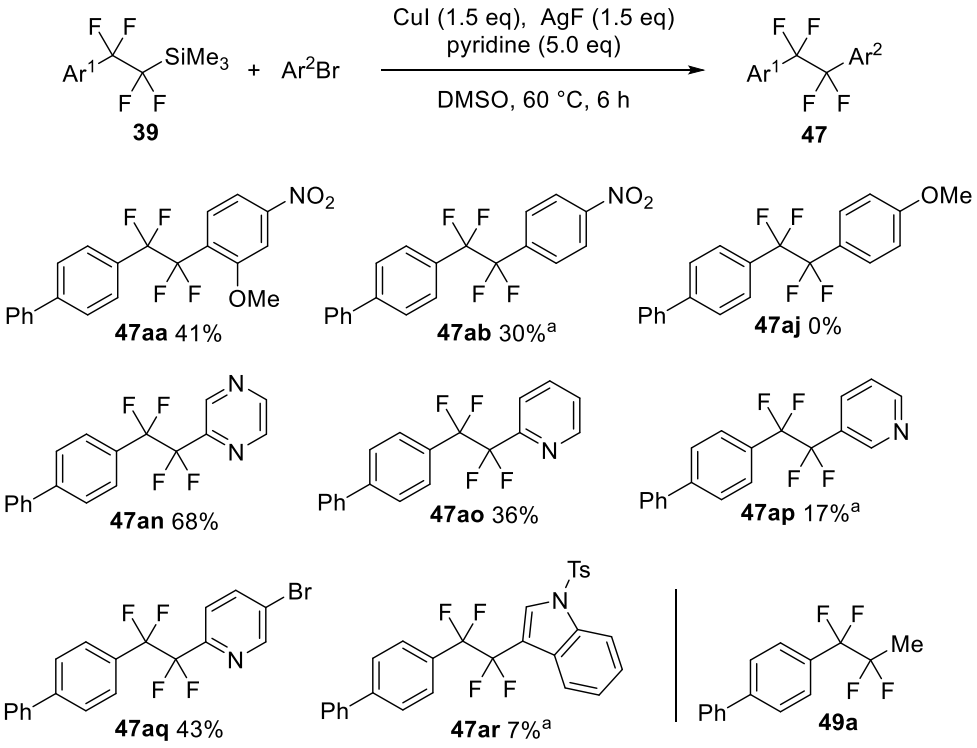
Conditions: 1.2 eq **39a** (0.24 mmol), 1.0 eq ArI (0.2 mmol), 1.5 eq CuI, 1.5 eq AgF, 5.0 eq pyridine, DMSO, rt, 6 h. Yields are of isolated products unless stated otherwise. [a] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq α,α,α-trifluorotoluene.

Scheme 89 Cross-coupling of 39a with aryl iodides at room temperature

5.2.3.3 Copper-Mediated Cross-Coupling of [2-Aryl-1,1,2,2-tetrafluoroethyl] (trimethyl)silanes with Aryl Bromides

Due to the lower cost and wider availability of (hetero)aryl bromides, we extended our method to representative (hetero)aryl bromides (Scheme 90). Yields are significantly lower than for aryl iodides and increasing the reaction time did not lead to an increase of yield, as the starting material was completely consumed after 6 hours. The by-products observed were a large amount of protodesilylated by-product **16a** and some elimination product **45a**. Interestingly, a significant amount of what we have tentatively assigned as 4-(1,1,2,2-tetrafluoropropyl)biphenyl **49a** is formed as a further by-product from methylation of the 2-biphenyl-1,1,2,2-tetrafluoroethide intermediate. Our assignment was based on high

resolution mass spectrometry (m/z = 268.0874) and a triplet of triplets in the ^{1}H NMR at 1.82 ppm with coupling constants of 18.5 Hz and 1.5 Hz, which is indicative of a methyl group coupling to two geminal and two vicinal fluorine nuclei. The $^{2}J_{HF}$ coupling of 18.5 Hz can also be seen in the ^{19}F NMR, in a quartet at −107.06 ppm for the geminal fluorines, while the benzylic fluorine substituents appear as a singlet at −111.95 ppm. This by-product is not observed in the reactions with aryl iodides. DMSO is known to act as a methylating reagent in the presence of base, but generally strong bases like sodium hydride and potassium *tert*-butoxide are necessary to form the dimsyl anion which then acts as an ylide-type methylating reagent.[231] Recently, Jiang *et al.* achieved the *N*-methylation of amines with a combination of DMSO and formic acid at 150 °C *via* a putitative DMS cation intermediate.[232] It is conceivable that under our conditions DMSO is sufficiently activated to methylate the tetrafluoroethide intermediate resulting from desilylation of **39a**. We postulate that this is kinetically unfavourable with aryl iodides, but becomes possible in the presence of the less reactive aryl bromides. Despite the lower yields, the reactivity trends with aryl bromides are similar to those observed with aryl iodides. An exception are electron-rich aryl bromides, which are unreactive under the reaction conditions. As with the corresponding iodides, 2-bromopyridine is more reactive than 3-bromopyridine, allowing for the selective synthesis of **47aq** from 2,5-dibromopyridine.

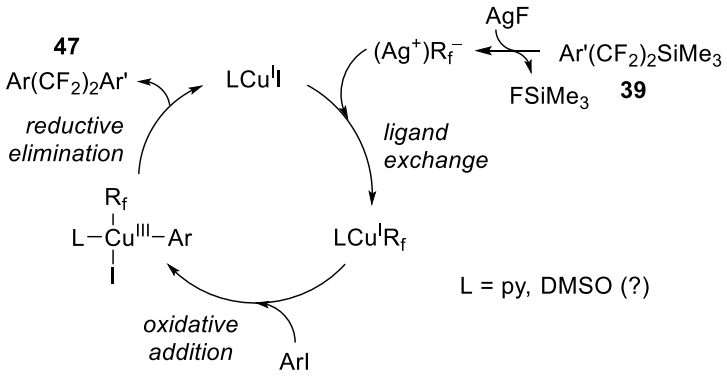


Conditions: 1.2 eq **39a** (0.24 mmol), 1.0 eq ArBr (0.2 mmol), 1.5 eq CuI, 1.5 eq AgF, 5.0 eq pyridine, DMSO, 60 °C, 6 h. Yields of isolated products unless stated otherwise. [a] ^{19}F NMR yields, determined by integration of the product peak(s) relative to 1.0 eq α,α,α-trifluorotoluene.

Scheme 90 Cross-coupling of [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes with aryl bromides

5.2.3.4 Mechanistic Considerations

In accordance with Grushin's findings (see section 3.2.2),[105] we propose the following mechanism for our reaction (Scheme 91): (1) Activation of [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silane **39** by silver fluoride to afford a potentially silver-stabilised tetrafluoroethide anion; (2) nucleophilic addition or transmetallation of this stabilised anion onto copper(I) iodide; (3) oxidative addition of the aryl iodide coupling partner to the resulting copper complex; (4) reductive elimination to afford 1,1,2,2-tetrafluoro-1,2-arylethane **47** as the cross-coupling product.

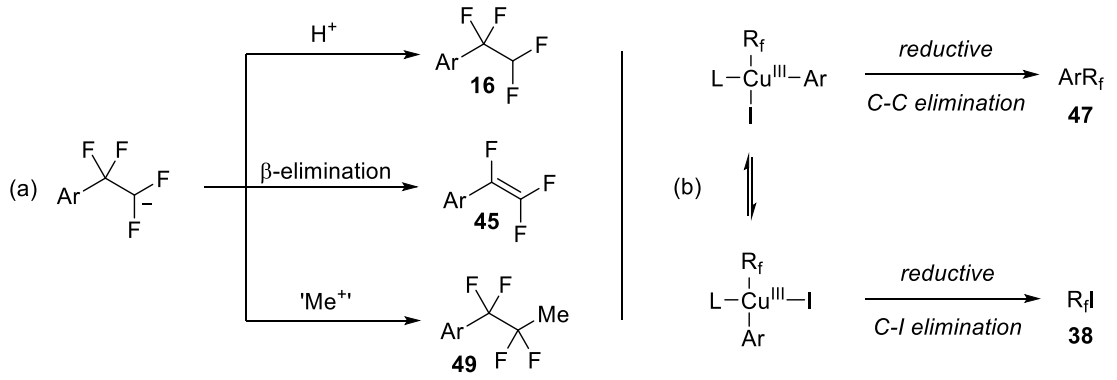


Scheme 91 Proposed mechanism

In-depth mechanistic studies are necessary to confirm this theory, but the following indications have been observed:

The affinity of fluoride for silicon is well-known and thus fluoride activation is widely believed to be the first step in copper-mediated cross-coupling reactions of Me_3SiCF_3 with aryl iodides. In our reaction, the formation of fluoro(trimethyl)silane was observed by ^{19}F NMR of the crude reaction mixture as an apparent octet at −157.8 ppm ($^3J_{FH}$ = 7.0 Hz). Furthermore, by-products **16**, **45** and **49** may be explained by protonation, β-fluoride elimination and methylation of the tetrafluoroethide intermediate respectively (Scheme 92a). This anionic intermediate may be stabilised by silver, as suggested by Weng *et al.*[97] ^{19}F NMR experiments were carried out to investigate the presence of a AgR_f or a CuR_f complex in the crude reaction mixture by monitoring the reaction of **39a** in the presence of either CuI or AgF, or a combination of both metals, without addition of an aryl iodide coupling partner, but no conclusive results were obtained. Separate synthesis of the two metal-R_f complexes and investigation of their reactivity is necessary to gain further insight into the mechanism. The role of pyridine may also be better understood if a series of metal-R_f complexes are synthesised with different stabilising ligands, including 1,10-phenanthroline and pyridine. Formation of iodinated by-product **38** is presumably due to competing reductive C–I elimination instead of the desired reductive C–C elimination

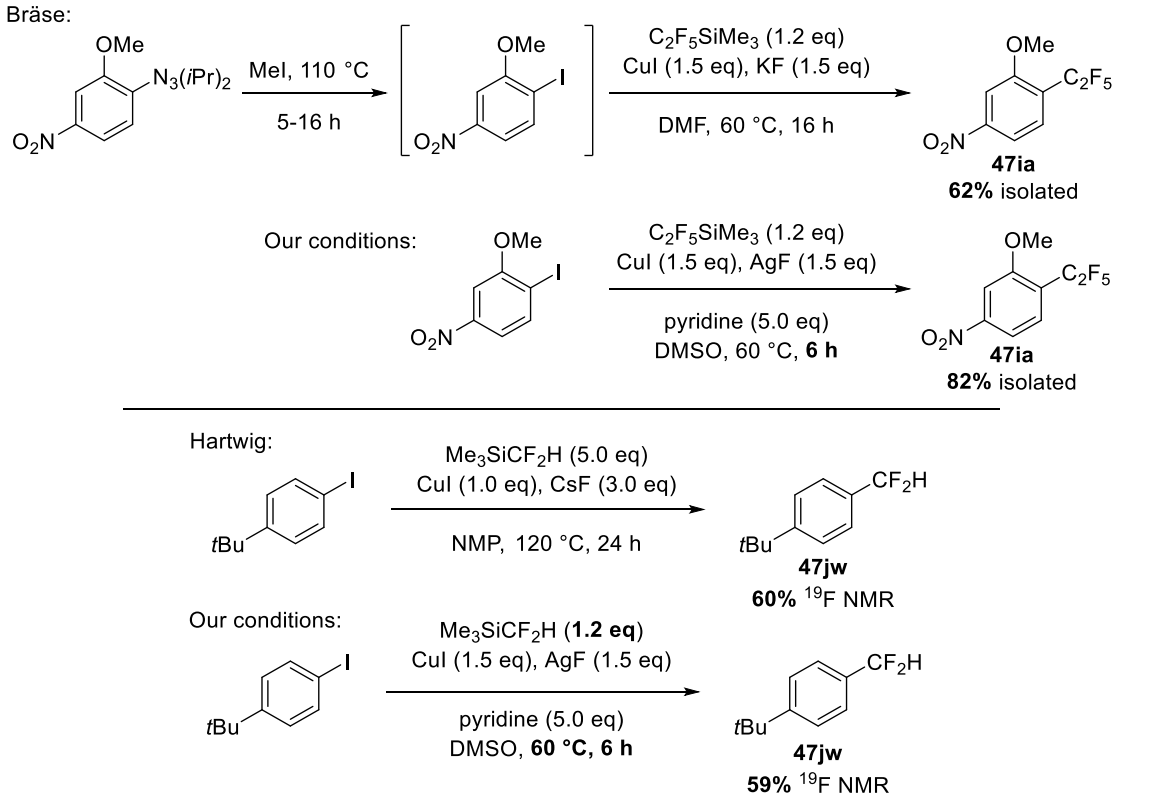
(Scheme 92b). By-product **38** is formed under the standard reaction conditions, with aryl bromides, and with copper catalysts other than copper iodide (*e.g.* CuCl, CuBr). This suggests that the source of iodine may be both CuI or the aryl iodide coupling partner.



Scheme 92 Proposed by-product formation (a) from trifluoromethide intermediate and (b) from reductive elimination

5.3 Conclusion

We have presented the synthesis and reactivity of [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes, $Me_3Si(CF_2)_2Ar$. Like the Ruppert-Prakash reagent Me_3SiCF_3, this new class of reagents takes part in fluoride-activated addition reactions to aldehydes, affording tetrafluoroethylated alcohols in good to very good yields. Furthermore, an operationally simple procedure for the silver/copper-mediated cross-coupling of these reagents with a wide range of (hetero)aryl iodides and bromides has been developed, furnishing 1,1,2,2-tetrafluoro-1,2-arylethanes in moderate to good yields. This protocol is an improvement over current fluoroalkylation methods due the mild reaction conditions that allow for cross-coupling at room temperature to 60 °C in 6 hours. The use of pyridine as an alternative to 1,10-phenanthroline enabled us to reduce side-reactions and improve on some known fluoroalkylation methods, both in terms of yield and reaction efficiency (Scheme 93).[94, 228]



Scheme 93 Improved results compared to other fluoroalkylation methods

The synthesis of the [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silane reagents is currently low yielding; especially the final silylation step requires further optimisation before this methodology will be of significant use to process chemistry. In addition, the mechanism of cross-coupling requires further elucidation: As alluded to in the previous section, the separate synthesis of LMR_f complexes (L = phen, py; M = Ag, Cu; R_f = $(CF_2)_2Ar$) is advisable. This would allow for structural studies by X-ray crystallography and NMR, as well as reactivity studies to help establish the cross-coupling mechanism and the role of pyridine as a ligand. Low-temperature synthesis of the tetrafluoroethide intermediate and its analysis by NMR and X-ray crystallography would also be interesting. Preliminary results indicate that the development of a catalytic variant of our cross-coupling methodology should also be feasible.

Chapter 6

Experimental Data and Analysis

Chapter 6: Experimental Data and Analysis

6.1 General Experimental Information

All solvents and chemicals were used as purchased unless stated otherwise. 1-(Pentafluoroethyl)-1,2-benziodoxol-3(1*H*)-one (Togni's reagent **19c**) was synthesised by S. Verhoog following a literature procedure.[206] *N*-Tosyl-3-iodo-*1H*-indole and *N*-tosyl-3-bromo-indole were provided by N. Taylor. NBS was recrystallized from boiling water, 2,2'-bipyridine was recrystallized from boiling PET 40/60, and aldehydes were distilled before use. All NMR spectra were recorded on Bruker DPX200, DPX250, AV400, AVIII400, AVIIIHD 500 or AVIIIHD 600 spectrometers. NMR data were processed using TOPSPIN 3.1 and 3.2 software. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to residual undeuterated solvent peak using the Bruker internal referencing procedure (edlock). Fluorine-19 NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. Coupling constants (*J*) are reported in units of hertz (Hz) and are rounded to the nearest 0.5 for ^{1}H and ^{19}F NMR and the nearest 1.0 for ^{13}C NMR. The following abbreviations are used to describe multiplets: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sex (sextet), sept (septet), m (multiplet), br (broad). High resolution mass spectra (HRMS, *m*/*z*) were recorded on a Bruker MicroTOF spectrometer using positive electrospray ionization (ESI), a Micromass GCT spectrometer using chemical ionisation (CI), or a Waters GCT TOF (temperature programmed solid's prope) spectrometer using field ionisation (FI) or electron impact (EI). Infrared spectra were recorded as neat compound using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm^{-1}) and only peaks of interest are reported. Melting points of solids were measured on a Griffin apparatus and are uncorrected. IUPAC

names were obtained using the ACD I-Lab 2.0 service. All reactions were performed in dried apparatus with magnetic stirring under an inert atmosphere of argon or nitrogen. All solvents were dried on a column of alumina prior to use. Thin layer chromatography (TLC) was performed using Merck aluminium-foil baked plates precoated with Kieselgel 60 F245. The products were visualized using UV fluorescence (254 nm) or potassium permanganate stain. ^{19}F NMR yields were obtained by integrating the product peak(s) relative to 1.0 equivalent internal standard. The relaxation time D1 was set to 10s for these experiments. Flash column chromatography was performed over Merck silica gel C60 (40-60 μm) using eluent systems as described for each experiment. Known compounds have been checked against literature references and only three pieces of analytical data are given.

General information for radiochemical procedures at the Siemens Organic Molecular Imaging Laboratory (SOMIL), University of Oxford.

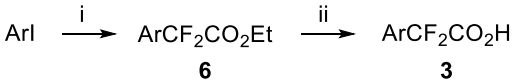
[^{18}F]Fluoride was produced by Erigal Ltd (Keele, UK) *via* the $^{18}O(p,n)^{18}F$ reaction and delivered as [^{18}F]fluoride in [^{18}O]water. Radiosynthesis and azeotropic drying was performed on a NanoTek® automated microfluidic device (Advion). [^{18}F]Fluoride was separated from ^{18}O-enriched-water using anion exchange cartridges (MP1, ORTG, Tennessee, USA) and subsequently released with 550 μL of a solution of K_2CO_3 (3mg) and $K_{2.2.2}$ (15mg) in MeCN/H_2O (4:1, 1 mL) into the concentrator to form [^{18}F]KF/$K_{2.2.2}$. Alternatively, [^{18}F]TEAF was prepared by releasing the [^{18}F]fluoride with 550 μL of a solution of tetraethylammonium bicarbonate (8 mg) in MeCN/H_2O (4:1, 1 mL). The solution was dried with five cycles of azeotropic drying with acetonitrile (300 μL) and redissolved in anhydrous acetonitrile (1000 μL). [^{18}F]KF/$K_{2.2.2}$ or [^{18}F]TEAF (*ca.* 30 MBq) was dispensed in as aliquots of this stock solution into a V-vial containing a magnetic stirrer and the MeCN was removed from the vial by heating to 100°C under a stream of N_2.

For all reactions, an aliquot was removed for analysis by radio-TLC and radio-HPLC. Radio-TLC was carried out on Merck Kiesegel 60 F254 plates in EtOAc:Hexane (1:1) or MeOH and analysed using a plastic scintillator/PMT detector. HPLC analysis was performed using a Dionex Ultimate 3000 dual channel HPLC system with a shared autosampler, parallel UV-detectors and LabLogic NaI/PMT-radiodetectors with Flowram analogue output. (HPLC System 1: A = Water, B = MeCN. HPLC System 2: A = Water + 0.1 % TFA, B = MeCN + 0.1 % TFA. HPLC Gradient Settings: 1 mL/min, Waters Nova-Pak C18 Column, 4 μm, 3.9 x 150 mm. 0–1 min (5% B) isocratic, 1–11 min (5% B to 95% B) linear increase, 11–15 min (95% B) isocratic, 15–17 min (95% B to 5% B) linear decrease, 17–18 min (5% B) isocratic.) Reported radiochemical yields are decay corrected and calculated by radio-TLC taking into account the radiochemical purity as determined by radio-HPLC.

6.2 Experimental Procedures and Characterisation Data

6.2.1 Electrophilic Fluorodecarboxylation

6.2.1.1 Synthesis of α,α-Difluoroaryl acetic acids 3



Conditions: (i) Cu (2.6 eq), $BrCF_2CO_2Et$ (1.0 eq), DMSO, 60°C, 12 h; (ii) K_2CO_3, H_2O/MeOH, rt, 2 h.

NB. Substrates denoted by an asterix (*) were synthesised by Dr. J. Wolstenhulme.

General Procedure 1-A: Ullmann coupling of aryl iodides with ethyl bromodifluoroacetate[60]

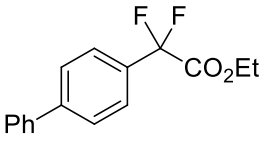
Copper powder was stirred vigorously in 1 M HCl for 10 minutes at rt and filtered, after which it was washed with water, MeOH and acetone successively. The activated copper powder was dried thoroughly under vacuum before use.

In a 50 mL round bottom flask under an atmosphere of N_2, aryl iodide (10.0 mmol, 1.0 eq) and 1.3 mL ethyl bromodifluoroacetate (10.0 mmol, 1.0 eq) were added to a suspension of 1.7 g activated Cu powder (26.0 mmol, 2.6 eq) in 26 mL DMSO (0.4 M). The reaction mixture was stirred at 60 °C for 12 h, after which it was poured into a mixture of ice and saturated $NH_4Cl_{(aq)}$, and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with $NH_4Cl_{(aq)}$ and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by silica flash column chromatography.

General Procedure 1-B: Hydrolysis of α,α-difluoroacetates

In a 50 mL round bottom flask, ethyl α,α-difluoroaryl acetate (5.0 mmol, 1.0 eq) obtained by GP 1-A was added to a mixture of 15 mL MeOH (0.3 M) and 15 mL 1 M K_2CO_3 and stirred at rt for 2 h. The reaction was then poured into 1 M HCl to acidify to pH 1, and the aqueous phase was extracted with EtOAc. The organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Crude products were purified by trituration with PET 30/40.

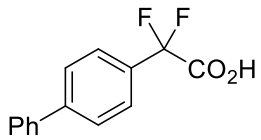
Ethyl biphenyl-4-yl(difluoro)acetate (6a)[222]



Synthesised from 4-iodobiphenyl following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 5% Et_2O in PET 30/40) to give 2.05 g (79% yield) of **6a** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.0 Hz, 3H), 4.18 (q, *J* = 7.0 Hz,

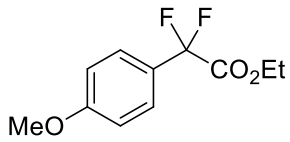
2H), 7.22−7.26 (m, 1H), 7.30−7.33 (m, 2H), 7.44−7.47 (m, 2H), 7.52-7.58 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 63.3, 113.6 (t, *J* = 252 Hz), 126.0 (t, *J* = 6 Hz), 127.3, 127.4, 128.1, 129.0, 131.7 (t, *J* = 26 Hz), 140.0, 144.0, 164.3 (t, *J* = 26 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −103.45 (s).

Biphenyl-4-yl(difluoro)acetic acid (3a)



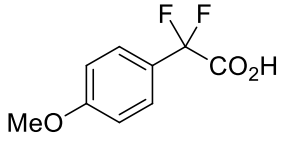
Synthesised from **6a** following GP 1-B (7.4 mmol scale), yielding 1.75 g (85% yield) of **3a** as an off-white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.43 (tt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.49−7.57 (m, 2H), 7.67−7.73 (m, 4H), 7.84 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 114.1 (t, *J* = 249 Hz), 126.2 (t, *J* = 6 Hz), 127.4, 127.7, 128.7, 129.5, 132.1 (t, *J* = 25 Hz), 139.4, 143.4, 165.4 (t, *J* = 34 Hz); **^{19}F NMR** (376.5 MHz, $(CD_3)_2SO$) δ −102.37 (s); **IR** (neat) ν 3516, 1702, 1324, 1263, 1143, 1125, 1102, 840, 739, 697; **HRMS** (ESI) calculated for $C_{14}H_9F_2O_2$ $[M-H]^-$ 247.0576, found 247.0577; **Mp** 114−117 °C.

Ethyl difluoro-2-(4-methoxyphenyl)acetate (6b)[233]



Synthesised from 4-iodoanisole following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 5% EtOAc in PET 30/40) to give 846 mg (37% yield) of **6b** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.0 Hz, 3H), 3.86 (s, 3H), 4.32 (q, *J* = 7.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.56 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 55.4, 63.0, 113.6 (t, *J* = 252 Hz), 114.0, 124.9 (t, *J* = 27 Hz), 127.1 (t, *J* = 6 Hz), 161.6, 164.5 (t, *J* = 36 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −102.6 (s).

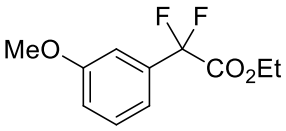
Difluoro(4-methoxyphenyl)acetic acid (3b)*



Synthesised from **6b** following GP 1-B (3.7 mmol scale), yielding 588 mg (79% yield) of **3b** as a yellow solid. **^{1}H NMR** (400 MHz,

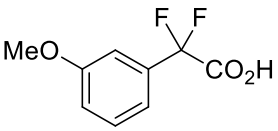
$(CD_3)_2SO$) δ 3.80 (s, 3H), 7.07 (d, *J* = 9.0 Hz, 2H), 7.51 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 55.8, 114.2 (t, *J* = 251 Hz), 114.7, 125.1 (t, *J* = 26 Hz), 127.3 (t, *J* = 6 Hz), 161.7, 165.7 (t, *J* = 35 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −101.0 (s); **IR** (neat) ν 1739, 1610, 1514, 1439, 1252, 1177, 1141, 1098, 1030, 988, 890, 829, 744, 693, 638; **HRMS** (ESI) calculated for $C_9H_7F_2O_3$ $[M-H]^-$ 201.0369, found 201.0361; **Mp** 72−74 °C.

Ethyl difluoro(3-methoxyphenyl)acetate (6c)



Synthesised from 3-iodoanisole following GP 1-A (5.0 mmol scale). Purified by silica flash column chromatography (eluent: 5% EtOAc in PET 30/40) to give 897 mg (78% yield) of **6c** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.0 Hz, 3H), 3.84 (s, 3H), 4.31 (q, *J* = 7.0 Hz, 2H), 7.03 (dd, *J* = 8.5 Hz, J = 2.5 Hz, 1H), 7.14 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 55.4, 63.2, 110.7 (t, *J* = 7 Hz), 113.2 (t, *J* = 254 Hz), 116.9, 117.7 (t, *J* = 6 Hz), 129.8, 134.1 (t, *J* = 26 Hz), 159.7, 164.2 (t, *J* = 35 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −103.8 (s); **IR** (neat) ν 1764, 1605, 1493, 1456, 1278, 1218, 1101, 1047, 1019, 859, 792, 747, 693; **HRMS** (ESI) calculated for $C_{11}H_{12}F_2NaO_3$ $[M+Na]^+$ 253.0647, found 253.0642.

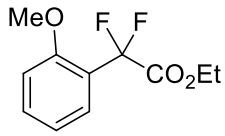
Difluoro(3-methoxyphenyl)acetic acid (3c)*



Synthesised from **6c** following GP 1-B (3.9 mmol scale), yielding 436 mg (55% yield) of **3c** as a pale yellow solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 3.81 (s, 3H), 7.07 (t, *J* = 2.0 Hz, 1H), 7.13−7.15 (m, 1H), 7.15−7.17 (m, 1H), 7.46 (t, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 55.8, 111.0 (t, *J* = 6 Hz), 113.8 (t, *J* = 251 Hz), 117.1, 117.6 (t, *J* = 6 Hz), 130.8, 134.6 (t, *J* = 25 Hz), 159.8, 165.3 (t, *J* = 34 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −102.4 (s, 2F); **IR** (neat) ν 1743, 1602, 1493, 1466, 1329, 1294, 1274, 1215, 1145, 1113,

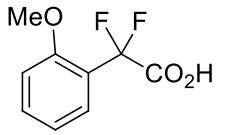
1082, 1039, 1012, 917, 847, 790, 734, 686; **HRMS** (ESI) calculated for $C_9H_8F_2NaO_3$ $[M+Na]^+$ 225.0334, found 225.0326; **Mp** 63−66 °C.

Ethyl difluoro(2-methoxyphenyl)acetate (6d)



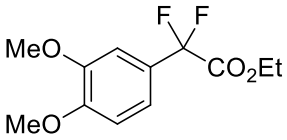
Synthesised from 2-iodoanisole following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 5% to 10% EtOAc in Hex) to give 1.5 g (66% yield) of **6d** as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.0 Hz, 3H), 3.80 (s, 3H), 4.32 (q, *J* = 7.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.8, 55.6, 62.6, 111.4, 112.3 (t, *J* = 248 Hz), 120.6, 121.9 (t, *J* = 24 Hz), 126.2 (t, *J* = 8 Hz), 132.4, 156.7 (t, *J* = 5 Hz), 164.1 (t, *J* = 34 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −102.6 (s); **IR** (neat) ν 2360, 1773, 1495, 1468, 1283, 1257, 1101, 1071, 1048, 1020, 755, 672; **HRMS** (ESI) calculated for $C_{11}H_{12}F_2NaO_3$ $[M+Na]^+$ 253.0647, found 253.0649.

Difluoro(2-methoxyphenyl)acetic acid (3d)



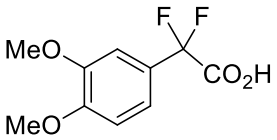
Synthesised from **6d** following GP 1-B (5.8 mmol scale), yielding 1.15 g (98 % yield) of **3d** as a pale yellow solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 3.79 (s, 3H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.51-7.58 (m, 2H); **^{13}C NMR** (125 MHz, $(CD_3)_2SO$) δ 55.9, 112.2, 112.5 (t, *J* = 246 Hz), 120.4, 121.6 (t, *J* = 24 Hz), 125.6 (t, *J* = 7 Hz), 132.5, 156.6 (t, *J* = 5 Hz), 164.6 (t, *J* = 28 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −101.8 (s); **IR** (neat) ν 1775, 1606, 1495, 1470, 1298, 1261, 1213, 1109, 1080, 1048, 995, 843, 774, 748, 731, 663, 608; **HRMS** (ESI) calculated for $C_9H_7F_2O_3$ $[M-H]^-$ 201.0369, found 201.0365; **Mp** 96−99 °C.

Ethyl (3,3-Dimethoxyphenyl)(difluoro)acetate (6e)[234]



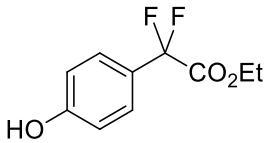
Synthesised from 3,4-dimethoxy-1-iodobenzene following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 10% EtOAc in PET 30/40) to give 1.63 g (63% yield) of **6e** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.0 Hz, 3H), 3.93 (s, 3H), 3.93 (s, 3H), 4.32 (q, *J* = 7.0 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 2.0 Hz, 1H), 7.18−7.22 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 56.0, 56.0, 63.0, 108.3 (t, *J* = 6 Hz), 110.8, 113.4 (t, *J* = 253 Hz), 118.5 (t, *J* = 7 Hz), 125.1 (t, *J* = 26 Hz), 149.0, 151.1, 164.4 (t, *J* = 36 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −102.7 (s).

(3,3-Dimethoxyphenyl)(difluoro)acetic acid (3e)*



Synthesised from **6e** following GP 1-B (6.3 mmol scale), yielding 1.16 g (80% yield) of **3e** as an off-white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 3.80 (s, 3H), 3.81 (s, 3H), 7.06 (d, *J* = 2.0 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 7.13 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 56.1, 56.1, 108.6 (t, *J* = 6 Hz), 112.0, 114.1 (t, *J* = 254 Hz), 118.6 (t, *J* = 6 Hz), 125.2 (t, *J* = 26 Hz), 149.2, 151.3, 165.6 (t, *J* = 35 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −100.8 (s); **IR** (neat) ν 1770, 1521, 1466, 1452, 1297, 1267, 1208, 1173, 1151, 1102, 1046, 1019, 865, 801, 767, 729, 641; **HRMS** (ESI) calculated for $C_{10}H_9F_2O_4$ $[M-H]^-$ 231.0474, found 231.0476; **Mp** 62−65 °C.

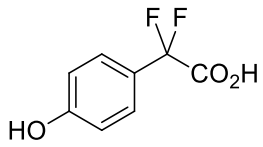
Ethyl difluoro(4-hydroxyphenyl)acetate (6f)



Synthesised from 4-iodophenol following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 15% EtOAc in PET 30/40) to give 820 mg (38% yield) of **6f** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.0 Hz, 3H), 4.31 (q, *J* = 7.0 Hz, 2H), 6.89 (d, *J* = 8.5 Hz), 7.49 (d, *J* = 8.5 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 13.9, 63.2,

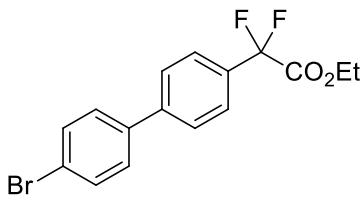
113.5 (t, *J* = 252 Hz, 2H), 115.5, 125.0 (t, *J* = 26 Hz, 2H), 127.3 (t, *J* = 6 Hz), 157.9, 164.7 (t, *J* = 37 Hz); **^{19}F NMR** (376.6 MHz, $CDCl_3$) δ –102.6 (s); **IR** (neat) ν 3411, 1740, 1598, 1518, 1444, 1266, 1210, 1164, 1139, 1095, 1021, 839, 760, 646; **HRMS** (FI) calculated for $C_{10}H_{10}O_3F_2$ $[M]^+$ 216.0598, found 216.0601.

(4-Hydroxyphenyl)(difluoro)acetic acid (3f)*



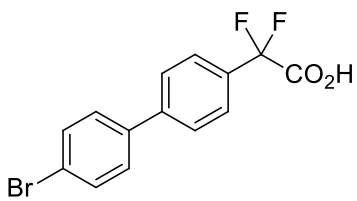
Synthesised from **6f** following GP 1-B (3.0 mmol scale). Product is not benchtop stable and decomposes to black sludge within minutes of workup.

Ethyl (4'-bromobiphenyl-4-yl)(difluoro)acetate (6g)



Synthesised from 4-bromo-4'-iodobiphenyl following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 2% EtOAc in PET 30/40) to give 1.91 g (54% yield) of **6g** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.0 Hz, 3H), 4.35 (q, *J* = 7.0 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 63.2, 113.4 (t, *J* = 256 Hz), 122.5, 126.1 (t, *J* = 6 Hz), 127.2, 128.8, 132.1 (t, *J* = 26 Hz), 132.1, 138.9, 142.7, 164.1 (t, *J* = 36 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −103.7 (s); **IR** (neat) ν 1762, 1484, 1266, 1099, 1034, 1003, 856, 815, 772, 758, 679; **HRMS** (FI) calculated for $C_{16}H_{13}F_2Br\ O_2$ $[M]^+$ 354.0067, found 354.0063.

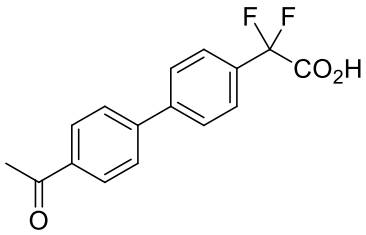
(4'-Bromobiphenyl-4-yl)(difluoro)acetic acid (3g)*



Synthesised from **6g** following GP 1-B (1.6 mmol scale), yielding 241 mg (68% yield) of **3g** as an off-white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.65–7.72 (m, 6H), 7.83 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 114.0 (t, *J* = 252 Hz), 122.3, 126.3

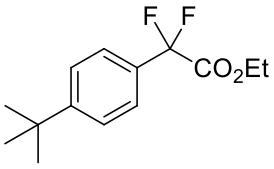
(t, *J* = 6 Hz), 127.6, 129.5, 132.4, 132.4 (t, *J* = 25 Hz), 138.6, 142.1, 165.3 (t, *J* = 35 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −102.5 (s, 2F); **IR** (neat) ν 1751, 1268, 1152, 1110, 1075, 991, 897, 852, 815, 747, 671; **HRMS** (ESI) calculated for $C_{14}H_8F_2BrO_2$ $[M-H]^-$ 324.9681, found 324.9689; **Mp** 150−153 °C.

(4'-Acetylbiphenyl-4-yl)(difluoro)acetic acid (3h)



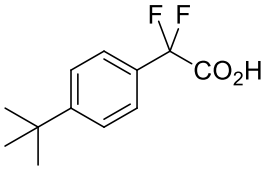
To a suspension of 2 mg $PdCl_2$ (0.0115 mmol, 0.5 mol%) and 636 mg K_2CO_3 (4.6 mmol, 2.0 eq) in 18 mL DMF/H_2O (*v*/*v* 1:1, 0.13 M) were added 645 mg ethyl (3-bromophenyl)(difluoro)acetate (2.3 mmol, 1.0 eq) and 574 mg 3-acetylphenylboronic acid (3.5 mmol, 1.5 eq). The reaction was stirred at rt overnight, after which it was filtered through celite. The mixture was extracted with Et_2O to remove any organic impurities. The Et_2O layer was discarded and the aqueous layer was acidified to pH 1 with 1 M HCl and extracted with EtOAc. The combined EtOAc layers were dried over $MgSO_4$, concentrated *in vacuo*, re-suspended in 50 mL Et_2O and stirred vigorously for 1 h to remove any unreacted boronic acid. The product was filtered off and dried *in vacuo* to yield 385 mg (58% yield) of pure **3h** as a white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 2.50 (s, 3H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.74 (tt, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.98 (tt, *J* = 8.5 Hz, 2.0 Hz, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 25.9, 113.7 (t, *J* = 250 Hz), 126.1 (t, *J* = 7 Hz), 127.3, 127.6, 128.9, 133.0 (t, *J* = 26 Hz), 138.7, 142.5, 143.9, 164.6 (t, *J* = 34 Hz), 196.7; **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −104.28 (s); **IR** (neat) ν 1680, 1605, 1292, 1265, 1117, 1101, 1022, 953, 822, 754, 687; **HRMS** (FI) calculated for $[M]^+$ 290.0755, found 290.0754; **Mp** 82–83 °C.

Ethyl (4-*tert*-butylphenyl)(difluoro)acetate (6i)



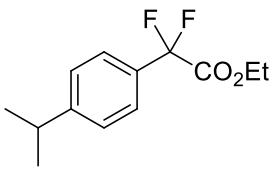
Synthesised from 4-*tert*-butyl-iodobenzene following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 2% EtOAc in PET 30/40) to give 1.21 g (47% yield) of the **6i** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.0 Hz, 3H), 1.34 (s, 9H), 4.31 (q, *J* = 7.0 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 31.2, 34.9, 63.0, 113.6 (t, *J* = 252 Hz), 125.2 (t, *J* = 6 Hz), 125.6, 129.9 (t, *J* = 26 Hz), 154.3, 164.4 (t, *J* = 35.5 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −103.2 (s); **IR** (neat) ν 2966, 1765, 1271, 1144, 1098, 1013, 991, 834, 706; **HRMS** (ESI) calculated for $C_{14}H_{18}F_2NaO_2$ $[M+Na]^+$ 279.1167, found 279.1162.

(4-*tert*-Butylphenyl)(difluoro)acetic acid (3i)



Synthesised from **6i** following GP 1-B (4.7 mmol scale), yielding 713 mg (66% yield) of **3i** as an off-white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 1.29 (s, 9H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 31.3, 35.1, 114.1 (t, *J* = 250 Hz), 125.4 (t, *J* = 6 Hz), 126.2, 130.3 (t, *J* = 26 Hz), 154.3, 165.5 (t, *J* = 34 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −102.1 (s); **IR** (neat) ν 1740, 1269, 1148, 1106, 992, 916, 840, 691; **HRMS** (ESI) calculated for $C_{14}H_{18}F_2NaO_2$ $[M+Na]^+$ 279.1167, found 279.1162; **Mp** 80–82 °C.

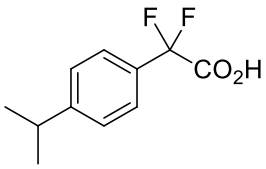
Ethyl difluoro[4-(propan-2-yl)phenyl]acetate (6j)



Synthesised from 4-*iso*-propyl-iodobenzene following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 2% EtOAc in PET 30/40) to give 1.07 g (44% yield) of **6j** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.29 (d, *J* = 7.0 Hz, 6H), 1.34 (t, *J* = 7.0 Hz, 3H), 2.98 (sept, *J* = 7.0 Hz, 1H), 4.33 (q, *J* = 7.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 23.8, 34.0, 63.0, 113.6

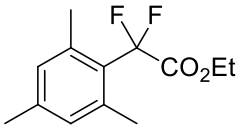
(t, *J* = 251 Hz), 125.5 (t, *J* = 6 Hz), 126.7, 130.3 (t, *J* = 26 Hz), 152.0, 164.4 (t, *J* = 36 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −103.2 (s); **IR** (neat) ν 1764, 1269, 1096, 1056, 1013, 992, 835; **HRMS** (ESI) calculated for $C_{13}H_{16}F_2NaO_2$ $[M+Na]^+$ 265.1011, found 265.1007.

Difluoro[4-(propan-2-yl)phenyl]acetic acid (3j)*



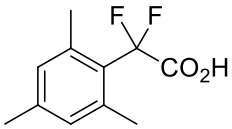
Synthesised from **6j** following GP 1-B (4.4 mmol scale), yielding 707 mg (75% yield) of **3j** as a white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 1.21 (d, *J* = 7.0 Hz, 6H), 2.94 (sept, *J* = 7.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100.6 MHz, $(CD_3)_2SO$) δ 24.0, 33.8, 114.1 (t, *J* = 252 Hz), 125.6 (t, *J* = 6 Hz), 127.3, 130.7 (t, *J* = 26 Hz), 152.1, 165.6 (t, *J* = 34.1 Hz); **^{19}F NMR** (376.6 MHz, $(CD_3)_2SO$) δ −102.0 (s); **IR** (neat) ν 1739, 1268, 1143, 1113, 1058, 993, 916, 836, 750, 695; **HRMS** (ESI) calculated for $C_{13}H_{16}O_2F_2Na$ $[M+Na]^+$ 265.1011, found 265.1007; **Mp** 32–34 °C.

Ethyl 2,2-difluoro-2-mesitylacetate (6k)



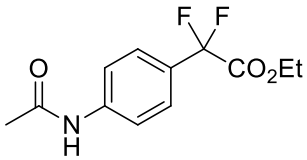
Synthesised from 2-iodo-1,3,5-trimethylbenzene following GP 1-A (6.0 mmol scale). Purified by silica flash column chromatography (eluent: 2% EtOAc in PET 30/40) to give 950 mg (65% yield) of **6k** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.0 Hz, 3H), 2.29 (s, 3H), 2.44 (t, *J* = 4.5 Hz, 6H), 4.32 (q, *J* = 7.0 Hz, 2H), 6.88 (s, 2H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 13.9, 20.8, 21.6 (t, *J* = 6 Hz), 63.0, 116.3 (t, *J* = 253 Hz), 126.9 (t, *J* = 23 Hz), 131.1, 137.6 (t, *J* = 4 Hz), 139.9, 164.6 (t, *J* = 36 Hz); **^{19}F NMR** (376.6 MHz, $CDCl_3$) δ −94.7 (s); **IR** (neat) ν 1762, 1278, 1242, 1170, 1093, 1017, 986, 956, 855, 835; **HRMS** (ESI) calculated for $C_{13}H_{16}F_2NaO_2$ $[M+Na]^+$ 265.1011, found 265.1010.

Difluoro(2,4,6-trimethylphenyl)acetic acid (3k)*



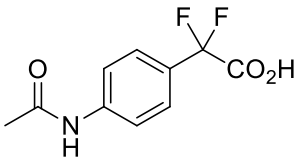
Synthesised from **6k** following GP 1-B (3.9 mmol scale), yielding 336 mg (40% yield) of **3k** as a white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 2.23 (s, 3H), 2.37 (t, *J* = 4.0 Hz, 6H), 6.93 (s, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 20.7, 21.5 (t, *J* = 6 Hz), 116.8 (t, *J* = 252 Hz), 127.4 (t, *J* = 22 Hz), 131.3, 137.2 (t, *J* = 3 Hz), 139.9, 165.8 (t, *J* = 34 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −94.2 (s); **IR** (neat) ν 1739, 1426, 1284, 1236, 1128, 1102, 688; **HRMS** (FI) calculated for $C_{11}H_{12}O_2F_2$ $[M]^+$ 214.0805, found 214.0802; **Mp** 97–99 °C.

Ethyl [4-(acetylamino)phenyl](difluoro)acetate (6l)



Synthesised from 4-acetamide-iodobenzene following GP 1-A (5.0 mmol scale). Purified by silica flash column chromatography (eluent: 30% EtOAc in PET 30/40) to give 1.10 g (86% yield) of **6l** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.0 Hz, 3H), 2.11 (s, 3H), 4.22 (q, *J* = 7.0 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.96 (brs, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 24.5, 63.2, 113.3 (t, *J* = 252 Hz), 119.7, 126.4 (t, *J* = 6 Hz), 128.1 (t, *J* = 26 Hz), 140.5, 164.3 (t, *J* = 35 Hz), 169.0; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −103.22 (s); **IR** (neat) ν 1763, 1672, 1603, 1533, 1409, 1371, 1317, 1265, 1184, 1142, 1099, 1028, 1011, 992, 834, 761, 689; **HRMS** (ESI) calculated for $C_{12}H_{13}F_2NNaO_3$ $[M+Na]^+$ 280.0756, found 280.0749.

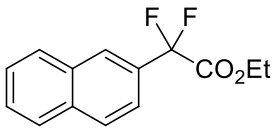
[4-(Acetylamino)phenyl](difluoro)acetic acid (3l)



Synthesised from **6l** following GP 1-B (4.0 mmol scale), yielding 576 mg (48% yield) of **3l** as a pale yellow solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 2.07 (s, 3H), 7.51 (d, *J* = 9.0 Hz, 2H), 7.73 (d, *J* = 9.0 Hz, 2H), 10.2 (s, N*H*); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 24.5, 114.1 (t, *J* = 252 Hz), 119.2, 126.4 (t, *J* = 6 Hz), 127.6 (t, *J* = 26 Hz), 142.2, 165.5 (t, *J* = 34 Hz),

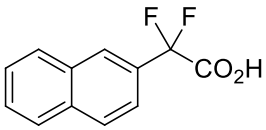
169.2; **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −101.5 (s); **IR** (neat) ν 3347, 1924, 1715, 1592, 1540, 1411, 1375, 1257, 1187, 1116, 1073, 996, 969, 838, 785, 755, 726, 688, 629, 609; **HRMS** (ESI) calculated for $C_{10}H_8F_2NO_3$ $[M-H]^-$ 228.0478, found 228.0487; **Mp** 154–156 °C.

Ethyl difluoro(naphthalen-2-yl)acetate (6m)



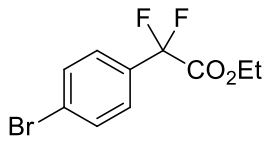
Synthesised from 2-iodonaphthalene following GP 1-A (5.0 mmol scale). Purified by silica flash column chromatography (eluent: 5% Et_2O in PET 30/40) to give 420 mg (34% yield) of **6m** as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.0 Hz, 3H), 4.24 (q, *J* = 7.0 Hz, 2H), 7.46-7.53 (m, 2H), 7.58 (dd, *J* = 2.0 Hz, 9.0 Hz, 1H), 7.79−7.89 (m, 3H), 8.05 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.9, 63.2, 113.6 (t, *J* = 252 Hz), 121.9 (t, *J* = 6 Hz), 125.7 (t, *J* = 7 Hz), 126.9, 127.7, 127.8, 128.8 (2C), 130.0 (t, *J* = 26 Hz), 132.4, 134.2, 164.2 (t, *J* = 35 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −103.6 (s); **IR** (neat) ν 2361, 1764, 1280, 1098; **HRMS** (CI) calculated for $C_{14}H_{12}O_2F_2$ $[M]^+$ 250.0805, found 250.0802.

Difluoro(naphthalen-2-yl)acetic acid (3m)



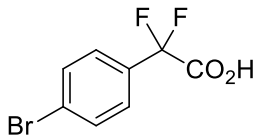
Synthesised from **6m** following GP 1-B (1.6 mmol scale), yielding 241 mg (68% yield) of **3m** as an off-white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.61−7.68 (m, 3H), 8.02 (d, *J* = 7.0 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 7.0 Hz, 1H), 8.23 (s, 1H); **^{13}C NMR** (125 MHz, $(CD_3)_2SO$) δ 121.7 (t, *J* = 5 Hz), 125.2 (t, *J* = 6 Hz), 127.2, 127.7, 127.9, 128.7, 128.9, 130.0 (t, *J* = 25 Hz), 132.0, 133.7; **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −102.1 (s); **IR** (neat) ν 1740, 1227, 1194, 1163, 1126, 1106, 1015, 906, 868, 827, 747, 717; **HRMS** (ESI) calculated for $C_{12}H_7F_2O_2$ $[M-H]^-$ 221.0420, found 221.0410; **Mp** 120−121 °C.

Ethyl (3-Bromophenyl)(difluoro)acetate (6n)[233]



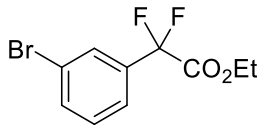
Synthesised from 4-bromo-1-iodobenzene following GP 1-A (5.0 mmol scale). Purified by silica flash column chromatography (eluent: 3% EtOAc in PET 30/40) to give 433 mg (31% yield) of **6n** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 3H), 4.23 (q, *J* = 7.0 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 63.4, 113.0 (t, *J* = 253 Hz), 125.7, 127.2 (t, *J* = 6 Hz), 131.8 (t, *J* = 26 Hz), 132.0, 163.8 (t, *J* = 35 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −104.1 (s).

