A Novel Route to Fluoroarenes from Trifluoroethanol

by

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Submitted to the Department of Pure and Applied Chemistry for the Degree of Doctor of Philosphy.

September 2014

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed:

Date: 19 September 2014

Abstract

This Thesis describes the preparation of fluoroarenes using a palladium-catalysed coupling/electrocyclisation methodology.

Difluoroenolzinc coupling partners, 1-(*N*,*N*-diethylcarbamoyloxy)-2,2-difluoro-1-zinc chloride and 2,2-difluoro-1-(2'-methoxy-ethoxymethoxy)-1-zinc chloride were prepared from trifluoroethanol at near ambient temperature and underwent Negishi coupling with a range of aryl-halides. A co-solvent (*N*,*N*-dimethylpropylene urea) was necessary to generate 2,2-difluoro-1-(2'-methoxy-ethoxymethoxy)-1-zinc chloride in good yield. The zinc coupling partners were also converted to (iodo)difluoroenols which participated in Suzuki-Miyaura coupling with a range of aryl-boronic acids and potassium aryl-trifluoroborates. Side reactions of the Suzuki-Miyaura couplings were circumvented by using tertiary butanol as the reaction solvent. Low temperature preparation of trifluoroborate coupling partners, potassium 2,2-difluoro-1-(*N*,*N*-diethylcarbamoyloxy)ethenyl trifluoroborate and potassium 2,2-difluoro-1-(2'-methoxy-ethoxymethoxy)ethenyl trifluoroborate, from trifluoroethanol was also accomplished. The trifluoroborates underwent Suzuki-Miyaura coupling with a range of aryl-halides. This Suzuki-Miyaura coupling protocol was used to prepare a range of fluorinated electrocyclisation precursors in modest to good yield. Subsequent electrocyclisation afforded fluorobenzene, fluoronaphthalene and fluorophenanthrene species. The electrocyclisations were investigated computationally in an attempt to rationalise the ease/difficulty of cyclisation.

Acknowledgements

I would like to thank Professor Jonathan Percy for his help and guidance throughout this PhD. Thanks also to Dr Joanna Redmond of GlaxoSmithKline for some extremely useful provisions and advice.

Thanks also to my colleagues within the JMP research group and the technical staff within the department, especially Gavin Bain, Denise Gilmour, Craig Irving and Patricia Keating.

I also wish to thank the EPSRC Pharma Synthesis Studentship Scheme and GlaxoSmithKline for funding this research.

Thanks to family and friends.

Abbreviations

Aq	aqueous
ASE	aromatic stabilisation energy
Ar	aryl
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
bmim	1-butyl-3-methylimidazolium
n-Bu	*n*-butyl
t-Bu	*t*-butyl
n-BuLi	*n*-butyllithium
t-BuLi	*t*-butyllithium
Ca	circa, approximately
Cy	cyclohexyl
d	days
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCM	dichloromethane
DEA	diethanolamine
DEC	*N*,*N*-diethylcarbamoyl
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMSO	dimethylsulfoxide
DoM	Directed *ortho*-Metallation

dppf	1,1'-*bis*(diphenylphosphino)ferrocene
dppp	1,3-*bis*(diphenylphosphino)ferrocene
EDG	electron donating group
emim	1-ethyl-3-methylimidazolium
eq.	equivalents
Et	ethyl
EWG	electron withdrawing group
GC	gas chromatography
h	hours
aHF	anhydrous hydrogen fluoride
HMBC	Homonuclear Multiple Bond Correlation
HMPA	hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HSQC	Heteronuclear Single Quantum Correlation
Hz	hertz
i-Pr	*iso*propyl
LC	Liquid Chromatography
LDA	lithium di*iso*propylamide
L_n	ligand (s)
Me	methyl
MEM	2-methoxyethoxymethyl
MIDA	*N*-methyliminodiacetic acid

min	minutes
mol	moles
MS	Mass Spectrometry
NHC	*N*-heterocyclic carbene
NICS	Nucleus Independent Chemical Shift
NMP	1-methyl-2-pyrrolidinone
NMR	Nuclear Magnetic Resonance
PDC	phthaloyl dichloride
Ph	phenyl
ppm	parts per million
PTFE	polytetrafluoroethylene
RT	room temperature
S_NAr	Nucleophilic Aromatic Substitution
TEA	triethylamine
Tf	trifluoromethane sulfonyl
THF	Tetrahydrofuran
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TS	transition state
UV	ultra violet
vide infra	see below
vide supra	see above