(3-Bromophenyl)(difluoro)acetic acid (3n)*



Synthesised from **6n** following GP 1-B (1.5 mmol scale), yielding 286 mg (76% yield) of **3n** as an off-white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.54 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 113.6 (t, *J* = 250 Hz), 125.3, 127.8 (t, *J* = 6 Hz), 132.5 (t, *J* = 27 Hz), 132.5, 165.0 (t, *J* = 33 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −102.7 (s); **IR** (neat) ν 1748, 1595, 1486, 1437, 1398, 1263, 1139, 1100, 1071, 989, 898, 828, 746, 721, 673; **HRMS** (ESI) calculated for $C_8H_4BrF_2O_2$ $[M-H]^-$ 248.9368, found 248.9358; **Mp** 95−97 °C.

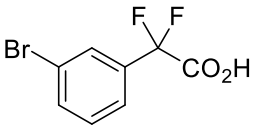
Ethyl (1-Bromophenyl)(difluoro)acetate (6o)



Synthesised from 3-bromo-1-iodobenzene following GP 1-A (5.0 mmol scale). Purified by silica flash column chromatography (eluent: 3% EtOAc in PET 30/40) to give 688 mg (49% yield) of **6o** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.0 Hz, 3H), 4.32 (q, *J* = 7.0 Hz, 2H), 7.35 (t, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 13.9, 63.4, 112.5 (t, *J* = 254 Hz), 122.7, 124.2 (t, *J* = 6 Hz), 128.7 (t, *J* = 7 Hz), 130.3, 134.2, 134.8 (t, *J* = 36 Hz), 163.5 (t, *J* = 35 Hz); **^{19}F NMR** (376.6 MHz,

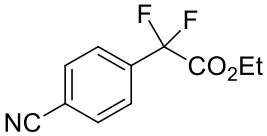
$CDCl_3$) δ –104.1 (s); **IR** (neat) ν 1765, 1372, 1298, 1251, 1105, 1021, 796, 726, 679; **HRMS** (FI) calculated for $C_{10}H_9O_2F_2Br$ $[M]^+$ 277.9754, found 277.9752.

(1-Bromophenyl)(difluoro)acetic acid (3o)*



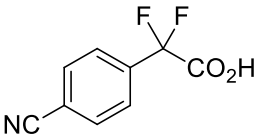
Synthesised from **6o** following GP 1-B (2.5 mmol scale), yielding 337 mg (54% yield) of **3o** as an off-white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.52 (t, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.73 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100.6 MHz, $(CD_3)_2SO$) δ 113.1 (t, *J* = 250 Hz), 122.4, 124.9 (t, *J* = 6 Hz), 128.2 (t, *J* = 6 Hz), 131.8, 134.7, 135.4 (t, *J* = 26 Hz), 164.9 (t, *J* = 32 Hz); **^{19}F NMR** (376.6 MHz, $(CD_3)_2SO$) δ –102.7 (s); **IR** (neat) ν 1744, 1423, 1280, 1252, 1146, 1117, 1007, 995, 888, 795, 710, 670, 654; **HRMS** calculated for $C_8H_5O_2F_2Br$ $[M]^+$ 249.9441, found 249.9451; **Mp** 67–69°C.

Ethyl (3-Cyanophenyl)(difluoro)acetate (6p)[222]



Synthesised from 4-iodobenzonitrile following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 9% EtOAc in PET 30/40) to give 1.61 g (71% yield) of **6p** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.0 Hz, 3H), 4.33 (q, *J* = 7.0 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 63.7, 112.4 (t, *J* = 253 Hz), 115.2, 117.8, 126.5 (t, *J* = 6 Hz), 132.5, 137.2 (t, *J* = 26 Hz), 163.2 (t, *J* = 35 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −104.9 (s).

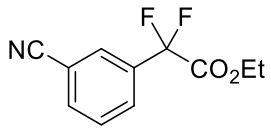
(3-Cyanophenyl)(difluoro)acetic acid (3p)



Synthesised from **6p** following GP 1-B (7.1 mmol scale), yielding 1.20 g (86% yield) of **3p** as a white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.79 (d, *J* = 8.5 Hz, 2H), 8.03 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 113.2 (t, *J* = 251 Hz), 114.5, 118.4, 126.7 (t, *J* = 6 Hz), 133.5, 137.6 (t,

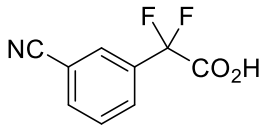
J = 26 Hz), 164.7 (t, *J* = 33 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −103.5 (s); **IR** (neat) ν 2251, 1770, 1408, 1263, 1242, 1143, 1103, 990, 843, 733, 680; **HRMS** (FI) calculated for $C_9H_5NO_2F_2$ $[M]^+$ 197.0288, found 197.0287; **Mp** 116−118 °C.

Ethyl (1-Cyanophenyl)(difluoro)acetate (6q)[222]



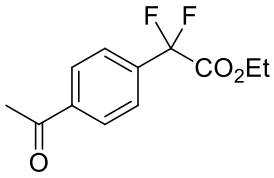
Synthesised from 3-iodobenzonitrile following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 9% EtOAc in PET 30/40) to give 1.50 g (67% yield) of **6q** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.0 Hz, 3H), 4.33 (q, *J* = 7.0 Hz, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.92 (s, 1H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 13.9, 63.7, 112.2 (t, *J* = 253 Hz), 113.3, 117.7, 129.4 (t, *J* = 7 Hz), 129.7, 129.9 (t, *J* = 6 Hz), 134.4 (t, *J* = 27 Hz), 134.5, 163.2 (t, *J* = 35 Hz); **^{19}F NMR** (376.6 MHz, $CDCl_3$) δ −104.4 (s).

(1-Cyanophenyl)(difluoro)acetic acid (3q)



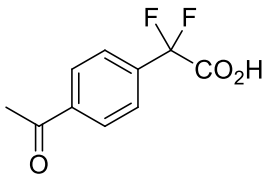
Synthesised from **6q** following GP 1-B (5.0 mmol scale), yielding 456 mg (46% yield) of **3q** as an off-white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.76 (t, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 8.05–8.07 (m, 2H); **^{13}C NMR** (125 MHz, $(CD_3)_2SO$) δ 112.2, 112.7 (t, *J* = 252 Hz), 117.8, 128.9 (t, *J* = 6 Hz), 130.1 (t, *J* = 6 Hz), 130.3, 134.4 (t, *J* = 27 Hz), 134.9, 164.2 (t, *J* = 33); **^{19}F NMR** (376.5 MHz, $(CD_3)_2SO$) δ –102.62 (s); **IR** (neat) ν 2251, 1769, 1281, 1234, 1175, 1142, 1108, 1091, 1019, 909, 836, 807, 714, 682; **HRMS** (FI) calculated for $C_9H_5NO_2F_2$ $[M]^+$ 197.0288, found 197.0286; **Mp** 105–106°C.

Ethyl difluoro(3-Acetophenone)acetate (6r)



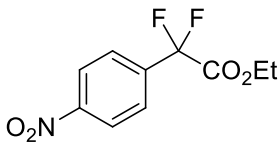
Synthesised from 1-(4-iodophenyl)ethanone following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 10% Et_2O in PET 30/40) to give 2.2 g (92% yield) of **6r** as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.0 Hz, 3H), 2.60 (s, 3H), 4.28 (q, *J* = 7.0 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 8.01 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.8, 26.7, 63.4, 112.9 (t, *J* = 252 Hz), 125.9 (t, *J* = 6 Hz), 128.5, 136.9 (t, *J* = 26 Hz), 139.0, 163.2 (t, *J* = 35 Hz), 197.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −104.5 (s); **IR** (neat) ν 2361, 1763, 1690, 1408, 1360, 1264, 1142, 1098, 1011, 993, 959, 833, 770, 752, 702, 628; **HRMS** (ESI) calculated for $C_{12}H_{12}O_3F_2$ $[M+Na]^+$ 265.0755, found 265.0697.

Difluoro(3-Acetophenone)acetic acid (3r)



Synthesised from **6r** following GP 1-B (9.0 mmol scale), yielding 1.02 g (53% yield) of **3r** as a pale red solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 2.63 (s, 3H), 7.73 (d, *J* = 8.0 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 27.4, 113.7 (t, *J* = 251.0 Hz), 126.1 (t, *J* = 6.0 Hz), 129.2, 137.1 (t, *J* = 25 Hz), 139.3, 165.0 (t, *J* = 33 Hz), 197.9; **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −103.8 (s); **IR** (neat) ν 2623, 1766, 1650, 1407, 1246, 1141, 1117, 1097, 994, 969, 845, 830, 778, 740, 689, 635; **HRMS** (ESI) calculated for $C_{10}H_8O_3F_2$ $[M-H]^-$ 213.0369, found 213.0452. **Mp** 129–131°C.

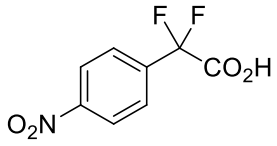
Ethyl difluoro-2-(4-nitrophenyl)acetate (6s)[222]



Synthesised from 4-nitro-1-iodobenzene following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 9% EtOAc in PET 30/40) to give 1.63 g (66% yield) of **6s** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.0 Hz, 3H), 4.35

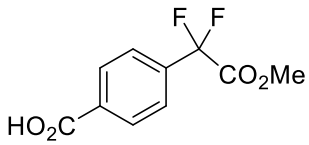
(q, *J* = 7.0 Hz, 2H), 7.84 (d, *J* = 9.0 Hz, 2H), 8.35 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 63.8, 112.4 (t, *J* = 254 Hz), 123.9, 127.0 (t, *J* = 6 Hz), 138.8 (t, *J* = 27 Hz), 149.6, 163.1 (t, *J* = 34 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −104.5 (s).

Difluoro(4-nitrophenyl)acetic acid (3s)*



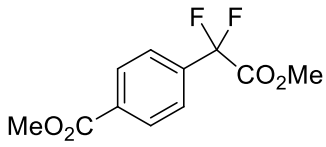
Synthesised from **6s** following GP 1-B (6.6 mmol scale), yielding 1.24 g (87% yield) of **3s** as a pale yellow solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.89 (d, *J* = 9.0 Hz, 2H), 8.38 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 113.2 (t, *J* = 252 Hz), 124.6, 127.5 (t, *J* = 6 Hz), 139.1 (t, *J* = 26 Hz), 149.7, 164.6 (t, *J* = 33 Hz); **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ −103.2 (s, 2F); **IR** (neat) ν 1755, 1525, 1348, 1291, 1262, 1153, 1122, 1106, 992, 865, 851, 706; **HRMS** (FI) calculated for $C_8H_5NO_4F_2$ $[M]^+$ 217.0187, found 217.0181; **Mp** 162−164 °C.

4-(2-Ethoxy-1,1-difluoro-2-oxoethyl)benzoic acid (6t)



Synthesised from 4-iodobenzoic acid following GP 1-A (5.0 mmol scale), yielding 1.20 g (98% yield) of the crude product as a white solid, which was taken through to the next step (esterification) without further purification. (Esterification was carried out to facilitate purification.) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 3H), 4.25 (q, *J* = 7.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 8.14 (d, *J* = 8.0 Hz, 2H), 9.9 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 63.5, 112.9 (t, *J* = 254 Hz), 125.9 (t, *J* = 6 Hz), 130.5, 134.0, 137.9 (t, *J* = 26 Hz), 136.6 (t, *J* = 34 Hz), 171.1; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –104.60 (s).

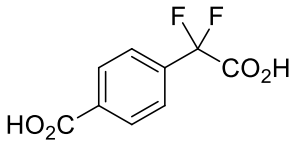
Methyl 4-(1,1-difluoro-2-methoxy-2-oxoethyl)benzoate



To a solution of 1.20 g crude 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoic acid **6t** (4.9 mmol, 1.0 eq) in 22 mL MeOH

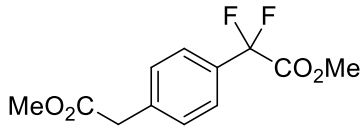
(0.2 M) was added dropwise 1.8 mL thionyl chloride (24.8 mmol, 5.0 eq) at 0 °C. The mixture was allowed to warm to rt while stirring overnight, after which it was concentrated *in vacuo* and the crude product was purified by silica flash column chromatography (eluent: 10% EtOAc in Hex) to give 725 mg (59% yield over 2 steps) of the title compound as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.88 (s, 3H), 7.62 (d, *J* = 8.5 Hz, 2H), 8.06 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 52.5, 53.8, 113.0 (t, *J* = 253 Hz), 125.7 (t, *J* = 6 Hz), 129.9, 132.7, 136.8 (t, *J* = 26 Hz), 164.2 (t, *J* = 35 Hz), 166.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −104.29 (s); **IR** (neat) ν 1770, 1729, 1281, 1193, 1002; **HRMS** (ESI) calculated for $C_{11}H_{10}F_2NaO_4$ $[M+Na]^+$ 267.0439, found 267.0442; **Mp** 40−42 °C.

4-[Carboxy(difluoro)methyl]benzoic acid (3t)



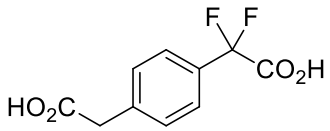
In a 50 mL round bottom flask, 600 mg methyl 4-(1,1-difluoro-2-methoxy-2-oxoethyl)benzoate (2.6 mmol, 1.0 eq) was added to a mixture of 8 mL MeOH (0.3 M) and 15 mL 1 M NaOH (15.0 mmol, 3.0 eq) and stirred for 5 h at rt. The reaction mixture was then poured into 1 M HCl to acidify to pH 1, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 418 mg (74% yield) of **3t** as a white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.72 (d, *J* = 8.5 Hz, 2H), 8.09 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $(CD_3)_2SO$) δ 113.2 (t, *J* = 253 Hz), 125.5 (t, *J* = 6 Hz), 129.8, 133.3, 136.6 (t, *J* = 26 Hz), 164.5 (t, *J* = 33 Hz), 166.5; **^{19}F NMR** (376.5 MHz, $(CD_3)_2SO$) δ –103.01 (s); **IR** (neat) ν 1721, 1581, 1425, 1309, 1281, 1264, 1148, 1108, 993, 955, 865, 729, 704; **HRMS** (ESI) calculated for $C_9H_5F_2O_4$ $[M–H]^–$ 215.0161, found 215.0162; **Mp** 240–241 °C.

Methyl difluoro[4-(2-methoxy-2-oxoethyl)phenyl]acetate



2-[4-(2-Ethoxy-1,1-difluoro-2-oxoethyl)phenyl]acetic acid (**6u**) was synthesised following GP 1-A (10.0 mmol). The crude reaction product was dissolved in 25 mL MeOH (0.4 M) and 2.6 mL thionyl chloride (50.0 mmol, 5.0 eq) was added dropwise at 0 °C. The mixture was allowed to warm to rt while stirring overnight, after which it was concentrated *in vacuo* and the crude product was purified by silica flash column chromatography (eluent: 10% EtOAc in Hex) to give 990 mg (37% yield over 2 steps) of the title compound as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.67 (s, 2H), 3.69 (s, 3H), 3.83 (s, 3H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, CDCl3) δ 40.7, 52.1, 53.5, 113.3 (t, *J* = 251 Hz), 125.7 (t, *J* = 7 Hz), 129.6, 131.5 (t, *J* = 26 Hz), 137.1, 164.5 (t, *J* = 36 Hz), 171.2; **^{19}F NMR** (377 MHz, CDCl3) δ −103.6 (s); **IR** (neat) ν 2360, 2170, 1735, 1487, 1435, 1253, 1158, 1009, 800; **HRMS** (ESI) calculated for $C_{12}H_{12}F_2NaO_4$ $[M+Na]^+$ 281.0596, found 281.0604.

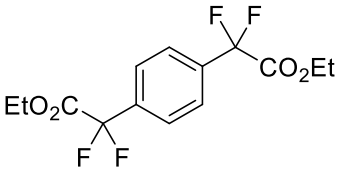
[4-(Carboxymethyl)phenyl](difluoro)acetic acid (3u)



In a 50 mL round bottom flask, 900 mg methyl difluoro[4-(2-methoxy-2-oxoethyl)phenyl]acetate (7.0 mmol, 1.0 eq) was added to a mixture of 10 mL MeOH and 15 mL 1 M NaOH and stirred at rt for 5 h. The reaction mixture was then poured into 1 M HCl to acidify to pH 1, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by trituration with PET 30/40 to give 700 mg (43% yield) of **3u** as a white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 3.61 (s, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 40.3, 113.6 (t, *J* = 249 Hz), 125.1 (t, *J* = 6 Hz), 130.0, 131.1 (t, *J* = 26 Hz), 165.0 (t, *J* = 34 Hz), 172.3; **^{19}F NMR** (377 MHz, $(CD_3)_2SO$) δ –102.2 (s); **IR** (neat) ν 2900, 2675, 1703, 1421, 1293, 1266, 1144, 1120, 994, 940, 829,

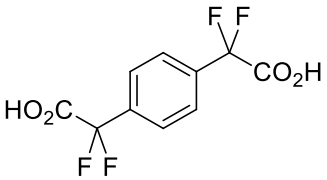
724, 670; **HRMS** (ESI) calculated for $C_{10}H_7F_2O_4$ $[M–H]^-$ 229.0318, found 229.0314; **Mp** 107–108 °C.

Diethyl 2,2'-benzene-1,3-Diylbis(difluoroacetate) (6v)



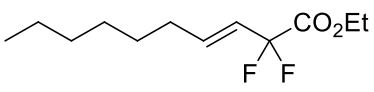
Synthesised from 1,4-diiodobenzene following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 5%–10% EtOAc in Hex) to give 1.40 g (44% yield) of **6v** as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.0 Hz, 6H), 4.31 (q, *J* = 7.0 Hz, 4H), 7.73 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.7, 77.0 (t, *J* = 32 Hz), 112.8 (t, *J* = 253 Hz), 126.0 (t, *J* = 6 Hz), 135.6 (t, *J* = 26 Hz), 163.6 (t, *J* = 35 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –104.29 (s); **IR** (neat) ν 1763, 1266, 1147, 1094, 1033, 1011, 989, 835, 736; **HRMS** (FI) calculated for $C_{14}H_{14}O_4F_4$ $[M]^+$ 322.0828, found 322.0815.

2,2'-Benzene-1,3-Diylbis(difluoroacetic acid) (3v)



Synthesised from **6v** following GP 1-B (4.0 mmol scale), yielding 1.0 g (94% yield) of **3v** an off-white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.77 (s, 4H); **^{13}C NMR** (100.6 MHz, $(CD_3)_2SO$) δ 113.5 (t, *J* = 251 Hz), 126.4 (t, *J* = 6 Hz), 135.9 (t, *J* = 25 Hz), 165.0 (t, *J* = 31 Hz); **^{19}F NMR** (376.6 MHz, $(CD_3)_2SO$) δ –102.9 (s); **IR** (neat) ν 1741, 1442, 1416, 1288, 1267, 1151, 1121, 1101, 990, 907, 849, 713; **HRMS** (ESI) calculated for $C_{10}H_4F_4NaO_4$ $[M–2H+Na]^-$ 286.9949, found 286.9945; **Mp** 199–202°C.

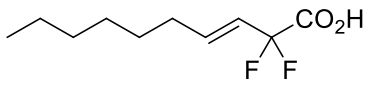
Ethyl (3*E*)-2,2-difluorodec-3-enoate (6w)



Synthesised from (1*E*)-1-iodooct-1-ene following GP 1-A (4.2 mmol scale). Purified by silica flash column chromatography (eluent: PET 30/40) to give 676 mg (69% yield) of **6w** as a yellow oil.

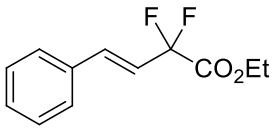
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.0 Hz, 3H), 1.18–1.25 (m, 6H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.32–1.39 (m, 2H), 2.03–2.11 (m, 2H), 4.25 (q, *J* = 7.0 Hz, 2H), 5.60 (dtt, *J* = 16.0 Hz, 11.0 Hz, 1.5 Hz, 1H), 6.21 (dtt, *J* = 16.0 Hz, 7.0 Hz, 2.5 Hz, 1H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 14.0, 14.1, 22.5, 28.1, 28.7, 31.6, 31.9, 62.9, 112.4 (t, *J* = 247 Hz), 120.9 (t, *J* = 25 Hz), 104.1 (t, *J* = 10 Hz), 164.2 (t, *J* = 35 Hz); **^{19}F NMR** (376.6 MHz, $CDCl_3$) δ –102.94 (dq, *J* = 11.0 Hz, 2.5 Hz); **IR** (neat) ν 1767, 1288, 1227, 1077, 968; **HRMS** (ESI) calculated for $C_{12}H_{20}F_2NaO_2$ $[M+Na]^+$ 257.1324, found 257.1331.

(3*E*)-2,2-Difluorodec-3-enoic acid (3w)



Synthesised from **6w** following GP 1-B (2.8 mmol scale), yielding 452 mg (78% yield) of **3w** as a brown oil. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 0.81 (t, *J* = 7.0 Hz, 3H), 1.15-1.30 (m, 6H), 1.33–1.40 (m, 2H), 2.05-2.12 (m, 2H), 5.61 (dtt, *J* = 15.5 Hz, 11.0 Hz, 1.5 Hz, 1H), 6.28 (dtt, *J* = 15.5 Hz, 7.0 Hz, 2.5 Hz, 1H), 10.67 (brs, 1H, CO_2H); **^{13}C NMR** (100.6 MHz, $(CD_3)_2SO$) δ 14.0, 22.5, 28.0, 28.7, 31.5, 31.9, 112.1 (t, *J* = 250 Hz), 120.1 (t, *J* = 25 Hz), 141.2 (t, *J* = 9 Hz), 169.2 (t, *J* = 36 Hz); **^{19}F NMR** (376.6 MHz, $(CD_3)_2SO$) δ −103.99 (d, *J* = 11.0 Hz); **IR** (neat) ν 2929, 2859, 2361, 1750, 1213, 1085, 967; **HRMS** (ESI) calculated for $C_{10}H_{15}F_2O_2$ $[M–H]^–$ 205.1046, found 205.1039.

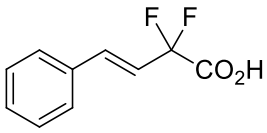
Ethyl (3*E*)-2,2-difluoro-4-phenylbut-3-enoate (6x)[235]



Synthesised from β-bromostyrene (mixture of isomers) following GP 1-A (10.0 mmol scale). Purified by silica flash column chromatography (eluent: 10% Et_2O in PET 30/40) to give 1.87 g (83% yield) of **6x** as a colourless oil in a 17:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.04 (t, *J* = 7.0 Hz, 3H, *Z*), 1.28 (t, *J* = 7.0 Hz, 3H, *E*), 3.94 (q, *J* = 7.0 Hz, 2H, *Z*), 4.26 (q, *J* = 7.0 Hz, 2H, *E*), 5.79 (q, *J* = 13.0 Hz, 1H, *Z*), 6.22 (dt, *J* = 16.0 Hz, 11.5 Hz, 1H, *E*), 6.87 (dt, *J* = 13.0 Hz, 1.5 Hz,

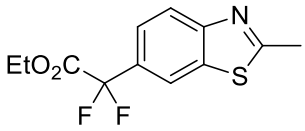
1H, *Z*), 7.00 (dt, *J* = 16.0 Hz, 2.5 Hz, 1H, *E*), 7.21-7.32 (m, 3H, *E*, *Z*), 7.34–7.39 (m, 2H, *E*, *Z*); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 14.0 (*E*), 15.3 (*Z*), 63.1 (*E*), 65.9 (*Z*), 112.8 (t, *J* = 250 Hz, *E*), 118.9 (t, *J* = 25 Hz, *E*), 122.0 (t, *J* = 28 Hz, *Z*), 127.5 (*E*), 128.2 (*Z*), 128.7 (*Z*), 128.9 (*E*), 128.9 (*Z*), 129.7 (*E*), 134.1 (*E*), 136.9 (t, *J* = 9 Hz, *E*), 138.8 (t, *J* = 9 Hz, *Z*), 163.9 (t, *J* = 35 Hz, *E*); **^{19}F NMR** (376.6 MHz, $CDCl_3$) δ –103.20 (dd, *J* = 11.5 Hz, 2.0 Hz).

(3*E*)-2,2-Difluoro-4-phenylbut-3-enoic acid (3x)[235]



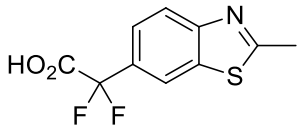
Synthesised from **6x** following GP 1-B (8.3 mmol scale), yielding 871 mg (53% yield) of **3x** as a white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 6.64 (dt, *J* = 16.5 Hz, 11.5 Hz, 1H), 7.09 (dt, *J* = 16.5 Hz, 2.5 Hz, 1H), 7.36–7.43 (m, 3H), 7.65 (dd, *J* = 7.5 Hz, 2.0 Hz, 2H); **^{13}C NMR** (100.6 MHz, $(CD_3)_2SO$) δ 113.7 (t, *J* = 247 Hz), 120.0 (t, *J* = 25 Hz), 128.0, 129.3, 130.0, 134.3, 136.4 (t, *J* = 10 Hz), 165.2 (t, *J* = 34 Hz); **^{19}F NMR** (376.6 MHz, $(CD_3)_2SO$) δ –101.85 (d, *J* = 11.5 Hz).

Ethyl difluoro(2-methyl-1,1-benzothiazol-6-yl)acetate (6y)



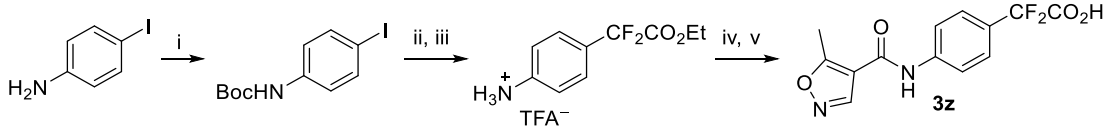
Synthesised from 6-iodo-2-methyl-1,3-benzothiazole following GP 1-A (2.0 mmol scale). Purified by silica flash column chromatography (eluent: 30% EtOAc in Hex) to give 205 mg (38% yield) of **6y** as a colourless oil. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 1.23 (t, *J* = 7.0 Hz, 3H), 2.80 (s, 3H), 4.24 (q, *J* = 7.0 Hz, 2H), 7.60 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 8.04 (d, *J* = 1.0 Hz, 1H); **^{13}C NMR** (100.6 MHz, $(CD_3)_2SO$) δ 13.9, 20.3, 63.3, 113.4 (t, *J* = 253 Hz), 119.2 (t, *J* = 7 Hz), 122.6, 123.3 (t, *J* = 7 Hz), 129.3 (t, *J* = 26 Hz), 135.9, 155.0, 164.1 (t, *J* = 35 Hz), 169.8; **^{19}F NMR** (376.6 MHz, $(CD_3)_2SO$) δ –102.69 (s); **HRMS** (FI) calculated for $C_{12}H_{11}F_2NO_2S$ $[M]^+$ 271.0479, found 271.0479.

Difluoro(2-methyl-1,1-Benzothiazol-6-yl)acetic acid (3y)



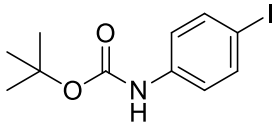
Synthesised from **6y** following GP 1-B (0.5 mmol scale), yielding 124 mg (89% yield) of **3y** as a yellow solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 2.84 (s, 3H), 7.65 (dd, *J* = 8.5 Hz, 21.5 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 8.38 (d, *J* = 1.5 Hz, 1H); **^{13}C NMR** (100.6 MHz, $(CD_3)_2SO$) δ 20.4, 113.5 (t, *J* = 252 Hz), 120.2 (t, *J* = 7 Hz), 122.7, 123.4 (t, *J* = 5 Hz), 129.4 (t, *J* = 25 Hz), 136.1, 155.0, 165.7, 171.0; **^{19}F NMR** (376.6 MHz, $(CD_3)_2SO$) δ –101.07 (s); **IR** (neat) ν 1746, 1503, 1461, 1407, 1373, 1326, 1294, 1255, 1241, 1188, 1145, 1106, 1061, 1011, 884, 826, 781, 747, 711, 679; **HRMS** (FI) calculated for $C_{10}H_7F_2NO_2S$ $[M]^+$ 243.0166, found 243.0166; **Mp** 194–195 °C.

6.2.1.1.1 Synthesis of Leflunomide precursor 3z



Conditions: (i) Boc_2O (2.0 eq), NEt_3/MeOH, 50 °C, 18 h; (ii) Cu (2.6 eq), $BrCF_2CO_2Et$ (1.0 eq), DMSO, 60°C, 16 h; (iii) TFA (6.0 eq), DCM, rt, 3 h; (iv) ArC(O)Cl (0.97 eq), $NaHCO_3$ (2.0 eq), DMA (0.21 eq), Toluene, 40°C to reflux, 4 h; (v) K_2CO_3, H_2O/MeOH, rt, 2 h.

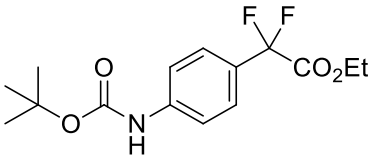
***tert*-Butyl (4-iodophenyl)carbamate[236]**



A solution of 4.4 g 4-iodoaniline (20.0 mmol, 1.0 eq) and 8.7 g di-*tert*-butyl dicarbonate (40.0 mmol, 2.0 eq) in 33 mL 10% (v/v) NEt_3/MeOH (0.6 M) was stirred at 50 °C for 18 h, after which the mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with water and dried over $MgSO_4$. The crude product was purified by silica flash column chromatography (eluent: DCM/Hexane 1:2) to give 5.0 g (78% yield) of the title compound as a white crystalline solid. **^{1}H NMR** (400 MHz, $CDCl_3$); δ 1.43 (s, 9H), 6.43 (brs, 1H, N*H*), 7.07 (d, *J* = 9.0 Hz,

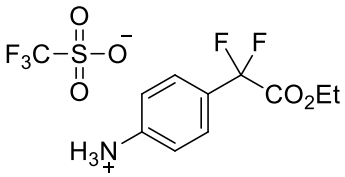
2H), 7.49 (dt, *J* = 9.0 Hz, 2.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$); δ 28.3, 80.9, 85.7, 120.4, 137.8, 138.2, 152.5; **HRMS** (FI) calculated for $C_{11}H_{14}INNaO_2$ $[M+Na]^+$ 341.9961, found 341.9962.

Ethyl {4-[(*tert*-butoxycarbonyl)amino]phenyl}(difluoro)acetate



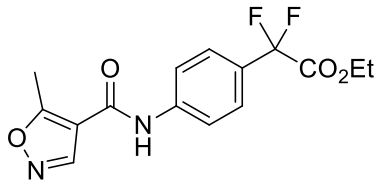
Synthesised from *tert*-butyl (4-iodophenyl)carbamate following GP 1-A (15.0 mmol scale). Purified by silica flash column chromatography (eluent: 5% Et_2O in PET 30/40) to give 3.14 g (66% yield) of the title compound as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.0 Hz, 3H), 1.50 (s, 9H), 4.28 (q, J = 7.0 Hz, 2H), 7.08 (brs, 1H, N*H*), 7.46–7.52 (m, 4H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 13.8, 28.2, 63.1, 81.0, 113.4 (t, *J* = 252 Hz), 118.1, 126.3 (t, *J* = 6 Hz), 126.8 (t, J = 26 Hz), 141.2 (t, J = 2 Hz), 152.6, 164.4 (t, *J* = 36 Hz); **^{19}F NMR** (376.6 MHz, $CDCl_3$) δ –10.311 (s); **IR** (neat) ν 1764, 1704, 1615, 1598, 1526, 1410, 1369, 1318, 1269, 1232, 1154, 1099, 1053, 1029, 991, 839, 763, 659; **HRMS** (EI) calculated for $C_{15}H_{19}F_2NNaO_4$ $[M+Na]^+$ 338.1174, found 338.1161.

Ethyl (3-aminophenyl)(difluoro)acetate triflate salt



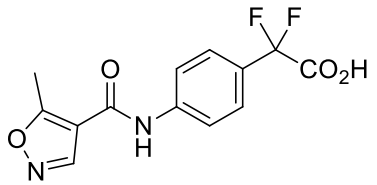
3.1 g Ethyl {4-[(*tert*-butoxycarbonyl)amino]phenyl}(difluoro)acetate (9.8 mmol, 1.0 eq) and 4.6 mL TFA (60.0 mmol, 6.0 eq) were stirred in 4.6 mL DCM (2 M) at rt for 3 h, after which the solvent was evaporated to yield 3.2 g (99% yield) of the product as a brown oil which was used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.0 Hz, 3H), 4.31 (q, *J* = 7.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 9.87 (brs, 3H, N*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$); δ 13.6, 63.9, 112.5 (t, *J* = 251 Hz), 123.2, 127.6 (t, *J* = 6 Hz), 132.5, 134.0 (t, *J* = 26 Hz), 161.3 (q, *J* = 40 Hz, *C*$F_3SO_3^-$), 163.9 (t, *J* = 35 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$); δ –104.13 (s, 2F), –67.17 (s, 3F).

Ethyl difluoro(4-{[(5-methyl-1,2-oxazol-4-yl)carbonyl]amino}phenyl)acetate (6z)



6z was synthesised following a literature procedure.[237] 1.2 g 5-Methyl-1,2-oxazole-3-Carboxylic acid (9.4 mmol) was refluxed at 80 °C in 7.0 mL thionyl chloride (9.4 mmol) for 3 h, after which the solvent was evaporated *in vacuo*, yielding the correspondent acid chloride as a dark yellow oil. 3.2 g ethyl (3-aminophenyl)(difluoro)acetate triflate salt (9.7 mmol, 1.0 eq) was dissolved in a mixture of 1.6 g $NaHCO_3$ (19.4 mmol, 2.0 eq), 0.2 mL *N*,*N*-dimethylacetamide (2.0 mmol, 0.21 eq) and 20 mL toluene (0.5 M). The mixture was warmed to 40°C and 1.4 g of the crude 5-methyl-1,2-oxazole-3-carbonyl chloride (9.4 mmol, 0.97 eq) was added dropwise over 10 minutes. The mixture was stirred at this temperature for another 3 h, and then heated to reflux for 1 h. The hot mixture was washed with water and the organic phase was allowed to cool to rt which caused the product to precipitate as a white solid (2.58 mg, 82 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 3H), 2.69 (s, 3H), 4.23 (q, J = 7.0 Hz, 2H), 7.50 (dd, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.92 (brs, 1H, N*H*), 8.46 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 12.6, 13.9, 63.3, 111.8, 113.2 (t, *J* = 252 Hz), 120.2, 126.6 (t, *J* = 6 Hz), 128.8, 139.8, 147.6, 159.5, 174.1; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −103.42 – −103.39 (m); **IR** (neat) ν 1748, 1683, 1607, 1536, 1320, 1306, 1272, 1249, 1142, 1088, 1027, 1006, 841, 829, 761, 706, 644; **HRMS** (ESI) calculated for $C_{15}H_{14}F_2N_2NaO_4$ $[M+Na]^+$ 347.0814, found 347.0796; **Mp** 105–106°C.

Difluoro(4-{[(5-methyl-1,2-oxazol-4-yl)carbonyl]amino}phenyl)acetic acid (3z)

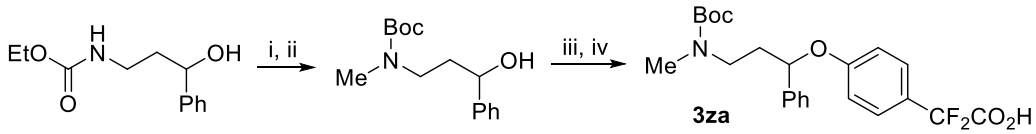


Synthesised from **6z** following GP 1-B (2.1 mmol scale), yielding 479 mg (77% yield) of **3z** as an off-white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 2.29 (s, 3H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 10.6 (brs, 1H, N*H*); (Note: isoxazole H not

observed); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 23.4, 81.3, 114.0 (t, *J* = 252 Hz), 120.6 (t, *J* = 3 Hz), 121.8, 126.2 (t, *J* = 6 Hz), 128.4 (t, *J* = 26 Hz), 140.6, 165.5 (t, *J* = 35 Hz), 167.0, 187.6; **^{19}F NMR** (376.5 MHz, $(CD_3)_2SO$) δ –101.80 (s); **IR** (neat) ν 2225, 1676, 1642, 1599, 1552, 1418, 1245, 1181, 984, 779, 727, 660; **HRMS** (EI) calculated for $C_{13}H_{14}F_2N_3O_4$ $[M+NH_4]^+$ 314.0952, found 314.0940; **Mp** 130–133°C.

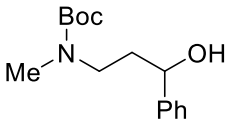
6.2.1.1.2 Synthesis of Fluoxetine precursor 3za

NB. The synthesis of Fluoxetine precursor **3za** was carried out by Dr. S. Mizuta.



Conditions: (i) LAH (2.3 eq), THF, reflux, 1 h; (ii) Boc_2O (1.0 eq), NEt_3/MeOH, reflux, 6 h; (iii) ethyl difluoro(4-hydroxyphenyl)acetate (1.2 eq), DIAD (1.5 eq), PPh_3 (1.5 eq), Et_2O, rt, 1 h; (iv) K_2CO_3, MeOH, rt, 2 h..

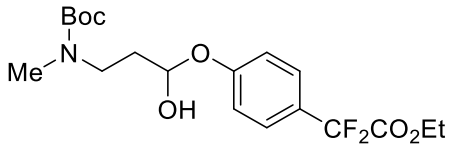
***tert*-Butyl (3-hydroxy-3-phenylpropyl)methylcarbamate**



Synthesised following a literature procedure:[238] To a solution of 112 mg LiAlH (3.0 mmol, 2.3 eq) in 5 mL dry THF (0.26 M) under N_2 at rt was added dropwise a solution of 300 mg *N*-(ethoxycarbonyl)-1-amino-1-phenyl-1-propanol (1.3 mmol, 1.0 eq) in 10 mL dry THF (0.13 M). The mixture was heated to reflux and stirred for 1 h, after which it was cooled to rt and 1 mL EtOAc was slowly added. The resultant mixture was filtered and the residue was washed with EtOAc. The combined filtrates were evaporated under reduced pressure. The residue was added to a 50 mL three-necked flask, to which was added 10 mL MeOH (0.13 M), 308 µL di-*tert*-butyl carbonate (1.3 mmol, 1.0 eq) and 37 µL Et_3N (0.13 mmol. 0.1 eq). The mixture was heated to reflux and stirred for 6 h, after which the reaction was was cooled to rt. The solvent was evaporated and the residue was purified by silica flash column chromatography (eluent:

30% EtOAc in Hex) to afford 113 mg (32 % yield) of the title compound as a pale yellow oil. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.69–2.05 (m, 2H), 2.89 (s, 3H), 3.00–3.16 (m, 1H), 3.68–4.03 (m, 1H), 4.62 (dd, *J* = 9.5 Hz, 3.0 Hz, 1H), 7.28–7.41 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 28.4, 34.3, 37.2, 45.1, 69.9, 80.1, 125. 6, 127.0, 128.3, 144.1, 157.2; **IR** (neat) ν 3419, 2976, 1667, 1482, 1452, 1394, 1366, 1248, 1166, 1061, 880, 670; **HRMS** (ESI) calculated for $C_{15}H_{23}N_2NaO_3$ $[M+Na]^+$ 288.1566, found 288.1570.

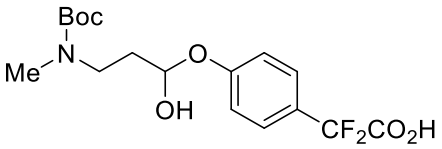
Ethyl (4-{3-[(*tert*-butoxycarbonyl)(methyl)amino]-1-phenylpropoxy}phenyl) (difluoro)acetate (6za)



Synthesised following a literature procedure:[238] 44.5 µL diisopropyl azodicarboxylate (0.23 mmol, 1.5 eq) in 0.1 mL dry Et_2O was slowly added to a solution of 59.3 mg triphenyl phosphine (0.23 mmol, 1.5 eq) in 0.6 mL dry Et_2O at 0 ˚C to form a betaine complex. After 20 min at 0 ˚C 38.9 mg ethyl difluoro(4-hydroxyphenyl)acetate (0.18 mmol, 1.2 eq) in 0.2 mL dry Et_2O was added. To the resultant mixture was added 40.0 mg *tert*-butyl (3-hydroxy-3-phenylpropyl)methylcarbamate (0.15 mmol, 1.0 eq) in 0.5 mL dry Et_2O and the reaction was allowed to warm to rt. After completion of the reaction as indicated by TLC (1 h) the solvent was evaporated and the residue was purified by silica flash column chromatography (eluent: 15% EtOAc in Hex) to afford 34.6 mg (50% yield) of the title compound as colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.0 Hz, 3H), 1.38 (brs, 9H), 2.03–2.23 (m, 2H), 2.85 (s, 3H), 3.27–3.53 (m, 2H), 4.26 (q, *J* = 7.0 Hz, 2H), 5.15 (dd, *J* = 8.5 Hz, 3.5 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 7.29–7.35 (m, 5H), 7.42 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.9, 28.3, 34.5, 37.2, 45.7, 62.9, 78.2, 79.4, 113.4 (t, *J* = 250 Hz), 115.7, 124.9 (t, *J* = 27 Hz), 125.6, 126.9 (t, *J* = 6 Hz), 127.8, 128.8, 141.0, 155.7, 160.0, 164.4 (t, *J* = 36 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −102.5 (s, 2F); **IR** (neat) ν 2978, 1764, 1691, 1611, 1512,

1454, 1393, 1366, 1245, 1175, 1142, 1098, 1024, 987; **HRMS** (ESI) calculated for $C_{25}H_{31}F_2NNaO_5$ $[M+Na]^+$ 486.2055, found 486.2063.

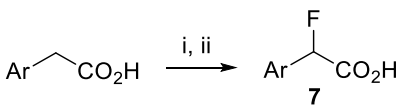
(4-{3-[(tert-Butoxycarbonyl)(methyl)amino]-1-phenylpropoxy}phenyl)(difluoro) acetic acid (3za)



Synthesised following GP 1-B (0.17 mmol scale) to afford 57 mg (77% yield) of the title compound as a white solid. **^{1}H NMR** (500 MHz, toluene-d8, 367 K) δ 1.29 (s, 9H), 1.88–1.99 (m, 1H), 2.07–2.09 (m, 1H), 2.56 (s, 3H), 3.15–3.30 (m, 2H), 5.09 (dd, *J* = 8.0 Hz, 4.0 Hz, 1H), 6.77 (d, *J* = 8.5 Hz,2 H), 7.06–7.10 (m, 3H), 7.20 (d, *J* = 7.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 8.45 (brs, CO_2H); **^{13}C NMR** (125 MHz, toluene-d8, 367K) δ 28.6, 34.5, 37.3, 46.3, 78.7, 80.5, 116.53, 126.3, 127.7 (t, *J* = 6 Hz), 129.1, 141.8, 156.7, 160.8, 165.6 (t, *J* = 35 Hz), (Note: The CF_2 carbon was not observed); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –103.5 (m, 2F); **IR** (neat) ν 1760, 1612, 1152, 1243, 1368, 1243, 1176, 1106, 989, 835, 757, 735, 701; **HRMS** calculated for $C_{23}H_{27}F_2NNaO_5$ $[M+Na]^+$ 458.1729, found 458.1750; **Mp** 32 °C.

6.2.1.2 Synthesis of α-monofluoroaryl acetic acids 7

NB. The synthesis of the α-monofluoroaryl acetic acids (with the exception of **7d**) was carried out by Dr. J. Wolstenhulme, as indicated by an asterix (*).



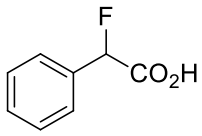
7

Conditions: (i) TBSCl (2.3 eq), LiHMDS (2.2 eq), THF, rt, 16 h; (ii) Selectfluor (1.3 eq), MeCN, rt, 15 min.

General Procedure 1-C: Synthesis of α-monofluoroaryl acetic acids[239]

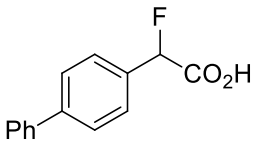
To a solution of arylacetic acid (5.0 mmol, 1.0 eq) and 1.73 g TBSCl (11.5 mmol, 2.3 eq) in 10 mL THF (0.5 M) at 0 °C was added 11.0 mL LiHMDS (1 M solution in THF, 11.0 mmol, 2.2 eq) slowly. The reaction was stirred overnight, during which it was allowed to warm to room temperature, before concentrating *in vacuo*. The crude bis-silylketeneacetal was dissolved in 25 mL hexane and the LiCl was filtered off and washed with hexane before evaporating the combined solution under reduced pressure. The residue was redissolved in 10 mL acetonitrile and added to a solution of 2.30 g Selectfluor (6.5 mmol, 1.3 eq) in 20 mL acetonitrile (0.3 M) at rt. After stirring for 15 minutes the reaction mixture was poured into a 1 M HCl solution (50 mL) and extracted into ether. The combined ether layers were extracted with 1 M NaOH and the combined basic phases were subsequently washed with ether. The organic extracts were discarded and the aqueous phase was acidified with 6 M HCl to pH 1. The acidic phase was then extracted with ether and the combined ether layers were dried over $MgSO_4$ and evaporated under reduced pressure to afford the corresponding α-monofluoroaryl acetic acids which were triturated with PET 30/40 for purification purposes.

Fluoro(phenyl)acetic acid (7a)[240] *



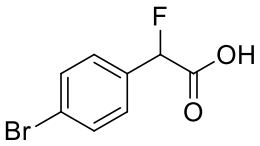
Synthesised from phenylacetic acid following GP 1-C, yielding 650 mg (84% yield) of **7a** as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.65 (d, *J* = 47.5 Hz, 1H), 7.22–7.27 (m, 3H), 7.28–7.33 (m, 2H), 9.52 (br. s, 1H, CO_2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 88.8 (d, *J* = 187 Hz), 126.7 (d, *J* = 6 Hz), 128.9, 130.0 (d, *J* = 2 Hz), 133.4 (d, *J* = 21 Hz), 174.2 (d, *J* = 28 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −180.9 (d, *J* = 47.5 Hz).

Biphenyl-4-yl(fluoro)acetic acid (7b)[241] *



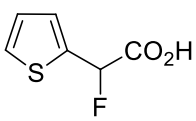
Synthesised from biphenyl-4-ylacetic acid following GP 1-C, yielding 926 mg (80% yield) of **7b** as a pale yellow solid. **^{1}H NMR** (400 MHz, CD_3CN) δ 5.74 (d, *J* = 47.5 Hz, 1H), 7.21 (tt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.26–7.32 (m, 2H), 7.36 (dd, *J* = 8.0 Hz, 1.5 Hz, 2H), 7.46–7.50 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 9.56 (brs, 1H, CO_2H); **^{13}C NMR** (100 MHz, CD_3CN) δ 89.3 (d, *J* = 182 Hz), 127.6, 128.0, 128.1 (d, *J* = 6 Hz), 128.5, 129.5, 134.3 (d, *J* = 20 Hz), 140.5, 142.9, 169.4 (d, *J* = 28 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −177.7 (d, *J* = 47.5 Hz).

Fluoro(3-Bromo)acetic acid (7c)*



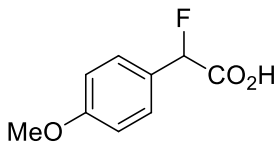
Synthesised from (4-bromophenyl)acetic acid following GP 1-C, yielding 959 mg (82% yield) of **7c** as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.81 (d, *J* = 47.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 9.82 (brs, 1H, CO_2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 88.1 (d, *J* = 188 Hz), 124.3 (d, *J* = 3 Hz), 128.2 (d, *J* = 6 Hz), 132.2, 132.3 (d, *J* = 21 Hz), 173.6 (d, *J* = 28 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −182.4 (d, *J* = 47.0 Hz); **IR** (neat) ν 3516, 1702, 1324, 1263, 1143, 1125, 1102, 840, 739, 697; **HRMS** (ESI) calculated for $C_{14}H_9F_2O_2$ $[M-H]^-$ 247.0576, found 247.0577; **Mp** 114−117 °C.

Fluoro(thiophen-2-yl)acetic acid (7d)



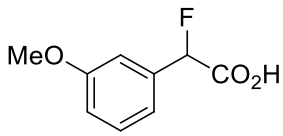
Synthesised from thiophen-2-ylacetic acid following GP 1-C. Product is not benchtop stable and decomposes to black sludge within minutes of workup.

Fluoro(4-methoxyphenyl)acetic acid (7e)*



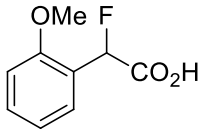
Synthesised from (4-methoxyphenyl)acetic acid following GP 1-C. Product is not benchtop stable and decomposes to black sludge within minutes of workup.

Fluoro(3-methoxyphenyl)acetic acid (7f)[242] *



Synthesised from (3-methoxyphenyl)acetic acid following GP 1-C, yielding 800 mg (87% yield) of **7f** as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.82 (d, *J* = 47.5 Hz, 1H), 6.96–7.01 (m, 1H), 7.05 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 10.8 (brs, 1H, CO_2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.4, 88.7 (d, *J* = 187 Hz), 111.9 (d, *J* = 7 Hz), 115.7 (d, *J* = 2 Hz), 118.9 (d, *J* = 6 Hz), 130.0, 134.8 (d, *J* = 21 Hz), 159.9, 173.9 (d, *J* = 28 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −181.2 (d, *J* = 47.5 Hz).

Fluoro(2-methoxyphenyl)acetic acid (7g)*



Synthesised from (2-methoxyphenyl)acetic acid following GP 1-C, yielding **7g** as a pale yellow solid. The title compound is not benchtop stable, and rapidly decomposes to black sludge within a few hours after work-up.

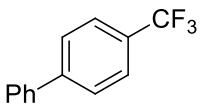
6.2.1.3 Fluorodecarboxylation

General Procedure 1-D: Silver catalysed fluorodecarboxylation[47]

To a Schlenck tube containing a magnetic stirrer bar were added the carboxylic acid (0.2 mmol, 1.0 eq), 142 mg Selectfluor (0.4 mmol, 2.0 eq) and 14 mg silver nitrate (0.08 mmol, 20 mol%). The Schlenck tube was closed with a rubber septum, equipped with a nitrogen balloon, and the system was purged with nitrogen. 4 mL acetone/H_2O (1:1 v/v,

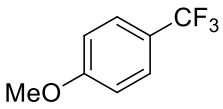
0.05 M) was added and the reaction was stirred at 55 °C for 1 h, before diluting with water. The reaction mixture was extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo*. Crude ^{19}F NMR yields were determined by integration of the product peak(s) relative to 1.0 eq (0.2 mmol, 0.21 µL) 1-fluoro-3-nitrobenzene which was added to the reaction after workup as the internal standard. The crude mixture was purified by silica flash column chromatography using the indicated solvent systems.

4-(Trifluoromethyl)biphenyl (4a)[243]



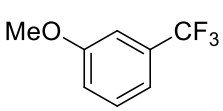
Synthesised from **3a** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: PET 30/40) to give 38 mg (86% yield) of **4a** as a white solid. Increasing the scale to 2.0 mmol afforded 378 mg (85% yield) of **4a**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27–7.31 (m, 1H), 7.36–7.40 (m, 2H), 7.49–7.52 (m, 2H), 7.60 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 124.4 (q, *J* = 273 Hz), 125.7 (q, *J* = 4 Hz), 127.3, 127.4, 128.2, 129.0, 129.4 (q, *J* = 32 Hz), 139.8, 144.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.4 (s).

1-Methoxy-4-(trifluoromethyl)benzene (4b)[244]



Synthesised from **3b** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: PET 30/40) to give 29 mg (82% yield) of **4b** as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 54.4, 112.9, 123.4 (q. *J* = 270 Hz), 121.8 (q, *J* = 33 Hz), 125.8 (q, *J* = 4 Hz), 161.0; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −61.47 (s).

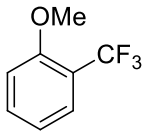
1-Methoxy-3-(trifluoromethyl)benzene (4c)[244]



Synthesised from **3c** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: PET 30/40 to 10% Et_2O in PET)

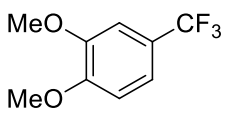
to give 30 mg (85% yield) of **4c** as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.05 (brs, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.4, 110.6 (q, *J* = 4 Hz), 117.4 (q, *J* = 4 Hz), 117.6, 124.0 (q, *J* = 273 Hz), 129.9, 131.8 (q, *J* = 33 Hz), 159.7; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.7 (s).

1-Methoxy-2-(trifluoromethyl)benzene (4d)[113]



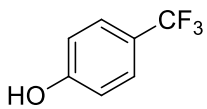
Synthesised from **3d** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: PET 30/40 to 10% Et_2O in PET) to give 31 mg (88% yield) of **4d** as a yellow oil. Increasing the scale to 2.0 mmol afforded 314 mg (89% yield) of **4d**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 6.82-6.86 (m, 2H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.7, 111.9, 118.7 (q, *J* = 31 Hz), 120.0, 123.9 (q, *J* = 272 Hz), 127.0 (q, *J* = 6 Hz), 133.4, 157.5 (q, *J* = 2 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.4 (s).

1-Methoxy-2-(trifluoromethyl)benzene (4e)



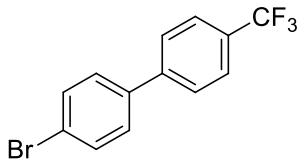
The reaction of **3e** following GP 1-D did not afford **4e**. Competitive fluorination of the aromatic ring was observed instead.

4-(Trifluoromethyl)phenol (4f)



Carboxylic acid **3f** was unstable towards decomposition, so GP 1-D could not be carried out.

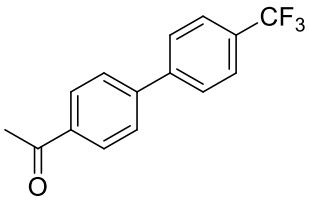
3-Bromo-4'-(trifluoromethyl)biphenyl (4g)[243]



Synthesised from **3g** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: PET 30/40) to give

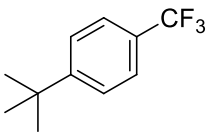
50 mg (83% yield) of **4g** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (dt, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.51 (dt, J = 8.5 Hz, 2.0 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 122.6, 124.2 (q, *J* = 273 Hz), 125.9 (q, *J* = 4.0 Hz), 127.2, 128.8, 129.7 (q, *J* = 32 Hz), 132.2, 138.7, 143.5; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.46 (s).

1-[4'-(trifluoromethyl)biphenyl-4-yl]ethanone (4h)



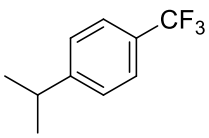
Synthesised from **3h** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: 50% Et_2O in hexane) to give 44 mg (83% yield) of **4h** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.57 (s, 3H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.64 (s, 4H), 7.98 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 25.7, 123.1 (q, *J* = 272 Hz), 124.9 (q, *J* = 4 Hz), 126.4, 126.6, 128.0, 129.2 (q, *J* = 33 Hz), 135.5, 142.3, 143.1, 196.6; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.52 (s); **IR** (neat) ν 1685, 1326, 1159, 1129, 1071, 823, 729; **HRMS** (FI) calculated for $C_{15}H_{11}F_3O$ $[M]^+$ 264.0762, found 264.0766; **Mp** 95–96°C.

1-*tert*-Butyl-4-(trifluoromethyl)benzene (4i)[244]



Synthesised from **3i** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: PET 30/40) to give 31 mg (77% yield) of **4i** as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 31.1, 35.0, 124.4 (q, *J* = 272 Hz), 125.0 (q, *J* = 4 Hz), 125.6, 127.7 (q, *J* = 33 Hz), 155.2; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.30 (s).

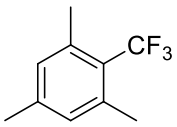
1-Isopropyl-4-(trifluoromethyl)benzene (4j)



Synthesised from **3j** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: PET 30/40) to give 25 mg

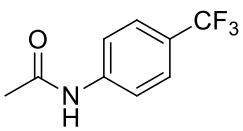
(66% yield) of **4j** as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.20 (s, 3H), 2.89 (sept, *J* = 7.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 23.7, 34.1, 124.4 (q, *J* = 271 Hz), 125.3 (q, *J* = 4 Hz), 126.7, 128.2, 152.9; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.3 (s); **IR** (neat) ν 2923, 2361, 2341, 1261, 1019, 800, 669; **HRMS** (ESI) calculated for $C_{13}H_{16}O_2F_2Na$ $[M+Na]^+$ 265.1011, found 265.1007.

1,2,4-Trimethyl-5-(trifluoromethyl)benzene (4k)[243]



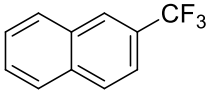
Synthesised from **3k** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: 5% Et_2O in PET 30/40) to give 21 mg (56% yield) of **4k** as a yellow oil. (Note: **4k** was obtained in 93% ^{19}F NMR yield. The loss of product upon isolation is due to volatility.) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.36 (q, *J* = 3.5 Hz, 6H), 6.82 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 20.6, 21.1 (q, *J* = 4 Hz), 124.6 (q, *J* = 29 Hz), 126.0 (q, *J* = 276 Hz), 130.7, 137.1 (q, *J* = 2 Hz), 140.7; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −53.7 (qn, *J* = 3.5 Hz).

***N*-[4-(Trifluoromethyl)phenyl]acetamide (4l)[240]**



Synthesised from **3l** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: 30%-50% EtOAc in PET 30/40) to give 35 mg (86% yield) of **4l** as an off-white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 24.7, 119.3, 124.1 (q, *J* = 272 Hz), 126.0 (q, *J* = 33 Hz), 226.3 (q, *J* = 4 Hz), 140.9, 168.7; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.1 (s).

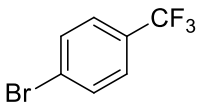
2-(Trifluoromethyl)naphthalene (4m)[244]



Synthesised from **3m** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: PET 30/40) to give 20 mg (51% yield) of **4m** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48-7.58 (m, 3H), 7.81-

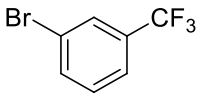
7.88 (m, 3H), 8.07 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 121.4 (q, *J* = 3 Hz), 124.4 (q, *J* = 270 H), 125.7 (q, *J* = 5 Hz), 127.2, 127.8 (q, *J* = 27 Hz), 127.9, 128.0, 128.8, 129.0, 132.2, 134.6; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.2 (s).

1-Bromo-4-(trifluoromethyl)benzene (4n)[240]



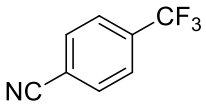
Synthesised from **3n** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: PET 30/40) to give 15 mg (33% yield) of **4n** as a white solid. The reaction with 4.0 eq Selectfluor in H_2O/acetone 1:4 (otherwise following GP 1-D) afforded 22 mg of **4n** (49% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 123.8 (q, *J* = 273 Hz), 125.9 (q, *J* = 4 Hz), 126.4, 129.5 (q, *J* = 34 Hz), 131.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.74 (s).

1-Bromo-3-(trifluoromethyl)benzene (4o)[245]



Synthesised from **3o** following GP 1-D (0.2 mmol) to give **4o** in 25% yield by ^{19}F NMR. The reaction with 4.0 eq Selectfluor in H_2O/acetone 1:4 (otherwise following GP 1-D) afforded **4o** in 46% yield by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49-7.48 (m, 2H), 7.68 (brs, 1H), 7.83 (dt, *J* = 8.5 Hz, 2.5 Hz, 1H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –63.40 (s).

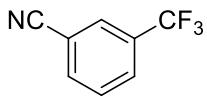
4-(trifluoromethyl)benzonitrile (4p)[47]



Synthesised from **3p** following GP 1-D (0.2 mmol) to give **4p** in 12% yield by ^{19}F NMR. Increasing the reaction time to 5 h increased the yield to 26% by ^{19}F NMR. The reaction with 4.0 eq Selectfluor in H_2O/acetone 1:4 (otherwise following GP 1-D) afforded **4p** in 41% yield by ^{19}F NMR. Purification by silica flash column chromatography (eluent: 2% Et_2O in PET 30/40) gave 10 mg (29% yield) of the product as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5 Hz, 2H), 7.82 (d,

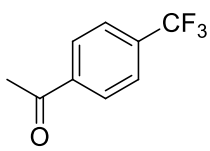
J = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 116.0, 117.4, 123 (q, *J* = 273 Hz), 126.2 (q, *J* = 4 Hz), 132.7, 434.6 (q, *J* = 34 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −63.51 (s).

3-(Trifluoromethyl)benzonitrile (4q)[222]



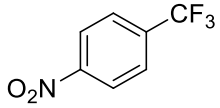
Synthesised from **3q** following GP 1-D (0.2 mmol), to give **4q** in 15% yield by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (t, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 8.05-8.07 (m, 2H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –63.63 (s).

1-[4-(Trifluoromethyl)phenyl]ethanone (4r)[244]



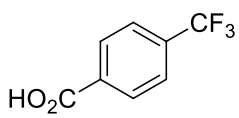
Synthesised from **3r** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: 20% Et_2O in hexane) to give 13 mg (21% yield) of **4r** as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.99 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 26.8, 125.7 (q, *J* = 4.0 Hz), 128.6, 134.3, 139.7, 197.0, (Note: CF_3 signal was not detected); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –63.11 (s).

1-Nitro-4-(trifluoromethyl)benzene (4s)



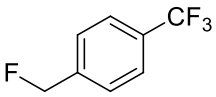
The reaction of **3a** following GP 1-D did not afford **4s**. Unreacted starting material was recovered.

4-(Trifluoromethyl)benzoic acid (4t)[246]



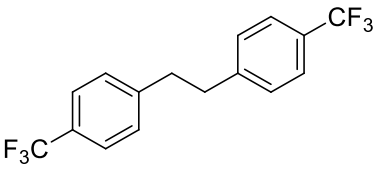
Synthesised from **3t** following GP 1-D (0.2 mmol), to give **4t** in 49% yield by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.5 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 2H), 8.24 (brs, 1H, CO_2H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −63.59 (s).

1-(Fluoromethyl)-4-(trifluoromethyl)benzene (4u)[247]



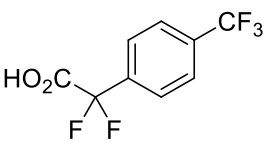
Synthesised from **3u** following GP 1-D (0.2 mmol) to give **4u** in 16% yield by ^{19}F NMR. The reaction with 4.0 eq Selectfluor and 40 mol% $AgNO_3$ (otherwise following GP 1-D) afforded a quantitative yield of **4u** by ^{19}F NMR. **4u** dimerised to form 1,1'-propane-1,1-diylbis[4-(trifluoromethyl)benzene] (see below) upon purification on silica or alumina. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.38 (d, *J* = 47.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 83.5 (d, *J* = 170 Hz), 125.6 (q, *J* = 4 Hz) 127.0, 127.1 (q, *J* = 271 Hz), 128.8, 145.0; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –212.76 (t, *J* = 47.0 Hz, 1F), –62.33 (s, 3F).

1,1'-Propane-1,1-Diylbis[4-(trifluoromethyl)benzene][248]



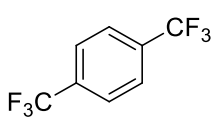
1-(Fluoromethyl)-4-(trifluoromethyl)benzene (**4u**), synthesised following GP 1-D (0.2 mmol), dimerised to form 1,1'-propane-1,1-diylbis[4-(trifluoromethyl)benzene] upon all attempts at purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.92 (s, 4H), 7.41 (d, *J* = 8.0 Hz, 4H), 7.59 (d, *J* = 8.0 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 37.2, 125.4 (q, *J* = 4 Hz), 127.0, 127.1 (q, *J* = 271 Hz), 128.8, 145.0; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –62.67 (s).

Difluoro[4-(trifluoromethyl)phenyl]acetic acid (4v-i)[249]



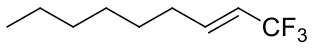
Synthesised from **3v** following GP 1-D (0.2 mmol) to give **4v-i** in 62% yield by ^{19}F NMR, together with 2% **4v-ii**. The reaction with 4.0 eq Selectfluor and 40 mol% $AgNO_3$ (otherwise following GP 1-D) afforded **4v-i** in 73% yield by ^{19}F NMR, together with 26% **4v-ii**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.0 Hz, 4H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –63.51 (s, 3F), −105.33 (s, 2F).

1,3-Bis(trifluoromethyl)benzene (4v-ii)[113]



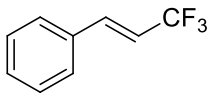
Synthesised from **3v** following GP 1-D (0.2 mmol) to give **4v-ii** in 2% yield by ^{19}F NMR, together with 62% **4v-i**. The reaction with 4.0 eq Selectfluor and 40 mol% $AgNO_3$ (otherwise following GP 1-D) afforded **4v-ii** in 26% yield by ^{19}F NMR, together with 73% **4v-i**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (s, 4H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –63.68 (s).

(2*E*)-1,1,1-Trifluorononon-2-ene (4w)[106]



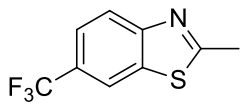
Synthesised from **3w** following GP 1-D (0.2 mmol) to give **4w** in 10% yield by ^{19}F NMR (in a 9:1 *E*:*Z* ratio, starting from pure *E*-**3w**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.67 (t, *J* = 7.0 Hz, 3H), 1.20–1.29 (m, 6H), 1.34–1.43 (m, 2H), 2.10–2.13 (m, 2H), 6.11–6.24 (m, 1H), 6.91–7.06 (m, 1H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −64.76–−64.72 (m).

[(1*E*)-3,3,3-Trifluoroprop-1-en-1-yl]benzene (4x)[250]



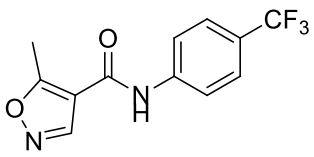
Synthesised from **3x** following GP 1-D (0.2 mmol) to give **4x** in 18% yield by ^{19}F NMR (in a 17:1 *E*:*Z* ratio, starting from pure *E*-**3x**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.97 (dq, *J* = 11.5 Hz, 6.5 Hz, 1H, *Z*), 6.15 (dq, *J* = 16.0 Hz, 6.5 Hz, 1H, *E*) , 6.74 (dq, *J* = 16.0 Hz, 2.0 Hz, 1H, *E*), 6.84 (dq, *J* = 11.5 Hz, 2.0 Hz, 1H, *Z*), 7.36–7.43 (m, 3H), 7.65 (dd, *J* = 7.5 Hz, 2.0 Hz, 2H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −63.48 (dd, *J* = 7.0 Hz, 2.0 Hz).

2-Methyl-6-(trifluoromethyl)-1,1-Benzothiazole (4y)



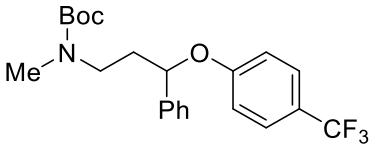
The reaction of **3y** following GP 1-D did not afford **4y**. Instead, oxidatively induced rupture of the aromatic ring-structure was observed.

5-Methyl-N-[4-(trifluoromethyl)phenyl]-1,2-oxazole-3-Carboxamide (Leflunomide) (4z)



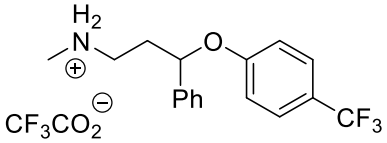
The reaction of **3z** following GP 1-D did not afford **4z**. Instead, oxidatively induced rupture of the aromatic ring structure was observed.

***tert*-Butyl methyl{3-phenyl-3-[4-(trifluoromethyl)phenoxy]propyl}carbamate (4za)** (**NB.** Synthesised by Dr. S. Mizuta.)



Synthesised from **3za** following GP 1-D (0.06 mmol scale), yielding 13.2 mg (59 %) of the product as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) (both rotamers) δ 1.38 (brs, 9H), 2.05-2.24 (m, 2H), 2.86 (s, 3H), 3.30-3.53 (m, 2H), 5.17 (dd, *J* = 8.0 Hz, 3.5 Hz 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 7.28-7.37 (m, 5H), 7.43 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) (both rotamers) δ 27.7, 28.4, 34.6, 36.2, 36.6, 37.2, 45.2, 47.2, 79.4, 82.9, 118.2, 118.4, 125.7, 125.9, 127.7, 127.8, 128.6, 128.8, 138.0, 138.1, 141.0, 141.2, 153.3, 155.7, 157.8, 158.0. (Note: The CF_3 carbon was not observed); **^{19}F NMR** (376.5 MHz, $CDCl_3$) (both rotamers) δ –61.6 (s, 3F); **IR** (neat) ν 2930, 2360, 1693, 1324, 1249, 1159, 1111, 1068, 1050, 1010, 835, 760, 701; **HRMS** calculated for $C_{22}H_{26}F_3NNaO_3$ $[M+Na]^+$ 432.1756, found 458.1757.

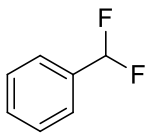
***N*-Methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine trifluoroacetic acid salt** (**NB.** Synthesised by Dr. S. Mizuta.)



To a solution of 120 mg *tert*-butyl methyl{3-phenyl-[4-(trifluoromethyl)phenoxy]propyl}carbamate (0.29 mmol, 1.0 eq) in 250 µL DCM (1.16 M) was added 250 µL TFA (3.26 mmol, 11.0 eq) and the mixture was stirred at rt for 1 h. The excess TFA was

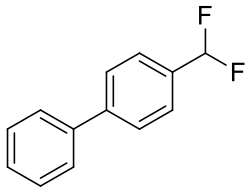
evaporated off and the residue was dried in *vacuo* to give 122 mg (quantitative yield) of the title compound as a colourless oil. **^{1}H NMR** (250 MHz, $CDCl_3$): δ 2.19-2.46 (m, 2H), 2.63(s, 3H), 3.08-3.26 (m, 2H), 5.32 (dd, *J* = 8.0 Hz, 4.0 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 7.25-7.37 (m, 5H), 7.42 (d, *J* = 9.0 Hz, 2H), 9.22 (brs, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 33.1, 34.6, 46.3, 77.1, 115.7, 123.3 (q, *J* = 32 Hz), 124.2 (q, *J* = 269 Hz), 125.5, 126.8 (q, *J* = 4 Hz), 128.4, 129.1, 139.0, 159.6, 161.7 (q, *J* = 30 Hz), (Note: The TFA CF_3 carbon was not observed); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –75.8 (s, 3F), –61.7 (s, 3F); **IR** (neat) ν 2821, 1670, 1614, 1517, 1325, 1245, 1109, 1067, 835, 722, 701; **HRMS** calculated for $C_{17}H_{19}F_3NO$ $[M+H]^+$ 310.1405, found 310.1413.

(Difluoromethyl)benzene (8a)[240]



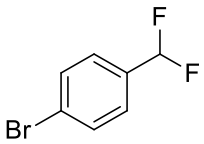
Synthesised from **7a** following GP 1-D (0.2 mmol), to give **8a** in 72% yield by ^{19}F NMR. The compound was not isolated due to its high volatility. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.59 (t, *J* = 56.6 Hz, 1H), 7.35–7.44 (m, 5H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –110.86 (d, *J* = 56.5 Hz);

4-(Difluoromethyl)biphenyl (8b)[241]



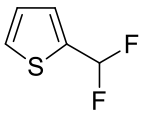
Synthesised from **7b** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: 5% Et_2O in PET 30/40) to give 37 mg (91 %) of **6b** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.61 (t, *J* = 56.5 Hz, 1H), 7.30 (tt, *J* = 7.5 Hz, 2.0 Hz, 1H), 7.35–7.40 (m, 2H), 7.48–7.52 (m, 4H), 7.59 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 114.8 (t, *J* = 239 Hz), 126.1 (t, *J* = 6.0 Hz), 127.3, 127.5, 127.8, 128.9, 133.2 (t, *J* = 23 Hz), 140.2, 143.7 (t, *J* = 2.0 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –110.29 (d, *J* = 55.5 Hz).

1-Bromo-4-(difluoromethyl)benzene (8c)[222]



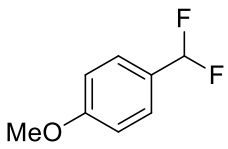
Synthesised from **7c** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: PET 30/40) to give 34 mg (82% yield) of **8c** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.54 (t, *J* = 56.0 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 114.1 (t, *J* = 239 Hz), 125.1 (t, *J* = 3 Hz), 127.2 (t, *J* = 6 Hz), 132.0, 133.3 (t, *J* = 23 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ –111.06 (d, *J* = 56.0 Hz).

2-(Difluoromethyl)thiophene (8d)



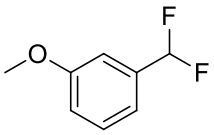
Substrate **7d** was unstable towards decomposition, so GP 1-D could not be carried out.

1-(Difluoromethyl)-4-methoxybenzene (8e)



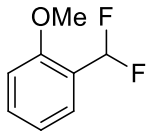
Substrate **7e** was unstable towards decomposition, so GP 1-D could not be carried out.

1-(Difluoromethyl)-3-methoxybenzene (8f)[242]



Synthesised from **7f** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: 5% Et_2O in PET 30/40) to give 26 mg (83% yield) of **8f** as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.53 (t, *J* = 56.5 Hz, 1H), 6.91–6.94 (m, 1H), 6.96 (s, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.4, 110.6 (t, *J* = 6 Hz), 114.6 (t, *J* = 236 Hz), 116.6 (t, *J* = 2 Hz), 117.8 (t, *J* = 6 Hz), 129.9, 135.7 (t, *J* = 22 Hz), 159.8; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –110.62 (d, *J* = 56.5 Hz).

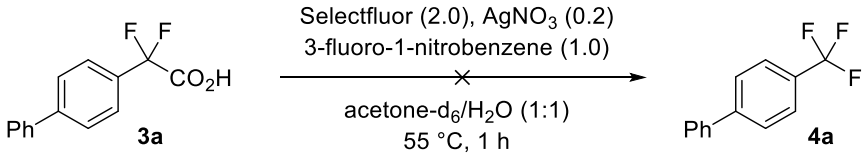
1-(Difluoromethyl)-2-methoxybenzene (8g)[94]



Synthesised from **7g** following GP 1-D (0.2 mmol). Purified by silica flash column chromatography (eluent: 5% Et_2O in PET 30/40) to give 21 mg (60%) of **8g** as a yellow oil. (Note: The relatively low yield is due to rapid decomposition of starting material **7g**.) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.88 (t, *J* = 55.5 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 7.33–7.37 (m, 1H), 7.49 (d, *J* = 7.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 54.7, 110.5 (t, *J* = 236 Hz), 109.8, 112.9, 119.5, 125.2 (t, *J* = 6 Hz), 130.9 (t, *J* = 2 Hz), 137.1, 156.2; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –115.38 (d, *J* = 55.7 Hz).

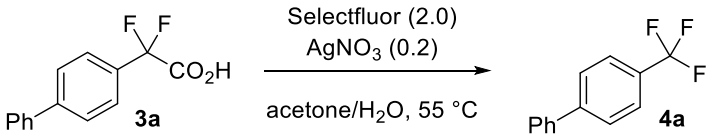
6.2.1.4 Control Experiments

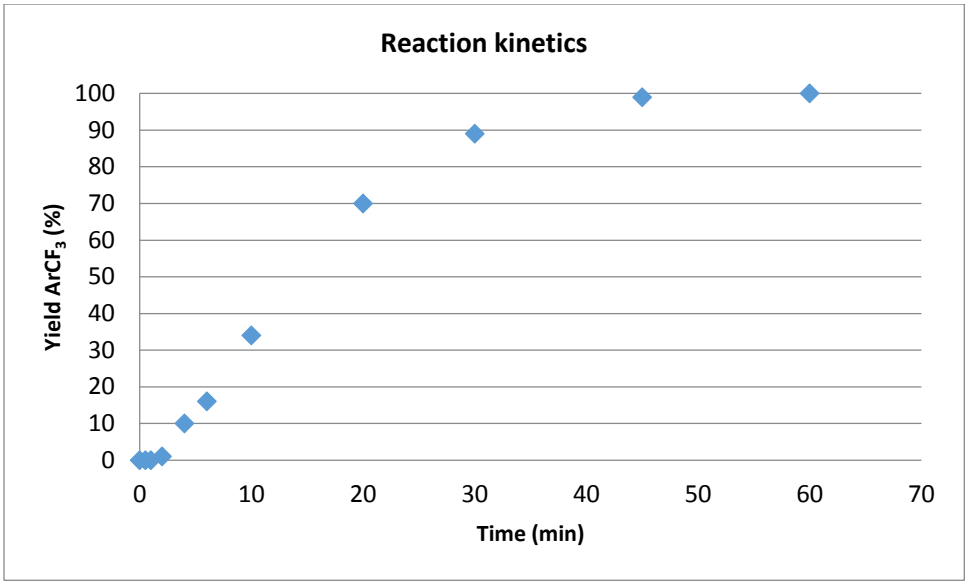
6.2.1.4.1 Reaction in the presence of 3-fluoro-1-nitrobenzene



A control reaction showed that the fluorodecarboxylation of **3a** under standard conditions with 2.0 eq Selectfluor and 20 mol% $AgNO_3$ in acetone-d_6/H_2O (1:1) did not proceed in the presence of 1.0 eq 3-fluoro-1-nitrobenzene. This result suggests that the nitro group may be acting as a radical quencher, inhibiting the reaction.

6.2.1.4.2 Reaction Kinetics





The reaction was run under standard conditions, with aliquots taken at the indicated time-points. ^{19}F NMR yields were determined by proton-decoupled ^{19}F NMR (relaxation time D1 = 10 s), integrating the starting material (−101.04 ppm, s) and product (−60.31 ppm, s) peaks relative to 1.0 eq of 3-fluoro-1-nitrobenzene (−110.20 ppm, m).

6.2.1.4.3 Formation of acyl fluoride by-product 5a

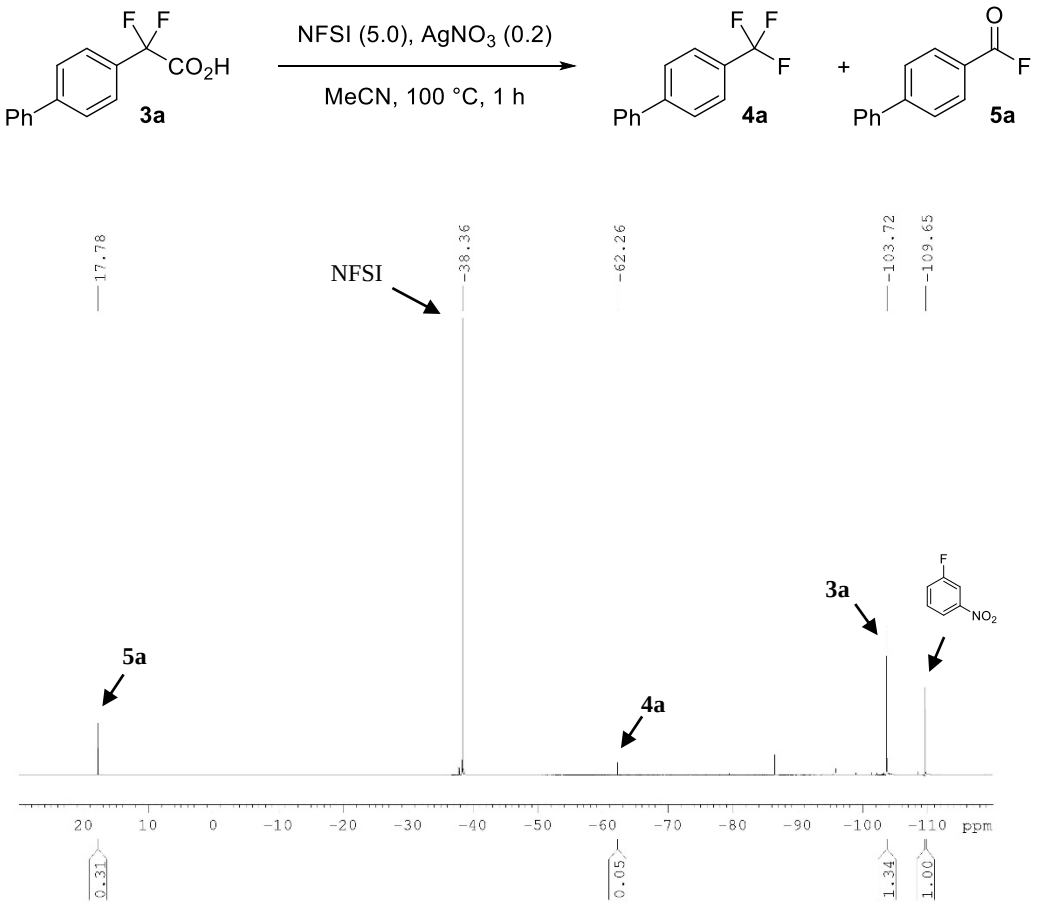
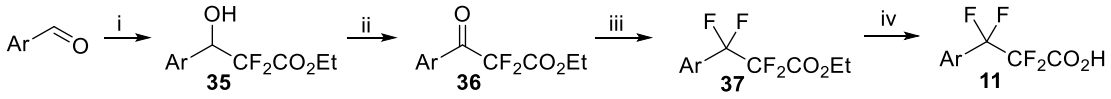


Figure 10 ^{19}F NMR spectrum of the crude reaction mixture from the reaction of 4a with 5.0 eq NFSI

Figure 10 shows the crude ^{19}F NMR spectrum for the reaction of **4a** with 5.0 eq NFSI and 20 mol% $AgNO_3$ in acetonitrile at 100 °C (see Table 3, Entry 13). 1.0 eq 3-fluoro-1-nitrobenzene (–109.65 ppm) was used as an internal NMR standard. Integration of the relevant peaks and comparison with the internal standard shows formation of 31% **5a** (+17.78 ppm) together with 5% **4a** (–62.26 ppm). The rest of the mass balance is made up by unreacted starting material **3a** (–103.72 ppm).

6.2.1.5 Synthesis of 3-(biphenyl-4-yl)-2,2,3,3-tetrafluoropropanoic acids 11



Conditions: (i) $BrCF_2CO_2Et$ (1.2 eq), Zn (1.5 eq), THF, reflux, 30 min; (ii) Dess-Martin periodinane (2.0 eq), DCM, rt, 3 h; (iii) DAST (1.2 eq), DCM, rt, 16 h; (iv) LiOH, $EtOH/H_2O$, rt, 16 h.

General procedure 1-E: Reformatskii coupling of aromatic aldehydes with ethyl bromodifluoroacetate[251]

To 981 mg Zn dust (15.0 mmol, 1.5 eq) suspended in 11 mL (0.9 M) THF at reflux, one drop of trimethylsilyl chloride and one drop of dibromoethane were added to activate the metal. A solution of 1.54 mL (12.0 mmol, 1.2 eq) ethyl dibromodifluoroacetate and 10.0 mmol (1.0 eq) aldehyde in 11 mL THF (0.9 M) was slowly added to the reaction mixture, maintaining vigorous reflux. The reaction was cooled to rt after 30 minutes, quenched with saturated $NaHCO_3$(aq), 1 M $KHSO_4$ (aq) and Et_2O and left to stir for another 15 min. After this time the reaction was extracted with Et_2O, washed with brine, dried over $MgSO_4$ and evaporated. Crude products were purified by silica flash column chromatography.

General procedure 1-F: Oxidation of 2,2-difluoro-3-hydroxypropanoates[252]

A solution of 2,2-difluoro-3-hydroxypropanoate **35** (1.0 mmol, 1.0 eq) in 2 mL DCM (0.5 M) was added to a stirred suspension of 848 mg Dess-Martin periodinane (2.0 mmol, 2.0 eq) in 20 mL DCM (0.05 M) at room temperature. The reaction was stirred for 3 h, after which it was diluted with Et_2O and poured into *ca.* 60 mL $NaHCO_{3(aq)}$ containing 1.74 g $Na_2S_2O_3$ (7.0 mmol, 7.0 eq) and then stirred for another 10 min. The reaction was washed with $NaHCO_{3(aq)}$ and water, extracted with Et_2O, dried over $MgSO_4$ and reduced *in vacuo*. The crude products were purified by silica flash column chromatography.

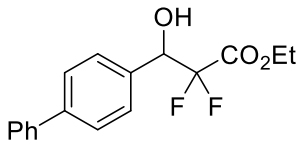
General procedure 1-G: Fluorination of 2,2-difluoro-3-ketones

To a solution of ketone **36** (8.7 mmol, 1.0 eq) in 30 mL DCM (0.33 M) was added 1.4 mL DAST (10.4 mmol, 1.2 eq). The reaction was stirred at room temperature for 24 h, after which it was carefully quenched with saturated $NaHCO_{3(aq)}$, extracted with DCM, dried over $MgSO_4$ and evaporated. The crude products were purified by silica flash column chromatography.

General procedure 1-H: Hydrolysis of 2,2,3,3-tetrafluoropropanoates

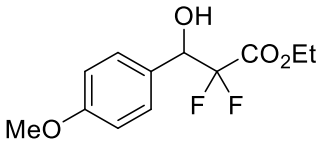
2,2,3,3-Tetrafluoropropanoate **37** (0.7 mmol, 1.0 eq) was stirred in a solution of 176 mg LiOH (4.2 mmol, 6.6 eq) in 5 mL EtOH and 0.5 mL H_2O overnight at room temperature. The mixture was acidified with 2 M HCl, extracted with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo*. The crude products were purified by trituration with PET 30/40.

Ethyl 3-(biphenyl-4-yl)-2,2-difluoro-3-hydroxypropanoate (35a)



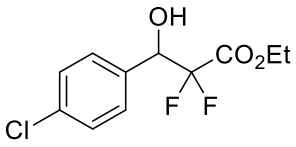
Synthesised from biphenyl-4-carbaldehyde following GP 1-E (20.0 mmol scale). Purification by silica flash column chromatography (eluent: 10% EtOAc/Hexane) afforded 5.79 g (94% yield) of the product as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.0 Hz, 3H), 2.94–2.98 (m, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 5.10 (ddd, *J* = 16.0 Hz, 8.0 Hz, 5.5 Hz, 1H), 7.26 (tt, *J* = 7.0 Hz, 2.0 Hz, 1H), 7.32–7.36 (m, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.47–7.52 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 63.3, 73.6 (dd, *J* = 28 Hz, 24.5 Hz), 113.8 (dd, *J* = 258 Hz, 254.0 Hz), 127.2 (2C), 127.7, 128.2, 128.9, 133.5, 140.4, 142.2, 163.7 (t, *J* = 31.5 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −113.41 (dd, *J* = 261.5 Hz, 8.0 Hz, 1F), –120.47 (dd, *J* = 261.5 Hz, 16.0 Hz, 1F); **IR** (neat) ν 1698, 1604, 1214, 1170, 1007, 837, 761, 730, 696; **HRMS** (FI) calculated for $C_{17}H_{16}O_3F_2$ $[M]^+$ 306.1068, found 306.1069; **Mp** 53–54 °C.

Ethyl 2,2-difluoro-3-hydroxy-3-(4-methoxyphenyl)propanoate (35b)[253]



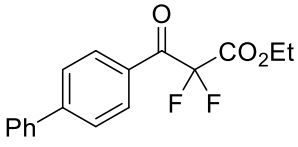
Synthesised from 4-methoxybenzaldehyde following GP 1-E (6.0 mmol scale). Purification by silica flash column chromatography (10% EOAc in hexane to 40% EtOAc) afforded 1.56 g (quantitative yield) of the title product as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.0 Hz, 3H), 3.59 (brs, 1H, O*H*), 3.78 (s, 3H), 4.28 (q, *J* = 7.0 Hz, 2H), 5.08 (dd, *J* = 15.5 Hz, 8.0 Hz, 1H), 6.87-6.91 (m, 2H), 7.32-7.36 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.8, 55.2, 63.1, 73.2 (dd, *J* = 28 Hz, 24 Hz), 113.8, 114.0 (dd, *J* = 259 Hz, 254 Hz), 126.8 (d, *J* = 2 Hz), 129.1, 160.1, 136.8 (t, *J* = 32 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –114.16 (dd, *J* = 259.0 Hz, 8.0 Hz, 1F), –120.57 (dd, *J* = 259.0 Hz, 15.5 Hz, 1F).

Ethyl 3-(3-Chlorophenyl)-2,2-difluoro-3-hydroxypropanoate (35c)[254]



Synthesised from 4-chlorobenzaldehyde following GP 1-E (6.0 mmol scale). Purification by silica flash column chromatography (10% EOAc in hexane to 20% EtOAc) afforded 1.59 g (quantitative yield) of the title product as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.0 Hz, 3H), 3.30 (brs, 1H, O*H*), 4.19 (q, *J* = 7.0 Hz, 2H), 5.03 (dd, *J* = 15.5 Hz, 7.5 Hz, 1H), 7.26 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.8, 63.4, 73.0 (dd, *J* = 28 Hz, 25 Hz), 113.6 (dd, *J* = 260 Hz, 254 Hz), 128.6, 129.1, 133.0, 135.2, 163.6 (dd, *J* = 32 Hz, 31 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –113.21 (dd, *J* = 262.5 Hz, 7.5 Hz, 1F), –120.72 (dd, *J* = 262.5 Hz, 15.5 Hz, 1F).

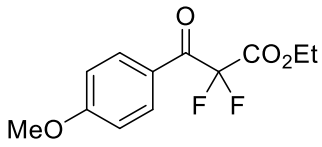
Ethyl 3-(biphenyl-4-yl)-2,2-difluoro-3-oxopropanoate (36a)



Synthesised from **35a** following GP 1-F (1.0 mmol scale). Purification by silica flash column chromatography (10% Et_2O in PET 30/40) afforded 271 mg (89% yield) of the title product as a

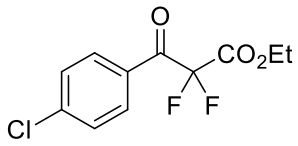
white solid. **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 1.33 (t, *J* = 7.0 Hz, 3H), 4.41 (q, *J* = 7.0 Hz, 2H), 7.45 (tt, *J* = 7.0 Hz, 2.0 Hz, 1H), 7.50–7.53 (m, 2H), 7.67–7.70 (m, 2H), 7.79 (dt, *J* = 8.5 Hz, 2.0 Hz, 2H), 8.17 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 14.0, 64.4, 110.3 (t, *J* = 264 Hz), 127.7, 127.9, 129.2, 129.5, 130.1, 130.9 (t, *J* = 9 Hz), 139.6, 148.1, 162.2 (t, *J* = 31 Hz), 158.3 (t, *J* = 28 Hz); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –106.0 (s); **IR** (neat) ν 1772, 1695, 1603, 1313, 1157, 1099, 748, 695; **HRMS** (ESI) calculated for $C_{17}H_{14}F_2NaO_3$ $[M+Na]^+$ 327.0803, found 327.0803; **Mp** 34–35°C.

Ethyl 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate (36b)[255]



Synthesised from **35b** following GP 1-F (5.3 mmol scale). Purification by silica flash column chromatography (10% Et_2O in Hexane to 20% Et_2O) afforded 994 mg (73% yield) of the title product as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.0 Hz, 3H), 3.81 (s, 3H), 4.29 (q, *J* = 7.0 Hz, 2H), 6.87–6.91 (m, 2H), 7.96–8.00 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.8, 55.6, 63.7, 110.1 (t, *J* = 265 Hz), 114.3, 123.9, 132.3 (t, *J* = 3 Hz), 162.1 (t, *J* = 31 Hz), 165.1, 183.8 (t, *J* = 27 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –107.28 (s).

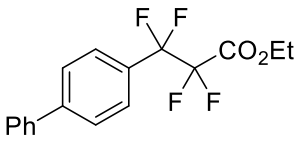
Ethyl 3-(3-Chlorophenyl)-2,2-difluoro-3-oxopropanoate (36c)



Synthesised from **35c** following GP 1-F (5.2 mmol scale). Purification by silica flash column chromatography (5% Et_2O in Hexane to 10% Et_2O) afforded 1.05 g (77% yield) of the title product as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.0 Hz, 3H), 4.30 (q, *J* = 7.0 Hz, 2H), 7.39–7.42 (m, 2H), 7.91–7.95 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.8, 63.4, 109.7 (t, *J* = 264 Hz), 129.3, 129.4, 131.3 (t, *J* = 3 Hz), 141.9, 161.5 (t, *J* = 31 Hz), 184.4 (t, *J* = 28 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ -107.68 (s); **IR** (neat) ν

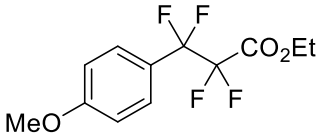
1773, 1703, 1589, 1311, 1254, 1158, 1088, 1013, 922, 847, 830, 784, 744; **HRMS** (FI) calculated for $C_{11}H_9O_3ClF_2$ $[M]^+$ 262.0208, found 262.0208.

Ethyl 3-(biphenyl-4-yl)-2,2,3,3-tetrafluoropropanoate (37a)



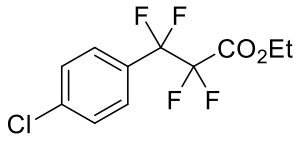
Synthesised from **36a** following GP 1-G (8.7 mmol scale). Purification by silica flash column chromatography (PET 30/40 to 3% Et_2O in PET 30/40) afforded 2.51 g (88% yield) of the product as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.0 Hz, 3H), 4.27 (q, *J* = 7.0 Hz, 2H), 7.26 (t, *J* = 7.0 Hz, 2.0 Hz, 1H), 7.31–7.36 (m, 2H), 7.45–7.49 (m, 2H), 7.52–7.57 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.8, 63.9, 109.4 (tt, *J* = 263 Hz, 40 Hz), 115.8 (tt, *J* = 254 Hz, 32 Hz), 127.2, 127.3, 127.3, 128.2 (s), 128.2 (t, *J* = 24 Hz), 129.0, 139.8, 144.5, 160.5 (t, *J* = 30 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –111.11 (t, *J* = 6.0 Hz, 2F), –118.62 (t, *J* = 6.0 Hz, 2F); **IR** (neat) ν 1769, 1320, 907, 729, 698, 650; **HRMS** (ESI) calculated for $C_{17}H_{14}F_4NaO_2$ $[M+Na]^+$ 349.0822, found 349.0823; **Mp** 67–69°C.

Ethyl 2,2,3,3-tetrafluoro-3-(4-methoxyphenyl)propanoate (37b)



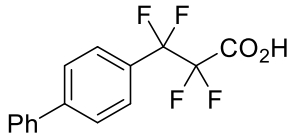
Synthesised from **36b** following GP 1-G (3.7 mmol scale). Purification by silica flash column chromatography (PET 30/40 to 10% Et_2O in PET 30/40) afforded 682 mg (66% yield) of the product as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.0 Hz, 3H), 3.69 (s, 3H), 4.24 (q, *J* = 7.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 7.37 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.7, 55.2, 63.7, 109.4 (tt, *J* = 262 Hz, 41 Hz), 113.9, 115.9 (tt, *J* = 255 Hz, 32 Hz), 121.3 (t, *J* = 25 Hz), 128.3 (t, *J* = 7 Hz), 160.5 (t, *J* = 30 Hz), 162.1; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –110.44 (t, *J* = 5.5 Hz, 2F), –118.98 (t, *J* = 5.5 Hz, 2F); **IR** (neat) ν 1769, 1615, 1518, 1318, 1258, 1168, 1129, 1099, 1079, 1054, 1029, 832; **HRMS** (FI) calculated for $C_{12}H_{12}O_3F_4$ $[M]^+$ 280.0723, found 280.0722.

Ethyl 2,2,3,3-tetrafluoro-3-(3-Chlorophenyl)propanoate (37c)



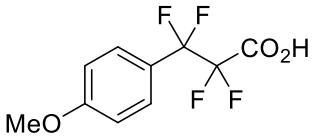
Synthesised from **36c** following GP 1-G (3.5 mmol scale). Purification by silica flash column chromatography (PET 30/40 to 5% Et_2O in PET 30/40) afforded 595 mg (60% yield) of the product as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.0 Hz, 3H), 4.31 (q, *J* = 7.0 Hz, 2H), 7.37-7.45 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.8, 63.9, 109.1 (tt, *J* = 262 Hz, 39 Hz), 115.4 (tt, *J* = 255 Hz, 32 Hz), 127.9 (t, *J* = 25 Hz), 128.3 (t, *J* = 7 Hz), 128.8, 138.1 (t, *J* = 2 Hz), 160.2 (t, *J* = 31 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –111.35 (t, *J* = 7 Hz, 2F), –118.64 (t, *J* = 7 Hz, 2F); **IR** (neat) ν 1770, 1318, 1284, 1231, 1170, 1131, 1094, 1077, 1053, 1016, 957, 940, 923, 824, 736, 686; **HRMS** (FI) calculated for $C_{11}H_9O_2ClF_4$ $[M]^+$ 284.0227, found 284.0226.

3-(Biphenyl-4-yl)-2,2,3,3-tetrafluoropropanoic acid (11a)



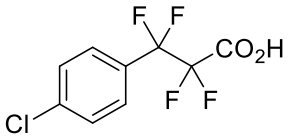
Synthesised from **37a** following GP 1-H (0.7 mmol scale). Purification by trituration with PET 30/40 afforded 192 mg (92% yield) of the title compound as a white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 7.43 (t, *J* = 7.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.67 (d, *J* = 7.5 Hz, 2H), 7.74 (t, *J* = 7.5 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 115.7 (tt, *J* = 253 Hz, 32 Hz), 127.3, 127.3, 127.3, 127.8 (t, *J* = 25 Hz), 128.2, 129.0, 139.8, 144.6, 162.5 (t, *J* = 31 Hz), (Note: CF_2 not detected); **^{19}F NMR** (376.5 MHz, $(CD_3)_2SO$) δ –110.20 (d, *J* = 3.5 Hz, 2F), –118.4 (d, *J* = 4.0 Hz, 2F); **IR** (neat) ν 1752, 1301, 1141, 731, 683; **HRMS** calculated for $C_{15}H_{10}F_4NaO_2$ $[M+Na]^+$ 321.0509, found 321.0503; **Mp** 124–125 °C.

Ethyl 2,2,3,3-tetrafluoro-3-(4-methoxyphenyl)propanoate (11b)



Synthesised from **37b** following GP 1-H (2.4 mmol scale). Purification by trituration with PET 30/40 afforded 490 mg (81% yield) of the product as an off-white solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 3.87 (s, 3H), 7.04–7.08 (m, 2H), 7.48–7.53 (m, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 55.8, 109.6 (tt, *J* = 261 Hz, 3 Hz), 114.6, 116.3 (tt, *J* = 253 Hz, 32 Hz), 121.2 (t, *J* = 25 Hz), 128.5 (t, *J* = 6 Hz), 161.7 (t, *J* = 29 Hz), 162.2; **^{19}F NMR** (376.5 MHz, CD_3OD) δ –111.84 (s, 2F), –120.69 (t, *J* = 2.0 Hz, 2F); **IR** (neat) ν 1764, 1615, 1518, 1294, 1259, 1168, 1142, 1101, 1080, 1028, 916, 833; **HRMS** (FI) calculated for $C_{10}H_8O_3F_4$ $[M]^+$ 252.0410, found 252.0413; **Mp** 64–66 °C.