Contents

1 Introduction

In recent history, fluorinated compounds have played a significant role in the enhancement of everyday life.[1] Since discovery of the remarkable properties of fluoropolymers, an ever expanding number of applications have been found. An array of uses such as non-stick coatings for cooking utensils, lubricants, fuel tanks/lines, waterproofing and chemical reactor linings, to name but a few, have contributed to a multi-billion dollar industry. Interest in the properties that fluorine imparts upon organic molecules has also received significant attention.[2]

Over 25% of the pharmaceuticals on the market in 2011 contained fluorine, one of which was Pfizer's atorvastatin **1**, the best-selling drug globally in 2008.[2] Other successful fluorinated drugs are the antibacterial ciprofloxacin **2** from Bayer, GSK's anticancer drug Lapatinib **3** and Eli-Lily's Prasugrel **4** (Figure **1**).

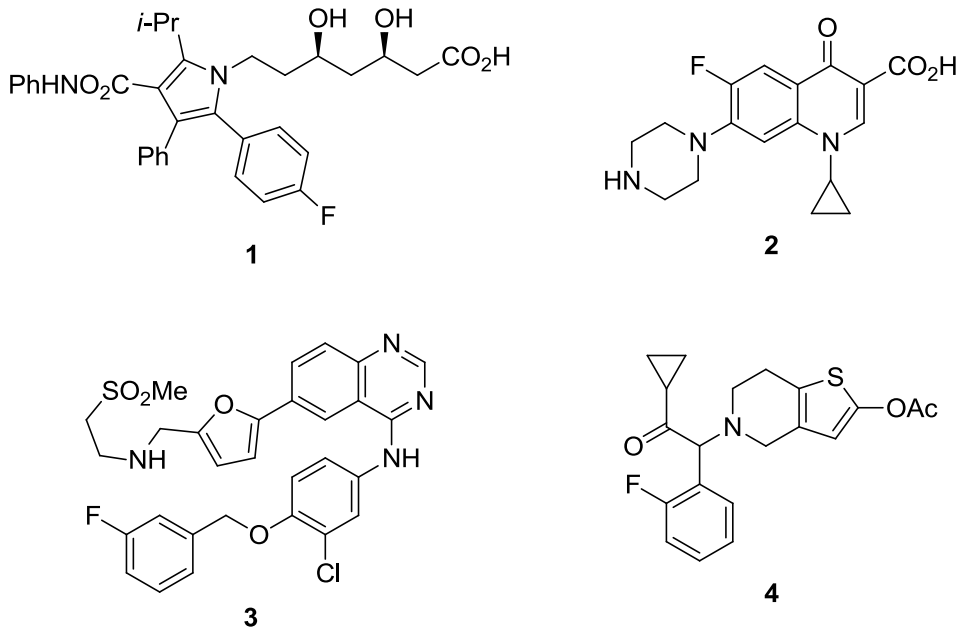


Figure **1**: Successful pharmaceuticals containing fluoroarenes

A common fluorinated motif present in modern pharmaceuticals is a fluoroarene.[2] The properties of the fluorine atom have the potential to enhance the efficacy of a drug through several channels (Figure **2**).[3] The high electron withdrawing nature of fluorine can Alter the pH of a drug, which can increase bioavailability.[4] Bioavailability can also be enhanced by blocking metabolism pathways with strategic introduction of a strong C-F bond[4] and increasing lipophilicity with the insertion of aromatic fluorines.[5]