Ethyl 2,2,3,3-tetrafluoro-3-(3-Chlorophenyl)propanoate (11c)



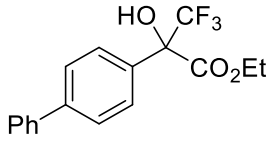
Synthesised from **37c** following GP 1-H (1.8 mmol scale). Purification by trituration with PET 30/40 afforded 255 mg (55% yield) of the product as a white solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.54–7.60 (m, 4H); **^{13}C NMR** (100 MHz, CD_3OD) δ 109.3 (tt, *J* = 261 Hz, 36 Hz), 115.4 (tt, *J* = 252 Hz, 34 Hz), 128.1 (t, *J* = 6 Hz), 128.4, 128.6, 137.7, 161.2 (t, *J* = 30 Hz); **^{19}F NMR** (376.5 MHz, CD_3OD) δ –112.85 (s, 2F), –120.51 (s, 2F); **IR** (neat) ν 1719, 1331, 1288, 1170, 1145, 1105, 1094, 1075, 826; **HRMS** (FI) calculated for $C_9H_5O_2ClF_4$ $[M]^+$ 255.9914, found 255.9920; **Mp** 42–44 °C.

6.2.1.6 Synthesis of 2-(biphenyl-4-yl)-2,3,3,3-tetrafluoropropanoic acid 13

13

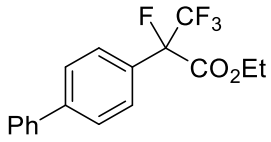
Conditions: (i) BuLi (1.0 eq), THF, –70 °C, 30 min; (ii) $CF_3C(O)CO_2Et$ (1.1 eq), THF, –75 °C to rt, 1 h; (iii) DAST (1.28 eq), DCM, 0 °C, 30 min; (iv) KOH, MeOH, rt, 2 h.

Ethyl 2-(biphenyl-4-yl)-3,3,3-trifluoro-2-hydroxypropanoate



Synthesised following a literature procedure:[256] 4.0 mL *n*BuLi (2.5 M in hexane, 10.0 mmol, 1.0 eq) was added to a solution of 2.33 g 4-bromobiphenyl (10.0 mmol, 1.0 eq) in 50 mL THF (0.2 M) at −75 °C. After stirring for 30 min, 1.46 mL ethyl trifluoropyruvate (11.0 mmol, 1.1 eq) was added to the reaction and the mixture was allowed to warm to rt. After 1h, the reaction was quenched with $NH_4Cl_{(aq)}$, extracted with Et_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by silica flash column chromatography (DCM/hexane 1:9 to 3:7) to give 1.2 g (37% yield) of the product as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.0 Hz, 3H), 4.22–4.38 (m, 2H), 7.21-7.25 (m, 1H), 7.29–7.33 (m, 2H), 7.45–7.52 (m, 4H), 7.76 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 13.9, 64.5, 77.84 (q, *J* = 30 Hz), 123.2 (q, *J* = 286 Hz), 127.2, 127.2, 127.3 (q, *J* = 3 Hz), 127.8, 128.9, 131.9, 140.2, 142.5, 169; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –76.22 (s); **IR** (neat) ν 1736, 1165, 1105, 746, 695; **HRMS** (ESI) calculated for $C_{17}H_{15}F_3NaO_3$ $[M+Na]^+$ 347.0866, found 347.0865; **Mp** 41–42 °C.

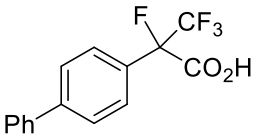
Ethyl 2-(biphenyl-4-yl)-2,3,3,3-tetrafluoropropanoate



0.61 mL DAST (4.58 mmol, 1.28 eq) was added to 1.16 g ethyl 2-(biphenyl-4-yl)-3,3,3-trifluoro-2-hydroxypropanoate (3.58 mmol, 1.0 eq) in 7 mL dry DCM (0.5 M) at 0 °C. The reaction mixture was stirred for 30 min, after which water was added carefully. The resulting mixture was extracted with DCM, washer with water, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by silica flash column chromatography (Et_2O/PET 30/40 1:9) to give 1.1 g (94% yield) of the product as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.43 (t, *J* = 7.0 Hz, 3H), 4.42–4.54 (qd, *J* = 7.0 Hz, 3.0 Hz, 2H), 7.46 (tt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.51–7.56 (m, 2H), 7.66–7.69 (m, 2H), 7.75–7.77 (m, 2H), 7.85 (d, *J* = 8.5 Hz, 2H);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.9, 63.5, 92.5 (dq, *J* = 203 Hz, 33 Hz), 121.5 (dq, *J* = 286 Hz, 30.0 Hz), 126.22 (d, *J* = 9 Hz), 127.2, 127.5 (d, *J* = 2 Hz), 128.1, 128.48 (d, *J* = 22 Hz), 129.0, 139.9, 143.5, 163.9 (d, *J* = 24 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −172.63 (q, *J* = 8.0 Hz, 1F), −76.98 (d, *J* = 8.0 Hz, 3F); **IR** (neat) ν 1755, 1260, 1185, 1035, 747, 697; **HRMS** (ESI) calculated for $C_{17}H_{14}F_4NaO_2$ $[M+Na]^+$ 349.0822, found 349.0824; **Mp** 36–37 °C.

2-(biphenyl-4-yl)-2,3,3,3-tetrafluoropropanoic acid (13)



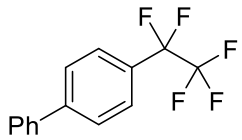
Synthesised following a literature procedure:[256] 979 mg ethyl 2-(biphenyl-4-yl)-2,3,3,3-tetrafluoropropanoate (3.0 mmol, 1.0 eq) was stirred in 75 mL 5% methanolic KOH for 2 h, after which it was concentrated *in vacuo*. The solid was dissolved in H_2O, and extracted with Et_2O. The aqueous layer was acidified to pH 1 with conc. HCl and extracted with EtOAc. The combined EtOAc layers were dried over $MgSO_4$, evaporated and recrystallized from EtOAc to afford 45 mg (5% yield) of the title compound as a yellow solid. **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.40–7.44 (m, 1H), 7.48–7.52 (m, 2H), 7.70–7.73 (m, 2H), 7.79–7.87 (m, 4H); **^{13}C NMR** (100.6 MHz, $(CD_3)_2CO$) δ 93.2 (dq, *J* = 188 Hz, 33 Hz), 122.6 (dq, *J* = 285 Hz, 32 Hz), 127.1 (d, *J* = 10 Hz), 127.9, 128.3, 129.0, 129.9, 140.4, 144.2, 164.9 (d, *J* = 24 Hz); **^{19}F NMR** (376.5 MHz, $(CD_3)_2CO$) δ –171.83 (q, *J* = 7.5 Hz, 1F), –77.75 (d, *J* = 7.5 Hz, 3F); **IR** (neat) ν 1756, 1194, 734, 697; **HRMS** (ESI) calculated for $C_{15}H_{10}F_4NaO_2$ $[M+Na]^+$ 321.0509, found 321.0502; **Mp** 83–85 °C.

6.2.1.7 Fluorodecarboxylation of 11

General procedure 1-I: Fluorodecarboxylation with XeF_2 and HF

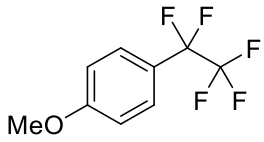
To a solution of carboxylic acid **11** (0.5 mmol, 1.0 eq) in 7 mL (0.07 M) DCM in a 15 mL polyethylene Falcon tube were added 169 mg XeF_2 (1.0 mmol, 2.0 eq) and – when the xenon difluoride had completely dissolved – 26µL HF/pyridine (70% HF, 30% pyridine, 1.0 mmol, 2.0 eq). The reaction was stirred at rt for 16 h, after which it was carefully quenched with saturated $NaHCO_{3(aq)}$, extracted with DCM, dried over $MgSO_4$, and concentrated *in vacuo*. ^{19}F NMR yields were obtained by addition of 53 µL (0.5 mmol, 1.0 eq) 3-fluoro-1-nitrobenzene as an internal standard. Crude products were purified by silica flash column chromatography (eluent: pentane).

4-(Pentafluoroethyl)biphenyl (12a)[36]



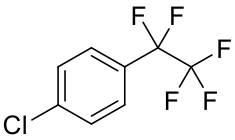
Synthesised from **11a** following GP 1-I (0.5 mmol scale) to give **12a** in 70% yield by ^{19}F NMR. Purification by silica flash column chromatography (eluent: pentane) afforded 64 mg (47% yield) of the product as a white solid. (The low isolated yield is due to difficulties in separating the fluorodecarboxylated product from the protodecarboxylated by-product.) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (tt, *J* = 7.0 Hz, 2.0 Hz, 1H), 7.37–7.41 (m, 2H), 7.50–7.53 (m, 2H), 7.57–7.64 (m, 4H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –84.70 (s, 3F), –114.69 (s, 2F); **IR** (neat) ν 1204, 1094, 768; **HRMS** (FI) calculated for $C_{14}H_9F_5$ $[M]^+$ 272.0624, found 272.0624; **Mp** 51–53 °C.

1-Methoxy-4-(pentafluoroethyl)benzene (12b)[257]



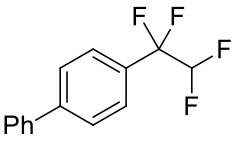
Synthesised from **11b** following GP 1-I (0.5 mmol scale) to give **12b** in 50% yield by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.97–7.00 (m, 2H), 7.17–7.20 (m, 2H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –84.87 (t, *J* = 1.5 Hz, 3F), –114.07 (s, 2F).

1-Chloro-4-(pentafluoroethyl)benzene (12c)



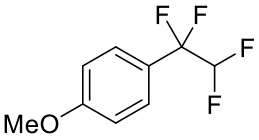
Synthesised from **11c** following GP 1-I (0.5 mmol scale) to give **12c** in 52% yield by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50–7.60 (m, 4H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –85.00 (s, 3F), –115.01 (s, 3F).

4-(1,1,2,2-tetrafluoroethyl)biphenyl (16a)[258]



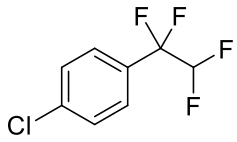
Synthesised from **11a** following GP 1-I (0.5 mmol scale) to afford 28% of **16a** by ^{19}F NMR. The reaction was purified by silica flash column chromatography (eluent: pentane) to afford 24 mg (19% yield) of the title compound as an off-white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.86 (tt, *J* = 54.0 Hz, 2.5 Hz, 1H), 7.29–7.33 (m, 1H), 7.36–7.40 (m, 2H), 7.50–7.56 (m, 4H), 7.59–7.62 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 109.2 (tt, *J* = 251 Hz, 43.5 Hz), 114.6 (tt, *J* = 248 Hz, 29 Hz), 125.9 (t, *J* = 6 Hz), 126.2, 126.3, 127.0, 127.5 (t, *J* = 25 Hz), 127.9, 138.9, 143.2 (t, *J* = 2 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −113.36 (q, *J* = 3.5 Hz, 2F), −134.03 (dt, *J* = 54.0 Hz, 3.5 Hz, 2F).

4-(1,1,2,2-tetrafluoroethyl)methoxyphenyl (16b)[258]



Synthesised from **11b** following GP 1-I (0.5 mmol scale) to afford 10% of **16b** by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 5.89 (tt, *J* = 54.0 Hz, 3.0 Hz, 1H), 6.96–7.01 (m, 2H), 7.17–7.20 (m, 2H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –112.47 (q, *J* = 3.0 Hz, 2F), –133.95 (dt, *J* = 54.0 Hz, 3.0 Hz, 2F).

4-(1,1,2,2-tetrafluoroethyl)chlorophenyl (16c)



Synthesised from **11c** following GP 1-I (0.5 mmol scale) to afford 18% of **16c** by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.02 (tt, *J* = 54.0 Hz, 2.0 Hz, 1H), 6.92–6.96 (m, 2H), 7.31–7.34 (m, 2H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –113.54 (q, *J* = 3.0 Hz, 2F), –134.23 (dt, *J* = 54.0 Hz, 3.0 Hz, 2F).

6.2.3 Photocatalytic Trifluoromethylation of Vinylsilanes

6.2.3.1 Synthesis of Alkenyl- and Alkynylsilanes

NB. Substrates denoted by an asterix (*) were synthesised by Dr. K. M. Engle.

General Procedure 2-A: Sonogashira coupling of aryl iodides with ethynyltrimethylsilane[183]

To a suspension of aryl iodide (10.0 mmol, 1.0 eq), copper(I) iodide (19 mg, 0.1 mmol, 1 mol%), bis(triphenylphosphine)palladium(II) dichloride (140 mg, 0.2 mmol, 2 mol%) and ethynyltrimethylsilane (2.12 mL, 15.0 mmol, 1.5 eq) in THF (25 mL, 0.4 M), was added diisopropylamine (2.8 mL, 20.0 mmol, 2.0 eq) dropwise. After stirring for 1.5 h at room temperature, the brown/grey sludge was poured into ice water. The crude product was extracted with hexane, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude products were purified by flash column chromatography (eluent: pentane).

General Procedure 2-B: Trimethylsilylation of terminal alkynes with *n*-butyllithium[259]

To a solution of alkyne (5.0 mmol, 1.0 eq) in THF (13 mL, 0.4 M) at 0 °C was added dropwise a 1.6 M solution of *n*-butyllithium in hexane (3.75 mL, 6.0 mmol, 1.2 eq). The

mixture was stirred at 0 °C for 45 min before adding chlorotrimethylsilane (1.1 mL, 8.5 mmol, 1.7 eq) dropwise. The reaction was allowed to warm to room temperature overnight. The reaction mixture was then quenched with H_2O, extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude products were purified by flash column chromatography (eluent: pentane).

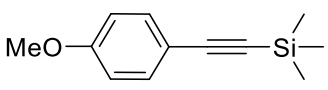
General Procedure 2-C: DIBAL reduction of aromatic trimethylsilylalkynes to *E*-alkenes[184]

DIBAL (1.0 M in hexane, 3 mL, 3.0 mmol, 3.0 eq) was added dropwise to the aromatic trimethylsilylalkyne (1.0 mmol, 1.0 eq). The reaction mixture was stirred for 21 h at room temperature and very carefully quenched with cold 10% aq H_2SO_4 on ice. The organic layer was separated, and the aqueous layers were extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude products were purified by flash column chromatography (eluent: pentane).

General Procedure 2-D: Hydrosilylation of terminal alkynes[188]

$PtCl_2$ (66.5 mg, 0.25 mmol, 5 mol%) and XPhos (238.36 mg, 0.5 mmol, 10 mol%) in THF (2.5 mL, 2 M) were heated at 60 °C for 15 min. Then, alkyne (0.7 mL, 5.0 mmol, 1.0 eq) and triethylsilane (1.2 mL, 7.5 mmol, 1.5 eq) were successively added *via* syringe and the mixture was stirred at 60 °C for 1 h, after which the solvent was removed *in vacuo* and the crude mixture was purified by column chromatography (eluent: pentane).

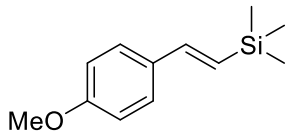
2-(4-Methoxyphenyl)-1-trimethylsilyl-ethyne (21a)[260]



Synthesised from 4-iodoanisol following GP 2-A (6.0 mmol scale). Purified by flash column chromatography (eluent: 10% Et_2O in hexane) to give 1.0 g (82% yield) of the title compound as an orange oil.

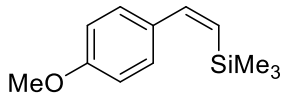
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H), 3.71 (s, 3H), 6.71–6.75 (m, 2H), 7.30–7.33 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.0, 55.2, 92.3, 105.1, 113.7, 115.2, 133.4, 159.6.

[(*E*)-2-(4-Methoxyphenyl)ethenyl]trimethylsilane ((*E*)-22a)[190, 261]



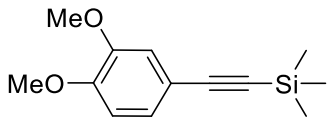
Synthesised from **21a** following GP 2-C (1.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to give 174 mg (71% yield) of the title compound as a white solid in an 11:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.17 (s, 9H), 3.83 (s, 3H), 6.33 (d, *J* = 19.0 Hz, 1H), 6.84 (d, *J* = 19.0 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –1.0, 55.4, 114.0, 126.8, 127.7, 131.5, 143.2, 159.7.

[(*Z*)-2-(4-Methoxyphenyl)ethenyl]trimethylsilane ((*Z*)-22a)[262]*



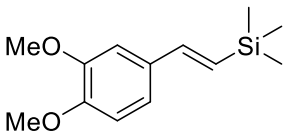
Synthesised from **21a** following GP 2-C (1.0 mmol scale) in Et_2O. Purified by flash column chromatography (eluent: pentane) to give 140 mg (68% yield) of the title compound as a white solid in a 3.5:1 *Z*:*E* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.09 (s, 9H), 3.83 (s, 3H), 5.73 (d, *J* = 15.0 Hz, 1H), 6.84–6.88 (m, 2H), 7.22–7.25 (m, 2H), 7.30 (d, *J* = 15.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ –0.6, 55.3, 113.7, 126.3, 127.5, 131.5, 134.1, 159.7.

[(3,3-Dimethoxyphenyl)ethynyl](trimethyl)silane (21b)[263]*



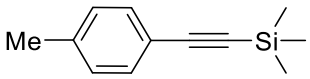
Synthesised from 4-iodoveratrole following GP 2-A (10.0 mmol scale). Purification by flash column chromatography (eluent: 5% Et_2O in Hexane) afforded 2.53 g (99% yield) of the title compound as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.24 (s, 9H), 3.87 (s, 6H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 1.5 Hz, 1H), 7.07 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.2, 56.0, 92.5, 105.4, 110.9, 114.7, 115.4, 125.5, 148.6, 147.8.

[(*E*)-2-(3,3-Dimethoxyphenyl)ethenyl]trimethylsilane (22b)



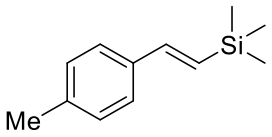
Synthesised from **21b** following GP 2-C (1.0 mmol scale). Purified by flash column chromatography (eluent: pentane to 5% Et_2O in pentane) to give 166 mg (70% yield) of the title compound as a pale yellow oil in a 1.7:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.17 (s, 9H, *Z*), 0.18 (s, 9H, *E*), 3.87 (s, 3H, *Z*), 3.89 (s, 3H, *E*), 3.91 (s, 3H, *Z*), 3.93 (s, 3H, E), 6.30 (dd, *J* = 19.0 Hz, 4.0 Hz, 1H, *Z*), 6.34 (d, *J* = 19.0 Hz, 1H, *E*), 6.73-7.32 (m, 8H, *E* and *Z*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 1.2 (*E*), 0.3 (*Z*), 55.8 (*E*), 55.8 (*Z*), 55.9 (*E*), 55.9 (*Z*), 108.0 (*Z*), 108.4 (*E*), 110.9 (*E*), 114.3 (*Z*), 119.8 (*E*), 120.4 (*Z*), 126.4 (*Z*), 126.9 (*E*), 131.2 (*Z*), 131.6 (*E*), 145.8 (*Z*), 146.6 (*Z*), 149.0 (*E*), 149.1 (*E*); **IR** (neat) ν 2360, 2342, 1264, 1246, 839, 866; **HRMS** (ESI) calculated for $C_{13}H_{20}NaOSi$ $[M+Na]^+$ 259.1125, found 259.1118.

Trimethyl[(4-methylphenyl)ethynyl]silane (21c)[264] *



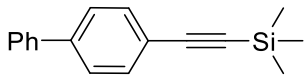
Synthesised from 4-iodotoluene following GP 2-A (10.0 mmol scale). Purified by flash column chromatography (eluent: 2% Et_2O in hexane) to afford 1.70 g (90% yield) of the title compound as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.25 (s, 9H), 2.34 (s, 3H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.2, 21.6, 93.4, 105.5, 120.2, 129.1, 132.0, 138.7.

Trimethyl[(*E*)-2-(4-methylphenyl)ethenyl]silane (22c)[265]



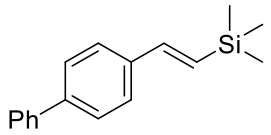
Synthesised from **21c** following GP 2-C (1.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to give 149 mg (78% yield) of the title compound as a colourless oil in an *E*:*Z* ratio > 20:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.23 (s, 9H), 2.41 (s, 3H), 6.49 (d, *J* = 19.0 Hz, 1H), 6.93 (d, *J* = 19.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 1.1, 21.3, 126.3, 128.1, 129.3, 135.7, 137.8, 143.6.

(Biphenyl-4-ylethynyl)(trimethyl)silane (21d)[266] *



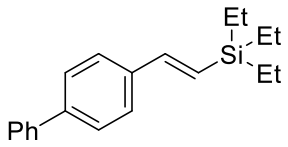
Synthesised from 4-iodobiphenyl following GP 2-A (10.0 mmol scale). Purified by flash column chromatography (eluent: hexane to 5% Et_2O/hexane) to give 1.75 g (70% yield) of the title compound as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.28 (s, 9H), 7.34–7.38 (m, 1H), 7.42–7.47 (m, 2H), 7.54 (s, 4H), 7.58–7.60 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.14, 95.0, 105.1, 122.1, 127.0, 127.2, 127.8, 129.0, 132.5, 140.4, 141.3.

[(*E*)-2-(biphenyl-4-yl)ethenyl](trimethyl)silane (22d)



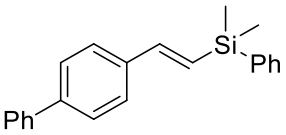
Synthesised from **21d** following GP 2-C (2.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to give 443 mg (88% yield) of the title compound as a white solid in an *E*:*Z* ratio >20:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.21 (s, 9H), 6.56 (d, *J* = 19.0 Hz, 1H), 6.95 (d, *J* = 19.0 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.59-7.65 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –1.2, 126.8, 127.0, 127.2, 127.3, 128.8, 129.7, 137.4, 140.6, 140.7, 143.1; **IR** (neat) ν 2361, 2341, 1250; **HRMS** (FI) calculated for $C_{17}H_{20}Si$ $[M]^+$ 252.1334, found 252.1328; **Mp** 94–96 °C.

[(*E*)-2-(biphenyl-4-yl)ethenyl](triethyl)silane (23d)



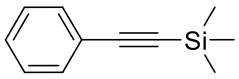
Synthesised from 4-iodobiphenyl following GP 2-D (2.0 mmol scale). Purification by column chromatography (eluent: pentane) afforded 510 mg (87% yield) of the title compound as a white solid (*E*/*Z* > 20). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.60 (q, *J* = 8.0 Hz, 6H), 0.92 (t, *J* = 8.0 Hz, 9H), 6.40 (d, *J* = 19.5 Hz, 1H), 6.85 (d, *J* = 19.5 Hz, 2H), 7.25 (tt, *J* = 7.5 Hz, 2.0 Hz, 1H), 7.32–7.37 (m, 2H), 7.42–7.53 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 3.6, 7.5, 126.2, 126.8, 127.0, 127.3, 127.3, 128.8, 137.6, 140.7, 140.8, 144.3; **IR** (neat) ν 2361, 2340, 1269, 754; **HRMS** (FI) calculated for $C_{20}H_{26}Si$ $[M]^+$ 294.1804, found 294.1795; **Mp** 42–44 °C.

[(*E*)-2-(biphenyl-4-yl)ethenyl](dimethyl)phenylsilane (28d)



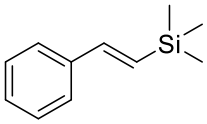
Synthesised from 4-iodobiphenyl following GP 2-D (2.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to yield 494 mg (79% yield) of the title compound as a white solid (*E*/*Z* > 20). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.48 (s, 6H), 6.66 (d, *J* = 19.0 Hz, 1H), 6.91 (d, *J* = 19.0 Hz, 1H), 7.36 (tt, *J* = 7.5 Hz, 2.0 Hz, 1H), 7.39–7.42 (m, 2H), 7.44–7.48 (m, 2H), 7.54–7.56 (m, 3H), 7.59–7.60 (m, 2H), 7.61–7.64 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –2.4, 127.1, 127.1, 127.4, 127.4, 127.5 128.0, 128.9, 129.2, 134.1, 137.3, 138.7, 140.8, 141.0, 144.9; **IR** (neat) ν 2361, 2342, 1248, 757; **HRMS** (FI) calculated for $C_{22}H_{22}Si$ $[M]^+$ 314.1491, found 314.1493; **Mp** 78–80 °C.

Trimethyl(2-phenylethenyl)silane (21e)[267]



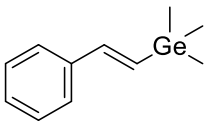
Synthesised from iodobenzene following GP 2-A (10.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to give 1.74 g (>99% yield) of the title compound as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.30 (s, 9H), 7.28–7.31 (m, 1H), 7.31–7.34 (m, 2H), 7.48–7.53 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.0, 94.1, 105.2, 123.2, 128.2, 128.5, 132.0.

Trimethyl[(*E*)-2-phenylethenyl]silane ((*E*)-22e)[190]



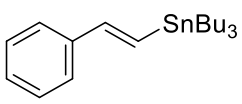
Synthesised from **21e** following GP 2-C (10.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to give 1.30 g (74% yield) of the title compound as a colourless oil in an *E*:*Z* ratio > 20:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.26 (s, 9H), 6.57 (d, *J* = 19.0 Hz, 1H), 6.97 (d, *J* = 19.0 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 7.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –1.1, 126.4, 128.0, 128.6, 129.5, 138.4, 143.7.

Trimethyl[(*E*)-2-phenylethenyl]germane (29e)



To a solution of 0.4 mL *trans*-bromostyrene (mixture of isomers, 3.0 mmol, 1.0 eq) in 10 mL dry Et_2O (0.3 M) at –78 °C under argon was added 4.13 mL *tert*-butyllithium (1.6 M in pentane, 6.6 mmol, 2.2 eq) slowly and the yellow solution was stirred for 1 hour. Addition of 0.4 mL chlorotrimethylgermane (3.0 mmol, 1.0 eq) followed and the solution was warmed to rt over 4 h. After stirring overnight, the mixture was quenched with MeOH (0.25 mL) and water (12.5 mL). The organic layer was extracted with Et_2O, the combined extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (eluent: 1% NEt_3 in pentane) afforded 630 mg (95 %) of the title compound as a colourless oil in an 11:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.0 (s, 9H, *Z*), 0.10 (s, 9H, *E*), 5.79 (d, *J* = 14.0 Hz, 1H, *Z*), 6.48 (d, *J* = 14.0 Hz, 1H, *Z*), 6.48 (d, *J* = 19.0 Hz, 1H, *E*), 6.63 (d, *J* = 19.0 Hz, 1H, *E*), 7.01–7.08 (m, 1H, *E*, *Z*), 7.08–7.17 (m, 2H, *E*, *Z*), 7.20–7.24 (m, 2H, *E*, *Z*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.0 (*E*), 1.71 (*Z*), 127.9 (*E*), 129.0 (*Z*), 129.5 (*E*), 129.7 (*Z*), 129.7 (*Z*), 130.3 (*E*), 133.0 (*E*), 136.3 (*Z*), 140.0 (*E*), 141.7 (*Z*), 143.8 (*E*), 146.5 (*Z*); **IR** ($CHCl_3$) ν 2361, 2343, 723, 689; **HRMS** (FI) calculated for $C_{11}H_{16}Ge$ $[M]^+$ 222.0464, found 222.0468.

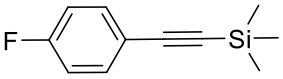
Tributyl[(E)-2-phenylethenyl]stannane (30e)



To a solution of 0.4 mL *trans*-bromostyrene (mixture of isomers, 3.0 mmol, 1.0 eq) in 10 mL dry Et_2O (0.3 M) at –78 °C under argon was added 4.13 mL *tert*-butyllithium (1.6 M in pentane, 6.6 mmol, 2.2 eq) slowly and the yellow solution was stirred for 1 hour. Addition of 0.8 mL tributyltin chloride (3.0 mmol, 1.0 eq) was followed and the solution warmed to rt over 4 h. After stirring overnight, the mixture was quenched with MeOH (0.25 mL) and water (12.5 mL). The organic layer was extracted with Et_2O and the combined extracts dried over $MgSO_4$. And concentrated *in vacuo*. Purification by flash column chromatography (eluent: 1% NEt_3 in pentane) afforded

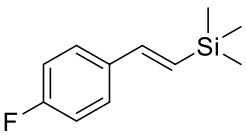
1.1 g (89% yield) of the title compound as a colourless oil (*E*/*Z* > 20). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.5 Hz, 8H), 0.99-1.04 (m, 6H), 1.39 (sex, *J* = 7.5 Hz, 6H), 1.56–1.64 (m, 6H), 6.92 (s, 2H), 7.25–7.29 (m, 1H), 7.35–7.39 (m, 2H), 7.46–7.48 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 9.6, 13.8, 27.4, 29.2, 126.0, 127.5, 128.5, 129.6, 138.8, 146.0.

[(4-Fluorophenyl)ethynyl](trimethyl)silane (21f)[264] *



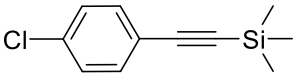
Synthesised from 4-fluoroiodobenzene following GP 2-A (10.0 mmol scale). Purified by flash column chromatography (eluent: hexane) to give 1.76 g (92% yield) of the title compound as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.24 (s, 9H), 6.96–7.01 (m, 2H), 7.42–7.47 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.1, 94.0, 104.1, 115.6 (d, *J* = 22 Hz), 119.4 (d, *J* = 4 Hz), 134.0 (d, *J* = 9 Hz), 162.7 (d, *J* = 250 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −110.44–−110.51 (m).

[(*E*)-2-(4-Fluorophenyl)ethenyl]trimethylsilane (22f)[190]



Synthesised from **21f** following GP 2-C (1.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to give 132 mg (68% yield) of the title compound as a colourless oil in an *E*:*Z* ratio > 20:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.20 (s, 9H), 6.42 (d, *J* = 19.0 Hz, 1H), 6.87 (d, *J* = 19.0 Hz, 1H), 7.04 (t, *J* = 8.5 Hz, 2H), 7.41–7.45 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –1.2, 115.4 (d, *J* = 21 Hz), 127.8 (d, *J* = 8 Hz), 129.2 (d, *J* = 2 Hz), 134.6 (d, *J* = 3 Hz), 142.3, 161.5 (d, *J* = 147 Hz); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ −114.00–−114.08 (m).

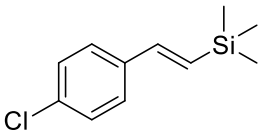
[(3-Chlorophenyl)ethynyl](trimethyl)silane (21g)[264] *



Synthesised from 3-chloroiodobenzene following GP 2-A (10.0 mmol scale). Purified by flash column chromatography (eluent: 5% Et_2O in hexane) to give 1.97 g (94% yield) of the title compound as an off-

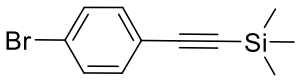
white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.06, 7.06–7.09 (m, 2H), 7.18–7.21 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.0, 95.5, 104.0, 121.8, 128.7, 133.3, 134.6.

[(*E*)-2-(3-Chlorophenyl)ethenyl]trimethylsilane (22g)[190]



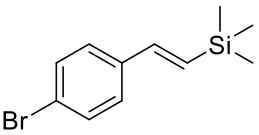
Synthesised from **21g** following GP 2-C (1.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to give 173 mg (82% yield) of the title compound as a white solid in an *E*:*Z* ratio > 20:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.18 (s, 9H), 6.47 (d, *J* = 19.0 Hz, 2H), 6.83 (d, *J* = 19.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –1.3, 127.6, 128.6, 130.4, 133.5, 136.8, 142.2.

[(3-Bromophenyl)ethynyl](trimethyl)silane (21h)[268] ∗



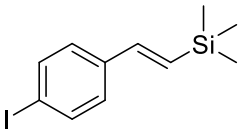
Synthesised from 1-bromo-4-iodobenzene following GP 2-A (10.0 mmol scale). Purified by flash column chromatography (eluent: hexane) to give 1.15 g (45% yield) of the title compound as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.25 (s, 9H), 7.30–7.33 (m, 2H), 7.41–7.45 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.0, 95.7, 104.0, 122.2, 122.9, 131.6, 133.5.

[(*E*)-2-(3-Bromophenyl)ethenyl]trimethylsilane (22h)[261, 269]



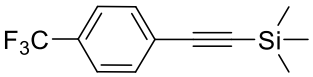
Synthesised from **21h** following GP 2-C (1.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to give 194 mg (76% yield) of the title compound as a white solid in an *E*:*Z* ratio > 20:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.17 (s, 9H), 6.48 (d, *J* = 19.0 Hz, 2H), 6.81 (d, *J* = 19.0 Hz, 2H), 7.29–7.32 (m, 2H), 7.44–7.47 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –1.3, 121.7, 127.9, 130.7, 131.6, 137.3, 142.2.

[(*E*)-2-(4-Iodophenyl)ethenyl]trimethylsilane (22i)[269]



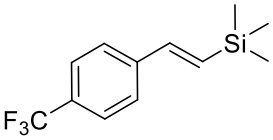
Synthesised from (4-iodophenylethynyl)trimethylsilane following GP 2-C (1.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to give 228 mg (75% yield) of the title compound as a pale yellow oil in an *E*:*Z* ratio > 20:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.20 (s, 9H), 6.52 (d, *J* = 19.0 Hz), 6.82 (d, *J* = 19.0 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –1.2, 93.4, 128.1, 130.8, 137.6, 137.8, 142.4.

Trimethyl({2-[4-(trifluoromethyl)phenyl]ethenyl})silane (21j)[270]



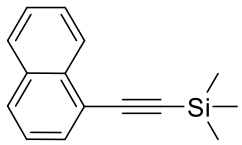
Synthesised from iodobenzene following GP 2-A (5.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to give 1.2 g (99% yield) of the title compound as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.28 (s, 9H), 7.56 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.2, 97.1, 103.4, 123.9 (q, *J* = 273 Hz), 125.1 (q, *J* = 4 Hz), 126.9, 130.1 (q, *J* = 31 Hz), 132.1; **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –63.27 (s).

Trimethyl-[(*E*)-2-[4-(trifluoromethyl)phenyl]ethenyl]silane (22j)



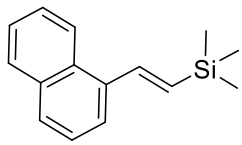
Synthesised from **21j** following GP 2-C (2.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to give 307 mg (63% yield) of the title compound as a colourless oil in a 4:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.21 (s, 9H), 6.64 (d, *J* = 19.0 Hz, 1H), 6.92 (d, *J* = 19.0 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –1.4, 124.2 (q, *J* = 272 Hz), 125.4 (q, *J* = 4 Hz), 126.3, 128.5, 129.6 (d, *J* = 33 Hz), 133.1, 142.0; **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –62.83 (s); **IR** (neat) ν 2361, 2342, 1249, 1068, 867; **HRMS** (FI) calculated for $C_{12}H_{15}SiF_3$ $[M]^+$ 244.0895, found 244.0892.

Trimethyl(naphthalen-1-ylethynyl)silane (21k)[271] *



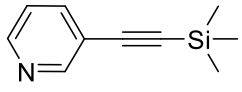
Synthesised from 1-iodonaphthalene following GP 2-A (10.0 mmol scale). Purified by flash column chromatography (eluent: hexane) to give 2.09 g (93% yield) of the title compound as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.35 (s, 9H), 7.41 (dd, *J* = 8.0 Hz, 7.5 Hz, 1H), 7.50–7.54 (m, 1H), 7.57–7.61 (m, 1H), 7.71–7.72 (m, 1H), 7.83 (d, *J* = 7.5 Hz, 2H), 8.35 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.2, 99.6, 103.2, 120.9, 125.2, 126.3, 126.5, 127.0, 128.4, 129.1, 130.9, 133.2, 133.5.

Trimethyl[(*E*)-2-(naphthalen-1-yl)ethenyl]silane (22k)[272]



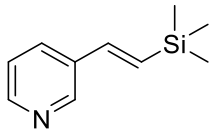
Synthesised from **21k** following GP 2-C (2.0 mmol scale). Purified by flash column chromatography (eluent: pentane) to give 308 mg (68% yield) of the title compound as a colourless oil in an *E*:*Z* ratio > 20:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.31 (s, 9H), 6.63 (d, *J* = 19.0 Hz, 1H, 7.50–7.60 (m, 3H), 7.74 (d, *J* = 7.0 Hz, 1H), 7.75 (d, *J* = 19.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –1.1, 123.59, 123.61, 125.67, 125.71, 126.0, 128.1, 128.6, 131.0, 133.7, 133.9, 136.6, 140.7.

3-[(Trimethylsilyl)ethynyl]pyridine (21l)[273] *



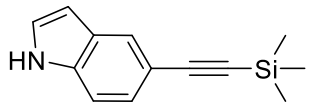
Synthesised from 3-iodopyridine following GP 2-A (10.0 mmol scale). Purified by flash column chromatography (eluent: 20% EtOAc in hexane) to give 1.65 g (94% yield) of the title compound as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.25 (s, 9H), 7.23–7.26 (m, 1H), 7.72–7.75 (m, 1H), 8.52 (brs, 1H), 8.68 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –0.1, 98.5, 101.5, 120.5, 123.1, 139.1, 148.6, 152.6.

3-[(*E*)-2-(Trimethylsilyl)ethenyl]pyridine (22l)[190]



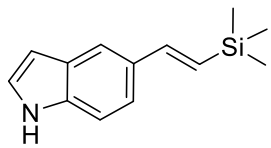
Synthesised from **21l** following GP 2-C (1.0 mmol scale). Purified by flash column chromatography (eluent: 20% EtOAc in Hexane) to give 51 mg (29% yield) of the title compound as a brown oil in an *E*:*Z* ratio > 20:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.14 (s, 9H), 6.55 (d, *J* = 19.0 Hz, 2H), 6.82 (d, *J* = 19.0 Hz, 2H), 7.21 (dd, *J* = 4.5 Hz, 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 8.44 (d, *J* = 4.5 Hz, 1H), 8.60 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –1.4, 123.4, 132.6, 132.7, 133.7, 139.9, 148.5, 148.8.

5-[(Trimethylsilyl)ethynyl]-1*H*-indole (21m)[274]*



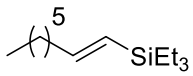
Synthesised from 5-iodoindole following GP 2-A (10.0 mmol scale). Purified by flash column chromatography (eluent: 10% Et_2O in hexane to 50% Et_2O/hexane) to give 1.53 g (72% yield) of the title compound as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.25 (s, 9H), 7.23–7.26 (m, 1H), 7.72–7.75 (m, 1H), 8.52 (brs, 1H), 8.68 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ −0.1, 98.5, 101.5, 120.5, 123.1, 139.1, 148.6, 152.6.

5-[(*E*)-2-(Trimethylsilyl)ethenyl]-1*H*-indole (22m)



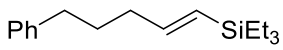
Synthesised from **21m** following GP 2-C (2.0 mmol scale). Purified by flash column chromatography (eluent: 10% EtOAc in Hexane) to give 98 mg (30% yield) of the title compound as a brown oil in a 9:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.24 (s, 9H), 6.47 (d, *J* = 19.0 Hz, 2H), 6.58 (dd, *J* = 2.5 Hz, 2.5 Hz, 1H), 7.06 (d, *J* = 19.0 Hz, 2H), 7.15 (dd, *J* = 2.5 Hz, 2.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.74 (s, 1H), 8.09 (brs, 1H, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –1.0, 103.0, 111.1, 119.5, 120.5, 124.7, 125.9, 128.1, 130.8, 135.8, 144.8; **IR** (neat) ν 3414, 2361, 2341, 1247, 986; **HRMS** (ESI) calculated for $C_{13}H_{16}NSi$ $[M–H]^+$ 214.1057, found 214.2060.

Triethyl[(1*E*)-oct-1-en-1-yl]silane (23n)[275, 276]



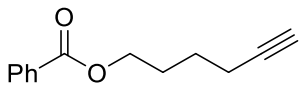
Synthesised from 1-octyne following GP 2-D (5.0 mmol scale). Purification by silica flash column chromatography (eluent: pentane) afforded 1.07 g (94% yield) of the title compound as a colourless oil (*E*/*Z* > 20). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.55 (q, *J* = 8.0 Hz, 6H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 1.29–1.33 (m, 4H), 1.38–1.41 (m, 2H), 2.10–2.15 (m, 2H), 5.54 (dt, *J* = 18.5 Hz, 1.5 Hz, 1H), 6.04 (d, *J* = 18.5 Hz, 6.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 3.7, 7.5, 14.2, 22.8, 29.0 (2C), 31.9, 37.3, 125.6, 149.0.

Triethyl[(1*E*)-5-phenylpent-1-en-1-yl]silane (23o)[276]



Synthesised 5-phenyl-1-pentyne following GP 2-D (2.0 mmol scale) from. Purification by silica flash column chromatography (eluent: pentane) afforded 520 mg (>99% yield) of the title compound as a colourless oil in a 5.6:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.57 (q, *J* = 8.0 Hz, 6H), 0.95 (t, *J* = 8.0 Hz, 9H), 1.72-1.79 (m, 2H), 2.16-2.22 (m, 2H), 2.62-2.67 (m, 2H), 5.60 (dt, *J* = 18.5 Hz, 1.5 Hz, 1H), 6.07 (dt, *J* = 18.5 Hz, 6.0 Hz, 1H), 7.19–7.22 (m, 3H), 7.27–7.32 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 3.7, 7.5, 30.8, 35.5, 36.6, 125.8, 126.4, 128.4, 128.6, 142.7, 148.2.

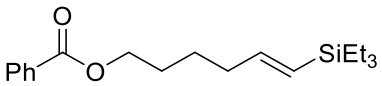
6-Benzoyloxy-1-hexyne (34p)[277]



To a solution of 5-hexyn-1-ol (0.55 mL, 5.0 mmol, 1.0 eq) in DCM (10 mL, 0.5 M) at 0 °C was added DMAP (61.1 mg, 0.5 mmol, 0.1 eq), pyridine (2.21 mL, 15.0 mmol, 3.0 eq) and benzoyl chloride (1.16 mL, 10.0 mmol, 2.0 eq) dropwise. The reaction was allowed to warm to room temperature, and stirred for 1.5 hours, after which it was quenched with H_2O and extracted with DCM. The combined organics were washed with H_2O and brine, dried over $MgSO_4$, filtered and evaporated. Purification by silica flash column chromatography (eluent: 6% EtOAc in Hexane) afforded 1.0 g (99% yield) of the title compound as a pale yellow oil. **^{1}H NMR**

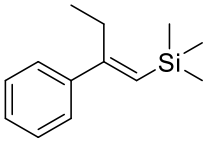
(400 MHz, $CDCl_3$) δ 1.71 (tt, *J* = 8.0 Hz, 2H), 1.92 (tt, *J* = 7.0 Hz, 2H), 2.0 (t, *J* = 3.0 Hz, 1H), 2.30 (dt, *J* = 7.0 Hz, 3.0 Hz, 2H), 4.36 (t, *J* = 6.5 Hz, 2H), 7.45 (tt, *J* = 7.5 Hz, 1.5 Hz, 2H), 7.57 (tt, *J* = 7.5 Hz, 1.5 Hz, 1H), 8.06 (dt, *J* = 7.5 Hz, 1.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.1, 25.1, 27.8, 64.4, 68.8, 83.9, 128.4, 129.5, 130.3, 132.9, 166.6.

(5*E*)-6-(Triethylsilyl)hex-5-en-1-yl benzoate (23p)



Synthesised from **34p** following GP 2-D (2.3 mmol). Purification by silica flash column chromatography (eluent: PET 40/60 to 2% Et_2O in PET) afforded 586 mg (80% yield) of the title compound as a colourless oil (*E*/*Z* > 20). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.55 (q, *J* = 8.0 Hz, 6H), 0.93 (t, *J* = 8.0 Hz, 9H), 1.55–1.61 (m, 2H), 1.75–1.80 (m, 2H), 2.18–2.24 (m, 2H), 4.33 (t, *J* = 6.4 Hz, 2H), 5.59 (dt, *J* = 18.5 Hz, 1.5 Hz, 1H), 6.04 (dt, *J* = 18.5 Hz, 6.0 Hz, 1H), 7.42–7.46 (m, 2H), 7.54–7.56 (m, 1H), 8.04–8.06 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 3.6, 7.5, 25.3, 28.3, 36.6, 65.0, 126.6, 128.4, 129.7, 130.6, 132.9, 147.9, 166.8; **IR** (neat) ν 2953, 2361, 1721, 1617, 1273, 1115, 710; **HRMS** (ESI) calculated for $C_{19}H_{30}NaO_2Si$ $[M+Na]^+$ 341.1907, found 341.1898.

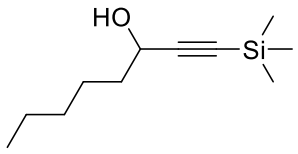
Trimethyl[(1*E*)-2-pehnylbut-1-en-1-yl]silane (22q)[187]



Synthesised following a literature procedure:[278] To a solution of 116 mg $Pd(PPh_3)_4$ (0.1 mmol, 2 mol%) and 0.5 mL phenylacetylene (5.0 mmol, 1.0 eq) in 10 mL 1,3-Dioxane (0.5 M), was added 5.0 mL diethylzinc (1M in hexane, 5.0 mmol, 1.0 eq) and 1.4 mL iodotrimethylsilane (10.0 mmol, 2.0 eq). The reaction was stirred at rt for 1 hour, before being poured onto ice, filtered through celite, extracted with hexane, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (eluent: pentane) to give 596 mg (58% yield) of the title compound as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.24 (s, 9H), 1.03 (t, *J* = 7.5 Hz, 3H), 2.68 (q, *J* = 7.5 Hz, 2H), 5.78 (s, 1H), 7.17–7.49

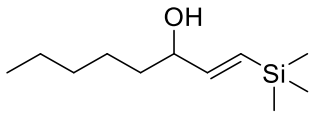
(m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.3, 14.1, 27.9, 126.2, 127.2, 127.2, 128.1, 143.3, 159.1.

1-(Trimethylsilyl)oct-1-yn-3-ol (21r)[186]



A solution of 1-octyn-3-ol (0.8 mL, 5.5 mmol, 1.0 eq) in ether (4.0 mL, 1.5 M) was added dropwise to ethyl magnesium bromide (4.0 mL, 12.1 mmol, 2.2 eq) in ether (4 mL) at 0 °C and stirred overnight at room temperature. Chlorotrimethylsilane (1.5 mL, 12.1 mmol, 2.2 eq) was added and the mixture was then heated to reflux for 7 h, before being cooled to 0 °C and quenched with 10% H_2SO_4. The organic phase was extracted with ether, washed with water, $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluent: 5% Et_2O in PET 30/40 to 20% Et_2O in PET) to afford 813 mg (75% yield) of the title compounds as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.16 (s, 9H), 0.98 (t, *J* = 7.0 Hz, 3H), 1.27–1.37 (m, 4H), 1.40–1.50 (m, 2H), 161–1.75 (m, 2H), 2.02 (brs, 1H, O*H*), 4.34 (t, *J* = 6.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –0.2, 13.9, 22.5, 24.8, 31.4, 37.6, 62.8, 89.2, 107.0.

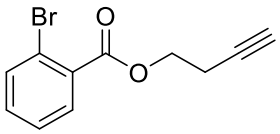
(1*E*)-1-(Trimethylsilyl)oct-1-en-3-ol (22r)[186]



To a solution of 1.54 mL Red-Al (65% by weight in toluene, 5.25 mmol, 1.75 eq) in 2 mL Et_2O (0.5 M) at 0 °C was added dropwise 595 mg 4-(trimethylsilyl)oct-1-yn-3-ol **21r** (3.0 mmol, 1.0 eq) in 2 mL Et_2O (0.5 M). The reaction was left stirring for 1 hour at room temperature, then cooled to 0 °C and quenched carefully with 10% H_2SO_4. The organic layer was extracted with Et_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluent: 5% Et_2O in pentane to 10% Et_2O in pentane) to afford 273 mg (45% yield) of the title compound as a colourless oil in an *E*:*Z* ratio > 20:1. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.07 (s, 9H), 0.89 (t, *J* = 7.0 Hz, 3H), 1.24–1.45 (m, 6H), 1.50 (dt,

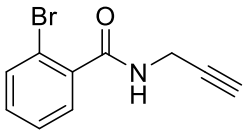
J = 7.0 Hz, 6.0 Hz, 2H), 1.67 (s, 1H, O*H*), 4.07 (ddt, *J* = 6.0 Hz, 5.5 Hz, 1.0 Hz, 1H), 5.84 (dd, *J* = 19.0 Hz, 1.0 Hz, 1H), 6.04 (dd, *J* = 19.0 Hz, 5.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –1.3, 14.0, 22.6, 25.0, 31.7, 36.9, 74.7, 129.1, 148.7.

But-3-yn-1-yl 2-bromobenzoate (34t)[176]



To a solution of 0.38 mL 3-butyn-1-ol (5.0 mmol, 1.0 eq) and 1.40 mL NEt_3 (10.0 mmol, 2.0 eq) in 35 mL DCM (0.14 M) at 0 °C was added 0.72 mL 3-Bromobenzoyl chloride (5.5 mmol, 1.1 eq). The reaction was stirred for 1 hour, before quenching with water. The mixture was extracted with DCM, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc in Hexane) afforded 1.26 g (>99% yield) of the title compound as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.97 (t, *J* = 2.5 Hz, 1H), 2.61 (dt, *J* = 7.0 Hz, 2.5 Hz, 2H), 4.38 (t, *J* = 7.0 Hz, 2H), 7.24–7.32 (m, 2H), 7.59 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.76 (dd, *J* = 7.5 Hz, 2.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 19.0, 63.2, 70.2, 79.9, 121.8, 127.2, 131.5, 131.8, 132.7, 134.4, 165.8; **IR** (neat) ν 3297, 1729, 1290, 1247, 1133, 1108, 1028, 743, 642; **HRMS** (CI) calculated for $C_{12}H_{10}BrO_2$ $[M+H]^+$ 252.9864, found 252.9871.

2-Bromo-*N*-(prop-2-yn-1-yl)benzamide (34u)[176]



To a solution of 0.32 mL propargylamine (5.0 mmol, 1.0 eq) and 1.40 mL NEt_3 (10.0 mmol, 2.0 eq) in 35 mL DCM (0.14 M) at 0 °C was added 0.72 mL 3-Bromobenzoyl chloride (5.5 mmol, 1.1 eq). The reaction was stirred for 3 hours, before quenching with water. The mixture was extracted with DCM, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (40% EtOAc in Hexane) gave 1.20 g (>99% yield) of the title compound as an off-white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.21 (t, *J* = 2.5 Hz, 1H), 4.15 (d, *J* = 2.5 Hz, 1H), 4.17 (d, *J* = 2.5 Hz, 1H), 6.31 (brs, 1H, N*H*), 7.20 (dt, *J* = 8.0 Hz, 2.0 Hz),

7.27 (dt, *J* = 7.5 Hz, 1.0 Hz), 7.44 (dd, *J* = 7.5 Hz, 2.0 Hz), 7.50 (dd, *J* = 8.0 Hz, 1.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 29.8, 72.1, 78.9, 119.4, 127.6, 129.7, 131.6, 133.5, 136.9, 167.2.

6.2.3.2 Photocatalytic Trifluoromethylation of Alkenyl- and Alkynylsilanes

General Procedure 2-E: Photocatalytic trifluoromethylation of vinyl- and alkynylsilanes

Alkenyl- or alkynylsilane (0.25 mmol, 1.0 eq), $Ru(bpy)_3Cl_2.6H_2O$ (18.7 mg, 0.025 mmol, 10 mol%), trifluoromethylating reagent (0.5 mmol, 2.0 eq) and solvent (1 mL, 0.25 M) were added to a vial which was exposed to a 14 W fluorescent household while stirring at rt for 24 h, before diluting with Et_2O. The reaction mixture was extracted with Et_2O and the combined organic phase was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture in THF (1 mL) was stirred with $TBAF{\cdot}3H_2O$ (2.0 eq) for 15 min at rt. The mixture was evaporated and ^{19}F NMR yield were determined by integrating the product peak(s) relative to 1.0 equivalents α,α,α-trifluorotoluene added as an internal standard. Purification by silica flash column chromatography or preparative TLC was difficult due to the non-polarity of the products.

NB. Conditions A: Togni's reagent **19a**, MeOH. Conditions B: Umemoto's reagent **18a**, MeOH. Conditions C: Togni's reagent **19a**, TFE. Conditions D: Togni's reagent **19c**, MeOH.

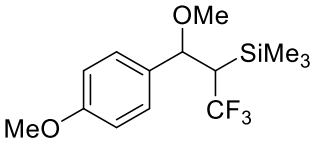
General Procedure 2-F: Hydrotrifluoromethylation of terminal alkynes

Alkyne (0.25 mmol, 1.0 eq), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (18.7 mg, 0.025 mmol, 10 mol%), Umemoto's reagent **18a** (181.0 mg, 0.5 mmol, 1.2 eq) and MeOH (1 mL) were added to a vial which was exposed to a 14 W fluorescent light bulb while stirring at rt for 24 h. The

reaction was quenched with saturated $NaHCO_{3(aq)}$, and extracted with Et_2O. The combined organic phases were washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated *invacuo*. Crude products were purified by silica flash column chromatography.

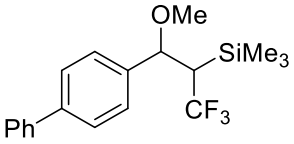
Figure 11 Reaction Setup

Trimethyl[1,1,1-trifluoro-3-methoxy-3-(4-methoxylphenyl)propan-2-yl]silane (24a)



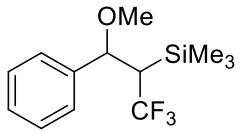
Intermediate formed during the reaction of **22a** under GP 2-E. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.11 (s, 9H), 3.28 (s, 3H), 3.79 (s, 3H), 3.99–4.05 (m, 1H), 4.41 (d, *J* = 5.5 Hz, 1H), 7.13–7.19 (m, 2H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –53.45 (d, *J* = 12.5 Hz).

Trimethyl(1,1,1-trifluoro-3-methoxy-3-biphenylpropan-2-yl)silane (24d)



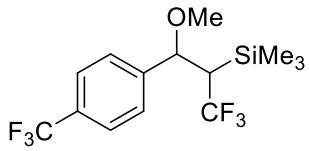
Intermediate formed during the reaction of **22d** under GP 2-E. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.06 (s, 9H), 3.16 (s, 3H), 3.74–3.76 (m, 1H), 4.41 (d, *J* = 5.0 Hz, 1H), 7.30–7.37 (m, 5H), 7.40–7.43 (m, 4H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –52.88 (d, *J* = 12.0 Hz).

Trimethyl(1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-yl)silane (24e)



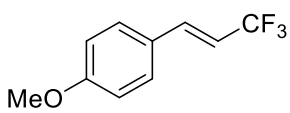
Intermediate formed during the reaction of **22e** under GP 2-E. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.11 (s, 9H), 3.27 (s, 3H), 3.95–4.01 (m, 1H), 4.43 (d, *J* = 5.0 Hz, 1H), 7.36–7.59 (m, 5H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ −52.29 ppm (d, *J* = 12.0 Hz).

Trimethyl[1,1,1-trifluoro-3-methoxy-3-(4-trifluoromethylphenyl)propan-2-yl]silane (24j)



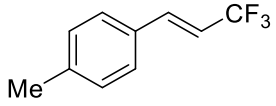
Intermediate formed during the reaction of **22j** under GP 2-E. **^{1}H NMR** (400 MHz, $CDCl_3$) δ –0.20 (s, 9H), 3.65 (s, 3H), 4.57–4.62 (m, 1H), 5.38 (d, *J* = 4.0 Hz, 1H), 7.34–7.42 (m, 4H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –53.13 (d, *J* = 12.0 Hz).

1-Methoxy-4-[(1*E*)-3,3,3-trifluoroprop-1-en-1-yl]benzene (25a)[279]



Synthesised from **22a** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH) afforded 40% of the title compound by ^{19}F NMR. Conditions B (Umemoto **18a**, MeOH) afforded 7% **38a** by ^{19}F NMR. When conditions A were applied to (*Z*)-**22a** (using 5 mol% $Ru(bpy)_3Cl_2 \cdot 6H_2O$), 39% **25a** was detected by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.06 (dq, *J* = 16.5 Hz, 6.5 Hz, 1H), 6.56–6.90 (m, 2H), 7.08 (dq, *J* = 16.5 Hz, 2.0 Hz, 1H), 7.36–7.41 (m, 2H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –63.19 (dd, *J* = 6.5 Hz, 2.0 Hz).

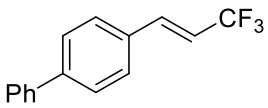
(*E*)-1-Methyl-4-(3,3,3-trifluoroprop-1-en-1-yl)benzene (25c)[279]



Synthesised from **22c** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH) afforded 39% of the title compound by ^{19}F NMR. In TFE (Conditions C: Togni **19a**, TFE), 28% **25c** was detected by ^{19}F NMR. Conditions B (Umemoto **18a**, MeOH) afforded 24% **25c** by ^{19}F NMR.

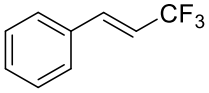
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 6.10 (dq, *J* = 16.0 Hz, 6.5 Hz, 1H), 7.06 (dq, *J* = 16.0 Hz, 2.0 Hz, 1H), 7.21–7.32 (m, 4H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ −63.60 (dd, *J* = 7.0 Hz, 2.0 Hz).

1-Phenyl-4-[(1*E*)-3,3,3-trifluoroprop-1-en-1-yl]benzene (25d)[39]



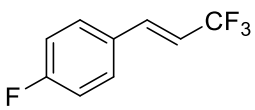
Synthesised from **22d** following GP 2-E (0.25 mmol). Conditions A (Togni **19a**, MeOH) afforded 65% of the title compound by ^{19}F NMR. Purification by silica flash column chromatography (eluent: pentane) gave 31 mg (50% yield) of the product as a white solid. In TFE (Conditions C: Togni **19a**, TFE), 52% **25d** was detected by ^{19}F NMR. Conditions B (Umemoto **18a**, MeOH) afforded 63% **25d** by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.25 (dq, *J* = 16.0 Hz, 6.5 Hz, 1H), 7.20 (dq, *J* = 16.0 Hz, 2.0 Hz, 1H), 7.36–7.40 (m, H), 7.45–7.49 (m, 2H), 7.52–7.54 (m, 2H), 7.60–7.64 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 115.8 (q, *J* = 34 Hz), 123.8 (q, *J* = 262 Hz), 127.2, 127.7, 128.0, 128.1, 129.1, 132.5, 137.3 (q, *J* = 7 Hz), 140.2, 143.0; **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –63.18 (dd, *J* = 6.5 Hz, 2.0 Hz).

[(1*E*)-3,3,3-Trifluoroprop-1-en-1-yl]benzene (25e)[280]



Synthesised from **22e** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH) afforded 57% of the title compound by ^{19}F NMR. In TFE (Conditions C: Togni **19a**, TFE), 62% **25e** was detected by ^{19}F NMR. Conditions B (Umemoto **18a**, MeOH) afforded 50% **25e** by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.12 (dq, *J* = 16.0 Hz, 6.5 Hz, 1H), 7.19 (dq, *J* = 16.0 Hz, 2.0 Hz, 1H), 7.36–7.59 (m, 5H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –63.76 (dd, *J* = 7.0 Hz, 2.0 Hz).

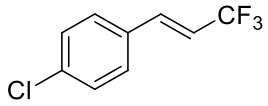
1-Fluoro-4-[(1*E*)-3,3,3-trifluoroprop-1-en-1-yl]benzene (25f)[250]



Synthesised from **22f** following GP 2-E (0.25 mmol scale). Conditions B (Umemoto **18a**, MeOH, 5 mol% $Ru(bpy)_3Cl_2 \cdot 6H_2O$)

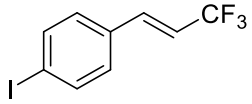
afforded 40% **25f** by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.96 (dq, *J* = 16.0 Hz, 6.5 Hz, 1H), 7.17 (dq, *J* = 16.0 Hz, 2.0 Hz, 1H), 6.76–7.74 (m, 4H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –63.85 (dd, *J* = 6.5 Hz, 2.0 Hz).

1-Chloro-4-[(1*E*)-3,3,3-trifluoroprop-1-en-1-yl]benzene (25g)[279]



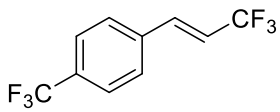
Synthesised from **22g** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH) afforded 45% of the title compound by ^{19}F NMR. In TFE (Conditions C: Togni **19a**, TFE), 73% **25g** was detected by ^{19}F NMR. Conditions B (Umemoto **18a**, MeOH) gave 52% **25g** by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.12 (dq, *J* = 16.0 Hz, 6.5 Hz, 1H), 7.00 (dq, *J* = 16.0 Hz, 2.0 Hz, 1H), 7.18–7.40 (m, 4H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –64.60 (dd, *J* = 6.5 Hz, 2.0 Hz).

1-Iodo-4-[(1*E*)-3,3,3-trifluoroprop-1-en-1-yl]benzene (25i)



Synthesised from **22i** following GP 2-E (0.25 mmol scale). Conditions B (Umemoto **18a**, MeOH) gave 58% **25i** by ^{19}F NMR. Purification by silica flash column chromatography (eluent: pentane) afforded 33 mg (44% yield) of the title compound as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.96 (dq, *J* = 16.0 Hz, 6.5 Hz, 1H), 6.82 (dq, *J* = 16.0 Hz, 2.0 Hz, 1H), 7.06–7.47 (m, 4H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –63.68 (dd, J = 6.5 Hz, 2.0 Hz).

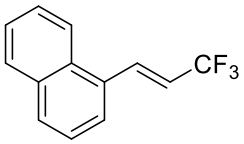
1,1,1-Trifluoro-4-[(1*E*)-3,3,3-trifluoroprop-1-en-1-yl]benzene (25j)[281]



Synthesised from **22j** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH) afforded 30% of the title compound by ^{19}F NMR. In TFE (Conditions C: Togni **19a**, TFE), 55% **25j** was detected by ^{19}F NMR. Conditions B (Umemoto **18a**, MeOH) gave 77% **25j** by ^{19}F NMR. Purification by silica flash column chromatography (eluent: pentane) afforded 20 mg (33% yield) of the product as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.14 (dq, *J* = 16.0 Hz,

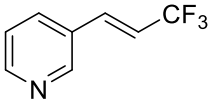
6.5 Hz, 1H), 7.08 (dq, *J* = 16.0 Hz, 2.0 Hz, 1H), 7.14–7.19 (m, 2H), 7.34–7.38 (m, 2H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) –63.60 (s, 3F), –64.50 (dd, J = 6.5 Hz, 2.0 Hz, 3F).

(*E*)-2-(3,3,3-Trifluoroprop-1-enyl)naphthalene (25k)[39]



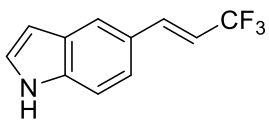
Synthesised from **22k** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH) afforded 20% of the title compound by ^{19}F NMR. In TFE (Conditions C: Togni **19a**, TFE), 10% **25k** was detected by ^{19}F NMR. Conditions B (Umemoto **18a**, MeOH) gave 25% **25k** by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.20 (dq, *J* = 16.0 Hz, 6.5 Hz, 1H), 7.40–8.76 (m, 7H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –63.25 (dd, *J* = 6.5 Hz, 2.0 Hz).

(*E*)-(3,3,3-Trifluoroprop-1-en-1-yl)pyridine (25l)[250]



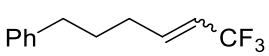
Synthesised from **22l** following GP 2-E (0.25 mmol scale). Conditions B (Umemoto **18a**, MeOH, 5 mol% $Ru(bpy)_3Cl_2 \cdot 6H_2O$) gave 22% **25l** by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.78 (dq, *J* = 16.0 Hz, 6.5 Hz, 1H), 7.13 (dq, *J* = 16.0 Hz, 2.0 Hz, 1H), 7.30–8.72 (m, 4H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –64.56 (dd, *J* = 6.5 Hz, 2.0 Hz).

(*E*)-5-(3,3,3-Trifluoroprop-1-en-1-yl)-1*H*-indole (25m)[250]



Synthesised from **22m** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH, 5 mol% $Ru(bpy)_3Cl_2 \cdot 6H_2O$) afforded 9% of the title compound by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.02 (dq, *J* = 16.0 Hz, 6.5 Hz, 1H), 7.08 (dq, *J* = 16.0 Hz, 2.0 Hz, 1H), 7.20–8.11 (m, 5H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –64.83 (dd, *J* = 6.5 Hz, 2.0 Hz).

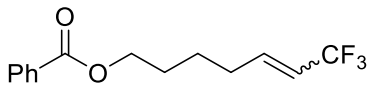
(6,6,6-Trifluorohex-3-En-1-yl)benzene (25o)[279]



Synthesised from **23o** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH) afforded 15% of **25o** by ^{19}F NMR in a 1:1.2 *E*:*Z* ratio.

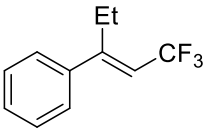
Hydrotrifluoromethylation of **34o** following GP 2-F (0.25 mmol) afforded 50% of **25o** by ^{19}F NMR in a 1:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.94–2.01 (m, 2H, *E*, *Z*), 2.17–2.22 (m, 2H, *E*, *Z*), 5.58–5.67 (m, 1H, *E*, *Z*), 5.69 (dt, *J* = 11.5 Hz, 8.0 Hz, 1H, *Z*), 6.34–6.43 (m, 1H, *E*), 7.10–7.30 (m, 5H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –56.53 (dt, *J* = 9.5 Hz, 2.0 Hz, 3F, *Z*), –66.01 (d, *J* = 8.0 Hz, 3F, *E*).

7,7,7-Trifluorohept-5-en-1-yl benzoate (25p)[176]



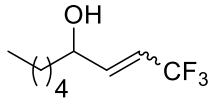
Synthesised from **23p** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH) afforded 9% of **25p** by ^{19}F NMR in a 1:1.4 *E*:*Z* ratio. In TFE (Conditions C: Togni **19a**, TFE), 6% **25p** was detected by ^{19}F NMR in a 2:1 *E*:*Z* ratio. Hydrosilylation of **34p** following GP 2-F and purification by silica flash column chromatography (eluent: 5% Et_2O in pentane) afforded 46 mg (68% yield) of the title compound as a colourless oil, in a 3.5:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.50–1.66 (m, 2H, *E*, Z), 1.69–1.88 (m, 2H, *E*, *Z*), 2.13–2.23 (m, 2H, *E*), 2.28–2.35 (m, 2H, *Z*), 4.25–4.31 (m, 2H, *E*, *Z*), 5.52–5.62 (m, 2H, *E*, *Z*), 5.92 (dt, *J* = 11.5 Hz, 8.0 Hz, 1H, Z), 6.31 (dtq, *J* = 16.0 Hz, 7.0 Hz, 2.0 Hz, 1H, *E*), 7.31–7.39 (m, 2H, *E*, *Z*), 7.47–7.50 (m, 1H, *E*, *Z*), 7.96–8.08 (m, 2H, *E*, *Z*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 24.6 (*E*), 25.4 (*Z*), 28.0 (*Z*), 28.2 (*E*), 28.2 (*Z*), 31.0 (*E*), 64.5 (*E*), 64.5 (*Z*), 118.9 (q, *J* = 34 Hz, *E*, *Z*), 123.0 (q, *J* = 267 Hz, *E*, *Z*), 128.4 (*E*, *Z*), 129.5 (*E*, *Z*), 130.3 (*E*, *Z*), 132.9 (*Z*), 133.0 (*E*), 140.0 (q, *J* = 7 Hz, *E*), 142.3 (q, *J* = 6 Hz, *Z*), 166.6 (*E*, *Z*); **^{19}F NMR** (376.5 MHz, CD_3Cl) δ −58.06 (dt, *J* = 8.0 Hz, 2.0 Hz, *Z*), −63.98 (dq, *J* = 5.5 Hz, 2.0 Hz, *E*); **IR** (neat) ν 1717, 1270, 1113, 711; **HRMS** (ESI) calculated for $C_{14}H_{15}F_3NaO_2$ $[M+Na]^+$ 295.0916, found 295.0911.

[(2*E*)-1,1,1-Trifluoropent-2-en-3-yl]benzene (25q)



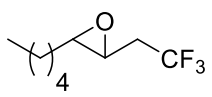
Synthesised following GP 2-E (0.25 mmol scale) from **22q**. Conditions A (Togni **19a**, MeOH) afforded 47% of the title compound by ^{19}F NMR. Purification by silica flash column chromatography (eluent: pentane) afforded 9 mg (17% yield) of **25q** as a colourless oil. (Note: **25q** is very volatile). In TFE (Conditions C: Togni **19a**, TFE), 13% **25q** was detected by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.0 Hz, 3H), 3.49 (d, *J* = 7.0 Hz, 2H), 5.75 (q, *J* = 8.5 Hz, 1H), 7.39 (brs, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 15.3, 65.9, 150.5 (q, *J* = 33.5 Hz), 126.6, 128.6, 128.8, 139.6, 155.6 (q, *J* = 6 Hz), (Note: CF_3 not detected); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –64.00 (dd, *J* = 6.5 Hz, 2.0 Hz); **IR** (neat) ν 1444, 1265, 697.

1,1,1-Trifluorononon-2-en-4-ol (25r)



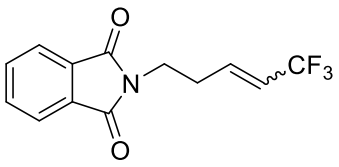
Synthesised from **34r** following GP 2-F (0.25 mmol scale). Purification by silica flash column chromatography (eluent: 10% Et_2O in PET 30/40) afforded 15 mg (31% yield) of the title compound as a colourless oil in a 9:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.86–0.94 (m, 3H, *E*, *Z*), 1.27–1.37 (m, 6H, *E*, *Z*), 1.55–1.60 (m, 2H, *E*, *Z*), 4.24–4.31 (m, 1H, *E*), 4.37 (dt, *J* = 6.5 Hz, 2.0 Hz, 1H, *Z*), 5.63 (ddq, *J* = 11.5 Hz, 8.5 Hz, 1.0 Hz, 1H, *Z*), 5.89 (ddq, *J* = 16.0 Hz, 6.5 Hz, 2.0 Hz, 1H, *E*), 5.91 (ddq, *J* = 17.0 Hz, 14.5 Hz, 2.0 Hz, 1H, *Z*), 6.40 (ddq, *J* = 16.0 Hz, 4.0 Hz, 2.0 Hz, 1H *E*); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ −63.99 (dt, *J* = 7.0 Hz, 2.0 Hz, 3F, *E*), −64.80 (t, *J* = 11.0 Hz, 3F, *Z*).

Trimethyl-[2,2,2-trifluoro-1-(3-methyloxiran-2-yl)ethyl]silane (31r)



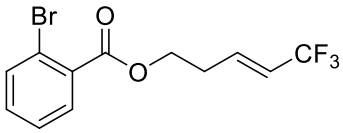
Synthesised from **22r** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH) afforded 19% of the title compound by ^{19}F NMR, as a 1:1 *cis*:*trans* mixture. **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –64.4 (t, *J* = 2.0 Hz, 3F, *cis*), –64.6 (t, *J* = 2.0 Hz, 3F, *trans*).

2-(5,5,5-Trifluoropent-3-en-1-yl)-1*H*-isoindole-1,3(2*H*)-dione (25s)[176]



Synthesised from **34s** following GP 2-F (0.25 mmol scale). Purification by silica flash column chromatography (eluent: 30% DCM in Hexane) afforded 40 mg (59% yield) of the title compound as a white solid, in a 3:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.46–2.53 (m, 1H, *E*), 2.61–2.69 (m, 1H, *Z*), 3.74–3.78 (m, 2H, *E*, *Z*), 5.56–5.67 (m, 1H, *E*, *Z*), 5.98 (dt, *J* = 11.5 Hz, 8.0 Hz, 1H, *Z*), 6.31 (dtq, *J* = 16.0 Hz, 7.0 Hz, 2.0 Hz, 1H, *E*), 7.63–7.68 (m, 2H, *E*, *Z*), 7.76–7.81 (m, 2H, *E*, *Z*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 30.6 (*E*, *Z*), 36.2 (*E*), 36.6 (*Z*), 121.0 (q, *J* = 34 Hz, *Z*), 121.1 (q, *J* = 34 Hz, *E*), 123.3 (*Z*), 123.4 (*E*), 131.9 (*Z*), 131.9 (*E*), 136.3 (q, *J* = 7 Hz, *E*), 138.4 (q, *J* = 6 Hz, *Z*), 168.1 (*E*, *Z*), (Note: CF_3 not detected); **^{19}F NMR** (376.5 MHz, CD_3Cl) δ –58.25 (dt, *J* = 8.0 Hz, 2.0 Hz, *Z*), −64.46 (dq, *J* = 4.5 Hz, 2.0 Hz, *E*); **IR** (neat) ν 1774, 1707, 1395, 1115, 719; **HRMS** (FI) calculated for $C_{13}H_{10}NO_2F_3$ $[M]^+$ 269.0664, found 269.0657.

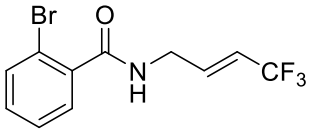
5,5,5-Trifluoropent-3-en-1-yl 2-bromobenzoate (25t)[176]



Synthesised from **34t** following GP 2-F (0.25 mmol scale). Purification by silica flash column chromatography (eluent: 1% Et_2O in PET 30/40) afforded 48 mg (59% yield) of the title compound as a pale yellow oil, in a 3:1 *E*:*Z* ratio. Further purification by preparative TLC (eluent: 5% Et_2O in PET 30/40) afforded 28 mg (35% yield) of the pure *E* isomer. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.54–2.61 (m, 2H), 4.38 (t, *J* = 6.5 Hz, 2H), 5.71 (dqt, *J* = 16.0 Hz, 6.5 Hz, 1.5 Hz, 1H), 6.39 (dqt, *J* = 16.0 Hz, 7.0 Hz, 2.0 Hz, 1H), 7.24–7.32 (m, 2H), 7.59 (dd, *J* = 7.5 Hz, 2.0 Hz, 1H), 7.68 (dd, *J* = 7.5 Hz, 2.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 30.8, 63.3, 121.1 (q, *J* = 34 Hz), 121.6, 122.7 (q, *J* = 269 Hz), 127.2, 131.3, 131.9, 132.7, 134.4, 136.1 (q, *J* = 7 Hz), 166.0; **^{19}F NMR** (376.5 MHz, CD_3Cl) δ –64.37 (dq, *J* = 5.5 Hz, 2.0 Hz); **IR**

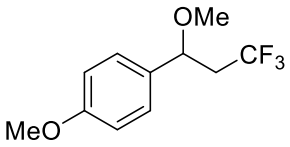
(neat) ν 1733, 1290, 1250, 1118, 745; **HRMS** (CI) calculated for $C_{12}H_{10}BrF_3O_2$ $[M+H]^+$ 322.9895, found 322.9893.

2-Bromo-*N*-[(2*E*)-4,4,4-trifluorobut-2-en-1-yl]benzamide (25u)[176]



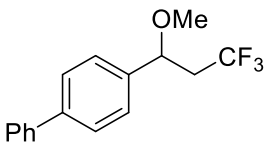
Synthesised from **34u** following GP 2-F (0.25 mmol scale). Purification by silica flash column chromatography (eluent: 10% EtOAc in PET 30/40) afforded 43 mg (56% yield) of the title compound as a white solid, in a 9:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.10–4.17 (m, 2H), 5.83 (dqt, *J* = 16.0 Hz, 6.5 Hz, 2.0 Hz, 1H), 6.28 (brs, 1H, N*H*), 6.40 (dqt, *J* = 16.0 Hz, 5.0 Hz, 2.0 Hz, 1H), 7.22 (dt, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.30 (dt, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.46 (dd, *J* = 7.5 Hz, 2.0 Hz, 1H), 7.52 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 40.0, 119.1, 119.8 (q, *J* = 34.0 Hz), 122.8 (q, *J* = 269.0 Hz), 127.7, 129.2, 131.6, 133.5, 135.9 (q, *J* = 6.5 Hz), 137.0, 167.6; **^{19}F NMR** (377 MHz, $CDCl_3$) δ −64.16 (dq, *J* = 9.0 Hz, 2.0 Hz); **IR** (neat) ν 1646, 1536, 1298, 1272, 1119, 961, 751; **HRMS** (CI) calculated for $C_{11}H_{13}N_2OBrF_3$ $[M+NH_4]^+$ 325.0163, found 325.0160; **Mp** 69–71 °C.

1-(3,3,3-trifluoro-1methoxypropyl)-4-(trifluoromethyl)benzene (26a)[282]



Synthesised from **22a** following GP 2-E in MeOH (0.25 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.18–2.39 (m, 1H), 2.47–2.70 (m, 1H), 3.12 (s, 3H), 3.72 (s, 3H), 4.34 (dd, *J* = 8.5 Hz, 4.5 Hz, 1H), 6.81–6.86 (m, 2H), 7.13–7.19 (m, 2H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ −64.00 (t, *J* = 10.5 Hz).

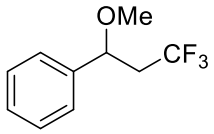
4-(3,3,3-Trifluoro-1-methoxypropyl)biphenyl (26d)



Synthesised from **22d** following GP 2-E in MeOH (0.25 mmol scale). Isolated by preparative TLC (eluent: pentane) to afford 14 mg (20% yield) of the title compound as an off-white solid.

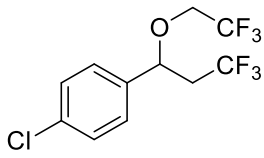
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35–2.48 (m, 1H), 2.62–2.76 (m, 1H), 3.27 (s, 3H), 4.51 (dd, *J* = 8.5 Hz, 4.0 Hz, 1H), 7.35–7.47 (m, 5H), 7.59–7.63 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 42.4 (q, *J* = 27 Hz), 56.9, 72.3, 127.1, 127.2, 127.6, 127.7, 129.0, 139.1, 140.7, 141.5, (Note: CF_3 not detected); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –63.67 (t, *J* = 10.5 Hz).

(3,3,3-Trifluoro-1-methoxypropyl)benzene (26e)[283]



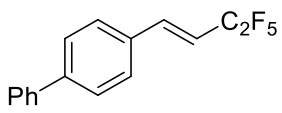
Synthesised from **22e** following GP 2-E in MeOH (0.25 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.30–2.41 (m, 1H), 2.60–2.66 (m, 1H), 3.21 (s, 3H), 4.44 (dd, *J* = 8.0 Hz, 4.0 Hz, 1H), 7.43-7.63 (m, 5H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –64.37 (t, *J* = 9.0 Hz).

1-Chloro-4-(3,3,3-trifluoro-1-methoxypropyl)benzene (26g)



Synthesised from **22g** following GP 2-E in TFE (0.25 mmol scale). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.23–3.43 (m, 1H), 2.56–2.72 (m, 1H), 3.62 (q, *J* = 10.0 Hz, 2H), 4.67 (dd, *J* = 8.5 Hz, 4.0 Hz, 1H), 7.19–7.23 (m, 2H), 7.28–7.32 (m, 2H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –64.29 (t, *J* = 10.5 Hz, 3F), –64.79 (t, *J* = 10.0 Hz, 3F).

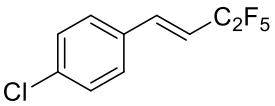
4-[(1*E*)-3,3,4,4,4-Pentafluorobut-1-en-1-yl]biphenyl (32d)[257]



Synthesised from **22d** following GP 2-E (0.25 mmol). Conditions D (Togni **19c**, MeOH) afforded 90% **45d** by ^{19}F NMR. Purification by silica flash column chromatography (eluent: pentane) followed by preparative TLC (eluent: pentane) gave 30 mg (40% yield) of the product as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.20 (dt, *J* = 16.0 Hz, 12.0 Hz, 1H), 7.21 (dt, *J* = 16.0 Hz, 2.0 Hz, 1H), 7.35–7.39 (m, 1H), 7.43–7.47 (m, 2H), 7.53–7.55 (m, 2H), 7.58–7.63 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 112.9 (tq, *J* = 249 Hz, 38 Hz), 114.0 (23 Hz), 119.2 (qt, *J* = 286 Hz, 40 Hz), 127.2, 127.7, 128.0, 128.2, 129.1, 132.6, 139.3 (t *J* = 9 Hz), 140.2,

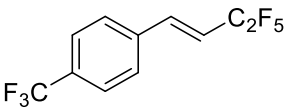
143.1; **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ −85.02 (t, *J* = 2.0 Hz, 3F), −114.76–−114.82 (m, 2F).

1-Chloro-4-[(1*E*)-3,3,4,4,4-pentafluorobut-1-en-1-yl]benzene (32g)



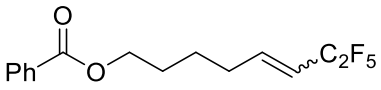
Synthesised from **22g** following GP 2-E (0.25 mmol scale). Conditions D (Togni **19c**, MeOH) afforded 81% of the title compound by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.12 (dq, *J* = 16.0 Hz, 6.5 Hz, 1H), 7.00 (dq, *J* = 16.0 Hz, 2.0 Hz, 1H), 7.18–7.40 (m, 4H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −85.23 (s, 3F), −115.20 (d, *J* = 9.0 Hz, 2F).

1,1,1-Trifluoro-4-[(1*E*)- 3,3,4,4,4-pentafluorobut-1-en-1-yl]benzene (32j)



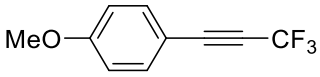
Synthesised from **22j** following GP 2-E (0.25 mmol scale). Conditions D (Togni **19c**, MeOH) afforded 63% of the title compound by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.15 (dt, *J* = 16.0 Hz, 12.0 Hz, 1H), 7.07 (dt, *J* = 16.0 Hz, 2.0 Hz, 1H), 7.29–7.32 (m, 2H), 7.37–7.39 (m, 2H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) –63.25 (s, 3F), –85.34 (t, J = 2.0 Hz, 3F), −115.67–−115.73 (m, 2F).

7,7,8,8,8-Pentafluorooct-5-en-1-yl benzoate (32p)



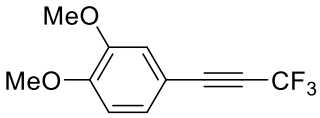
Synthesised from **23p** following GP 2-E (0.25 mmol scale). Conditions D (Togni **19c**, MeOH) afforded 33% **32p** by ^{19}F NMR in a 2.3:1 *E*:*Z* ratio. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.51 (dt, *J* = 18.5 Hz, 1.5 Hz, 1H, *E*), 5.56 (t, *J* = 11.5 Hz, 1H, *Z*), 5.96 (dt, *J* = 18.5 Hz, 6.0 Hz, 1H, *E*), 6.35 (dtt, *J* = 16.0 Hz, 7.0 Hz, 2.0 Hz, 1H, *Z*); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ −81.21 (s, 3F, *E*), –85.62 (s, 3F, *Z*), –115.38 (dt, *J* = 11.5 Hz, 2.0 Hz, 1F, *E*), –116.24 (d, *J* = 15.0 Hz, 1F, *E*), –119.0 (dd, *J* = 270.5 Hz, 16.0 Hz, 2F, *Z*).

1-Methoxy-4-(3,3,3-trifluoroprop-1-yn-1-yl)-benzene (33a)[284]



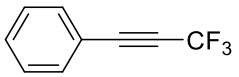
Synthesised from **21a** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH) afforded 40% **33a** by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 6.69–6.73 (m, 2H), 7.33–7.36 (m, 2H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –49.40 (s).

1,2-Dimethoxy-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene (33b)



Synthesised from **21b** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH) afforded 22% **33b** by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.85 (s, 6H), 6.75–7.10 (m, 3H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ –49.40 (s).

(3,3,3-Trifluoroprop-1-yn-1-yl)benzene (33e)[285]

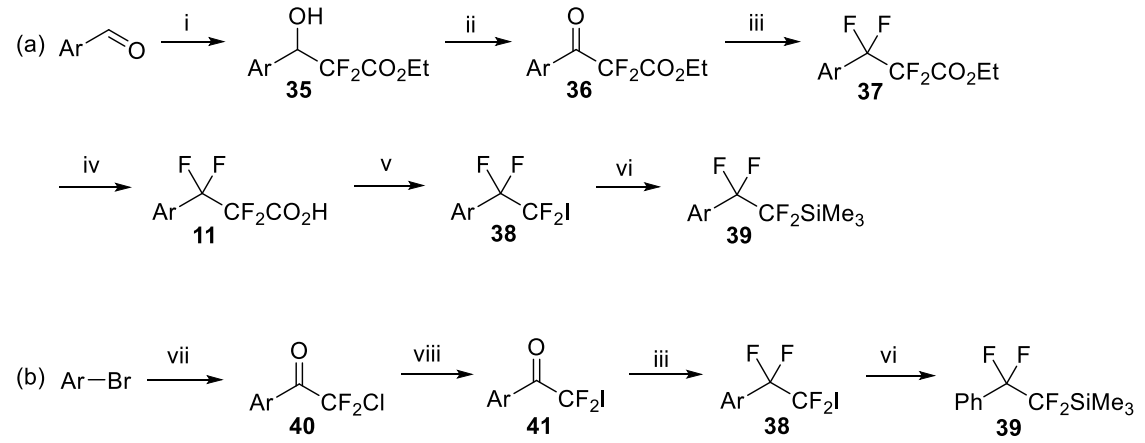


Synthesised from **21e** following GP 2-E (0.25 mmol scale). Conditions A (Togni **19a**, MeOH) afforded 4% **33e** by ^{19}F NMR. With Umemoto's reagent **18a** (Conditions B) 8% **33e** was detected by ^{19}F NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50–7.55 (m, 2H); **^{19}F NMR** (376.5 MHz, CD_2Cl_2) δ −49.80 (s).

6.2.4 Synthesis and Reactivity of 'Ruppert-Prakash' like Reagents

6.2.4.1 Synthesis of [2-Aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes 39

6.2.4.1.1 Before Optimisation

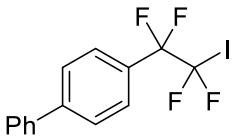


Conditions: (i) Zn, $BrCF_2CO_2Et$, THF, 70 °C, 2 h; (ii) Dess-Martin, DCM, rt, 3 h; (iii) DAST, DCM, rt, 16 h; (iv) LiOH, H_2O, EtOH, rt, 16 h; (v) DIH, DCE, hν, 85 °C, 16 h; (vi) Mg, TMSCl, DMF, rt, 16 h; (vii) 1. Mg, Et_2O, rt, 1h; 2. $ClCF_2CO_2H$, –10 °C, 1 h; (viii) 1. Zn, TMSCl, MeCN, rt, 3 h; 2. I_2, rt, 5 h.

Route (a):

For synthesis and analysis of **35a**, **36a**, **37a** and **11a** *via* route (a) see section 6.2.1.5.

4-(1,1,2,2-tetrafluoro-2-iodoethyl)biphenyl (38a)

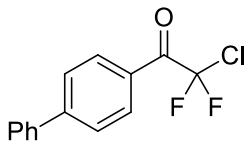


Synthesised following a literature procedure:[227] 298 mg **11a** (1.0 mmol, 1.0 eq) and 570 mg 1,3-diiodo-5,5-dimethylhydantoin (1.5 mmol, 1.5 eq) were refluxed in 4 mL (0.25 M) DCE for 24 h under UV irradiation. The reaction was cooled to rt and quenched with $NaHSO_{3(aq)}$. The mixture was extracted with DCM, washed with $NaHCO_3$, dried over MgSO4 and concentrated *in vacuo*. Purification by silica flash column chromatography (eluent: PET 30/40) afforded 185 mg (49% yield) of an inseparable 1:1 mixture of the desired product and periodinated side-products. These were separated by prep-HPLC to yield the title compound as a white solid. (Note: Compound **38a** is very unstable towards protodeiodination on silica gel and in light.

It is best used as soon as purified, or stored in the freezer, wrapped in tin foil.) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (tt, *J* = 7.0 Hz, 2.0 Hz, 1H), 7.35–7.40 (m, 2H), 7.49–7.52 (m, 2H), 7.54–7.60 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 97.9 (tt, *J* = 319 Hz, 48 Hz), 115.0 (tt, *J* = 254 Hz, 30 Hz), 126.5 Hz (t, *J* = 26 Hz), 127.2, 127.3, 127.7 (t, *J* = 6 Hz), 128.2, 129.0, 139.8, 144.6; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −58.57 (t, *J* = 7.0 Hz, 2F), −104.17 (t, *J* = 7.0 Hz, 2F); **IR** (neat) ν 1089, 801, 745; **HRMS** (FI) calculated for $C_{14}H_9F_4I$ $[M]^+$ 379.9685, found 379.9691; **Mp** 46–48 °C.

Route (b):

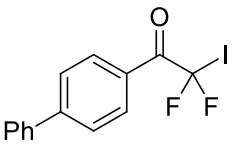
1-(Biphenyl-4-yl)-2-chloro-2,2-difluoroethanone (40a)



2.0 g magnesium turnings (84.0 mmol, 3.33 eq) were added to a two-neck round-bottom flask equipped with a reflux condenser and a magnetic stirrer bar. Dry THF was added until the turnings were fully covered (*ca.* 5 mL). The magnesium was activated by addition of dibromoethane and 2.0 g 3-bromobiphenyl (in 5 mL THF) was added neat. The mixture was stirred until the Grignard reaction began (if necessary, heat was applied to initiate the reaction). The remaining 17.3 g 3-bromobiphenyl (combined: 83.0 mmol, 3.3 eq) were added dropwise as a solution in 50 mL THF (end concentration: 1.38 M). After addition was complete, the mixture was allowed to stir for 1 hour at rt. It was then transferred dropwise (*via* cannula) to a solution of 2.1 mL chlorodifluoroacetic acid (25.0 mmol, 1.0 eq) in 31 mL THF (0.8 M) at –10 °C. The reaction was stirred at −10 °C for 1 hour, after which it was carefully quenched with $NH_4Cl_{(aq)}$ and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash silica column chromatography (eluent: pentane to 10% Et_2O in PET 30/40) to give 4.0 g (59% yield) of

the title compound as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29–7.38 (m, 3H), 7.49–7.52 (m, 2H), 7.59–7.62 (m, 2H), 8.06 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 120.3 (t, *J* = 305 Hz), 127.4, 127.5, 128.0, 128.9, 129.2, 131.2 (t, *J* = 3 Hz), 139.2, 147.9, 180.8 (t, *J* = 29 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –60.66 (s); **IR** (neat) ν 1708, 1601, 1154, 985, 889, 739, 693, 647; **HRMS** (FI) calculated for $C_{14}H_9OF_2Cl$ $[M]^+$ 266.0310, found 266.0309.

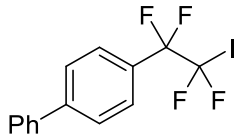
1-(Biphenyl-4-yl)-2,2-difluoro-2-iodoethanone (41a)



To a two-neck round-bottom flask equipped with a reflux condenser and a magnetic stirrer bar were added 1.16 g zinc powder (17.8 mol, 1.25 eq) and 11 mL MeCN (1.3 M). The zinc was activated with several drops of dibromoethane and chlorotrimethylsilane. When slight bubbling was observed, 2.3 mL chlorotrimethylsilane (17.8 mmol, 1.25 eq) was added, followed by 3.79 g 1-(biphenyl-4-yl)-2-chloro-2,2-difluoroethanone **40a** (14.2 mmol, 1.0 eq). The mixture was stirred for 3 hours at rt, after which 5.08 g iodine (20.0 mmol, 1.38 eq) was added and stirring continued for another 5 hours. The reaction was then quenched with aqueous sodium thiosulfate and extracted with Et_2O. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica flash column chromatography (eluent: 10% Et_2O in PET 30/40) to afford 2.65 g (52% yield) of the title compound as a dark red oil (together with ca. 10% 1-(biphenyl-4-yl)-2,2-difluoroethanone). (Note: Compound **41a** is unstable on silica gel and towards light. It is best used as soon as purified, or kept in the freezer, wrapped in tin foil.) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50–7.54 (m, 1H), 7.55–7.60 (m, 2H), 7.71–7.74 (m, 2H), 7.79–7.82 (m, 2H), 8.31–8.34 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 95.8 (t, *J* = 326 Hz), 127.4, 127.5, 128.9, 129.2, 131.5 (t, *J* = 3 Hz), 139.2, 147.7, 182.0 (t, *J* = 23 Hz); **^{19}F NMR**

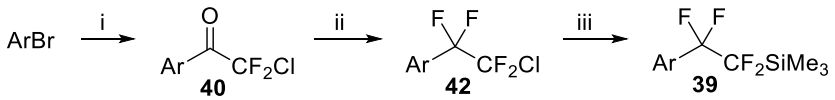
(376.5 MHz, $CDCl_3$) δ –53.93 (s); **IR** (neat) ν 1697, 1601, 1269, 1140, 960, 908, 865, 727, 689; **HRMS** (FI) calculated for $C_{14}H_9OI$ $[M]^+$ 357.9702, found 357.9670.

4-(1,1,2,2-tetrafluoro-2-iodoethyl)biphenyl (38a)



To a solution of 6.0 g (16.8 mmol, 1.0 eq) 1-(biphenyl-4-yl)-2,2-difluoro-2-iodoethanone **41a** in 56 mL DCM (0.33 M) was added 3.3 mL (25.2 mmol, 1.5 eq) DAST. The reaction was stirred at room temperature for 24 h, after which it was quenched with $NaHCO_{3(aq)}$, extracted with DCM, dried over $MgSO_4$ and evaporated. The crude product was purified by silica flash column chromatography (eluent: pentane) to afford 5.5 g (87% yield) of the title compound as a white solid. The compound is very unstable towards protodeiodination on silica gel and in light. For analytical data see above.

6.2.4.1.2 Optimised Conditions



Conditions: (i) 1. Mg, LiCl, THF, rt, 2 h; 2. $ClCF_2CO_2Me$, THF, –40 °C, 1h; (ii) DAST, $CHCl_3$, 60 °C, 16h; (iii) Mg, TMSCl, DMF, 0 °C to rt, 16 h.

NB. Substrates marked with an asterix (*) were synthesised by Dr. E. Dubost.

General procedure 3-A: Schlosser Grignard reaction for the formation of 1-aryl-2-halo-2,2-difluoroethanone

Magnesium turnings (1.5 eq) and LiCl (1.5 eq) were added to a Schlenck flask equipped with a magnetic stirrer bar. The flask was flame dried at 630 °C under vacuum and back-flushed with N_2 three times. Anhydrous THF was added until the turnings were fully covered. A solution of bromoaryl (1.0 eq) in the remaining anhydrous THF (final concentration 1.6 M) was slowly added to the flask and the mixture was stirred at room

temperature for 2 h. The reaction was then cooled to –40 °C and methyl chlorodifluoroacetate (1.1 eq) in anhydrous THF (1.8 M) was added dropwise. The reaction was stirred at –40 °C for 1 hour, after which it was carefully quenched with $NH_4Cl_{(aq)}$ and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography.

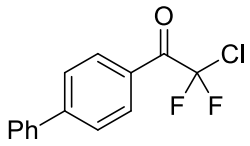
General procedure 3-B: Fluorination of 1-aryl-2-halo-2,2-difluoroethanone with DAST

In a two-neck flask equipped with a reflux condenser under nitrogen, DAST (2.0 eq) was added slowly to a solution of 1-aryl-2-halo-2,2-difluoroethanone (1.0 eq) in anhydrous chloroform (0.5 M) at room temperature. The mixture was stirred at 60 °C for 24 hours, after which it was cooled to 0 °C, carefully quenched with sat. $NaHCO_{3(aq)}$ and extracted with DCM. The organic layers were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude mixture was purified by silica flash column chromatography.

General procedure 3-C: Silylation of (2-chloro-1,1,2,2-tetrafluoroethyl)arenes

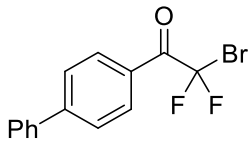
In a flame dried Schlenck tube, trimethylsilyl chloride (4.0 eq) was added to magnesium turnings (2.0 eq) in anhydrous DMF (0.3 M) at room temperature. A solution of (2-chloro-1,1,2,2-tetrafluoroethyl)arene (1.0 eq) in anhydrous DMF (2.0 M) was added dropwise at 0 °C and the reaction was stirred for 16 hours at room temperature. The reaction was quenched with $NH_4Cl_{(aq)}$, filtered over Celite and extracted with Et_2O. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude products were purified by silica flash column chromatography. If necessary, mixed fractions of product **39** and protodesilylated by-product **16** were left to recrystallise (neat) at room temperature to afford a further batch of pure **39**.

1-(Biphenyl-4-yl)-2-chloro-2,2-difluoroethanone (40a)



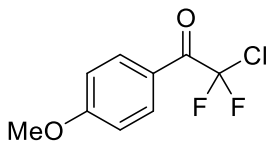
Synthesised from 4-bromo-1,1'-biphenyl following GP 3-A (30.0 mmol scale). Purification by flash silica column chromatography (eluent: 10% Et_2O in PET 40/60) afforded 5.45g of the title compound (68% yield) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45–7.54 (m, 3H), 7.66–7.677 (m, 2H), 7.75–7.77 (m, 2H), 8.22 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 120.4 (t, *J* = 305 Hz), 127.4, 127.6, 128.0, 129.0, 129.2, 131.3 (t, *J* = 3 Hz), 139.2, 148.0, 180.8 (t, *J* = 29 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −60.66 (s); **IR** (neat) ν 1708, 1601, 1154, 985, 889, 739, 693, 647; **HRMS** (FI) calculated for $C_{14}H_9OF_2Cl$ 266.0310, found 266.0309.

1-(Biphenyl-4-yl)-2-bromo-2,2-difluoroethanone



Synthesised from 4-bromo-1,1'-biphenyl and methyl bromodifluoroacetate following GP 3-A (30.0 mmol scale). Purification by flash silica column chromatography (eluent: PET 40/60 to 10% Et_2O in PET 40/60) gave 437 mg (28% yield) of the title compound as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (tt, *J* = 7.0 Hz, 2.0 Hz, 1H), 7.35–7.40 (m, 2H), 7.52–7.54 (m, 2H), 7.60–7.64 (m, 2H), 8.09–8.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 113.8 (t, *J* = 319 Hz), 127.4, 127.5, 127.7, 128.9, 129.2, 131.3 (t, *J* = 3 Hz), 139.2, 147.9, 181.0 (t, *J* = 26 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –57.58 (s); **IR** (neat) ν 1702, 1602, 1279, 1151, 972, 872, 730, 693; **HRMS** (EI) calculated for $C_{14}H_9OBrF_2$ $[M]^+$ 309.9805, found 309.9804.

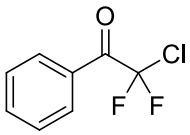
2-Chloro-2,2-difluoro-1-(4-methoxyphenyl)ethanone (40b)



Synthesised from 1-bromo-4-methoxybenzene following GP 3-A (10.0 mmol scale). Purification by silica flash column chromatography (eluent: PET 40/60 to 10% Et_2O in PET 40/60)

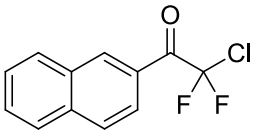
afforded 924 mg (42% yield) of the title compound as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.88 (dt, *J* = 9.0 Hz, 2.0 Hz, 2H), 7.97–8.01 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.6, 114.3, 121.9 (t, *J* = 153 Hz), 127.7, 133.1 (t, *J* = 3 Hz), 165.2, 179.7 (t, *J* = 29 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –60.26 (s); **IR** (neat) ν 1701, 1598, 1266, 1147, 1027, 981, 888, 842, 748; **HRMS** (ESI) calculated for $C_9H_7O_2ClF_2Na$ $[M+Na]^+$ 242.9995, found 242.9997.