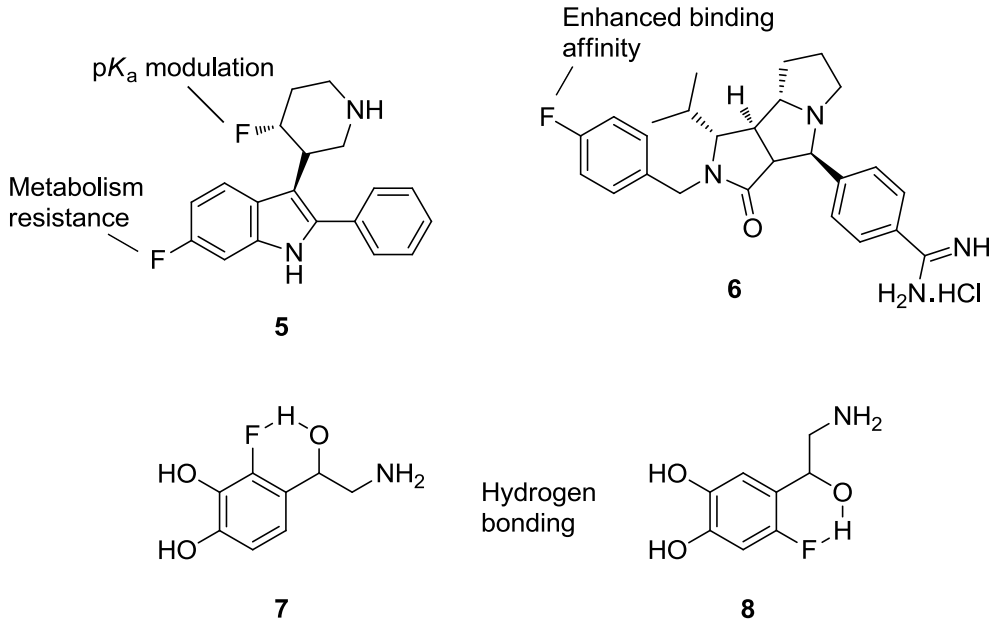


Figure **2**: Effect of fluorine substitution on biologically active compounds

Electrostatic interactions also play a role in drug efficacy; fluorine atoms have been observed to increase the potency of drugs by stronger binding to an active site on an enzyme.[6]

Weak F-H hydrogen bonding can also have a significant effect on the drug. Intramolecular F-H hydrogen bonding of fluorinated norepinephrine isomers **7** and **8** has been implicated in their selectivity for different (α or β) adrenergic receptors.[7]

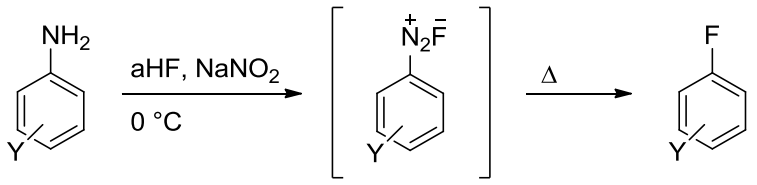
With a better understanding of fluorine atom effects in biological systems and an ever increasing interest in fluorinated, biologically active molecules, it is important to develop new and efficient methods for their synthesis.

1.1 Nucleophilic fluorination of arenes

Nucleophilic sources of fluorine have been routinely used to fluorinate aromatic compounds. Early methods which required harsh reaction conditions and toxic, difficult-to-handle fluoride sources have been superseded by more sophisticated techniques. A brief description of some of the most useful methods and their advances is described below.

1.1.1 Diazotisation/ fluorodediazoniation

Fluorination by displacement of a diazonium salt has been performed in anhydrous hydrogen fluoride (aHF).[8] Anilines were converted to diazonium salts **10** using sodium nitrite in neat aHF at 0 °C, then heated gently to promote decomposition to the fluorinated arenes (Table **1**).[8]



9 **10** **11**

Entry	Y	Yield of 11 (%)	Entry	Y	Yield of 11 (%)
1	H	87	**7**	4-OH	<10
2	2-Ph	82	**8**	2-Cl	<10
3	2-Me	73	**9**	3-Cl	81
4	3-Me	82	**10**	4-Cl	74
5	2-OH	<10	**11**	2-NO_2	<10
6	3-OH	46	**12**	3-NO_2	40

Table **1:** diazotisation/fluorodediazotisation of a range of substituted arenes

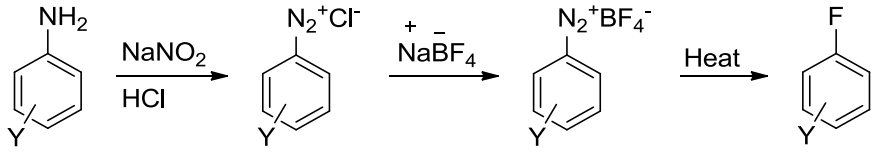
Dediazoniation becomes difficult when strong electron donating groups (OH) are present in the *ortho*- and *para*- positions. Nitro groups also have a deleterious effect on the yield when present *ortho* to the diazonium salt.

Fluoroarenes are prepared by this method on an industrial scale;[9] however, the highly corrosive nature of aHF requires expertise and specialist equipment to handle and so alternative sources of fluoride have been sought for fluorodeazoniation.