2-Chloro-2,2-difluoro-1-phenylethanone (40d)[286]



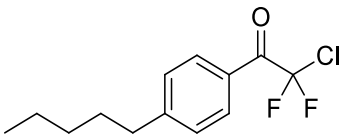
Synthesised from bromobenzene following GP 3-A (50.0 mmol scale). Purification by silica flash column chromatography (eluent: pentane to 10% Et_2O in pentane) to afford 8.47 g (89% yield) of the title compound as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55–7.60 (m, 2H), 7.71–7.75 (m, 1H), 8.14–8.17 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 120.2 (t, *J* = 306 Hz), 129.0, 129.4, 130.6 (t, *J* = 3 Hz), 135.2, 181.2 (t, *J* = 29 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –60.84 (s).

2-Chloro-2,2-difluoro-1-(naphthalen-2-yl)ethanone (40e)[287]



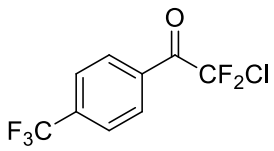
Synthesised from 2-bromonaphtalene following GP 3-A (10.0 mmol scale). Purification by flash silica column chromatography (eluent: pentane to 5% Et_2O in pentane) afforded 1.36 g of the title compound (56% yield) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (t, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.0 Hz, 1H), 7.85 (t, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 8.66 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 120.6 (t, *J* = 305 Hz), 124.7, 126.5, 127.3, 127.8, 128.9, 129.9, 130.1, 132.1, 133.4 (t, *J* = 3 Hz), 136.3, 181.1 (t, *J* = 29 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –60.09 (s).

2-Chloro-2,2-difluoro-1-(4-pentylphenyl)ethanone (40f)*



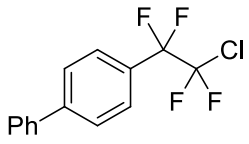
Synthesised from 1-bromo-4-pentylbenzene following GP 3-A (4.4 mmol scale). Purification by silica flash column chromatography (eluent: PET 40/60) afforded 703 mg of the title compound (61% yield) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.88–0.92 (m, 3H), 1.30–1.36 (m, 4H), 1.61–1.69 (m, 2H), 2.68–2.71 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.1, 22.6, 30.7, 31.6, 36.3, 120.5 (t, *J* = 303 Hz), 127.2, 129.2, 130.9 (t, *J* = 3 Hz), 151.7, 181.0 (t, *J* = 28 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −60.61 (s); **IR** (neat) ν 1711, 1606, 1156, 985, 891; **HRMS** (FI) calculated for $C_{13}H_{15}OF_2Cl$ 260.0779, found 260.0777.

2-Chloro-2,2-difluoro-1-[4-(trifluoromethyl)phenyl]ethanone (40g)[288]



Synthesised from 3-bromobenzotrifluoride *via* GP 3-A (10 mmol scale). The crude product was purified by silica flash column chromatography (eluent: PET 40/60 to 20% Et_2O in PET 30/40) to afford 1.34 g (54% yield) of the title compound as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 8.13 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 119.9 (t, *J* = 305 Hz), 123.2 (q, *J* = 272 Hz), 125.9 (q, *J* = 4 Hz), 130.8 (t, *J* = 3 Hz), 132.2, 136.2 (q, *J* = 33 Hz), 180.3 (t, *J* = 30 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –61.71 (t, *J* = 5.0 Hz, 2F), –63.81 (t, *J* = 6.0 Hz, 3F).

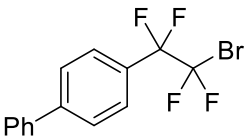
4-(2-Chloro-1,1,2,2-tetrafluoroethyl)biphenyl (42a)



Synthesised from **40a** following GP 3-B (22.3 mmol scale). Purification by silica flash column chromatography (eluent: pentane) afforded 6.17 g of the title compound (96% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43–7.47 (m, 1H), 7.49–7.54 (m, 2H), 7.63–7.66 (m, 2H), 7.71–7.75 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 115.2 (tt, *J* = 255 Hz, 34 Hz), 123.9 (tt,

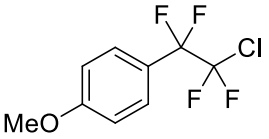
J = 300 Hz, 42 Hz), 127.4, 127.4, 127.6 (t, *J* = 7 Hz), 127.8 (t, *J* = 25 Hz), 128.4, 129.1, 139.8, 144.9; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −70.31 (s, 2F), −110.04 (s, 2F); **IR** (neat) ν 1153, 1099, 912, 828, 734, 697; **HRMS** (FI) calculated for $C_{14}H_9F_4Cl$ 288.0329, found 288.0327; **Mp** 62–63 °C.

4-(2-Bromo-1,1,2,2-tetrafluoroethyl)biphenyl (48a)



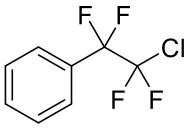
Synthesised from 1-(biphenyl-4-yl)-2-bromo-2,2-difluoroethanone following GP 3-B (1.07 mmol scale). Purification by silica flash column chromatography (eluent: pentane) afforded 331 mg (93% yield) of the title compound as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (tt, *J* = 7.5 Hz, 2.0 Hz, 1H), 7.37–7.42 (m, 2H), 7.52–7.55 (m, 2H), 7.58–7.64 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 115.0 (CF_2 – splitting not resolved), 117.9 (CF_2 – splitting not resolved), 127.4, 127.4, 127.5, 127.7 (t, *J* = 6 Hz), 128.4, 129.1, 139.9, 144.9; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −64.75 (t, *J* = 5.0 Hz, 2F), −107.83 (t, *J* = 5.0 Hz, 2F); **IR** (neat) ν 1280, 1150, 1097, 1004, 890, 860, 817, 748, 696; **HRMS** (EI) calculated for $C_{14}H_9BrF_4$ $[M]^+$ 331.9824, found 331.9828; **Mp** 51–52 °C.

1-(2-Chloro-1,1,2,2-tetrafluoroethyl)-4-methoxybenzene (42b)



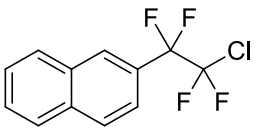
Synthesised from **40b** following GP 3-B (3.77 mmol). Purification by silica flash column chromatography (eluent: pentane) afforded 754 mg (82% yield) of the title compound as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 6.83 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.2, 113.9, 115.2 (tt, *J* = 256 Hz, 34 Hz), 120.8 (t, *J* = 25 Hz), 123.8 (tt, *J* = 298 Hz, 43 Hz), 128.6 (t, *J* = 6 Hz), 162.2; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –70.62 (t, *J* = 5 Hz, 2F), –109.48 (t, *J* = 5 Hz, 2F); **IR** (neat) ν 1615, 1518, 1311, 1289, 1262, 1242, 1181, 1151, 1095, 1059, 1023, 1005, 912, 865, 828, 789, 617; **HRMS** (EI) calculated for $C_9H_7OF_4Cl$ $[M]^+$ 242.0122, found 242.0125.

(2-Chloro-1,1,2,2-tetrafluoroethyl)benzene (42d)



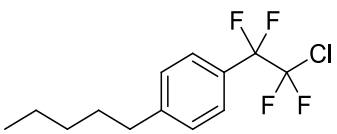
Synthesised from **40d** following GP 3-B (7.3 mmol scale). Purification by silica flash column chromatography (eluent: pentane) afforded 1.10 g of the title compound (59% yield) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.41 (m, 2H), 7.44–7.48 (m, 1H), 7.50–7.53 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 114.9 (tt, *J* = 255 Hz, 34 Hz), 123.7 (tt, *J* = 300 Hz, 42 Hz), 127.0 (t, *J* = 7 Hz), 128.5, 129.0 (t, *J* = 25 Hz), 131.7 (t, *J* = 2 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −70.49 (t, *J* = 3.5 Hz, 2F), −110.40 (t, *J* = 3.5 Hz, 2F); **IR** (neat) ν 1154, 1100, 1061, 1017, 909, 857, 702; **HRMS** (EI) calculated for $C_8H_5F_4Cl$ $[M]^+$ 212.0016, found 212.0016.

2-(2-Chloro-1,1,2,2-tetrafluoroethyl)naphthalene (42e)



Synthesised following GP 3-B from **40e** (5.3 mmol scale). Purification by silica flash column chromatography (eluent: pentane) afforded 1.18 g of the title compound (85% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58–7.66 (m, 3H), 7.91–7.93 (m, 1H), 7.94–7.97 (m, 2H), 8.17 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 115.3 (tt, *J* = 256 Hz, 33 Hz), 122.9 (t, *J* = 6 Hz), 124.0 (tt, *J* = 300 Hz, 42 Hz), 126.3 (t, *J* = 25 Hz), 127.2, 128.0, 128.1 (t, *J* = 7 Hz), 128.3, 128.7, 129.0, 132.4, 134.7; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –70.12 (t, *J* = 3.5 Hz, 2F), –109.73 (t, *J* = 3.5 Hz, 2F); **IR** (neat) ν 1289, 1153, 1129, 1095, 1032, 953, 921, 910, 888, 860, 815, 797, 745; **HRMS** (FI) calculated for $C_{12}H_7F_4Cl$ 262.0172, found 262.0175; **Mp** 30 °C.

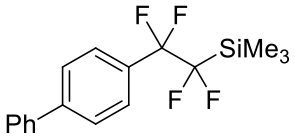
1-(2-Chloro-1,1,2,2-tetrafluoroethyl)-4-pentylbenzene (42f)*

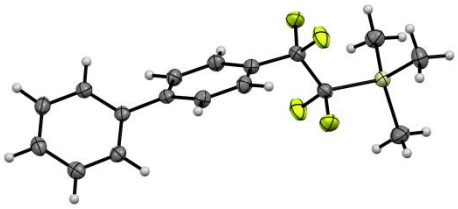


Synthesised from **40f** following GP 3-B (2.19 mmol scale). Purification by silica flash column chromatography (eluent: PET 30/40) afforded 590 mg of the title compound (95% yield) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3H), 1.29–1.38 (m, 4H), 1.60–1.67 (m, 2H), 2.66 (t, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz,

$CDCl_3$) δ 14.1, 22.6, 31.0, 31.6, 35.9, 115.3 (tt, *J* = 255 Hz, 33 Hz), 123.9 (tt, *J* = 300 Hz, 42 Hz), 126.4 (t, *J* = 25 Hz), 127.0 (t, *J* = 6 Hz), 128.7, 147.2; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –70.41 (t, *J* = 3.5 Hz, 2F), –109.92 (t, *J* = 3.5 Hz, 2F); **IR** (neat) ν 1287, 1246, 1157, 1100, 1032, 1013, 915, 879, 818, 668, 633; **HRMS** (FI) calculated for $C_{13}H_{15}F_4Cl$ 282.0798, found 282.0795.

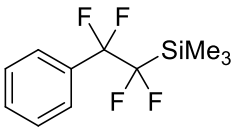
[2-(Biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl](trimethyl)silane (39a)





Synthesised following GP 3-C from **42a** (9.4 mmol scale). Purification by silica flash column chromatography (eluent: pentane) afforded 1.07 g of the title compound (35% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.36 (s, 9H), 7.40–7.43 (m, 1H), 7.47–7.51 (m, 2H), 7.64–7.67 (m, 2H), 7.69–7.71 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ –3.9, 119.4 (tt, *J* = 245 Hz, 31 Hz), 122.6 (tt, *J* = 271 Hz, 52 Hz), 127.0, 127.4, 127.5 (t, *J* = 7 Hz), 128.0, 129.0, 130.2 (t, *J* = 26 Hz), 140.4, 143.7; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –106.79 (s, 2F), –125.02 (s, 2F); **IR** (neat) ν 1271, 1090, 1066, 1027, 1007, 851, 838, 820, 767, 74, 729, 691; **HRMS** (FI) calculated for $C_{17}H_{18}F_4Si$ 326.1114, found 326.1120; **Mp** 52–53 °C. For single X-ray crystallography data see Appendix.

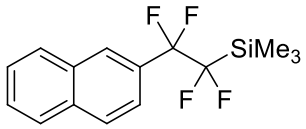
Trimethyl(1,1,2,2-tetrafluoro-2-phenylethyl)silane (39d)



Synthesised from **42d** following GP 3-C (1.0 mmol scale). Purification by silica flash column chromatography (eluent: pentane) afforded 97 mg (39% yield) of the title compound as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.30 (s, 9H), 7.42–7.51 (m, 3H), 7.54–7.57 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ −4.1,

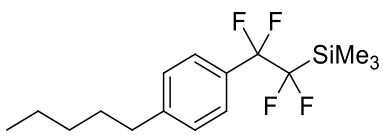
119.1 (tt, *J* = 246 Hz, 30 Hz), 122.4 (tt, *J* = 270 Hz, 51 Hz), 126.9 (tt, *J* = 7 Hz, 1 Hz), 128.1, 130.6 (t, *J* = 2 Hz), 131.3 (t, *J* = 26 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –107.16 (s, 2H), –125.25 (s, 2F); **IR** (neat) ν 1289, 1255, 1117, 1065, 1028, 850, 821, 754, 695; **HRMS** (FI) calculated for $C_{11}H_{14}SiF_4$ $[M]^+$ 250.0801, found 250.0791.

[1,1,2,2-Tetrafluoro-2-(naphthalen-2-yl)ethyl](trimethyl)silane (39e)



In a flame dried Schlenck tube, 0.11 mL trimethylsilyl chloride (0.87 mmol, 1.3 eq) was added to a solution of 176 mg **42e** (0.67 mmol, 1.0 eq) in 3.5 mL anhydrous THF (0.19 M). The reaction was cooled to −78 °C and 0.32 mL *n*-butyllithium (2.5 M in hexane, 0.80 mmol, 1.2 eq) was added dropwise over 10 minutes. The reaction was stirred at –78 °C for 2 hours and was allowed to warm to room temperature overnight. The reaction was quenched by addition of H_2O, extracted with Et_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica flash column chromatography (eluent: pentane) to afford 164 mg of the title compound (72% yield) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.33 (s, 9H), 7.5–-7.59 (m, 2H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.88–7.94 (m, 3H), 8.07 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –3.8, 119.5 (tt, *J* = 246 Hz, 31 Hz), 122.7 (tt, *J* = 270 Hz, 52 Hz), 123.6 (t, *J* = 6 Hz), 126.7, 127.4 (t, *J* = 8 Hz), 127.6, 127.9, 128.1, 128.7 (t, *J* = 26 Hz), 128.9, 132.5, 134.3; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –106.44 (s, 2F), −124.87 (s, 2F); **IR** (neat) ν 1291, 1256, 1101, 1060, 1030, 848, 819, 789, 756, 706; **HRMS** (FI) calculated for $C_{15}H_{16}F_4Si$ 300.0957, found 300.0960; **Mp** 38–39 °C.

[1,1,2,2-tetrafluoro-2-(4-pentylphenyl)ethyl](trimethyl)silane (39f)*



In a flame dried Schlenck tube, 0.25 mL trimethylsilyl chloride (1.93 mmol, 1.3 eq) was added to a solution of 420 mg **42f** (1.49 mmol, 1.0 eq) in 8 mL anhydrous THF (0.19 M). The reaction was cooled to –78 °C and 0.71 mL *n*-butyllithium (2.5 M in hexane,

1.78 mmol, 1.2 eq) was added dropwise over 10 minutes. The reaction was stirred at –78 °C for 2 hours and was allowed to warm to room temperature overnight. The reaction was quenched by addition of H_2O, extracted with Et_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica flash column chromatography (eluent: pentane) to afford 380 mg of the title compound (80% yield) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.25 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H), 1.26–1.34 (m, 4H), 1.56–1.64 (m, 2H), 2.59–2.63 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ –3.9, 14.1, 22.7, 31.1, 31.6, 35.9, 119.4 (tt, *J* = 246 Hz, 31 Hz), 122.6 (tt, *J* = 271 Hz, 52 Hz), 126.9 (t, *J* = 7 Hz), 128.3, 128.7 (t, *J* = 26 Hz), 145.9; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −106.72 (s, 2F), −125.28 (s, 2F); **IR** (neat) ν 1293, 1256, 1101, 1063, 1031, 847, 806, 783, 757, 629; **HRMS** (FI) calculated for $C_{16}H_{24}SiF_4$ 320.1583, found 320.1592.

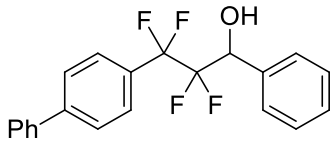
6.2.4.2 Addition of [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes to aldehydes

General procedure 3-D: Addition of $Ar(CF_2)_2SiMe_3$ to aldehydes

Caesium fluoride (0.05 mmol, 8 mg, 10 mol%) was flame dried in a Schlenck tube under high vacuum. [2-(Aryl)-1,1,2,2-tetrafluoroethyl](trimethyl)silane **39** (0.6 mmol, 1.2 eq.) was added and the tube was back-filled with N_2 three times. 0.5 mL Anhydrous THF (1 M) and freshly distilled aldehyde (0.5 mmol, 1.0 eq.) were added and the reaction was stirred for 1 hour at room temperature. Tetrabutylammonium fluoride (1 M in THF, 1.2 mmol, 1.2 mL, 1.2 eq) was added and the mixture stirred for a further 30 min at room temperature. The reaction was quenched with H_2O and extracted with Et_2O. The combined organic layers were were washed with brine and dried over $MgSO_4$. ^{19}F NMR yields were determined by integrating the product peak(s) relative to 1.0 eq $PhCF_3$. After concentration

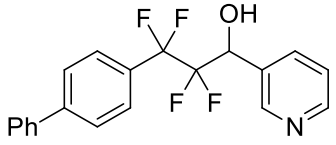
in vacuo, the crude product was purified by silica flash column chromatography. Alternatively, recrystallization from hot $CHCl_3$ is also possible.

3-(Biphenyl-4-yl)-2,2,3,3-tetrafluoro-1-phenylpropan-1-ol (43aa)



Synthesised from **39a** (0.24 mmol) and benzaldehyde (0.2 mmol) following GP 3-D. Purification by silica flash column chromatography (eluent: 10% EtOAc/pentane to 20% EtOAc/pentane) afforded 65 mg of the title compound (90% yield) as an off-white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.60 (d, *J* = 4.5 Hz, 1H, O*H*), 5.23 (ddd, *J* = 17.0 Hz, 7.0 Hz, 4.5 Hz, 1H), 7.39–7.44 (m, 4H), 7.47–7.51 (m, 4H), 7.61–7.64 (m, 2H), 7.68 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 72.4 (dd, *J* = 29 Hz, 23 Hz), 115.6 (ddt, *J* = 160 Hz, 154 Hz, 36 Hz), 117.5 (dt, *J* = 253 Hz, 34 Hz), 127.1, 127.3 (t, *J* = 7 Hz), 127.4, 128.1, 128.2, 128.5, 129.1, 129.3, 129.8 (t, *J* = 25 Hz), 135.4, 140.1, 144.1; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −108.76 (dt, *J* = 266.5 Hz, 3.0 Hz, 1F), −109.53 (dt, *J* = 266.5 Hz, 3.0 Hz, 1F), −117.52 (ddt, *J* = 275.5 Hz, 7.0 Hz, 3.0 Hz, 1F), −126.45 (ddt, *J* = 275.5 Hz, 17.0 Hz, 3.0 Hz, 1F); **IR** (neat) ν 1291, 1184, 1099, 1075, 841, 769, 750, 734, 696; **HRMS** (ESI) calculated for $C_{21}H_{16}OF_4Na$ 383.1030, found 383.1030; **Mp** 69–70 °C.

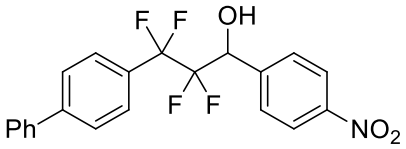
3-(Biphenyl-4-yl)-2,2,3,3-tetrafluoro-1-(pyridin-3-yl)propan-1-ol (43ab)



Synthesised from **39a** (0.6 mmol) and 3-pyridinecarboxaldehyde (0.5 mmol) following GP 3-D. Purification by silica flash column chromatography (eluent: hexane to 20% EtOAc in hexane) afforded 87 mg of the title compound (48% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.15 (dd, *J* = 19.0 Hz, 3.5 Hz, 1H), 525 (brs, 1H, O*H*), 7.33 (dd, *J* = 7.0 Hz, 5.0 Hz, 1H), 7.37–7.41 (m, 2H), 7.45–7.49 (m, 2H), 7.60–7.62 (m, 2H), 7.66–7.75 (m, 5H), 8.62 (d, *J* = 4.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 70.6 (dd, *J* = 30 Hz, 25 Hz), 115.8 (ddt, *J* = 263 Hz, 254 Hz, 34 Hz), 117.1 (tt, *J* = 254 Hz,

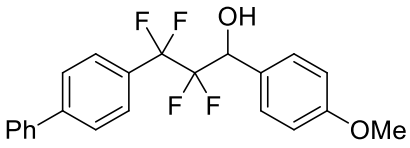
33 Hz), 123.3 (d, *J* = 4 Hz), 124.0, 127.0, 127.3, 127.3 (t, *J* = 6 Hz), 128.0, 129.0, 130.3 (t, *J* = 25 Hz), 136.8, 140.0, 143.8, 148.2, 152.5; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –108.90 (d, *J* = 266.0 Hz, 1F), –109.93 (dd, *J* = 266.0 Hz, 5.5 Hz, 1F), –116.45 (d, *J* = 273.5 Hz, 1F), –127.96 (ddd, *J* = 273.5 Hz, 19.0 Hz, 5.5 Hz, 1F); **IR** (neat) ν 2361, 2342, 1100, 1077, 669; **HRMS** (ESI) calculated for $C_{20}H_{16}ONF_4$ 362.1163, found 362.1168; **Mp** 98–99 °C.

3-(Biphenyl-4-yl)-2,2,3,3-tetrafluoro-1-(4-nitrophenyl)propan-1-ol (43ac)



Synthesised from **39a** (0.6 mmol) and 4-nitrobenzaldehyde (0.5 mmol) following GP 3-D. Purification by silica flash column chromatography (eluent: 20% EtOAc/pentane) afforded 147 mg of the title compound (73% yield) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.66 (brs, 1H, O*H*), 5.33 (dd, *J* = 16.0 Hz, 7.0 Hz, 1H), 7.33 (tt, *J* = 7.0 Hz, 2.0 Hz, 1H), 7.38–7.42 (m, 2H), 7.51–7.57 (m, 4H), 7.0–7.63 (m, 4H), 8.18 (dt, *J* = 9.0 Hz, 2.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 71.6 (dd, *J* = 28 Hz, 24 Hz), 115.1 (ddt, *J* = 260 Hz, 255 Hz, 36 Hz), 117.66 (tt, *J* = 253 Hz, 35 Hz), 123.5, 127.3 (t, *J* = 7 Hz), 127.3, 127.4, 128.3, 129.0 (t, *J* = 25 Hz), 129.1, 129.3, 139.9, 142.0, 144.5, 148.5; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –108.77 (s, 2F), –117.09 (dd, *J* = 277.5 Hz, 6.0 Hz, 1F), –125.61 (dd, *J* = 277.5 Hz, 16.0 Hz, 1F); **IR** (neat) ν 2361, 2341, 1516, 1348, 1102, 1076, 839, 730, 694, 668; **HRMS** (ESI) calculated for $C_{21}H_{15}O_3NF_4Na$ 428.0880, found 428.0874; **Mp** 127–128 °C.

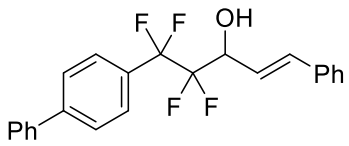
3-(Biphenyl-4-yl)-2,2,3,3-tetrafluoro-1-(4-methoxyphenyl)propan-1-ol (43ad)



Synthesised from **39a** (0.6 mmol) and *para*-anisaldehyde (0.5 mmol) following GP 3-D. Purification by silica flash column chromatography (eluent: 20% EtOAc/pentane) afforded 184 mg the title compound (94% yield) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.64 (d, *J* = 4.5 Hz, 1H, O*H*), 3.81 (s, 3H), 5.15 (ddd,

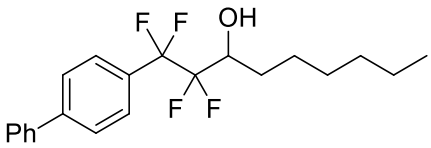
J = 17.0 Hz, 7.5 Hz, 4.0 Hz, 1H), 6.91–6.93 (m, 2H), 7.39-7.43 (m, 3H), 7.46–7.51 (m, 2H), 7.62–7.64 (m, 2H), 7.68 (brs, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.3, 71.9 (dd, *J* = 29 Hz, 23 Hz), 113.8, 115.7 (ddt, *J* = 260 Hz, 254 Hz, 36 Hz), 117.4 (tt, *J* = 253 Hz, 33 Hz), 127.0, 127.2 (t, *J* = 7 Hz), 127.3, 127.5, 128.1, 129.0, 129.4, 129.8 (t, *J* = 25 Hz), 140.0, 143.9, 160.2; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −108.76 (d, *J* = 266.0 Hz, 1F), −109.56 (d, *J* = 226.0 Hz, 1F), −117.85 (dd, *J* = 274.0 Hz, 7.5 Hz, 1F), −126.43 (dd, *J* = 274.0 Hz, 17.0 Hz, 1F); **IR** (neat) ν 2360, 2342, 1614, 1515, 1291, 1251, 1177, 1100, 1075, 1033, 907, 728; **HRMS** (ESI) calculated for $C_{22}H_{18}O_2F_4Na$ 413.1135, found 413.1136; **Mp** 87–88 °C.

(1*E*)-5-(Biphenyl-4-yl)-4,4,5,5-tetrafluoro-1-phenylpent-1-en-3-ol (43ae)



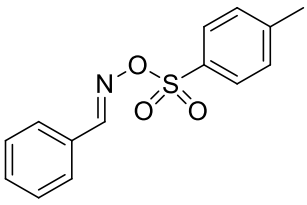
Synthesised from **39a** (0.24 mmol) and cinnamaldehyde (0.2 mmol) following GP 3-D. Purification by silica flash column chromatography (eluent: 10% EtOAc/Hexane) afforded 66 mg of the title compound (85% yield) as an off-white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.36 (d, *J* = 6.0 Hz, 1H, O*H*), 4.80 (ddd, *J* = 13.0 Hz, 9.0 Hz, 7.0 Hz, 6.0 Hz, 1H), 6.30 (dd, *J* = 16.0 Hz, 7.0 Hz, 1H), 6.81 (d, *J* = 16.0 Hz, 1H), 7.29–7.33 (m, 1H), 7.33–7.37 (m, 2H), 7.40–7.44 (m, 3H), 7.47–7.51 (m, 2H), 7.60–7.63 (m, 2H), 7.70 (brs, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 71.5 (dd, *J* = 27 Hz, 24 Hz), 115.9 (tt, *J* = 258 Hz, 35 Hz), 117.2 (tt, *J* = 253 Hz, 33 Hz), 122.1, 126.9, 127.1, 127.3 (t, *J* = 7 Hz), 127.3, 128.1, 128.5, 128.7, 129.0, 129.7 (t, *J* = 25 Hz), 135.5, 135.9, 140.0, 144.1; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −108.91 (dt, *J* = 266.5 Hz, 3.0 Hz, 1F), −109.88 (dt, *J* = 266.5 Hz, 3.0 Hz, 1F), −125.95 (ddt, *J* = 273.0 Hz, 9.0 Hz, 3.0 Hz, 1F), −125.05 (ddt, *J* = 273.0 Hz, 13.0 Hz, 3.0 Hz, 1F); **IR** (neat) ν 1099, 1074, 968, 833, 769, 751, 732, 692; **HRMS** (ESI) calculated for $C_{23}H_{18}OF_4Na$ 409.1186, found 409.1187; **Mp** 77–79 °C.

1-(Biphenyl-4-yl)-1,1,2,2-tetrafluorononan-3-ol (43af)



Synthesised from **39a** (0.24 mmol) and heptanal (0.2 mmol) fowing GP 3-D. Purification by silica flash column chromatography (eluent: pentane to 20% Et_2O in pentane) afforded 37 mg of the title compound (50% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.5 Hz, 3H), 1.31–1.42 (m, 7H), 1.58–1.69 (m, 2H), 1.77–1.85 (m, 1H), 1.89 (s, 1H), 4.07–4.11 (m, 1H), 7.38–7.42 (m, 1H), 7.45–7.50 (m, 2H), 7.60–7.63 (m, 2H), 7.64-7.70 (m, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.1, 22.7, 25.3, 29.1, 29.7, 31.8, 70.3 (dd, *J* = 28 Hz, 23 Hz), 116.5 (tt, *J* = 256 Hz, 36 Hz), 117.5 (tt, *J* = 253 Hz, 34 Hz), 127.2, 127.2 (t, *J* = 7 Hz), 127.4, 128.1, 129.1, 130.0 (t, *J* = 26 Hz), 140.1, 144.1; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −109.20 (d, *J* = 267.5 Hz, 1F), −110.02 (dt, *J* = 267.5 Hz, 3.5 Hz, 1F), −120.93 (d, *J* = 275.0 Hz, 1F), −127.18 (ddt, *J* = 275.0 Hz, 16.0 Hz, 3.5 Hz, 1F); **IR** (neat) ν 2361, 2338, 1293, 1196, 1099, 1078, 836, 768, 745, 693, 666; **HRMS** (ESI) calculated for $C_{21}H_{24}OF_4Na$ 391.1656, found 391.1656; **Mp** 49–51 °C.

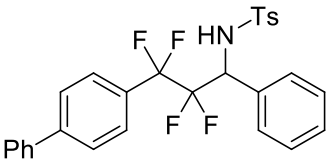
***N*-{[(4-Methylphenyl)sulfonyl]oxy}-1-phenylmethanimine[289]**



0.3 mL benzaldehyde (3.0 mmol, 1.0 eq), 514 mg *p*-toluenesulfonamide (3.0 mmol, 1.0 eq) and 492 mg sodium benzenesulfinate (3.0 mmol, 1.0 eq) was stirred in 10 mL formic acid and H_2O (1:1, 0.33 M) for 20 h at rt. A white solid precipitated out of solution and was collected by vacuum filtration, washed with H_2O and pentane, after which it was redissolved in 30 mL DCM (0.1 M). 21 mL saturated $NaHCO_{3(aq)}$ were added and the mixture was stirred for 3 h at rt. The aqueous phase was extracted with DCM, and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford 400 mg (51% yield) of the pure title compound as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.54 (tt, *J* = 7.5 Hz, 1.5 Hz,

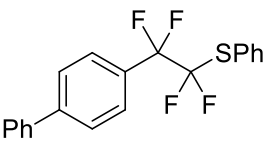
1H), 7.80–7.86 (m, 4H), 8.96 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.7, 128.1, 129.2, 129.8, 131.3, 132.4, 134.9, 135.2, 144.6, 170.1.

3-(Biphenyl-4-yl)-2,2,3,3-tetrafluoro-*N*-{[(4-methylphenyl)sulfonyl]oxy}-1-phenylpropan-1-amine (43ag)



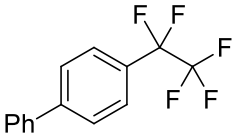
Synthesised from **39a** (0.24 mmol) and *N*-{[(4-methylphenyl)sulfonyl]oxy}-1-phenylmethanimine (0.2 mmol) following GP 3-D. Purification by silica flash column chromatography (eluent: pentane to 40% EtOAc in pentane) afforded 13 mg (13% yield) of the title compound as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 4.94–5.03 (m, 1H), 5.35 (d, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 7.02–7.05 (m, 2H), 7.06–7.11 (m, 2H), 7.13–7.17 (m, 1H), 7.28–7.34 (m, 1H), 7.36–7.43 (m, 4H), 7.46–7.58 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.6, 58.2 (dd, *J* = 27 Hz, 22 Hz), 115.8 (ddt, *J* = 259 Hz, 257 Hz, 36 Hz), 117.0 (tt, *J* = 254 Hz, 34 Hz), 127.1, 127.2, 127.4, 128.2, 128.5, 128.8, 129.1, 129.2, 129.4, 137.4, 140.0, 143.4, 143.7, 144.2, 144.8, 170.3; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −107.89 (dt, *J* = 267.5 Hz, 3.0 Hz, 1F), −108.92 (dt, *J* = 267.5 Hz, 5.0 Hz, 1F), −115.73 (dd, *J* = 274.5 Hz, 11.5 Hz, 1F), −118.15 (ddt, *J* = 274.5 Hz, 15.0 Hz, 5.0 Hz, 1F); **IR** (neat) ν 2361, 2338, 1335, 1286, 1162, 1096, 938, 734, 699, 667; **HRMS** (ESI) calculated for $C_{28}H_{23}O_2NF_4NaS$ $[M+Na]^+$ 536.1278, found 536.1278; **Mp** 148–149 °C.

2-(Biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl phenyl sulphide (43ah)



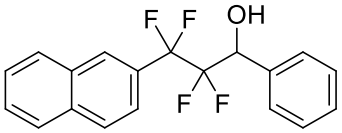
Diphenyl disulfide was unreactive towards GP 3-D.

4-(Pentafluoroethyl)biphenyl (43ai)



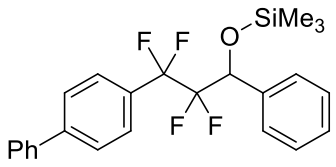
A literature procedure was followed:[224] To 19 mg XeF_2 (0.11 mmol, 1.1 eq) in 0.1 mL anhydrous DCM in a screw-cap vial at –40 °C was carefully added 33 mg **39a** (0.1 mmol, 1.0 eq) in 0.1 mL anhydrous DCM. The reaction was gradually allowed to warm to –5 °C and stirred for 1.5 hours, after which it was quenched with $NaHCO_{3(aq)}$, extracted with DCM, dried and concentrated *in vacuo*. ^{19}F NMR showed no formation of product **43ai**, with full recovery of unreacted starting material **51a**.

2,2,3,3-Tetrafluoro-3-(naphthalen-2-yl)-1-phenylpropan-1-ol (43ea)



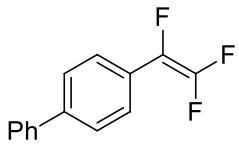
Synthesised from **39e** (0.6 mmol) and benzaldehyde (0.5 mmol) *via* GP 3-D. Purification by silica flash column chromatography (eluent: 20% EtOAc in pentane) afforded 164 mg (98% yield) of the title compound as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.70 (brs, 1H, O*H*), 5.22 (dd, *J* = 17.0 Hz, 6.5 Hz, 1H), 7.39–7.42 (m, 3H), 7.49–7.51 (m, 2H), 7.56–7.63 (m, 2H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.90–7.95 (m, 3H), 8.16 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 27.4 (dd, *J* = 29 Hz, 23 Hz), 115.7 (dtt, *J* = 261 Hz, 254 Hz, 36 Hz), 117.6 (tt, *J* = 254 Hz, 34 Hz), 123.1 (t, *J* = 6 Hz), 126.9, 127.4 (t, *J* = 8 Hz), 127.9, 128.2, 128.3 (t, *J* = 24 Hz), 128.4, 128.5, 128.9, 129.3, 132.4, 134.4, 135.4; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –108.28 (d, *J* = 265.5 Hz, 1F), –109.09 (dt, *J* = 265.0 Hz, 3.5 Hz, 1F), –117.28 (dd, *J* = 275.0 Hz, 7.0 Hz, 1F), –126.23 (ddt, *J* = 275.0 Hz, 17.0 Hz, 3.5 Hz, 1F); **IR** (neat) ν 2360, 2342, 1289, 1112, 1067, 933, 728, 698; **HRMS** (ESI) calculated for $C_{19}H_{13}OF_4$ $[M–H]^-$ 333.0908, found 333.0904.

[3-(Biphenyl-4-yl)-2,2,3,3-tetrafluoro-1-phenylpropoxy](trimethyl)silane (44aa)



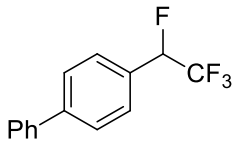
Intermediate formed in the reaction of **39a** with benzaldehyde following GP 3-D. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 5.15 (dd, *J* = 17.5 Hz, 6.0 Hz, 1F), 7.28–7.35 (m, 4H), 7.38–7.44 (m, 4H), 7.53–7.56 (m, 2H), 7.58–7.63 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.0, 73.1 (dd, *J* = 32 Hz, 23 Hz), 115.7 (ddt, *J* = 262 Hz, 250 Hz, 35 Hz), 117.3 (tt, *J* = 253 Hz, 34 Hz), 127.0, 127.4 (t, *J* = 7 Hz), 127.4, 128.1, 128.2, 128.6, 128.9, 129.1, 130.7 (t, *J* = 25 Hz), 136.6, 140.3, 143.8 (t, *J* = 2 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −108.38 (dt, *J* = 266.0, 6.0 Hz, 1F), −109.44 (ddd, *J* = 266.0 Hz, 7.0 Hz, 3.0 Hz, 1F), −115.16 (dq, *J* = 275.0 Hz, 5.0 Hz, 1F), −125.93 (ddt, *J* = 275.0 Hz, 17.5 Hz, 7.0 Hz, 1F); **IR** (neat) ν 1253, 1101, 1074, 876, 838, 768, 696; **HRMS** (ESI) calculated for $C_{24}H_{24}OF_4NaSi$ $[M+Na]^+$ 455.1425, found 455.1425; **Mp** 75–77 °C.

4-(1,2,2-Trifluorovinyl)biphenyl (45a)[290]



Desilylation/elimination by-product formed from **39a**. White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (tt, *J* = 7.0 Hz, 2.0 Hz, 1H), 7.37–7.42 (m, 2H), 7.46–7.49 (m, 2H), 7.52–7.55 (m, 2H), 7.57–7.61 (m, 2H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –99.47 (dd, *J* = 70.5 Hz, 32.0 Hz, 1F), –114.31 (dd, *J* = 109.0 Hz, 70.5 Hz, 1F), –176.92 (dd, *J* = 109.0 Hz, 32.5 Hz, 1F); **HRMS** (EI) calculated for $C_{14}H_9F_3$ 234.0656, found 234.0650.

4-(1,2,2,2-Tetrafluoroethyl)biphenyl (46)[36]



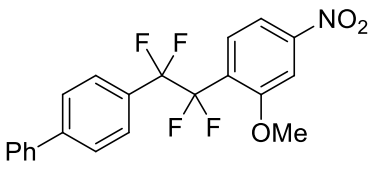
Elimination/hydrofluorination by-product, isolated as a 3:2 mixture with **16a** from the synthesis of **43af**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.65 (dq, *J* = 44.0 Hz, 6.0 Hz, 1H), 7.36–7.45 (m, 1H), 7.46–7.51 (m, 2H), 7.54–7.61 (m, 2H), 7.59–7.64 (m, 2H), 7.69–7.73 (m, 2H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –78.63 (dd, *J* = 13.0 Hz, 6.0 Hz, 3F), –104.08 (dq, *J* = 44.0 Hz, 13.0 Hz, 1F).

6.2.4.3 Cu-mediated cross-coupling of [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes

General procedure 3-E: Cu-mediated cross-coupling of $Ar(CF_2)_2SiMe_3$ with (hetero)aryl iodides and bromides

A flame dried Schenk tube was charged with [2-(aryl)-1,1,2,2-tetrafluoroethyl](trimethyl)silane **39** (0.24 mmol, 1.2 eq), copper(I) iodide (0.3 mmol, 57 mg, 1.5 eq), silver fluoride (0.3 mmol, 38 mg, 1.5 eq) and (hetero)aryl iodide or bromide (0.2 mmol, 1.0 eq). The tube was evacuated and back-filled with N_2 three times. Pyridine (1.0 mmol, 81 µL, 5.0 eq) and anhydrous DMSO (0.8 mL, 0.25 M) were added and the reaction was stirred at 60 °C for 6 h. The mixture was cooled to room temperature, quenched with $NH_4Cl_{(aq)}$ and extracted with Et_2O. The organics layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. ^{19}F NMR yields were determined by referencing against $PhCF_3$ (0.2 mmol, 25 µL, 1.0 eq.). The crude products were purified by silica flash column chromatography.

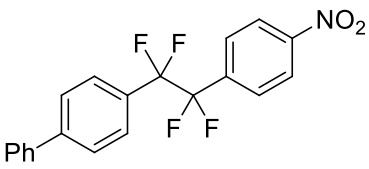
2-Methoxy-4-nitro-1-(trifluoromethyl)benzene (47aa)



Synthesised from **39a** (0.24 mmol) and 1-iodo-2-methoxy-4-nitrobenzene (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: PET 30/40 to 10% Et_2O/PET) afforded 63 mg of the title compound (78% yield) as a white solid. When GP 3-E was carried out at room temperature, 49 mg (60% yield) of **59aa** was isolated. The reaction with 1-bromo-2-methoxy-4-nitrobenzene (0.2 mmol) afforded 33 mg (41% yield) of the title compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 7.40 (tt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.46–7.50 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.60–7.62 (m, 2H), 7.65–7.69 (m, 3H), 7.75 (d, *J* = 1.5 Hz, 1H), 7.87 (dd, *J* 8.5 Hz, 2.0 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 65.4, 107.1, 114.9, 116.5 (tt, *J* = 256 Hz, 38 Hz), 116.9 (tt, *J* = 154 Hz, 35 Hz),

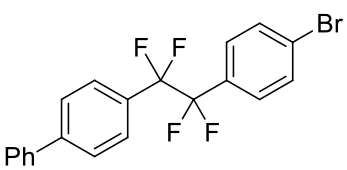
125.0 (t, *J* = 24 Hz), 127.0, 127.4, 127.6 (t, *J* = 6 Hz), 128.2, 129.1, 129.7 (t, *J* = 25 Hz), 130.9 (t, *J* = 9 Hz), 140.0, 144.2, 150.9, 159.0; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –109.25 (m, 2F), –111.40 (m, 2F); **IR** (neat) ν 1530, 1349, 1262, 1236, 1103, 1080, 886, 823, 754; **HRMS** (FI) calculated for $C_{21}H_{15}F_4NO_3$ 405.0977, found 405.0971; **Mp** 125–126 °C.

4-[1,1,2,2-Tetrafluoro-2-(4-nitrophenyl)ethyl]biphenyl (47ab)



Synthesised from **39a** (0.24 mmol) and 1-iodo-4-nitrobenzene (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: PET 30/40 to 5% Et_2O/PET) afforded 53 mg of the title compound (71% yield) as a white solid. When GP 3-E was carried out at room temperature, 56 mg (75% yield) of **47ab** was isolated. The reaction with 1-bromo-4-nitrobenzene (0.2 mmol) afforded 30% ^{19}F NMR yield of the title compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (tt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.47–7.51 (m, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.62–7.64 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 8.31 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 116.0 (tt, *J* = 254 Hz, 38 Hz), 116.6 (tt, *J* = 253 Hz, 35 Hz), 123.5, 127.2, 127.4, 127.5 (t, *J* = 6 Hz), 128.3, 128.6 (t, *J* = 6 Hz), 128.8 (t, *J* = 25 Hz), 129.1, 137.2 (t, *J* = 26 Hz), 139.8, 144.5, 149.7; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –110.87 (t, *J* = 5.0 Hz, 2F), −111.75 (t, *J* = 5.0 Hz, 2F); **IR** (neat) ν 1527, 1350, 1259, 1142, 1103, 1084, 899, 852, 830, 772, 752, 701; **HRMS** (FI) calculated for $C_{20}H_{13}NO_2F_4$ 375.0882, found 375.0891; **Mp** 125–126 °C.

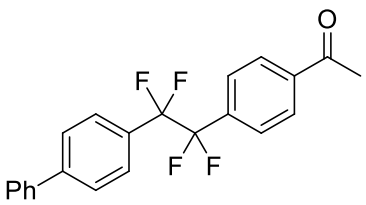
4-[2-(3-Bromophenyl)-1,1,2,2-tetrafluoroethyl]biphenyl (47bc)



Synthesisedfrom **39b** (0.24 mmol) and 3-bromo-1-iodobenzene (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane) afforded 52 mg of the title compound (64% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.42 (m, 3H), 7.45–7.50 (m, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.58 (d,

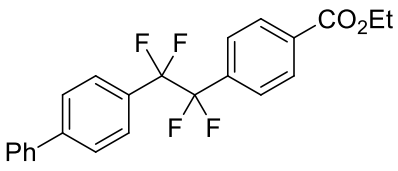
J = 8.5 Hz, 2H), 7.60–7.63 (m, 2H), 7.66 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 116.6 (tt, *J* = 235 Hz, 37 Hz), 116.7 (253 Hz, 36 Hz), 125.9, 127.0, 127.4, 127.5 (t, *J* = 6 Hz), 128.2, 128.3 (t, *J* = 6 Hz), 129.1, 129.4 (t, *J* = 25 Hz), 130.0 (t, 25 Hz), 131.6, 140.0, 144.1; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –111.35 (s, 2F), –111.65 (s, 2F); **IR** (neat) ν 1261, 1136, 1101, 1084, 895, 817, 769, 753, 726; **HRMS** (FI) calculated for $C_{20}H_{13}BrF_4$ 408.0137, found 408.0140; **Mp** 136–138 °C.

1-{4-[2-(Biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl]phenyl}ethanone (47ad)



Synthesised from **39a** (0.24 mmol) and 1-(4-iodophenyl)ethanone (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane to 5% Et_2O/pentane) afforded 62 mg of the title compound (84% yield) as a white solid. When GP 3-E was carried out at room temperature, 38 mg (51% yield) of **47ad** was isolated. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.65 (s, 3H), 7.40 (tt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.46–7.50 (m, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.60–7.63 (m, 4H), 7.66 (d, *J* = 8.5 Hz, 2H), 8.01 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 26.9, 116.4 (tt, *J* = 253 Hz, 37 Hz), 116.7 (tt, *J* = 253 Hz, 35 Hz), 127.1, 127.4, 127.5 (t, *J* = 6 Hz), 127.6 (t, *J* = 6 Hz), 128.1, 128.2, 129.1, 129.3 (t, *J* = 25 Hz), 135.3 (t, *J* = 25 Hz), 139.1, 140.0, 144.2, 197.5; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –111.15 (s, 2F), –111.91 (s, 2F); **IR** (neat) ν 1688, 1407, 1262, 1140, 1101, 1086, 903, 823, 726, 650; **HRMS** (ESI) calculated for $C_{22}H_{16}OF_4Na$ 395.1030, found 395.1033; **Mp** 156–158 °C.

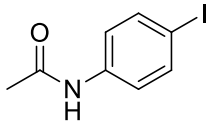
Ethyl 4-[2-(biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl]benzoate (47ae)



Synthesised from **39a** (0.24 mmol) and ethyl 4-iodobenzoate (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane to 5% Et_2O/pentane) afforded 55 mg of the title compound (68% yield) as

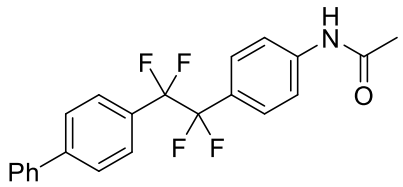
a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.0 Hz, 3H), 4.42 (q, *J* = 7.0 Hz, 2H), 7.38–7.42 (m, 1H), 7.45–7.49 (m, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.57–7.66 (m, 6H), 8.11 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 14.4, 61.6, 116.5 (tt, *J* = 253 Hz, 37 Hz), 116.7 (tt, *J* = 253 Hz, 36 Hz), 127.1, 127.3 (t, *J* = 6 Hz), 127.4, 127.6 (t, *J* = 6 Hz), 128.2, 129.1, 129.4 (t, *J* = 25 Hz), 129.4, 133.1, 135.2 (t, *J* = 25 Hz), 140.0, 144.2, 165.9; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –111.32 (s, 2F), –112.01 (s, 2F); **IR** (neat) ν 1718, 1286, 1259, 1132, 1094, 1082, 901, 829, 731, 716, 695; **HRMS** (ESI) calculated for $C_{23}H_{18}O_2F_4Na$ 425.1135, found 425.1138; **Mp** 120–121 °C.

_N_-(4-Iodophenyl)acetamide[291]



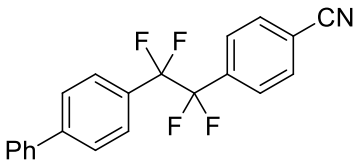
To a solution of 2.19 g 4-iodoaniline (10.0 mmol, 1.0 eq) and 2.8 mL NEt_3 (20.0 mmol, 2.0 eq) in 20 mL DCM (0.45M) at 0 °C was added 1.9 mL acetic anhydride (20.0 mmol, 2.0 eq) dropwise. The reaction was allowed to warm to rt and stirred for 2 h, after which volatiles were removed *in vacuo*. The crude product was recrystallized from hot DCM to afford 2.29 g (88% yield) of the title compound as a white solid. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 2.03 (s, 3H), 7.40–7.44 (m, 2H), 7.59–7.63 (m, 2H), 10.03 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 24.1, 86.3, 121.1, 137.3, 139.1, 168.5.