1.1.2 Balz-Schiemann reaction

Decomposition of diazonium tetrafluoroborate salts by Balz and Schiemann[10] demonstrated that fluorodeazoniation could be accomplished with a less hazardous

source of fluoride. A series of fluoroarenes, prepared by the Balz-Schiemann reaction, are displayed in Table **2**.[11]



9 **12** **13** **11**

R	Yield of 11 (%)		R	Yield of 11 (%)	
	ortho	***para***		***ortho***	***para***
H	100	100	CO_2H	19	-[a]
Me	90	97	CO_2Et	87	90
F	30	62	NO_2	19	58
Cl	85	-[a]	NEt_2	-[a]	20
Br	81	75	NMe_2	-[a]	17
OMe	67	67	OEt	36	53

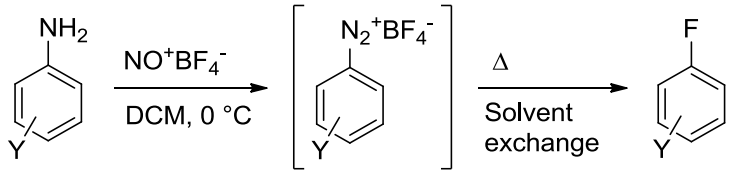
a) Reaction not performed

Table **2**: Balz-Schiemann reaction performed on a range of substituted arenes

As with fluoroarenes generated by fluorodediazoniation with aHF, lower yields were obtained using the Balz-Schiemann method when the aniline precursors were substituted with polar groups and Lewis basic groups (electron donating and withdrawing) in the *ortho*- or *para*- positions. Another problem encountered arises from the strong electron withdrawing nature of diazo-salts, which can encourage substitution of even moderate leaving groups from the *ortho*- position (particularly nitro groups) via an S_NAr process.

Isolation of the diazonium tetrafluoroborate salt is necessary and low yields can result if the intermediate is not dried thoroughly; decomposition in the presence of moisture can lead to the formation of phenols.[12] Recovery of tetrafluoroborate salts **13** from water can also be difficult, particularly when hydrophilic substituents are present on the ring.[12]

Milner demonstrated that aqueous acidic media was not needed to effect diazotisation of anilines, and that fluoroarenes could be prepared in one pot, without the inconvenience of isolating the diazonium salt intermediate.[13] Low temperature diazotisation (0 °C) was accomplished using nitrosonium tetrafluoroborate in DCM. A solvent exchange to a higher boiling solvent (1,2-dichlorobenzene) before subsequent thermal decomposition provided fluoroarenes in good yield (Table **3**).

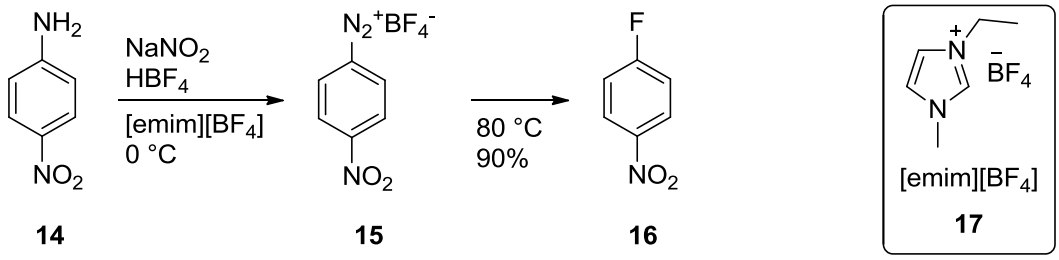


9 **13** **11**

Entry	Y	Yield of 11 (%)	Entry	Y	Yield of 11 (%)
1	H	72	**6**	2-Cl	90
2	4-NHAc	55	**7**	2-Br	90
3	2-OMe	70	**8**	3-F	52
4	2-OPh	63	**9**	2-NO_2	15
5	2-OH	58	**10**	3-NO_2	65

Table **3**: One-pot diazotisation/ fluorodediazoniation reactions

Low yields are still apparent with 2-nitro substituted derivatives. Laali has also reported one-pot diazotisation/fluorodediazoniation reactions, but in ionic liquids.[14] A noteworthy success of the use of ionic liquids is the high isolated yield (90%) obtained from the decomposition of a 4-nitro substituted diazonium tetrafluoroborate salt (Scheme **1**), although this example was not a one-pot procedure and an extensive study of other lone pair bearing *ortho*- and *para*-substituents was not undertaken.



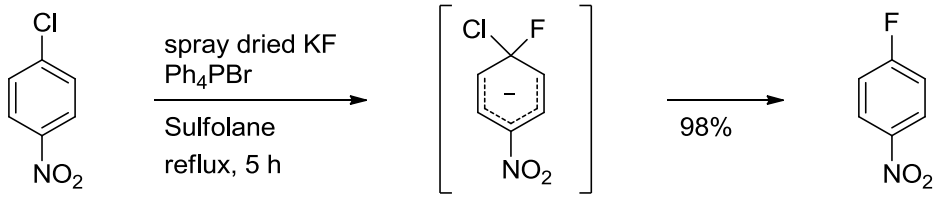
Scheme **1**: Diazotisation/fluorodediazoniation in ionic liquid [emim][BF_4]

Fluoroarene preparation by the decomposition of aryltriazenes is also a route of note; the first decomposition in acidic media (HCl and HF) to form chloro- and fluoroarenes was described by Wallach.[15,16]

Aryltriazenes are prepared by treating diazonium salts with an arylamine and are more stable than the salt precursors. Cleavage of the amine under acidic conditions releases the diazonium salt for fluorodediazoniation by HF[17] or $[BF_4]^-$.[18] Generally, aryltriazene decomposition affords fluoroarene product in lower yields than the Balz-Schiemann reaction.

1.1.3 S_NAr reactions with fluoride

Another established protocol for fluorinating arenes is the displacement of a halogen ion leaving group (halex reaction) by a fluoride anion nucleophile (Scheme **2**).[19,20] Substantial activation can be required, with the presence of one or more strong electron withdrawing groups, such as formyl, nitrile or nitro groups a common requirement. Alkali metal fluorides, which are hygroscopic and require careful drying are the usual sources of fluoride ion, and polar aprotic solvents such as dimethylsulfoxide (DMSO), tetramethylene sulfone (sulfolane) and *N*-methyl pyrrolidinone (NMP) are routinely used as reaction solvents.[21] High temperatures are required due to the poor solubility of the fluoride sources in non-aqueous solvents which makes the use of phase transfer catalysts very important.



18 **19** **16**

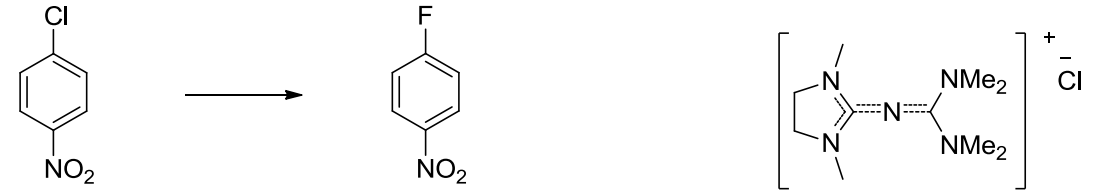
Scheme **2**: Halex reaction performed on 4-nitrochlorobenzene

Spray dried potassium fluoride (KF) has been used most often, normally delivering product in better yields than anhydrous KF; the greater surface area of the spray dried salt leads to a more efficient reaction. The surface area of the salt (hence the

rate of fluorination) can be increased still further by recrystalising KF from methanol.[22]

The use of phase transfer catalysts have allowed lower temperatures to be used (although temperatures of up to 200 °C are sometimes needed) and improved reaction yields. Effective catalysts include those of the 'onium' type such as Ph_4PBr[23] and Me_4NCl.[24] Crown ethers have also been shown to be effective phase transfer catalysts.[23] These catalysts can degrade at high temperatures and pressures, so more recently, alternative catalysts have been sought.[25] Pleschke demonstrated that azaallenium catalysts such as CNC^+ (**20**), which has high thermal stability and low dermal toxicity (Ph_4PBr has high dermal toxicity), are effective phase transfer catalysts (Table **4**). Pleschke admits however, that a general method for the halex reaction has not been found and that optimisation would be needed for each substrate.[25]

Microwave-mediated halex reactions have been attempted, proceeding in good yields in the presence of a polymeric imidazole catalyst (Scheme **3**).[26,27] Sulfolane, the solvent of choice for many halex reactions was found by Luo to be unstable under microwave conditions, degrading under the high temperatures generated at 200-350W; DMSO was found to be a suitable alternative. Although good yields were achieved, it should be noted that the substrates were highly activated by electron withdrawing nitro groups.