***N*-{4-[2-(biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl]phenyl}acetamide (47af)**



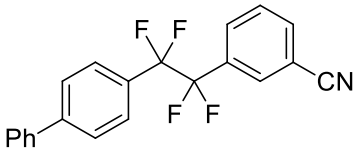
Synthesised from **39a** (0.24 mmol) and *N*-(4-iodophenyl)acetamide (0.2 mmol) following GP 3-E. The crude ^{19}F NMR yield was determined to be 24%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.99 (s, 3H), 7.18–7.57 (m, 13H), 8.58 (brs, 1H, N*H*); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –111.09 (s, 2F), –111.49 (s, 2F).

4-[2-(Biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl]benzonitrile (47ag)



Synthesised from **39a** (0.24 mmol) and 4-iodobenzonitrile (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane to 10% Et_2O/pentane) afforded 56 mg of the title compound (79% yield) as a white solid. When GP 3-E was carried out at room temperature, 46 mg (65% yield) of **47ag** was isolated. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.44 (m, 1H), 7.47–7.51 (m, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.62–7.69 (m, 6H), 7.75 (d, *J* = 8.5 Hz, 2H);**^{13}C NMR** (100 MHz, $CDCl_3$) δ 115.3, 116.0 (tt, *J* = 253 Hz, 38 Hz), 116.6 (tt, *J* = 253 Hz, 36 Hz), 118.0, 127.2, 127.4, 127.5 (t, *J* = 6 Hz), 128.1 (t, *J* = 6 Hz), 128.3, 128.9 (t, *J* = 25 Hz), 129.1, 132.2, 135.6 (t, *J* = 25 Hz), 140.0, 144.4; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –111.00 (t, *J* = 5.0 Hz, 2F), –112.23 (t, *J* = 5.0 Hz, 2F); **IR** (neat) ν 1259, 1134, 1080, 1023, 895, 825, 799, 767, 752, 735, 711, 696, 639; **HRMS** (ESI) calculated for $C_{21}H_{13}NF_4Na$ 378.0876, found 378.0877; **Mp** 140–141 °C.

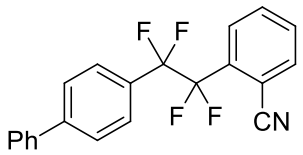
3-[2-(Biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl]benzonitrile (47ah)



Synthesised from **39a** (0.24 mmol) and 3-iodobenzonitrile (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane) afforded 46 mg of the title compound (65% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.42 (m, 1H), 7.46–7.50 (m, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.60–7.62 (m, 3H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.81–7.84 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 113.0, 115.8 (tt, *J* = 254 Hz, 39 Hz), 116.6 (tt, *J* = 253 Hz, 36 Hz), 117.9, 127.2, 127.4, 127.5 (t, *J* = 6 Hz), 128.3, 128.8 (t, *J* = 25 Hz), 129.1, 129.4, 130.9 (t, *J* = 7 Hz), 131.4 (t, *J* = 6 Hz), 132.7 (t, *J* = 26 Hz), 134.6, 139.9, 144.4; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −110.88 (t, *J* = 6.0 Hz, 2F), −111.76 (t, *J* = 6.0 Hz, 2F); **IR** (neat) ν 1268, 1178, 1141, 1098,

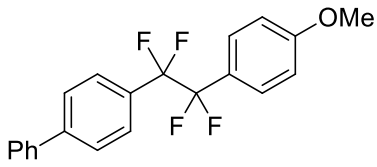
1083, 840, 817, 793, 797, 748; **HRMS** (ESI) calculated for $C_{21}H_{13}NF_4Na$ 378.0876, found 378.0877; **Mp** 122–123 °C.

2-[2-(Biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl]benzonitrile (47ai)



Synthesised from **39a** (0.24 mmol) and 2-iodobenzonitrile (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane to Et_2O/pentane 10/90) afforded 51 mg of the title compound (72% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.42 (m, 1H), 7.46–7.50 (m, 2H), 7.62–7.74 (m, 8H), 7.84 (d, *J* = 7.5 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 112.0 (t, *J* = 3 Hz), 115.9 (tt, *J* = 255 Hz, 39 Hz), 116.6, 116.9 (tt, *J* = 253 Hz, 36 Hz), 127.2, 127.4, 127.7 (t, *J* = 6 Hz), 128.2, 128.6 (t, *J* = 25 Hz), 129.1, 129.3 (t, *J* = 6Hz), 131.5, 132.4, 133.4 (t, *J* = 26 Hz), 134.9, 140.0, 144.5; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −108.49 (s, 2F), −109.65 (s, 2F); **IR** (neat) ν 1251, 1139, 1101, 1078, 899, 879, 835, 800, 767, 755, 739, 719, 698, 650; **HRMS** (ESI) calculated for $C_{21}H_{13}NF_4Na$ 378.0876, found 378.0879; **Mp** 155–156°C.

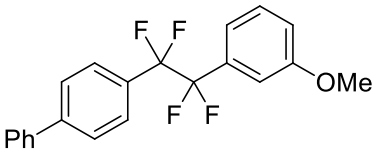
4-[1,1,2,2-Tetrafluoro-2-(4-methoxyphenyl)ethyl]biphenyl (47aj)



Synthesised from **39a** (0.24 mmol) and 1-iodo-4-methoxybenzene (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane to 5% Et_2O/pentane) afforded 64 mg of the title compound (89% yield) as a white solid. When GP 3-E was carried out at room temperature, 27% ^{19}F NMR yield of **47aj** was afforded. The reaction with 1-bromo-4-methoxybenzene gave no product. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.92 (d, *J* = 8.5 Hz, 2H), 7.37–7.41 (m, 3H), 7.45–7.52 (m, 4H), 7.60–7.64 (m, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 55.5, 113.7, 116.9 (tt, *J* = 252 Hz, 37 Hz), 117.0 (tt, *J* = 252 Hz, 36 Hz), 123.7 (t, *J* = 25 Hz), 126.9, 127.4, 127.6 (t, *J* = 6 Hz), 128.1, 128.7 (t, *J* = 6 Hz), 129.1, 130.0 (t, *J* = 25 Hz), 140.2, 143.8,

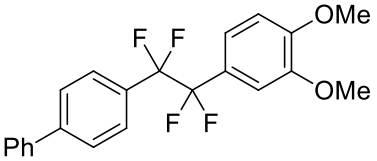
162.0; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –110.62 (d, *J* = 5.0 Hz, 2F), –111.51 (d, *J* = 5.0 Hz, 2F); **IR** (neat) ν 1262, 1181, 1096, 894, 832, 819, 794, 768, 751, 732; **HRMS** (FI) calculated for $C_{21}H_{16}OF_4$ $[M]^+$ 360.1137, found 360.1133; **Mp** 146–147°C.

4-[1,1,2,2-Tetrafluoro-2-(3-methoxyphenyl)ethyl]biphenyl (47ak)



Synthesised from **39a** (0.24 mmol) and 3-iodo-methoxybenzene (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane to 2% Et_2O/pentane) afforded 32 mg of the title compound (44% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 7.00 (s, 1H), 7.03–7.05 (m, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 7.32–7.36 (m, 1H), 7.38–7.42 (m, 1H), 7.46–7.50 (m, 2H), 7.53–7.55 (m, 2H), 7.61–7.66 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 55.5, 112.5 (t, *J* = 7 Hz), 116.7 (tt, *J* = 254 Hz, 37 Hz), 116.8 (tt, *J* = 254 Hz, 36 Hz), 117.0, 119.5 (t, *J* = 7 Hz), 126.9, 127.4, 127.6 (t, *J* = 6 Hz), 128.1, 129.1, 129.4, 129.8 (t, *J* = 25 Hz), 132.3 (t, *J* = 25 Hz), 140.2, 143.9, 159.4; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –114.42 (s, 2F), –114.94 (s, 2F); **IR** (neat) ν 1272, 1223, 1102, 1091, 1079, 1063, 1036, 1018, 1007, 844, 819, 793, 767, 749, 724, 691; **HRMS** (FI) calculated for $C_{21}H_{16}F_4O$ 360.1137, found 360.1137; **Mp** 85–87 °C.

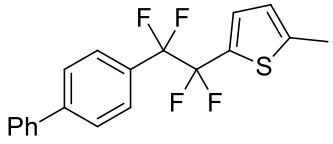
4-[2-(3,3-Dimethoxyphenyl)-1,1,2,2-tetrafluoroethyl]biphenyl (47al)



Synthesised from **39a** (0.24 mmol) and 4-iodo-1,2-dimethoxybenzene (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: 5% Et_2O/pentane to 10% Et_2O/pentane) afforded 46 mg of the title compound (59% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.92 (s, 3H), 6.86-6.89 (m, 2H), 7.06 (dd, *J* = 8.5 Hz, 1.5 Hz, 1H), 7.37–7.42 (m, 1H), 7.45–7.52 (m, 4H), 7.59–7.64 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 56.0, 56.0, 110.0 (t, *J* = 6 Hz), 110.4, 116.9

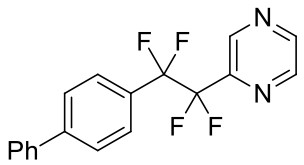
(tt, *J* = 253, 36 Hz), 116.9 (tt, *J* = 253 Hz, 37 Hz), 120.2 (t, *J* = 7 Hz), 123.1 (t, *J* = 26 Hz), 126.9, 127.4, 127.6 (t, *J* = 6 Hz), 128.1, 129.1, 129.9 (t, *J* = 126 Hz), 140.1, 143.9, 148.6, 151.1; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –110.97 (d, *J* = 6.0 Hz, 2F), −111.90 (d, *J* = 6.0 Hz, 2F); **IR** (neat) ν 1518, 1269, 1219, 1175, 1110, 1082, 1022, 915, 806, 733; **HRMS** (ESI) calculated for $C_{22}H_{18}O_2F_4Na$ 413.1135, found 413.1135; **Mp** 127–128 °C.

2-[2-(Biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl]-5-methylthiophene (47am)



Synthesised from **39a** (0.24 mmol) and 2-iodo-5-methylthiophene (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane) afforded 41 mg of the title compound (58% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 6.74-6.75 (m, 1H), 7.13 (d, *J* = 2.5 Hz, 1H), 7.41 (tt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.46–7.50 (m, 2H), 7.60–7.64 (m, 4H), 7.66–7.68 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 15.4, 115.7 (tt, *J* = 251 Hz, 38 Hz), 116.6 (tt, *J* = 253 Hz, 37 Hz), 125.4, 127.0, 127.4, 127.6 (t, *J* = 6 Hz), 128.1, 129.0, 129.1 (t, *J* = 30 Hz), 129.6 (t, *J* = 25 Hz), 129.8 (t, *J* = 6 Hz), 140.1, 144.0, 144.2; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –101.24 (s, 2F), –110.82 (s, 2F); **IR** (neat) ν 1099, 1077, 827, 810, 766, 746, 688; **HRMS** (FI) calculated for $C_{19}H_{14}F_4S$ 350.0752, found 350.0767; **Mp** 134–135 °C.

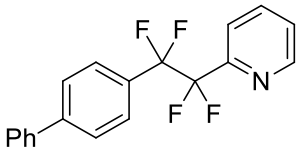
2-[2-(Biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl]pyrazine (47an)



Synthesised from **39a** (0.24 mmol) and 2-iodopyrazine (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: 10% Et_2O/pentane to 20% Et_2O/pentane) afforded 49 mg of the title compound (74% yield) as an off-white solid. When GP 3-E was carried out at room temperature, 46 mg (69% yield) of **47an** was isolated. The reaction with 1-bromopyrazine (0.2 mmol) afforded 45 mg (68% yield) of the title compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.42 (m, 1H), 7.46–7.49 (m, 2H),

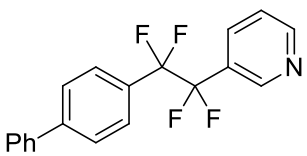
7.61–7.70 (m, 6H), 7.75 (brs, 1H), 8.82 (brs, 1H), 9.00 (brs, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 114.0 (tt, *J* = 255 Hz, 39 Hz), 116.7 (tt, *J* = 253 Hz, 35 Hz), 127.2, 127.3, 127.5 (t, *J* = 6 Hz), 128.2, 128.8 (t, *J* = 25 Hz), 129.0, 139.9, 144.0, 144.3 (brs), 144.4, 145.9 (brs), 146.7; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –110.62 (s, 2F), –115.01 (s, 2F); **IR** (neat) ν 1270, 1119, 1102, 1074, 1042, 1020, 902, 854, 760, 738, 717, 697; **HRMS** (FI) calculated for $C_{18}H_{13}N_2F_4$ 333.1009, found 333.1012; **Mp** 138–139 °C.

2-(2-([1,1'-biphenyl]-4-yl)-1,1,2,2-tetrafluoroethyl)pyridine (47ao)



Synthesised from **39a** (0.24 mmol) and 2-iodopyridine (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane to 15% Et_2O/pentane) afforded 60 mg of the title compound (91% yield) as a white solid. When GP 3-E was carried out at rt, 45 mg (68% yield) **47ao** was isolated. The reaction with 2-bromopyridine (0.2 mmol) afforded 24 mg (36% yield) of the title compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.41 (m, 1H), 7.43–7.49 (m, 3H), 7.60–7.62 (m, 4H), 7.65–7.68 (m, 3H), 7.83 (dt, *J* = 8.0 Hz, 1.0 Hz, 1H), 8.74 (d, 4.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 114.4 (tt, *J* = 253 Hz, 37 Hz), 116.9 (tt, *J* = 253 Hz, 36 Hz), 122.9, 125.7, 127.1, 127.4, 127.5 (t, *J* = 6 Hz), 128.1, 129.0, 129.6 (t, *J* = 25 Hz), 136.9, 140.1, 144.1, 149.6, 149.8 (t, *J* = 26 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −110.79 (t, *J* = 6.0 Hz, 2F), −114.60 (t, *J* = 6.0 Hz, 2F); **IR** (neat) ν 1269, 1132, 1099, 1083, 1072, 906, 891, 835, 768, 753, 724, 698, 688; **HRMS** (ESI) calculated for $C_{19}H_{14}NF_4$ 332.1057, found 332.1060; **Mp** 119–120 °C.

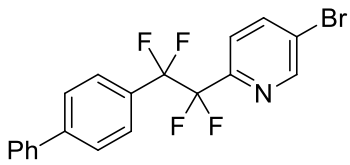
3-(2-([1,1'-biphenyl]-4-yl)-1,1,2,2-tetrafluoroethyl)pyridine (47ap)



Synthesised from **39a** (0.24 mmol) and 3-iodopyridine (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: 5% Et_2O/pentane to 20% Et_2O/pentane) afforded 51 mg of the title compound (77% yield) as a white solid. The

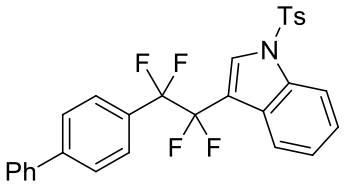
reaction with 3-bromopyridine (0.2 mmol) gave 17% ^{19}F NMR yield of the title compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.42 (m, 2H), 7.45–7.49 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 8.78 (s, 2H);**^{13}C NMR** (150 MHz, $CDCl_3$) δ 116.1 (tt, *J* = 253 Hz, 38 Hz), 116.6 (tt, *J* = 253 Hz, 35 Hz), 123.2, 127.2, 127.4, 127.5 (t, *J* = 6 Hz), 128.1, 128.2, 129.0 (t, *J* = 25 Hz), 129.1, 135.0 (t, *J* = 6 Hz), 140.0, 144.4, 148.3 (t, *J* = 6 Hz), 152.2; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –111.25 (s, 2F), –112.15 (s, 2F); **IR** (neat) ν 1265, 1099, 1085, 890, 835, 805, 768, 753, 725, 717, 689; **HRMS** (ESI) calculated for $C_{19}H_{14}NF_4$ 332.1057, found 332.1057; **Mp** 120–121 °C.

2-(2-([1,1'-biphenyl]-4-yl)-1,1,2,2-tetrafluoroethyl)-5-bromopyridine (47aq)



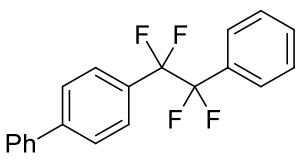
Synthesised from **39a** (0.24 mmol) and 5-bromo-2-iodopyridine (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: 5% Et_2O/pentane) afforded 68 mg of the title compound (83% yield) as a white solid. The reaction with 2,5-dibromopyridine (0.2 mmol) afforded 35 mg (43% yield) of the title compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.42 (m, 1H), 7.46–7.49 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.61–7.63 (m, 4H), 7.67–7.69 (m, 2H), 7.97 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 8.79 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 114.3 (tt, *J* = 255 Hz, 37 Hz), 116.7 (tt, *J* = 253 Hz, 35 Hz), 123.5, 124.1 (t, *J* = 4 Hz), 127.2, 127.4, 127.5 (t, *J* = 6 Hz), 128.2, 129.1, 129.3 (t, *J* = 25 Hz), 139.6, 140.0, 144.2, 148.3 (t, *J* = 27 Hz), 150.9; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −110.68 (t, *J* = 6.0 Hz, 2F), −114.35 (t, *J* = 6.0 Hz, 2F); **IR** (neat) ν 1269, 1124, 1098, 1088, 1010, 898, 830, 732, 708, 691; **HRMS** (EI) calculated for $C_{19}H_{12}BrF_4N$ 409.0089, found 409.0089; **Mp** 101–103 °C.

3-(2-([1,1'-Biphenyl]-4-yl)-1,1,2,2-tetrafluoroethyl)-1-tosyl-*1H*-indole (47ar)



Synthesised from **39a** (0.24 mmol) and *N*-tosyl-3-iodo-*1H*-indole (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: 5% Et_2O in pentane to 15% Et_2O/pentane) afforded 27 mg of the title compound (34% yield) as a white solid. The reaction with *N*-tosyl-3-bromo-*1H*-indole (0.2 mmol) afforded 7% ^{19}F NMR yield of the title compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.03–7.07 (m, 1H), 7.14–7.18 (m, 1H), 7.18–7.23 (m, 1H), 7.26–7.31 (m, 4H), 7.35–7.40 (m, 5H), 7.53–7.56 (m, 3H), 7.78 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 21.7, 113.4 (t, *J* = 30 Hz), 113.6, 116.3 (tt, *J* = 251 Hz, 38 Hz), 117.0 (tt, 253 Hz, 36 Hz), 121.4, 124.1, 125.5, 127.1, 127.1, 127.2, 127.4, 127.5 (t, *J* = 6 Hz), 127.5 (t, *J* = 6 Hz), 128.2, 129.1, 129.4 (t, *J* = 25 Hz), 130.2, 134.7, 134.9, 140.1, 144.1, 145.7; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –107.84 (s, 2F), –111.57 (s, 2F); **IR** (neat) ν 1448, 1379, 1283, 1175, 1138, 1115, 1090, 1076, 1008, 961, 749, 659; **HRMS** (ESI) calculated for $C_{29}H_{21}O_2NF_4NaS$ 546.1121, found 546.1121; **Mp** 55–57 °C.

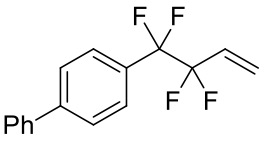
4-(1,1,2,2-Tetrafluoro-2-phenylethyl)biphenyl (47as)



Synthesised from **39a** (0.24 mmol) and iodobenzene (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane) afforded 46 mg of the title compound (70% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.41 (m, 1H), 7.43–7.54 (m, 9H), 7.60–7.65 (m, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 116.8 (tt, *J* = 252 Hz, 36 Hz), 116.9 (tt, *J* = 253 Hz, 36 Hz), 127.0, 127.2 (t, *J* = 6 Hz), 127.4, 127.6 (t, *J* = 6 Hz), 128.1, 128.3, 129.1, 129.8 (t, *J* = 25 Hz), 131.0 (t, *J* = 25 Hz), 131.1, 140.1, 144.0; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –111.45 (s, 2F), –111.62 (s, 2F); **IR** (neat) ν 1260,

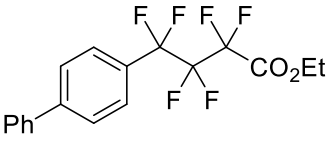
1098, 1082, 1068, 1027, 954, 834, 799, 763, 749, 698, 687; **HRMS** (FI) calculated for $C_{20}H_{14}F_4$ 330.1032, found 330.1029; **Mp** 149–151 °C.

4-(1,1,2,2-Tetrafluorobut-3-en-1-yl)biphenyl (47at)



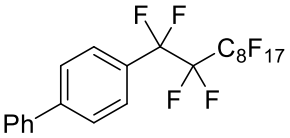
Synthesised from **39a** (0.24 mmol) and iodoethene (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane) afforded 46 mg of the title compound (82% yield) as a white solid (in 91% purity by ^{1}H NMR, with 9% of the protodesilylated by-product **16a**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.73 (d, *J* = 11.0 Hz, 1H), 5.86 (ddt, *J* = 17.5 Hz, 2.0 Hz, 0.5 Hz, 1H), 6.00–6.13 (m, 1H), 7.39–7.44 (m, 1H), 7.46–7.50 (m, 2H), 7.61–7.72 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 115.3 (tt, *J* = 248 Hz, 38 Hz), 166.6 (tt, *J* = 252 Hz, 36 Hz), 124.4 (t, *J* = 9 Hz), 126.9 (t, *J* = 25 Hz), 127.1, 127.4, 127.5 (t, *J* = 6 Hz), 128.2, 129.1, 129.7 (t, *J* = 25 Hz), 140.2, 144.2; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –111.72 (s, 2F), –114.24 (d, *J* = 11.0 Hz, 2F); **IR** (neat) ν 1612, 1489, 1421, 1303, 1209, 1100, 1074, 1007, 958, 919, 836, 754, 733, 688; **HRMS** (EI) calculated for $C_{16}H_{12}F_4$ 280.0875, found 280.0875; **Mp** 57–58 °C.

Ethyl 4-(biphenyl-4-yl)-2,2,3,3,4,4-hexafluorobutanoate (47au)



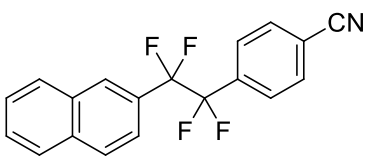
Ethyl iododifluoroacetate was unreactive under GP 3-E.

4-(Henicosafluorodecyl)biphenyl (47av)



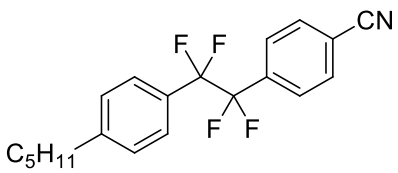
1-Iodo-perfluorooctane was unreactive under GP 3-E.

4-[1,1,2,2-Tetrafluoro-2-(naphthalen-2-yl)ethyl]benzonitrile (47eg)



Synthesised from **39e** (0.24 mmol) and 4-iodobenzonitrile (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane to 5% Et_2O/pentane) afforded 46 mg of the title compound (70% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.5 Hz, 1H), 7.56–7.64 (m, 4H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.89–7.91 (m, 3H), 8.01 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 115.3, 116.1 (tt, *J* = 254 Hz, 37 Hz), 116.7 (tt, *J* = 253 Hz, 36 Hz), 117.9, 123.1 (t, *J* = 6 Hz), 127.1, 127.4 (t, *J* = 25 Hz), 127.7 (t, *J* = 7 Hz), 127.9, 128.0 (t, *J* = 7 Hz), 128.1, 128.4, 128.9, 132.1, 132.3, 134.5, 135.6 (t, *J* = 26 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −110.73 (s, 2F), –112.11 (s, 2F); **IR** (neat) ν 1262, 1229, 1125, 1106, 1082, 921, 902, 865, 850, 832, 810, 743; **HRMS** (EI) calculated for $C_{19}H_{11}F_4N$ 329.0828, found 329.0828; **Mp** 120–121 °C.

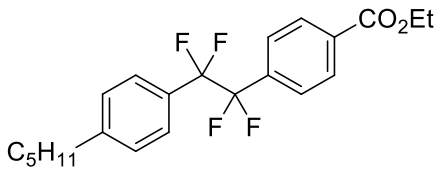
4-[1,1,2,2-Tetrafluoro-2-(4-pentylphenyl)ethyl]benzonitrile (47fg)



Synthesised from **39f** (0.24 mmol) and 4-iodobenzonitrile (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane to 2% Et_2O/pentane) afforded 54 mg of the title compound (77% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.17 (t, *J* = 7.0 Hz, 3H), 1.53–1.67 (m, 4H), 1.86–1.94 (m, 2H), 2.92 (dd, *J* = 8.0 Hz, 7.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.99 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 14.1, 22.6, 31.0, 31.5, 35.8, 115.2, 116.0 (tt, *J* = 253 Hz, 38 Hz), 116.7 (tt, *J* = 253 Hz, 36 Hz), 118.0, 126.9 (t, *J* = 7 Hz), 127.3 (t, *J* = 25 Hz), 128.0 (t, *J* = 7 Hz), 128.5, 132.0, 135.7 (t, *J* = 26 Hz), 146.7; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ −110.98 (s, 2F), –112.50 (s, 2F); **IR** (neat) ν 1258,

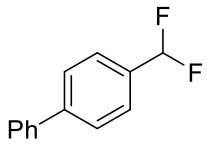
1142, 1107, 1083, 897, 819, 638; **HRMS** (ESI) calculated for $C_{20}H_{19}NF_4Na$ 372.1346, found 372.1346; **Mp** 69–70 °C.

Ethyl 4-[1,1,2,2-tetrafluoro-2-(4-pentylphenyl)ethyl]benzoate (47fe)[226]



Synthesised from **39f** (0.6 mmol) and ethyl 4-iodobenzoate (0.5 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane to 5% Et_2O/pentane) afforded 173 mg of the title compound (87% yield, 90% pure by ^{1}H NMR) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3H), 1.29–1.37 (m, 4H), 1.41 (t, *J* = 7.0 Hz, 3H), 1.60–1.66 (m, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 4.40 (q, *J* = 7.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 8.07 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.1, 14.3, 22.6, 30.9, 31.5, 35.8, 61.4, 116.5 (tt, *J* = 254 H, 37 Hz), 116.8 (tt, *J* = 253 Hz, 36 Hz), 127.0 (dt, *J* = 29 Hz, 6 Hz), 127.8 (t, *J* = 25 Hz), 128.3, 131.1, 132.9, 135.3 (t, *J* = 25 Hz), 137.7, 146.4, 165.7; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –111.26 (d, *J* = 2.5 Hz, 2F), −112.22 (d, *J* = 2.5 Hz, 2F).

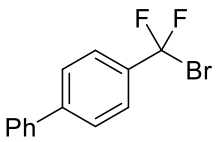
4-(Difluoromethyl)biphenyl[292]



To a solution of 1.8 g biphenyl-3-carbaldehyde (10.0 mmol, 1.0 eq) in 30 mL DCM (0.3 M) was carefully added 1.6 mL DAST (12.0 mmol, 1.2 eq). The reaction was stirred for 16 h, quenched with aqueous sodium bicarbonate, extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica flash column chromatography (eluent: Hexane to 10% Et_2O/Hexane) to afford 1.28 g (63% yield) of the title compound as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.61 (t, *J* = 56.5 Hz, 1H), 7.30 (tt, *J* = 7.5 Hz, 2.0 Hz, 1H), 7.35–7.40 (m, 2H), 7.48–7.52 (m, 4H), 7.59 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 114.8

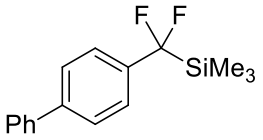
(t, *J* = 239 Hz), 126.1 (t, *J* = 6 Hz), 127.3, 127.5, 127.8, 128.9, 133.2 (t, *J* = 23 Hz), 140.2, 143.7 (t, *J* = 2 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –110.29 (d, *J* = 55.5 Hz).

4-[Bromo(difluoro)methyl]biphenyl



To a solution of 408 mg 4-(difluoromethyl)biphenyl (2.0 mmol, 1.0 eq) in 6 mL CCl_4 (0.36 M) was added 748 mg NBS (recrystallized from boiling H_2O, 4.2 mmol, 2.1 eq). The reaction was stirred at rt under UV irradiation for 16 h, after which it was quenched with $Na_2S_2O_{3(aq)}$ and extracted with DCM. The organic layer was dried over $MgSO_4$, evaporated and purified by silica flash column chromatography (eluent: pentane) to afford 563 mg (99% yield) of the title compound as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.35 (m, 1H), 7.38–7.43 (m, 2H), 7.51–7.55 (m, 2H), 7.58–7.63 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 118.4 (t, *J* = 304.0 Hz), 124.9 (t, *J* = 5 Hz), 127.3, 127.4, 128.2, 129.0, 137.0 (t, *J* = 24 Hz), 139.7, 144.2; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –43.16 (s); **IR** (neat) ν 1268, 1100, 1056, 881, 828, 769, 746, 715, 688, 660; **HRMS** (FI) calculated for $C_{13}H_9F_2Br$ [M^+] 281.9856, found 281.9861; **Mp** 53–55 °C.

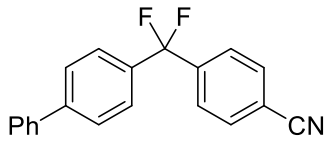
[Biphenyl-4-yl(difluoro)methyl](trimethyl)silane



To 5 mg Mg turnings (0.2 mmol, 2.0 eq) in 0.3 mL DMF (0.3 M) in a Schlenck tube was added 51 µL Me_3SiCl (0.4 mmol, 4.0 eq). 28 mg 4-[bromo(difluoro)methyl]biphenyl (0.1 mmol, 1.0 eq) in 0.1 mL DMF was added dropwise and the reaction was stirred at rt for 16 h. The reaction was quenched with H_2O, extracted with Et_2O and the organic layers were dried over $MgSO_4$ before concentrating *in vacuo*. The crude product was purified by silica flash column chromatography (eluent: pentane) to afford 17 mg (62% yield) of the title compound as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 7.17–7.21 (m, 1H), 7.22–7.25 (m, 2H), 7.25–7.30 (m,

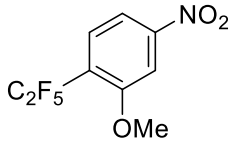
2H), 7.41–7.47 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ –4.8, 125.2 (t, *J* = 8 Hz), 127.0, 127.2, 127.6, 128.4 (t, *J* = 266 Hz), 128.9, 137.2 (t, *J* = 20 Hz), 140.4, 141.7 (t, *J* = 3 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –111.95 (s); **IR** (neat) ν 1484, 1249, 1074, 986, 837, 755, 690; **HRMS** (FI) calculated for $C_{16}H_{18}SiF_2$ $[M]^+$ 276.1146, found 276.1142; **Mp** 79–81 °C.

4-[Biphenyl-4-yl(difluoro)methyl]benzonitrile (47hg)



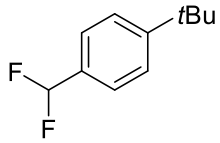
Synthesised from [biphenyl-4-yl(difluoro)methyl] (trimethyl)silane (0.24 mmol) and 4-iodobenzonitrile (0.2 mmol) following GP 3-E. The ^{19}F NMR yield was determined to be 4%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.11–7.61 (m, 13H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –110.34 (s, 2F), –110.49 (s, 2F).

2-Methoxy-4-nitro-1-(pentafluoroethyl)benzene (47ia)[228]



Synthesised from trimethyl(pentafluoroethyl)silane (0.24 mmol) and 1-iodo-2-methoxy-4-nitrobenzene (0.2 mmol) following GP 3-E. Purification by silica flash column chromatography (eluent: pentane to 5% Et_2O/pentane) afforded 44 mg of the title compound (82% yield) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.85 (s, 1H), 7.88–7.91 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 56.8, 107.5, 113.1 (tq, *J* = 257 Hz, 40.0 Hz), 115.2, 118.0 (tt, *J* = 287 Hz, 39 Hz), 122.8 (t, *J* = 23 Hz), 130.3 (t, *J* = 9 Hz), 151.5, 159.2 (t, *J* = 2 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –83.79 (t, *J* = 2.0 Hz, 3F), −112.66 (s, 2F).

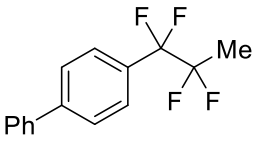
1-*tert*-Butyl-4-(difluoromethyl)benzene (47jw)[94]



Synthesised from (difluoromethyl)-trimethylsilane (0.24 mmol) and 1-*tert*-butyl-4-iodobenzene (0.2 mmol) following GP 3-E. The ^{19}F NMR yield was determined to be 59%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.25 (s, 9H), 6.53 (t, *J* = 56.5 Hz, 1H), 7.34–7.40 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$)

δ 31.2, 34.9, 115.0 (t, *J* = 238 Hz), 125.4 (t, *J* = 6 Hz), 125.7, 131.6 (t, *J* = 23 Hz), 154.1 (t, *J* = 2 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –109.75 (d, *J* = 56.5 Hz).

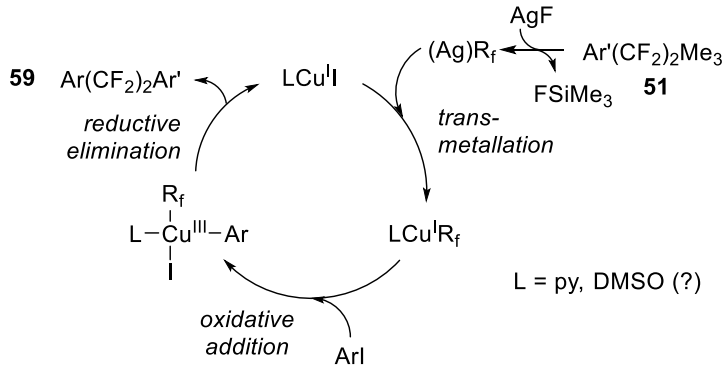
4-(1,1,2,2-Tetrafluoropropyl)biphenyl (49a)



Formed as a by-product in the copper-mediated cross-coupling of **39a** with aryl bromides. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.82 (tt, *J* = 18.5 Hz, 1.5 Hz, 3H), 7.38–7.42 (m, 1H), 7.45–7.49 (m, 2H), 7.60–7.64 (m, 4H), 7.67–7.71 (m, 2H); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –107.06 (q, *J* = 18.5 Hz, 2F), –111.95 (s, 2F); **HRMS** (EI) calculated for $C_{15}H_{12}F_4$ 268.0875, found 268.0874.

6.2.4.4 Mechanistic Considerations

Scheme 94 shows the reaction mechanism we have tentatively proposed for the cross-coupling of [2-aryl-1,1,2,2-tetrafluoroethyl](trimethyl)silanes with aryl iodides.



Scheme 94 Proposed mechanism

The crude ^{19}F NMR spectra for the reaction of **39a** with iodoarenes clearly show the formation of Me_3SiF as an apparent octet at –157.7 ppm with a $^3J_{HF}$ coupling of 7.0 Hz,[293] suggesting the fluoride-mediated formation of a CF_3 anion from Me_3SiCF_3 (Figure 12).

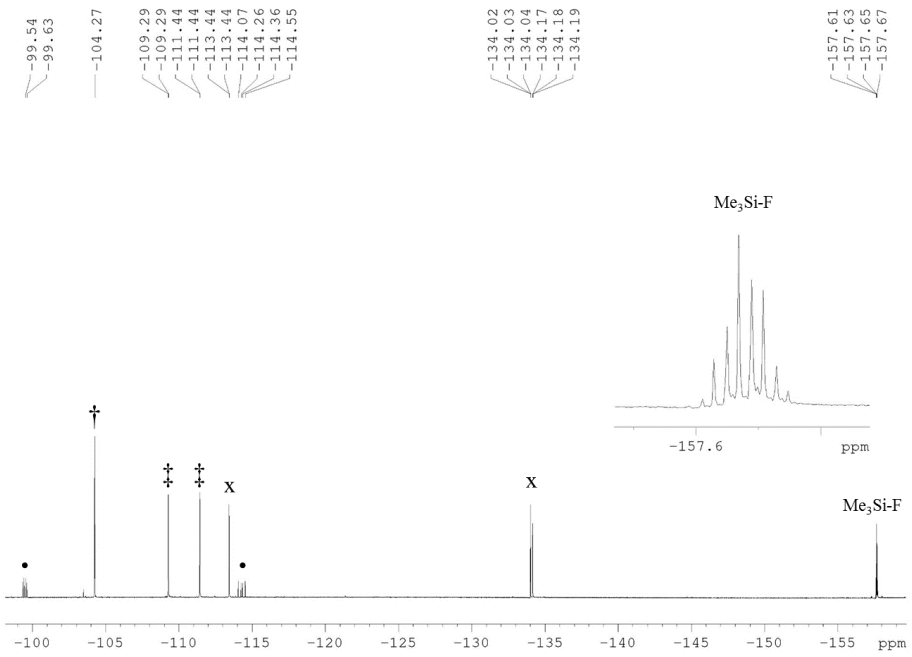


Figure 12 Crude ^{19}F NMR spectrum for the reaction of 39a with 1-iodo-2-methoxy-4-nitrobenzene, showing products 45a (•), 38a (†), 47aa (‡), 16a (x) and Me_3SiF

7. References

[1] D. O'Hagan, *Chemical Society Reviews* **2008**, *37*, 308-319.

[2] M. Pagliaro, R. Ciriminna, *Journal of Materials Chemistry* **2005**, *2005*, 4981-4991.

[3] P. Kirsch, *Modern Fluoroorganic Chemistry*, WILEY-VCH, Weinheim, Germany, **2004**.

[4] R. L. Wahl, *Principles and practice of PET and PET/CT*, Lippincott Williams & Wilkins, Philadelphia, **2002**.

[5] T. Liang, T. Ritter, in *Comprehensive Organic Synthesis II, Volume 6: Heteroatom Manipulation, Vol. 6* (Eds.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**, pp. 210–238.

[6] J. F. R. Robertson, S. E. Come, S. E. Jones, L. Beex, M. Kaufmann, A. Makris, J. W. R. Nortier, K. Possinger, L.-E. Rutqvist, *European Journal of Cancer* **2005**, *41*, 346-356.

[7] J.-P. Bégué, D. Bonnet-Delpon, in *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, Inc., Hoboken, New Jersey, **2008**.

[8] A. Studer, S. Hadida, R. Ferritto, S.-Y. Kim, P. Jeger, P. Wipf, D. P. Curran, *Science* **1997**, *275*, 823-826; D. P. Curran, *Synlett* **2001**, *2001*, 1488-1496; J.-M. Vincent, in *Flourous Chemistry* (Ed.: I. T. Horvath), Springer, Berlin Heidelberg, **2012**, pp. 153-174.

[9] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886.

[10] V. G. Nenajdenko, V. M. Muzalevskiy, A. V. Shastin, *Chemical Reviews* **2015**, *115*, 973-1050.

[11] R. D. Howells, H. Gilman, *Journal of Fluorine Chemistry* **1975**, *5*, 99-114; P. Tarrant, *Journal of Fluorine Chemistry* **1984**, *25*, 69-74; X.-Y. Li, X.-K. Jiang, H.-Q. Pan, J.-S. Hu, W.-M. Fu, *Pure and Applied Chemistry* **1987**, *59*, 1015-1020.

[12] A. Cheguillaume, J. Gillart, D. Labar, V. Grégoire, J. Marchand-Brynaert, *Bioorganic & Medicinal Chemistry* **2005**, *13*, 1357-1367.

[13] D. B. Harper, D. O'Hagan, *Natural Product Reports* **1994**, 123-133.

[14] D. O'Hagan, C. Schaffrath, S. L. Cobb, J. T. G. Hamilton, C. D. Murphy, *Nature* **2002**, *416*, 279-279; C. Schaffrath, S. L. Cobb, D. O'Hagan, *Angewandte Chemie International Edition* **2002**, *41*, 3913-3915.

[15] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chemical Society Reviews* **2008**, *2008*, 320-330.

[16] D. O'Hagan, *Journal of Fluorine Chemistry* **2010**, *131*, 1071-1081.

[17] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chemical Reviews* **2013**, *114*, 2432-2506.

[18] Z. B. Li, P. S. Conti, *Advanced Drug Delivery Reviews* **2010**, *62*, 1031-1051.

[19] Y. X. He, Q. Y. Guo, *Postgraduate Medical Journal* **2008**, *84*, 246-251.

[20] R. Littich, P. J. H. Scott, *Angewandte Chemie International Edition* **2012**, *51*, 1106-1109.

[21] G. Mees, R. Dierck, C. Vangestel, C. Van de Wiele, *European Journal of Nuclear Medicine and Molecular Imaging* **2009**, *36*, 1674-1686; L. S. Ziemer, S. M. Evans, A. Kachur, A. L. Shuman, C. A. Cardi, W. T. Jenkins, J. S. Karp, A. Alavi, W. R. Dolbier, C. J. Koch, *European Journal of Nuclear Medicine and Molecular Imaging* **2003**, *30*, 259-266; G. Komar, M. Seppanen, O. Eskola, P. Lindholm, T. J. Gronroos, S. Forsback, H. Sipila, S. M. Evans, O. Solin, H. Minn, *Journal of Nuclear Medicine* **2008**, *49*, 1944-1951.

[22] O. Eskola, T. J. Gronroos, S. Forsback, J. Tuomela, G. Komar, J. Bergman, P. Harkonen, M. Haaparanta, H. Minn, O. Solin, *Molecular Imaging and Biology* **2012**, *14*, 205-212.

[23] J. G. Rajendran, K. A. Krohn, *Seminars in Nuclear Medicine* **2015**, *45*, 151–162.

[24] M. Tredwell, V. Gouverneur, *Angewandte Chemie International Edition* **2012**, *51*, 11426-11437; T. Liang, C. N. Neumann, T. Ritter, *Angewandte Chemie International Edition* **2013**,

52, 8214-8264; S. H. Liang, N. Vasdev, *Angewandte Chemie International Edition* **2014**, *53*, 11416-11418; O. Jacobson, D. O. Kiesewetter, X. Chen, *Bioconjugate Chemistry* **2015**, *26*, 1-18.

[25] A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford, P. J. H. Scott, *Chemical Science* **2014**, 4545-4553.

[26] V. T. Lien, P. J. Riss, *BioMed Research International* **2014**, *2014*.

[27] P. Johnström, S. Stone-Elander, *Journal of Labelled Compounds and Radiopharmaceuticals* **1995**, *36*, 537-547.

[28] G. K. S. Prakash, M. M. Alauddin, J. Hu, P. S. Conti, G. A. Olah, *Journal of Labelled Compounds and Radiopharmaceuticals* **2003**, *46*, 1087-1092; W. R. Dolbier Jr, A.-R. Li, C. J. Koch, C.-Y. Shiue, A. V. Kachur, *Applied Radiation and Isotopes* **2001**, *54*, 73-80.

[29] J. Bergman, O. Solin, *Nuclear Medicine and Biology* **1997**, *24*, 677-683.

[30] P. J. Riss, F. I. Aigbirhio, *Chemical Communications* **2011**, *47*, 11873-11875.

[31] O. Josse, D. Labar, B. Georges, V. Gregoire, J. Marchand-Brynaert, *Bioorganic & Medicinal Chemistry* **2001**, *9*, 665-675.

[32] D. van der Born, J. D. M. Herscheid, R. V. A. Orru, D. J. Vugts, *Chemical Communications* **2013**, *49*, 4018-4020.

[33] M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur, J. Passchier, *Nature Chemistry* **2013**, *5*, 941-944.

[34] D. van der Born, C. Sweing, J. K. D. M. Herscheid, A. D. Windhorst, R. V. A. Orru, D. J. Vugts, *Angewandte Chemie International Edition* **2014**, *53*, 11046-11050.

[35] P. Ivashkin, G. Lemonnier, J. Cousin, V. Gregoire, D. Labar, P. Jubault, X. Pannecoucke, *Chemistry - A European Journal* **2014**, *20*, 9514-9518.

[36] E. Emer, J. Twilton, M. Tredwell, S. Calderwood, T. L. Collier, B. Liégault, M. Taillefer, V. Gouverneur, *Organic Letters* **2014**, *16*, 6004-6007.

[37] S. Rozen, E. Mishani, *Journal of the Chemical Society, Chemical Communications* **1994**, 2081-2081.

[38] Y. Hagooly, S. Rozen, *Organic Letters* **2012**, *14*, 1114-1117.

[39] S. Furuta, M. Kuroboshi, T. Hiyama, *Bulletin of the Chemical Society of Japan* **1999**, *72*, 805-819.

[40] T. B. Patrick, K. K. Johri, D. H. White, *The Journal of Organic Chemistry* **1983**, *48*, 4158-4159.

[41] T. B. Patrick, K. K. Johri, D. H. White, W. S. Bertrand, R. Mokhtar, M. R. Kilbourn, M. J. Welch, *Canadian Journal of Chemistry* **1986**, *64*, 138-141.

[42] T. B. Patrick, S. Khazaeli, S. Nadji, K. Hering-Smith, D. Reif, *The Journal of Organic Chemistry* **1993**, *58*, 705-708.

[43] M. A. Tius, *Tetrahedron* **1995**, *51*, 6605-6634.

[44] M. Eisenberg, D. D. DesMarteau, *Inorganic and Nuclear Chemistry Letters* **1970**, *6*, 29-34; D. D. DesMarteau, R. D. LeBlond, S. F. Hossain, D. Nothe, *Journal of the American Chemical Society* **1981**, *103*, 7734-7739.

[45] M. Rueda-Becerril, C. Chatalova Sazepin, J. C. T. Leung, T. Okbinoglu, P. Kennepohl, J.-F. Paquin, G. M. Sammis, *Journal of the American Chemical Society* **2012**, *134*, 4026-4029.

[46] J. C. T. Leung, C. Chatalova-Sazepin, J. G. West, M. Rueda-□□Becerril, J.-F. Paquin, G. M. Sammis, *Angewandte Chemie International Edition* **2012**, *51*, 10804-10807.

[47] F. Yin, Z. Wang, Z. Li, C. Li, *Journal of the American Chemical Society* **2012**, *134*, 10401-10404.

[48] M. Rueda-Becerril, O. Mahé, M. Drouin, M. B. Majewski, J. G. West, M. O. Wolf, G. M. Sammis, J.-F. Paquin, *Journal of the American Chemical Society* **2014**, *136*, 2637-2641.

[49] J. C. T. Leung, G. M. Sammis, *Chemistry - A European Journal* **2015**, 2197-2204.

[50] S. Ventre, F. R. Petronijevic, D. W. C. MacMillan, *Journal of the American Chemical Society* **2015**, *137*, 5654-5657.

[51] X. Huang, W. Liu, J. M. Hooker, J. T. Groves, *Angewandte Chemie International Edition* **2015**, *54*, 5241-5245.
[52] W. Liu, X. Huang, M.-J. Cheng, R. J. Nielsen, W. A. Goddard III, J. T. Groves, *Science* **2012**, *337*, 1322-1325; W. Liu, J. T. Groves, *Angewandte Chemie International Edition* **2013**, *52*, 6024-6027.
[53] L. Carroll, H. L. Evans, A. C. Spivey, E. O. Aboagye, *Chemical Communications* **2015**, *51*, 8439-8441.
[54] N. R. Patel, I. Flowers, Robert A., *Journal of Organic Chemistry* **2015**, *80*, 5834-5841.
[55] H. Teare, E. G. Robins, E. Arstad, S. K. Luthra, V. Gouverneur, *Chemical Communications* **2007**, 2330-2332; I. S. R. Stenhagen, A. K. Kirjavainen, S. J. Forsback, C. G. Jorgensen, E. G. Robins, S. K. Luthra, O. Solin, V. Gouverneur, *Chemical Communications* **2013**, *49*, 1386-1388.
[56] H. Teare, E. G. Robins, A. Kirjavainen, S. Forsback, G. Sandford, O. Solin, S. K. Luthra, V. Gouverneur, *Angewandte Chemie International Edition* **2010**, *49*, 6821-6824.
[57] W. R. Dolbier, *Chemical Reviews* **1996**, *96*, 1557-1584.
[58] L. D. Kispert, H. Liu, C. U. Pittman, *Journal of the American Chemical Society* **1973**, *95*, 1657-1659.
[59] I. V. Beregovaya, L. N. Shchegoleva, V. E. Platonov, *Bulletin of the Academy of Sciences of the USSR, Division of Chemical Science* **1990**, *39*, 956-961.
[60] K. Sato, M. Omote, A. Ando, I. Kumadaki, *Journal of Fluorine Chemistry* **2004**, *125*, 509-515.
[61] I. S. Stenhagen, *New Methods for the Construction of C-18F bonds*, **2013**.
[62] R. P. Singh, J. M. Shreeve, *Synthesis* **2002**, *2002*, 2561-2578.
[63] S. Lu, V. W. Pike, *Journal of Fluorine Chemistry* **2010**, *131*, 1032-1038.
[64] J. A. Morrison, L. L. Gerchman, R. Eujen, R. J. Lagow, *Journal of Fluorine Chemistry* **1977**, *10*, 333–339.
[65] L. J. Krause, J. A. Morrison, *Journal of the American Chemical Society* **1981**, *103*, 2995-3001.
[66] V. C. R. McLoughlin, J. Thrower, *Tetrahedron* **1969**, *25*, 5921-5940.
[67] N. Shibata, S. Mizuta, H. Kawai, *Tetrahedron - Asymmetry* **2008**, *19*, 2633-2644.
[68] X. Liu, C. Xu, M. Wang, Q. Liu, *Chemical Reviews* **2014**.
[69] O. A. Tomashenko, V. V. Grushin, *Chemical Reviews* **2011**, *111*, 4475-4521.
[70] O. R. Pierce, E. T. McBee, G. F. Judd, *Journal of the American Chemical Society* **1954**, *76*, 474-478.
[71] M. A. McClinton, D. A. McClinton, *Tetrahedron* **1992**, *48*, 6555-6666.
[72] I. Kieltsch, G. G. Dubinina, C. Hamacher, A. Kaiser, J. Torres-Nieto, J. M. Hutchison, A. Klein, Y. Budnikova, D. A. Vicic, *Organometallics* **2010**, *29*, 1451-1456.
[73] J. A. Pople, M. Gordon, *Journal of the American Chemical Society* **1967**, *89*, 4253-4261.
[74] A. Lishchynskyi, V. V. Grushin, *Journal of the American Chemical Society* **2013**, *135*, 12584-12587.
[75] *IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"), Vol. 71*, Blackwell Scientific Publications, Oxford, **1997**.
[76] K. G. Sharp, T. D. Coyle, *Inorganic Chemistry* **1972**, *11*, 1259-1264.
[77] R. Vianello, J. F. Liebman, Z. B. Maksic, *Chemistry - A European Journal* **2004**, *10*, 5751-5760.
[78] I. E. Charif, S. M. Mekelleche, D. Villemin, N. Mora-Diez, *Journal of Molecular Structure: THEOCHEM* **2007**, *818*, 1-6.
[79] W. H. Saunders Jr., *Journal of Organic Chemistry* **1999**, *64*, 861-865.
[80] F. G. Bordwell, *Accounts of chemical research* **1988**, *21*, 456-463.
[81] L. M. Yagupolskii, I. I. Maletina, N. V. Kondratenko, V. V. Orda, *Synthesis* **1978**, *1978*, 835-837.