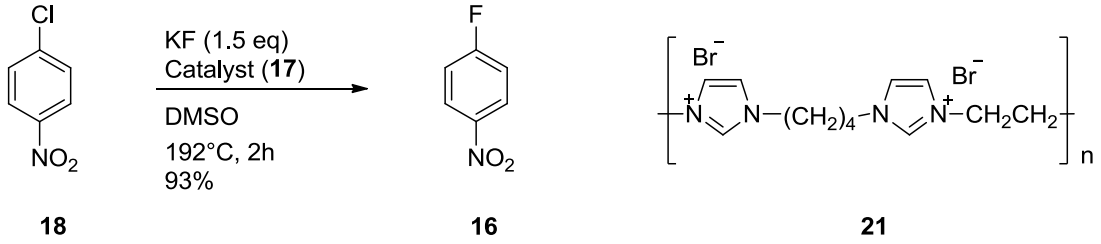


18 **16** **20**

Entry	Solvent (wt.%)	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%)
1	-	Ph_4PBr (1.3)	190	10	30[a]
2	Sulfolane (70)	Ph_4PBr (1.6)	180	5	40[a]
3	Sulfolane (250)	Ph_4PBr (1.6)	180	4	80
4	Me_2SO (130)	CNC^+ (1.0) (**20**)	170	5	96
5	Me_2SO (130)	Ph_4PBr (1.0)	170	6	89
6	Me_2SO (130)	$(Et_2N)_4PBr$ (1.0)	170	6	93

a) % conversion

Table **4**: Halex reactions using azaallenium salt catalysts

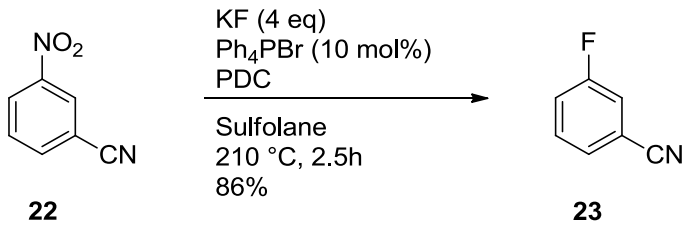


18 **16** **21**

Scheme **3**: Microwave-mediated halex reaction

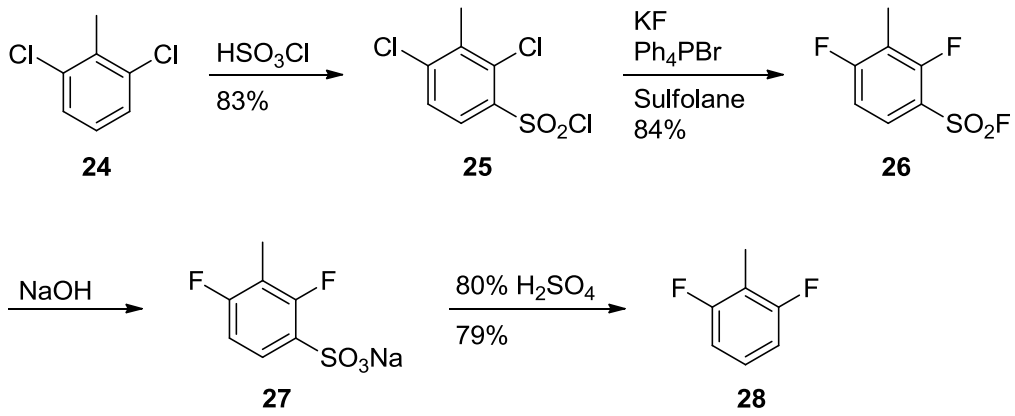
Substitution of a nitro group itself is possible due to the strongly electron withdrawing nature of the group.[28,29] The yields of this transformation can be modest; however, Kimura has shown that high yields of *meta*-fluoroarenes can be achieved by using Ph_4PBr as a phase transfer catalyst and phthaloyl dichloride (PDC) to trap the nitrite ion (Scheme **4**).[28] A higher temperature is necessary, presumably

because the Meisenheimer complex cannot be stabilised by this substitution pattern.