[82] C.-M. Chiang, C.-C. Cho, *Journal of Physical Chemistry B* **2005**, *109*, 21486-21488.
[83] A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *Journal of the American Chemical Society* **2011**, *133*, 20901-20913.
[84] A. Lishchynskyi, M. A. Novikov, E. Martin, E. C. Escudero-Adán, P. Novák, V. V. Grushin, *Journal of Organic Chemistry* **2013**, *78*, 11126-11146.
[85] B. Chen, D. A. Vicic, *Journal of Fluorine Chemistry* **2014**, *167*, 139–142.
[86] P. Chen, G. Liu, *Synthesis* **2013**, *45*, 2919-2939.
[87] D. M. Wiemers, D. J. Burton, *Journal of the American Chemical Society* **1986**, *108*, 832-834.
[88] A. Kütt, V. Movchun, T. Rodima, T. Dansauer, E. B. Rusanov, I. Leito, I. Kaljurand, J. Koppel, V. Pihl, I. Koppel, G. Ovsjannikov, L. Toom, M. Mishima, M. Medebielle, E. Lork, G.-V. Röschenthaler, I. A. Koppel, A. A. Kolomeitsev, *Journal of Organic Chemistry* **2008**, *73*, 2607-2620.
[89] G. G. Dubinina, H. Furutachi, D. A. Vicic, *Journal of the American Chemical Society* **2008**, *130*, 8600-8601; G. G. Dubinina, J. Ogikubo, D. A. Vicic, *Organometallics* **2008**, *27*, 6233-6235.
[90] H. Urata, T. Fuchikami, *Tetrahedron Letters* **1991**, *32*, 91-94.
[91] H. Morimoto, T. Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angewandte Chemie International Edition* **2011**, *50*, 3793-3798.
[92] N. D. Litvinas, P. S. Fier, J. F. Hartwig, *Angewandte Chemie International Edition* **2012**, *51*, 536-539.
[93] M. G. Mormino, P. S. Fier, J. F. Hartwig, *Organic Letters* **2014**, *16*, 1744-1747.
[94] P. S. Fier, J. F. Hartwig, *Journal of the American Chemical Society* **2012**, *134*, 5524-5527.
[95] Q.-Y. Chen, S.-W. Wu, *Journal of the Chemical Society, Chemical Communications* **1989**, 705-706.
[96] M. Oishi, H. Kondo, H. Amii, *Chemical Communications* **2009**, *0*, 1909-1911.
[97] Z. Weng, R. Lee, W. Jia, Y. Yuan, W. Wang, X. Feng, K.-W. Huang, *Organometallics* **2011**, *30*, 3229-3232.
[98] T. Knauber, F. Arikan, G.-V. Röschenthaler, L. J. Gooßen, *Chemistry – A European Journal* **2011**, *17*, 2689-2697.
[99] T. Billard, B. R. Langlois, G. Blond, *Tetrahedron Letters* **2000**, *41*, 8777–8780; H. Kondo, M. Oishi, K. Fujikawa, H. Amii, *Advanced Synthesis & Catalysis* **2011**, *353*, 1247-1252.
[100] Y. Li, T. Chen, H. Wang, R. Zhang, K. Jin, X. Wang, C. Duan, *Synlett* **2011**, *2011*, 1713-1716; T. Schareina, X.-F. Wu, A. Zapf, A. Cotte, M. Gotta, M. Beller, *Topics in Catalysis* **2012**, *55*, 426-431.
[101] I. Popov, S. Lindeman, O. Daugulis, *Journal of the American Chemical Society* **2011**, *133*, 9286-9289.
[102] T. Umemoto, *Chemical Reviews* **1996**, *96*, 1757-1778.
[103] P. Eisenberger, S. Gischig, A. Togni, *Chemistry – A European Journal* **2006**, *12*, 2579-2586.
[104] C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu, J.-C. Xiao, *Angewandte Chemie International Edition* **2011**, *50*, 1896-1900.
[105] A. I. Konovalov, A. Lishchynskyi, V. V. Grushin, *Journal of the American Chemical Society* **2014**, *136*, 13410-13425.
[106] L. Chu, F.-L. Qing, *Organic Letters* **2010**, *12*, 5060-5063.
[107] X. Jiang, L. Chu, F.-L. Qing, *Journal of Organic Chemistry* **2012**, *77*, 1251-1257.
[108] B. A. Khan, A. E. Buba, L. J. Gooßen, *Chemistry – A European Journal* **2012**, *18*, 1577-1581.
[109] C.-P. Zhang, J. Cai, C.-B. Zhou, X.-P. Wang, X. Zheng, Y.-C. Gu, J.-C. Xiao, *Chemical Communications* **2011**, *2011*, 9516-9518.
[110] J. Xu, D. F. Luo, B. Xiao, Z. J. Liu, T. J. Gong, Y. Fu, L. Liu, *Chemical Communications* **2011**, *47*, 4300-4302; T. F. Liu, Q. L. Shen, *Organic Letters* **2011**, *13*, 2342-2345.
[111] Y. Huang, X. Fang, X. Lin, H. Li, W. He, K.-W. Huang, Y. Yuan, Z. Weng, *Tetrahedron* **2012**, *68*, 9949–9953.

[112] Y. Li, L. Wu, H. Neumann, M. Beller, *Chemical Communications* **2013**, *49*, 2628-2630.
[113] Y. Ye, M. S. Sanford, *Journal of the American Chemical Society* **2012**, *134*, 9034-9037.
[114] L. Chu, F.-L. Qing, *Journal of the American Chemical Society* **2010**, *132*, 7262-7263.
[115] L. Chu, F.-L. Qing, *Journal of the American Chemical Society* **2012**, *134*, 1298-1304.
[116] R. Shimizu, H. Egami, T. Nagi, J. Chae, Y. Hamashima, M. Sodeoka, *Tetrahedron Letters* **2010**, *51*, 5947–5949.
[117] H. Egami, R. Shimizu, M. Sodeoka, *Tetrahedron Letters* **2012**, *53*, 5503-5506.
[118] S. Cai, C. Chen, Z. Sun, C. Xi, *Chemical Communications* **2013**, 4552-4554.
[119] E. Pair, N. Monteiro, D. Bouyssi, O. Baudoin, *Angewandte Chemie International Edition* **2013**, *52*, 5346-5349.
[120] N. O. Ilchenko, P. G. Janson, K. J. Szabó, *Chemical Communications* **2013**, 6614-6616; X. Wang, Y. Ye, G. Ji, Y. Xu, S. Zhang, J. Feng, Y. Zhang, J. Wang, *Organic Letters* **2013**, *15*, 3730-3733.
[121] P. M. Maitlis, F. G. A. Stone, *Chemistry & Insdustry* **1962**, 1865-1866; D. T. Rosevear, F. G. A. Stone, *Journal Of the Chemical Society A* **1968**, 164-167.
[122] D. Naumann, N. V. Kirij, N. Maggiarosa, W. Tyrra, Y. L. Yagupolskii, M. S. Wickleder, *Zeitschrift für anorganische und allgemeine Chemie* **2004**, *630*, 746-751.
[123] J. F. Hartwig, *Inorganic Chemistry* **2007**, *46*, 1936-1947.
[124] N. D. Ball, J. W. Kampf, M. S. Sanford, *Journal of the American Chemical Society* **2010**, *132*, 2878-2879.
[125] J. F. Hartwig, University Science Books, Sausatito, CA, **2010**.
[126] V. P. Ananikov, D. G. Musaev, K. Morokuma, *Journal of the American Chemical Society* **2002**, *124*, 2839-2852.
[127] X. Wang, L. Truesdale, J.-Q. Yu, *Journal of the American Chemical Society* **2010**, *132*, 3648-3649.
[128] X.-G. Zhang, H.-X. Dai, M. Wasa, J.-Q. Yu, *Journal of the American Chemical Society* **2012**, *134*, 11948-11951.
[129] L.-S. Zhang, K. Chen, G. Chen, B.-J. Li, S. Luo, Q.-Y. Guo, J.-B. Wei, Z.-J. Shi, *Organic Letters* **2012**, *15*, 10-13.
[130] X. Mu, S. Chen, X. Zhen, G. Liu, *Chemistry – A European Journal* **2011**, *17*, 6039-6042.
[131] X. Mu, T. Wu, H.-Y. Wang, Y.-l. Guo, G. Liu, *Journal of the American Chemical Society* **2011**, *134*, 878-881.
[132] V. V. Grushin, W. J. Marshall, *Journal of the American Chemical Society* **2006**, *128*, 12644-12645.
[133] E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679-1681.
[134] E. J. Cho, S. L. Buchwald, *Organic Letters* **2011**, *13*, 6552-6555.
[135] R. N. Loy, M. S. Sanford, *Organic Letters* **2011**, *13*, 2548-2551.
[136] D. W. McBride, E. Dudek, F. G. A. Stone, *Journal of the Chemical Society* **1964**, *1964*, 1752-1759.
[137] M. R. Churchill, T. A. O'Brien, *Journal of the Chemical Society A: Inorganic, Physical, Theoretical* **1970**, 161-167.
[138] H. Wang, D. A. Vicic, *Synlett* **2013**, *24*, 1887-1898.
[139] G. G. Dubinina, W. W. Brennessel, J. L. Miller, D. A. Vicic, *Organometallics* **2008**, *27*, 3933-3938.
[140] J. R. Bour, N. M. Camasso, M. S. Sanford, *Journal of the American Chemical Society* **2015**, *137*, 8034-8037.
[141] W. E. Tyrra, *Journal of Fluorine Chemistry* **2001**, *112*, 149–152.
[142] A. Hafner, N. Jung, S. Bräse, *Synthesis* **2014**, *46*, 1440-1447.
[143] W. Tyrra, D. Naumann, *Journal of Fluorine Chemistry* **2004**, *125*, 823–830.

[144] Y. Zeng, L. Zhang, Y. Zhao, C. Ni, J. Zhao, J. Hu, *Journal of the American Chemical Society* **2013**, *135*, 2955-2958.
[145] Y. Gu, D. Chang, X. Leng, Y. Gu, Q. Shen, *Organometallics* **2015**, *34*, 3065-3071.
[146] Y. Ye, S. H. Lee, M. S. Sanford, *Organic Letters* **2011**, *13*, 5464-5467.
[147] Y. Ye, M. S. Sanford, *Synlett* **2012**, *23*, 2005-2013.
[148] A. Hafner, S. Bräse, *Angewandte Chemie International Edition* **2012**, *51*, 3713-3715.
[149] A. Hafner, A. Bihlmeier, M. Nieger, W. Klopper, S. Bräse, *The Journal of Organic Chemistry* **2013**, *78*, 7938-7948.
[150] S. Seo, J. B. Taylor, M. F. Greaney, *Chemical Communications* **2013**.
[151] G. Shi, C. Shao, S. Pan, J. Yu, Y. Zhang, *Organic Letters* **2015**, *17*, 38-41; K. Monir, A. K. Bagdi, M. Ghosh, A. Hajra, *Journal of Organic Chemistry* **2015**, *80*, 1332-1337.
[152] X. Wang, Y. Xu, Y. Zhou, Y. Zhang, J. Wang, *Synthesis* **2014**, *46*, 2143-2148.
[153] J. W. Tucker, C. R. J. Stephenson, *Journal of Organic Chemistry* **2012**, *77*, 1617-1622.
[154] J. D. Nguyen, J. W. Tucker, M. D. Konieczynska, C. R. J. Stephenson, *Journal of the American Chemical Society* **2011**, *133*, 4160-4163.
[155] T. B. Demissie, K. Ruud, J. H. Hansen, *Organometallics* **2015**.
[156] R. N. Haszeldine, B. R. Steele, *Journal Of the Chemical Society* **1953**, 1199-1206.
[157] D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *Journal of the American Chemical Society* **2009**, *131*, 10875-10877.
[158] P. V. Pham, D. A. Nagib, D. W. C. MacMillan, *Angewandte Chemie-International Edition* **2011**, *50*, 6119-6122.
[159] D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77-80.
[160] D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224-228.
[161] N. Iqbal, S. Choi, E. Ko, E. J. Cho, *Tetrahedron Letters* **2012**, *53*, 2005–2008.
[162] J. Xie, X. Yuan, A. Abdukader, C. Zhu, J. Ma, *Organic Letters* **2014**, *16*, 1768-1771.
[163] N. J. W. Straathof, H. P. L. Gemoets, X. Wang, J. C. Schouten, Hessel, Volker, T. Noël, *ChemSusChem* **2014**, *7*, 1612-1617.
[164] N. Iqbal, S. Choi, E. Kim, E. J. Cho, *Journal of Organic Chemistry* **2012**, *77*, 11383-11387.
[165] Y. Yasu, T. Koike, M. Akita, *Chemical Communications* **2013**, *49*, 2037-2039.
[166] P. Xu, A. Abdukader, K. Hu, Y. Cheng, C. Zhu, *Chemical Communications* **2013**, *50*, 2308-2310.
[167] R. Tomita, Y. Yasu, T. Koike, M. Akita, *Beilstein Journal of Organic Chemistry* **2014**, *10*, 1099-1106.
[168] Q.-Y. Lin, X.-H. Xu, F.-L. Qing, *Journal of Organic Chemistry* **2014**, *79*, 10434-10446.
[169] L. M. Kreis, S. Krautwald, N. Pfeiffer, R. E. Martin, E. M. Carreira, *Organic Letters* **2013**, *15*, 1634-1637.
[170] R. Beniazza, F. Molton, C. Duboc, A. Tron, N. D. McClenaghan, D. Lastécouères, J.-M. Vincent, *Chemical Communications* **2015**, *51*, 9571-9574.
[171] W. J. Choi, S. Choi, K. Ohkubo, S. Fukuzumi, E. J. Cho, Y. You, *Chemical Science* **2014**, *6*, 1454-1464.
[172] D. J. Wilger, N. J. Gesmundo, D. A. Nicewicz, *Chemical Science* **2013**, *4*, 3160-3165; S. P. Pitre, C. D. McTiernan, H. Ismaili, J. C. Scaiano, *ACS Catalysis* **2014**, *4*, 2530-2535; Ł. Woźniak, J. J. Murphy, P. Melchiorre, *Journal Of the Chemical Society* **2015**, *137*, 5678-5681.
[173] X.-H. Xu, K. Matsuzaki, N. Shibata, *Chemical Reviews* **2014**, *115*, 731-764; A. Tlili, T. Billard, *Angewandte Chemie International Edition* **2013**, *52*, 6818-6819.
[174] G. Landelle, A. Panossian, F. R. Leroux, *Current Topics In Medicinal Chemistry* **2015**, *14*, 941-951.
[175] C. Alonso, E. Martínez de Marigorta, G. Rubiales, F. Palacios, *Chemical Reviews* **2015**, *115*, 1847-1935.

[176] S. Mizuta, S. Verhoog, K. M. Engle, T. Khotavivattana, M. O'Duill, K. Wheelhouse, G. Rassias, M. Medebielle, V. Gouverneur, *Journal of the American Chemical Society* **2013**, *135*, 2505-2508.
[177] S. Mizuta, K. M. Engle, S. Verhoog, O. Galicia-Lopez, M. O'Duill, M. Medebielle, K. Wheelhouse, G. Rassias, A. L. Thompson, V. Gouverneur, *Organic Letters* **2013**, *15*, 1250-1253.
[178] C. E. Masse, J. S. Panek, *Chemical Reviews* **1995**, *95*, 1293-1316.
[179] I. Fleming, A. Barbero, D. Walter, *Chemical Reviews* **1997**, *97*, 2063-2192.
[180] L. Chabaud, P. James, Y. Landais, *European Journal of Organic Chemistry* **2004**, *2004*, 3173-3199.
[181] J. B. Lambert, *Tetrahedron* **1990**, *46*, 2677–2689.
[182] S. Mizuta, S. Verhoog, X. Wang, N. Shibata, V. Gouverneur, M. Medebielle, *Journal of Fluorine Chemistry* **2013**, *155*, 124-131.
[183] M. Tsuji, *The Journal of Organic Chemistry* **2003**, *68*, 9589-9597.
[184] A. E. Sheshenev, M. S. Baird, I. G. Bolesov, A. S. Shashkov, *Tetrahedron* **2009**, *65*, 10552-10564.
[185] J. J. Eisch, M. W. Foxton, *Journal of Organic Chemistry* **1971**, *36*, 3520-3526.
[186] K. Igawa, K. Tomooka, *Angewandte Chemie-International Edition* **2006**, *45*, 232-234.
[187] S. S. P. Chou, H. L. Kuo, C. J. Wang, C. Y. Tsai, C. M. Sun, *The Journal of Organic Chemistry* **1989**, *54*, 868-872.
[188] A. Hamze, O. Provot, J.-D. Brion, M. Alami, *Journal of Organometallic Chemistry* **2008**, *693*, 2789-2797.
[189] A. Hafner, S. Bräse, *Advanced Synthesis & Catalysis* **2011**, *353*, 3044-3048.
[190] J. R. McAtee, S. E. S. Martin, D. T. Ahneman, K. A. Johnson, D. A. Watson, *Angewandte Chemie-International Edition* **2012**, *51*, 3663-3667.
[191] N. Vargas Alfredo, N. Espinosa Jalapa, S. Lopez Morales, A. D. Ryabov, R. Le Lagadec, L. Alexandrova, *Macromolecules* **2012**, *45*, 8135-8146.
[192] L. P. Hammett, *Journal of the American Chemical Society* **1937**, *59*, 96-103.
[193] I. Fleming, J. A. Langley, *Journal of the Chemical Society, Perkin Transactions 1* **1981**, 1421-1423; M. Ochiai, Y. Takaoka, T. Ukita, Y. Nagao, E. Fujita, *Journal of Organic Chemistry* **1989**, *54*, 2346-2350; B. S. Bandodakar, G. Nagendrappa, *Journal of Organometallic Chemistry* **1992**, *430*, 373–383; B. M. Trost, Z. T. Ball, T. Jöge, *Journal of the American Chemical Society* **2002**, *124*, 7922-7923; F. Lacombe, K. Radkowski, G. Seidel, A. Fürstner, *Tetrahedron* **2004**, *60*, 7315–7324.
[194] B. Yang, X.-H. Xu, F.-L. Qing, *Organic Letters* **2015**, *17*, 1906-1909.
[195] L. Eberson, M. P. Hartshorn, O. Persson, F. Radner, *Chemical Communications* **1996**, 2105-2112; I. A. Shuklov, N. V. Dubrovina, A. Börner, *Synthesis* **2007**, *2007*, 2925-2943.
[196] J. B. Lambert, G. T. Wang, D. H. Teramura, *Journal of Organic Chemistry* **1988**, *53*, 5422-5428.
[197] F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry. Part A: Structure and Mechanisms*, 5 ed., Springer, New York, **2007**.
[198] J. A. Kerr, *Chemical Reviews* **1966**, *66*, 465-500.
[199] X.-M. Zhang, *Journal of Organic Chemistry* **1998**, *63*, 3590-3594.
[200] J. A. Ma, D. Cahard, *Journal of Fluorine Chemistry* **2007**, *128*, 975-996.
[201] T. Umemoto, S. Ishihara, K. Adachi, *Journal of Fluorine Chemistry* **1995**, *74*, 77-82; N. Shibata, A. Matsnev, D. Cahard, *Beilstein Journal of Organic Chemistry* **2010**, *6*.
[202] G. K. S. Prakash, A. K. Yudin, *Chemical Reviews* **1997**, *97*, 757-786.
[203] I. Ruppert, K. Schlich, W. Volbach, *Tetrahedron Letters* **1984**, *25*, 2195-2198.
[204] G. K. S. Prakash, P. V. Jog, P. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324-1327.
[205] O. A. Tomashenko, E. C. Escudero-Adán, M. Martínez Belmonte, V. V. Grushin, *Angewandte Chemie International Edition* **2011**, *50*, 7655-7659; T. Umemoto, K. Adachi,

S. Ishihara, *The Journal of Organic Chemistry* **2007**, *72*, 6905-6917; I. Kieltsch, P. Eisenberger, A. Togni, *Angewandte Chemie-International Edition* **2007**, *46*, 754-757; C. Xu, J. Liu, W. Ming, Y. Liu, J. Liu, M. Wang, Q. Liu, *Chemistry – A European Journal* **2013**, *19*, 9104-9109.

[206] V. Matoušek, E. Pietrasiak, R. Schwenk, A. Togni, *The Journal of Organic Chemistry* **2013**, *78*, 6763-6768.

[207] V. V. Bardin, L. S. Pressman, V. F. Cherstkov, *Synthetic Communications* **1995**, *25*, 2425-2433.

[208] V. Broicher, D. Geffken, *Journal of Organometallic Chemistry* **1990**, *381*, 315-320.

[209] G. Pawelke, *Journal of Fluorine Chemistry* **1989**, *42*, 429-433; V. A. Petrov, *Journal of Fluorine Chemistry* **1995**, *73*, 17-19.

[210] M. Yoshida, D. Suzuki, M. Iyoda, *Chemistry Letters* **1994**, *23*, 2357-2360.

[211] G. K. S. Prakash, R. Krishnamurti, G. A. Olah, *Journal of the American Chemical Society* **1989**, *111*, 393-395.

[212] G. K. S. Prakash, F. Wang, Z. Zhang, R. Haiges, M. Rahm, K. O. Chrsite, T. Mathew, G. A. Olah, *Angewandte Chemie International Edition* **2014**, *53*, 11575-11578.

[213] R. Krishnamurti, D. R. Bellew, G. K. S. Prakash, *The Journal of Organic Chemistry* **1991**, *56*, 984-989.

[214] D. W. Nelson, N. J. O'Reilly, J. Speier, P. G. Gassman, *The Journal of Organic Chemistry* **1994**, *59*, 8157-8171; V. Broicher, D. Geffken, *Zeitschrift für Naturforschung B* **1990**, *45b*, 401-403; V. Broicher, D. Geffken, *Archiv der Pharmazie* **1990**, *323*, 929-931; Y. Carcenac, M. Tordeux, C. Wakselman, P. Diter, *Journal of Fluorine Chemistry* **2005**, *126*, 1347-1355; A. D. Dilman, D. E. Arkhipov, V. V. Levin, P. A. Belyakov, A. A. Korlyukov, M. I. Struchkova, V. A. Tartakovsky, *The Journal of Organic Chemistry* **2008**, *73*, 5643-5646.

[215] Y. Kawano, N. Kaneko, T. Mukaiyama, *Bulletin of the Chemical Society of Japan* **2006**, *79*, 1133-1145.

[216] F. Toulgoat, B. R. Langlois, M. Médebielle, J.-Y. Sanchez, *The Journal of Organic Chemistry* **2007**, *72*, 9046-9052.

[217] Y. Chernykh, K. Hlat-Glembova, B. Klepetarova, P. Beier, *European Journal of Organic Chemistry* **2011**, 4528-4531.

[218] J. Václavík, Y. Chernykh, B. Jurásek, P. Beier, *Journal of Fluorine Chemistry* **2015**, *169*, 24-31.

[219] P. Kirsch, M. Bremer, F. Huber, H. Lannert, A. Ruhl, M. Lieb, T. Wallmichrath, *Journal of the American Chemical Society* **2001**, *123*, 5414-5417; P. Kirsch, F. Huber, M. Lenges, A. Taugerbeck, *Journal of Fluorine Chemistry* **2001**, *112*, 69–72; P. Kirsch, M. Bremer, *ChemPhysChem* **2010**, *11*, 357-360; P. Kirsch, F. Huber, J. Krause, M. Heckmeier, D. Pauluth, Merck GmbH, US, **2003**.

[220] M. Hird, *Chemical Society Reviews* **2007**, 2070-2095.

[221] M. Zupan, A. Pollak, *Journal of Organic Chemistry* **1974**, *39*, 2646-2647; C. York, G. K. S. Prakash, G. A. Olah, *Journal of Organic Chemistry* **1994**, *59*, 6493-6494; R. P. Singh, U. Majumder, J. M. Shreeve, *Journal of Organic Chemistry* **2001**, *66*, 6263-6267; Y. Chang, A. Tewari, A.-I. Adi, C. Bae, *Tetrahedron* **2008**, *64*, 9837–9842; J. Gatenyo, S. Rozen, *Journal of Fluorine Chemistry* **2009**, *130*, 332–335.

[222] K. Fujikawa, Y. Fujioka, A. Kobayashi, H. Amii, *Organic Letters* **2011**, *13*, 5560-5563.

[223] K. Fujikawa, A. Kobayashi, H. Amii, *Synthesis* **2012**, *44*, 3015-3018.

[224] K. I. Petko, S. Y. Kot, L. M. Yagupolskii, *Journal of Fluorine Chemistry* **2008**, *129*, 301-306.

[225] J. Zhu, C. Ni, B. Gao, J. Hu, *Journal of Fluorine Chemistry* **2015**, *171*, 139–147; Y. Watanabe, T. Konno, *Journal of Fluorine Chemistry* **2015**, *174*, 102–107.

[226] H. Saijo, M. Ohashi, S. Ogoshi, *Journal of the American Chemical Society* **2014**, *136*, 15158-15161.

[227] K. Kulbitski, G. Nisnevich, M. Gandelman, *Advanced Synthesis & Catalysis* **2011**, *353*, 1438-1442.
[228] A. Hafner, S. Bräse, *Advanced Synthesis & Catalysis* **2013**, *355*, 996-1000.
[229] Z. Gonda, S. Kovács, C. Wéber, T. Gáti, A. Mészáros, A. Kotschy, Z. Novák, *Organic Letters* **2014**, *16*, 4268-4271.
[230] M. Chen, S. L. Buchwald, *Angewandte Chemie International Edition* **2013**, *52*, 11628-11631.
[231] G. Russell, A., S. A. Weiner, *Journal of Organic Chemistry* **1966**, *31*, 248-251.
[232] X. Jiang, C. Wang, Y. Wei, D. Xue, Z. Liu, J. Xiao, *Chemistry - A European Journal* **2014**, *20*, 58-63.
[233] J.-H. Lin, G. Zong, R.-B. Du, J.-C. Xiao, S. Liu, *Chemical Communications* **2012**, *48*, 7738-7740.
[234] E. Laurent, B. Marquet, R. Tardivel, *Tetrahedron* **1989**, *45*, 4431-4444.
[235] W. Ghattas, C. R. Hess, G. Iacazio, R. Hardré, J. P. Klinman, M. Réglier, *The Journal of Organic Chemistry* **2006**, *71*, 8618-8621.
[236] A. Yokoyama, T. Maruyama, K. Tagami, H. Masu, K. Katagiri, I. Azumaya, T. Yokozawa, *Organic Letters* **2008**, *10*, 3207-3210.
[237] A. Ilya, G. Neomi, L. Anita, US, **2002**.
[238] A. Kamal, G. B. R. Khanna, R. Ramu, *Tetrahedron: Asymmetry* **2002**, *13*, 2039-2051.
[239] F. Zhang, J. Z. Song, *Tetrahedron Letters* **2006**, *47*, 7641-7644.
[240] H. M. Peters, D. M. Feigl, H. S. Mosher, *The Journal of Organic Chemistry* **1968**, *33*, 4245-4250.
[241] K. Fuchibe, Y. Ohshima, K. Mitomi, T. Akiyama, *Organic Letters* **2007**, *9*, 1497-1499.
[242] R. P. Singh, D. Chakraborty, J. M. Shreeve, *Journal of Fluorine Chemistry* **2001**, *111*, 153-160.
[243] J.-Y. Yu, R. Kuwano, *Angewandte Chemie International Edition* **2009**, *48*, 7217-7220.
[244] P. Novák, A. Lishchynskyi, G. V. V., *Angewandte Chemie International Edition* **2012**, *51*, 7767-7770.
[245] G. A. Olah, Y. K. Mo, *The Journal of Organic Chemistry* **1973**, *38*, 2682-2685.
[246] M. M. Kremlev, W. Tyrra, A. I. Mushta, D. Naumann, Y. L. Yagupolskii, *Journal of Fluorine Chemistry* **2010**, *131*, 212-216.
[247] R. T. C. Brownlee, D. J. Craik, *Tetrahedron Letters* **1980**, *21*, 1681-1684.
[248] T. Chen, L. Yang, L. Li, K.-W. Huang, *Tetrahedron* **2012**, *68*, 6152-6157.
[249] W. J. Middleton, E. M. Bingham, *The Journal of Organic Chemistry* **1980**, *45*, 2883-2887.
[250] G. K. S. Prakash, H. S. Krishnan, P. V. Jog, A. P. Iyer, G. A. Olah, *Organic Letters* **2012**, *14*, 1146-1149.
[251] N. A. Fokina, A. M. Kornilov, V. P. Kukhar, *Journal of Fluorine Chemistry* **2001**, *111*, 69-76.
[252] R. J. Linderman, D. M. Graves, *Tetrahedron Letters* **1987**, *28*, 4259-4262.
[253] H. Zhou, Q. Xu, P. Chen, *Tetrahedron* **2008**, *64*, 6494-6499.
[254] Y. Shen, M. Qi, *Journal of Fluorine Chemistry* **1994**, *67*, 229-232.
[255] Z.-W. Mei, T. Omote, M. Mansour, H. Kawafuchi, Y. Takaguchi, A. Jutand, S. Tsuboi, T. Inokuchi, *Tetrahedron* **2008**, *64*, 10761-10766.
[256] G. Ricci, R. Ruzziconi, *The Journal of Organic Chemistry* **2005**, *70*, 611-623.
[257] H. Serizawa, K. Aikawa, K. Mikami, *Organic Letters* **2014**, *16*, 3456-3459.
[258] R. P. Singh, J. M. Shreeve, *Organic Letters* **2001**, *3*, 2713-2715.
[259] G. A. Molander, J. A. C. Romero, C. P. Corrette, *Journal of Organometallic Chemistry* **2002**, *647*, 225-235.
[260] A. Sagadevan, K. C. Hwang, *Advanced Synthesis & Catalysis* **2012**, *354*, 3421-3427.
[261] K. Karabelas, A. Hallberg, *The Journal of Organic Chemistry* **1986**, *51*, 5286-5290.
[262] J. M. Concellón, P. L. Bernad, E. Bardales, *Organic Letters* **2001**, *3*, 937-939.
[263] D. Mujahidin, S. Doye, *European Journal of Organic Chemistry* **2005**, *2005*, 2689-2693.

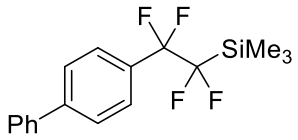
[264] C.-M. Che, W.-Y. Yu, P.-M. Chan, W.-C. Cheng, S.-M. Peng, K.-C. Lau, W.-K. Li, *Journal of the American Chemical Society* **2000**, *122*, 11380-11392.
[265] S. R. Cicco, G. M. Farinola, C. Martinelli, F. Naso, M. Tiecco, *European Journal of Organic Chemistry* **2010**, 2275-2279.
[266] H. Li, J. L. Petersen, K. K. Wang, *Journal of Organic Chemistry* **2001**, *66*, 7804-7810.
[267] Y. Nishihara, D. Saito, K. Tanemura, S. Noyori, K. Takagi, *Organic Letters* **2009**, *11*, 3546-3549.
[268] M. G. Steinmetz, C. Yu, L. Li, *Journal of the American Chemical Society* **1994**, *116*, 932-943.
[269] K. Kikukawa, K. Ikenaga, K. Kono, K. Toritani, F. Wada, T. Matsuda, *Journal of Organometallic Chemistry* **1984**, *270*, 277-282.
[270] R. J. Rahaim, J. T. Shaw, *The Journal of Organic Chemistry* **2008**, *73*, 2912-2915.
[271] G. Cahiez, C. Duplais, J. Buendia, *Angewandte Chemie International Edition* **2009**, *48*, 6731-6734.
[272] Y. Kido, S. Yoshimura, M. Yamaguchi, T. Uchimaru, *Bulletin of the Chemical Society of Japan* **1999**, *72*, 1445-1458.
[273] T. A. Zeidan, S. V. Kovalenko, M. Manoharan, R. J. Clark, I. Ghiviriga, I. V. Alabugin, *Journal of the American Chemical Society* **2005**, *127*, 4270-4285.
[274] C. Kub, J. Tolosa, A. J. Zucchero, P. L. McGrier, C. Subramani, A. Khorasani, V. M. Rotello, U. H. F. Bunz, *Macromolecules* **2010**, *43*, 2124-2129; C. Torborg, A. Zapf, M. Beller, *ChemSusChem* **2008**, *1*, 91-96.
[275] G. Stork, E. Colvin, *Journal of the American Chemical Society* **1971**, *93*, 2080-2081.
[276] R. Takeuchi, S. Nitta, D. Watanabe, *The Journal of Organic Chemistry* **1995**, *60*, 3045-3051.
[277] S. Atobe, H. Masuno, M. Sonoda, Y. Suzuki, H. Shinohara, S. Shibata, A. Ogawa, *Tetrahedron Letters* **2012**, *53*, 1764-1767.
[278] N. Chatani, N. Amishiro, T. Morii, T. Yamashita, S. Murai, *Journal of Organic Chemistry* **1995**, *60*, 1834-1840.
[279] A. T. Parsons, T. D. Senecal, S. L. Buchwald, *Angewandte Chemie-International Edition* **2012**, *51*, 2947-2950.
[280] A. Hafner, S. Brase, *Advanced Synthesis & Catalysis* **2011**, *353*, 3044-3048.
[281] T. Hanamoto, N. Morita, K. Shindo, *European Journal of Organic Chemistry* **2003**, 4279-4285.
[282] H. Egami, R. Shimizu, M. Sodeoka, *Tetrahedron Letters* **2012**, *53*, 5503-5506.
[283] Y. Yasu, T. Koike, M. Akita, *Angewandte Chemie International Edition* **2012**, *51*, 9567-9571.
[284] H. Zheng, Y. Huang, Z. Wang, H. Li, K.-W. Huang, Y. Yuan, Z. Weng, *Tetrahedron Letters* **2012**, *53*, 6646-6649.
[285] M. Presset, D. Oehlrich, F. Rombouts, G. A. Molander, *Journal of Organic Chemistry* **2013**, *78*, 12837-12843.
[286] M. Kuroboshi, T. Ishihara, *Bulletin of the Chemical Society of Japan* **1990**, *63*, 428-437.
[287] J. P. John, D. A. Colby, *The Journal of Organic Chemistry* **2011**, *76*, 9163-9168.
[288] F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V. Jog, S. K. Ganesh, G. K. S. Prakash, G. A. Olah, *Angewandte Chemie International Edition* **2011**, *50*, 7153-7157.
[289] F. Chemla, V. Hebbe, J.-F. Normant, *Synthesis* **2000**, *2000*, 75-77.
[290] C. Xu, S. Chen, L. Lu, Q. Shen, *The Journal of Organic Chemistry* **2012**, *77*, 10314-10320.
[291] J. S. Yadav, B. V. S. Reddy, U. V. S. Reddy, K. Praneeth, *Tetrahedron Letters* **2008**, *49*, 4742-4745.
[292] S. Mizuta, I. S. R. Stenhagen, M. O'Duill, J. Wolstenhulme, A. K. Kirjavainen, S. J. Forsback, M. Tredwell, G. Sandford, P. R. Moore, M. Huiban, S. K. Luthra, J. Passchier, O. Solin, V. Gouverneur, *Organic Letters* **2013**, *15*, 2648-2651.
[293] D. C. England, G. J. Weigert, J. C. Calabrese, *Journal of Organic Chemistry* **1984**, *49*, 4816-4819.

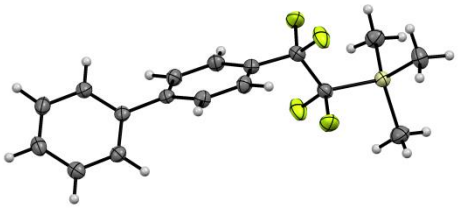
[294] J. Cosier, A. M. Lazer, *Journal of Applied Crystallography* **1986**, *19*, 105-107; N. E. Shevchenko, K. Vlasov, V. G. Nenajdenko, G.-V. Röschenthaler, *Tetrahedron* **2011**, *67*, 69-74.
[295] O. CrysAlisPro (Agilent Technologies, 2011).
[296] L. Palatinus, G. Chapuis, *Journal of Applied Crystallography* **2007**, *40*, 786-790.
[297] P. W. C. Betteridge, J. Robert, R. I. Cooper, K. Prout, D. J. Watkin, *Journal of Applied Crystallography* **2003**, *36*, 1487; P. Parois, R. I. Cooper, A. L. Thompson, *Chemistry Central Journal* **2015**, *9*, 30-44; A. L. Thompson, D. J. Watkin, *Journal of Applied Crystallography* **2011**, *44*, 1017-1022.
[298] R. I. Cooper, A. L. Thompson, D. J. Watkin, *Journal of Applied Crystallography* **2010**, *43*, 1100-1107.

Appendix

Appendix: X-Ray Crystallographic Data

[2-(Biphenyl-4-yl)-1,1,2,2-tetrafluoroethyl](trimethyl)silane (39a)





Low temperature (150 K)[294] single-crystal X-ray diffraction data were collected by L. Pfeifer using an Oxford Diffraction (Agilent) SuperNova A diffractometer. Raw frame data were reduced using the instrument manufacturer supplied software CrysAlisPro.[295] The structure could be solved ab initio using SuperFlip,[296] and full-matrix least-squares refinement was carried out using CRYSTALS.[297] All non-hydrogen atoms were refined using anisotropic displacement ellipsoids, and hydrogen atoms were visible in the difference map. Once the heavy atoms structure was complete, hydrogen atoms were positioned geometrically then refined separately using soft restraints prior to inclusion in the final refinement using a riding model.[298] The structure has been deposited with the Cambridge Crystallographic Data Centre (reference code CCDC 1401715); these data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 1: Crystal data and refinement details

Crystal identification	047lp14
CCDC number	1401715
Compound number	**39a**
Empirical formula	C17 H18 F4 Si
Formula weight	326.41
Temperature	150 K
Wavelength	1.54180 Å

Crystal system	triclinic
Space group	P 1
Unit cell dimensions	a =8.2789 (2) Å
	b = 8.4180 (3) Å
	c = 12.5528 (4) Å
	α = 77.074 (3)°
	β = 75.662 (3)°
	γ = 73.736 (3)°
Volume	802.38 (5) $Å^3$
Z	2
Density (calculated)	1.351 Mg/m^3
Absorption coefficient	1.621 mm^{-1}
F(000)	340
Crystal shape	block
Crystal colour	colourless
Crystal size	0.10 × 0.18 × 0.22 mm^3
Crystallization solvent	(neat)
Theta range for data collection (θ)	3.7 to 76.6°
Index ranges	−10≤h≥24, −9≤k≥10, −15≤l≥15
Reflections collected	21835
Independent reflections	3338
Completeness to theta max. (θ)	98.7%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.72 and 0.58
Refinement method	Full-matrix least-squares on F^2
Data/ restraints/ parameters	3323 / 0 / 199
Goodness-of-fit on F^2	0.9916
Final R indices [I>2sigma(I)]	R1 = 0.0295, wR2 = 0.0773
R indices (all data)	R1 = 0.0313,

	wR2 = 0.0789
Largest dif. peak and hole	−0.48 and 0.50 e. $Å^{-3}$

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($Å^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
C8	1.02286(15)	0.42581(14)	0.25719(9)	0.0245
C9	1.04683(15)	0.35562(15)	0.36498(10)	0.0278
C10	0.92095(15)	0.28794(15)	0.44122(10)	0.0267
C11	0.76791(15)	0.29051(14)	0.41186(9)	0.0232
C12	0.74684(15)	0.35957(15)	0.30312(10)	0.0268
C13	0.87273(16)	0.42661(15)	0.22620(10)	0.0273
C14	0.63028(15)	0.22435(14)	0.49522(9)	0.0236
C15	0.67001(16)	0.07526(15)	0.56889(10)	0.0284
C16	0.54097(17)	0.01224(16)	0.64542(10)	0.0317
C17	0.37089(17)	0.09910(16)	0.65136(10)	0.0311
C18	0.32999(16)	0.24911(16)	0.58004(10)	0.0292
C19	0.45825(15)	0.31037(15)	0.50136(10)	0.0257
Si1	1.29377(4)	0.82161(4)	0.09151(3)	0.0250
C2	1.12654(14)	0.69707(15)	0.17750(9)	0.0252
F3	0.96972(9)	0.77292(10)	0.14753(7)	0.0373
F4	1.10244(11)	0.71300(10)	0.28784(6)	0.0389
C5	1.15407(15)	0.50916(15)	0.17727(10)	0.0272
F6	1.31440(9)	0.43360(10)	0.19938(7)	0.0404
F7	1.16219(11)	0.49272(10)	0.07025(6)	0.0402
C20	1.19666(19)	1.03673(17)	0.12429(13)	0.0384
C21	1.49871(16)	0.72551(17)	0.14028(12)	0.0350
C22	1.31589(18)	0.81421(19)	-0.05788(11)	0.0366

Table 3: Atomic coordinates and equivalent isotropic thermal parameters (Å^2) of hydrogen atoms

Atom	x	y	z	U_{equiv}
H91	1.1465	0.3564	0.3866	0.0337
H101	0.9384	0.2428	0.5140	0.0323
H121	0.6460	0.3587	0.2812	0.0316
H131	0.8566	0.4727	0.1527	0.0332
H151	0.7864	0.0157	0.5652	0.0339
H161	0.5717	-0.0906	0.6925	0.0385
H171	0.2833	0.0556	0.7042	0.0375
H181	0.2148	0.3110	0.5849	0.0352
H191	0.4300	0.4130	0.4527	0.0307
H201	1.0991	1.0864	0.0933	0.0601
H202	1.2768	1.1056	0.0932	0.0591
H203	1.1634	1.0382	0.2022	0.0597
H211	1.5514	0.6199	0.1154	0.0524
H212	1.5762	0.7976	0.1112	0.0534
H213	1.4805	0.7105	0.2198	0.0532
H221	1.3649	0.7020	-0.0731	0.0555
H222	1.3899	0.8849	-0.1021	0.0569
H223	1.2074	0.8531	-0.0781	0.0562

Table 4: Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C8	0.0246(5)	0.0217(5)	0.0245(5)	-0.0042(4)	-0.0017(4)	-0.0036(4)
C9	0.0235(5)	0.0304(6)	0.0288(6)	-0.0029(5)	-0.0073(5)	-0.0049(5)
C10	0.0278(6)	0.0283(6)	0.0222(5)	-0.0010(4)	-0.0065(4)	-0.0048(5)
C11	0.0256(5)	0.0186(5)	0.0240(5)	-0.0044(4)	-0.0031(4)	-0.0038(4)
C12	0.0274(6)	0.0279(6)	0.0266(6)	-0.0027(5)	-0.0084(5)	-0.0077(5)

C13	0.0308(6)	0.0286(6)	0.0218(5)	-0.0013(4)	-0.0064(5)	-0.0073(5)
C14	0.0278(6)	0.0213(5)	0.0223(5)	-0.0057(4)	-0.0031(4)	-0.0070(4)
C15	0.0312(6)	0.0241(6)	0.0264(6)	-0.0039(5)	-0.0031(5)	-0.0035(5)
C16	0.0421(7)	0.0252(6)	0.0252(6)	-0.0013(5)	-0.0029(5)	-0.0095(5)
C17	0.0358(7)	0.0340(7)	0.0253(6)	-0.0069(5)	0.0015(5)	-0.0163(5)
C18	0.0270(6)	0.0318(6)	0.0309(6)	-0.0097(5)	-0.0036(5)	-0.0089(5)
C19	0.0284(6)	0.0226(5)	0.0277(6)	-0.0048(4)	-0.0066(5)	-0.0070(4)
Si1	0.02331(16)	0.02466(17)	0.02518(17)	-0.00264(12)	-0.00300(12)	-0.00570(12)
C2	0.0226(5)	0.0287(6)	0.0218(5)	-0.0051(4)	-0.0015(4)	-0.0040(4)
F3	0.0220(3)	0.0327(4)	0.0507(5)	0.0004(3)	-0.0062(3)	-0.0027(3)
F4	0.0518(5)	0.0432(5)	0.0242(4)	-0.0119(3)	0.0050(3)	-0.0211(4)
C5	0.0245(6)	0.0279(6)	0.0257(6)	-0.0052(5)	-0.0003(4)	-0.0040(5)
F6	0.0212(4)	0.0318(4)	0.0557(5)	0.0038(3)	0.0001(3)	-0.0018(3)
F7	0.0539(5)	0.0433(5)	0.0253(4)	-0.0131(3)	0.0085(3)	-0.0228(4)
C20	0.0379(7)	0.0270(6)	0.0479(8)	-0.0065(6)	-0.0054(6)	-0.0062(5)
C21	0.0286(6)	0.0338(7)	0.0433(7)	-0.0038(6)	-0.0106(5)	-0.0075(5)
C22	0.0384(7)	0.0443(8)	0.0262(6)	-0.0014(5)	-0.0022(5)	-0.0154(6)

Table 5: Bond Length (Å)

C8–C9	1.3888(16)	C18–H181	0.944
C8–C13	1.3893(17)	C19–H191	0.946
C8–C5	1.5004(16)	Si1–C2	1.9359(12)
C9–C10	1.3861(17)	Si1–C20	1.8571(14)
C9–H91	0.932	Si1–C21	1.8526(13)
C10–C11	1.3979(16)	Si1–C22	1.8520(13)
C10–H101	0.938	C2–F3	1.3802(13)
C11–C12	1.3920(16)	C2–F4	1.3811(13)
C11–C14	1.4859(15)	C2–C5	1.5342(17)
C12–C13	1.3871(17)	C5–F6	1.3690(14)

C12–H121	0.944	C5–F7	1.3644(14)
C13–H131	0.944	C20–H201	0.934
C14–C15	1.3923(16)	C20–H202	0.956
C14–C19	1.3970(16)	C20–H203	0.950
C15–C16	1.3881(17)	C21–H211	0.958
C15–H151	0.948	C21–H212	0.957
C16–C17	1.3851(19)	C21–H213	0.956
C16–H161	0.941	C22–H221	0.959
C17–C18	1.3841(18)	C22–H222	0.962
C17–H171	0.950	C22–H223	0.943
C18–C19	1.3886(17)		

Table 6: Bond Angles (°)

C9–C8–C13	119.60(11)	C2–Si1–C20	103.23(6)
C9–C8–C5	119.87(11)	C2–Si1–C21	108.19(6)
C13–C8–C5	120.43(10)	C20–Si1–C21	112.38(7)
C8–C9–C10	120.07(11)	C2–Si1–C22	108.29(6)
C8–C9–H91	120.0	C20–Si1–C22	112.18(7)
C10–C9–H91	119.9	C21–Si1–C22	112.04(7)
C9–C10–C11	120.99(11)	Si1–C2–F3	109.23(8)
C9–C10–H101	119.0	Si1–C2–F4	107.78(8)
C11–C10–H101	120.0	F3–C2–F4	105.24(9)
C10–C11–C12	118.18(10)	Si1–C2–C5	121.84(8)
C10–C11–C14	120.79(10)	F3–C2–C5	105.80(9)
C12–C11–C14	121.01(10)	F4–C2–C5	105.79(9)
C11–C12–C13	121.12(11)	C2–C5–C8	115.71(10)
C11–C12–H121	119.2	C2–C5–F6	106.49(10)
C13–C12–H121	119.6	C8–C5–F6	110.39(10)
C8–C13–C12	120.02(11)	C2–C5–F7	106.63(9)

C8–C13–H131	119.9	C8–C5–F7	111.10(10)
C12–C13–H131	120.1	F6–C5–F7	105.96(9)
C11–C14–C15	120.71(11)	Si1–C20–H201	110.9
C11–C14–C19	120.72(10)	Si1–C20–H202	109.8
C15–C14–C19	118.58(11)	H201–C20–H202	107.4
C14–C15–C16	120.59(12)	Si1–C20–H203	112.6
C14–C15–H151	119.3	H201–C20–H203	107.5
C16–C15–H151	120.1	H202–C20–H203	108.4
C15–C16–C17	120.37(11)	Si1–C21–H211	110.3
C15–C16–H161	118.6	Si1–C21–H212	110.1
C17–C16–H161	121.1	H211–C21–H212	108.5
C16–C17–C18	119.59(11)	Si1–C21–H213	110.8
C16–C17–H171	119.9	H211–C21–H213	110.0
C18–C17–H171	120.5	H212–C21–H213	107.0
C17–C18–C19	120.23(12)	Si1–C22–H221	111.0
C17–C18–H181	120.3	Si1–C22–H222	109.2
C19–C18–H181	119.5	H221–C22–H222	108.6
C14–C19–C18	120.61(11)	Si1–C22–H223	109.9
C14–C19–H191	119.3	H221–C22–H223	109.0
C18–C19–H191	120.1	H222–C22–H223	109.1