Scheme **4**: Halex reaction with NO_2 as the leaving group

An alternative option to having activating groups such as NO_2 already present on the arene ring is to utilise the disposable electron withdrawing group strategy developed by Kimura (Scheme **5**).[30,31]



Scheme **5**: Chlorosulfonyl group as a disposable activator for the halex reaction

Carbons 2 and 4 of **25** are activated for attack by fluoride in the halex reaction as a result of the introduction of the chlorosulfonyl moiety. The chlorosulfonyl group is

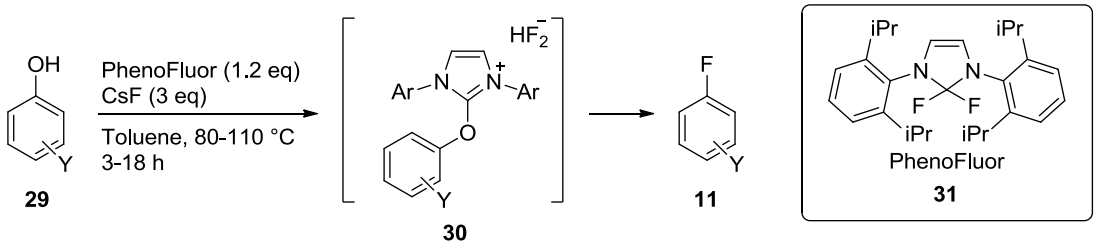
converted to a fluorosulfonyl group during the halex reaction. Subsequent reaction with aqueous sodium hydroxide generates a sodium sulfonate that is cleaved on exposure to 80% H_2SO_4. Owing to the unattractive scale-up implications arising from the use of excess strong acid, the Kimura group devised a milder cleavage of the sulfonate using sodium carbonate in 1,3-dimethyl-2-imidazolidinone (DMI), followed by desulfination by exposure to HCl.[31] This gave comparable yields, although an extra step is needed and the use of acid is still required.

The introduction of fluorine into an aromatic compound by an S_NAr type reaction is a direct and selective method but certain limitations hinder the widespread use of this operation. The fluoride source demands careful drying before use, and due to solubility issues, requires high temperatures and expensive phase transfer catalyst. Poor yields are often reported and electron withdrawing groups in a particular substitution pattern (*ortho*- and/or *para*-) are usually required to make the Meisenheimer complex energetically favourable. A considerable limitation of this approach is the lack of generality. No single set of conditions has been able to effect the transformation of both activated and non-activated substrates.

1.1.4 Conversion of phenols

An operationally simple, single step fluorination of phenols was developed by Ritter.[32] The fluorinating agent PhenoFluor **31** was prepared by treating *N*,*N*-1,3-*bis*(2',6'-di*iso*propylphenyl)-2-chloroimidazolium chloride with CsF. A wide range of substituted phenols underwent deoxyfluorination in good yield; a few examples are

displayed in Table **5**. Electron deficient phenols typically reacted more rapidly than electron rich phenols; however, nucleophilic fluorination of arenes bearing electron donating groups represents a significant advance in fluoroarene synthesis.



Entry	Y	Temperature (°C)	Time (h)	Yield (%)
1	4-NO_2	80	3	93
2	4-CF_3	80	3	92
3	4-OMe	110	20	82[a]
4	4-NH_2	110	20	75[a,b]
5	2-Me	110	20	55[a,b]
6	4-Me	110	20	81[a]

a) Determined by GC assay; b) 1,4-dioxane used as solvent.

Table **5**: Deoxyfluorination of phenols using imidazolium species PhenoFluor **31**

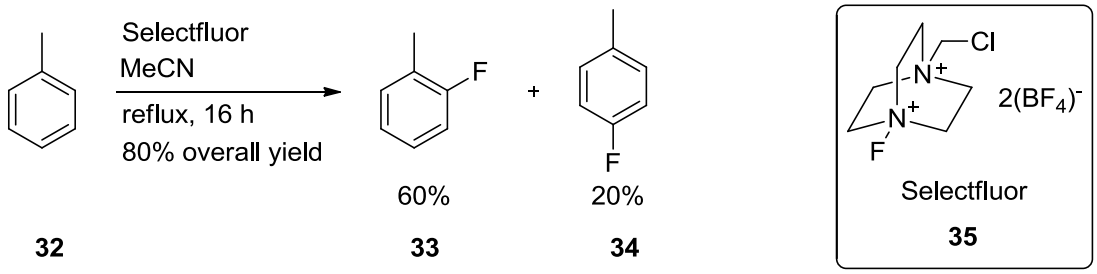
1.2 Electrophilic fluorination of arenes

Many electrophilic sources of fluorine such as elemental fluorine,[33] xenon difluoride[34] and organic hypofluorites[35] have been used in the synthesis of fluoroarenes. Issues with toxicity, ease of handling and reagent availability have seen these fluorinating agents relegated in favour of N-F reagents such as pyridinium fluorides and fluoro-diazoniabicyclo[2.2.2]octane salts (Selectfluor™). Many of the N-F salts are air stable and commercially available and, as a result, are

the most frequently used electrophilic fluorinating agents. A brief overview of their use in fluoroarene preparation is described below.

1.2.1 CH/CF exchange

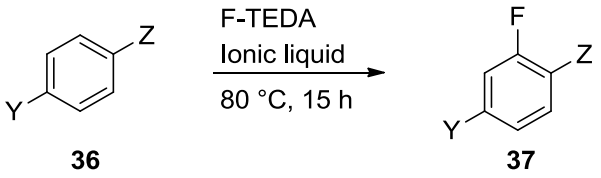
Direct C-H/C-F exchange of aromatic compounds by electrophilic aromatic substitution has been accomplished using *N*-fluoropyridinium species[36] and fluoro-diazoniabicyclo[2.2.2]octane salts (F-TEDA or Selectfluor™) developed by Banks *et al.*.[37] These reactions require directing groups and proceed with modest conversions, but result in poor selectivity. An example is shown in Scheme **6**.[38]



Scheme **6**: CH/CF exchange using F-TEDA

Attempts to improve the efficiency and yields of such fluorination reactions have seen the use of ionic liquids[39] and microwave irradiation[40] with limited success. Ionic liquids appear to offer no advantage in electrophilic fluorination. Modest (~50%) yields are generally obtained and due to the need for electron rich arenes, mixtures of *ortho*- and *para*- isomers are routinely recovered after the reaction.[39] Laali and co-workers have shown that the isomer ratio can be managed in favour of

the *ortho*- isomer by blocking *para*- substitution with a substituent already present on the molecule (Table **6**). Although selectivity is improved with this approach, a 'blocking' group must either be introduced or already present on the arene; this represents a significant limitation of the method as extra synthetic steps would be required to add and remove the blocking group.



36 **37**

Z	Y	Ionic liquid	Yield	Isomer Composition of Reaction Mixture (%)
OMe	Me	[emim][CF_3SO_3]	56%	2-fluoro (93), 3-fluoro (6)
OMe	Cl	[emim][CF_3SO_3]	50%	2-fluoro (95), 2,6-difluoro (5)
OMe	F	[emim][CF_3SO_3]	24%	2,4-difluoro (100)
Me	NO_2	[bmim][BF_4]	0	-

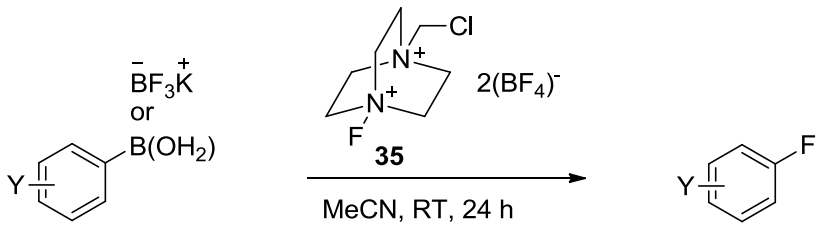
a) Determined by NMR assay.

Table **6**: *Ortho*- CH/CF exchange selectivity

The use of microwave reactors significantly reduces reaction times; however this method suffers from similarly poor yields and selectivity.[40]

1.2.2 From aryl boronic acids

Substitution of a small selection of aryl boronic acids and aryl trifluoroborates using Selectfluor has been accomplished by Lemaire (Table **7**).[41]



Entry	Y	B species	Conversion (%)[a]
1	4-*t*-Bu	$B(OH)_2$	75
2		BF_3K	53
3	4-NO_2	$B(OH)_2$	Traces
4		BF_3K	Traces
5	4-OBn	$B(OH)_2$	100
6	3-OBn	$B(OH)_2$	0
7	2-OBn	$B(OH)_2$	67

a) Measured by GC

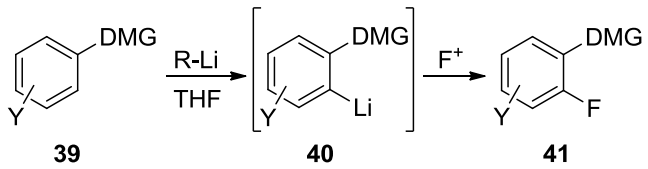
Table **7**: Electrophilic fluorination of aryl boronic acids and aryl trifluoroborates

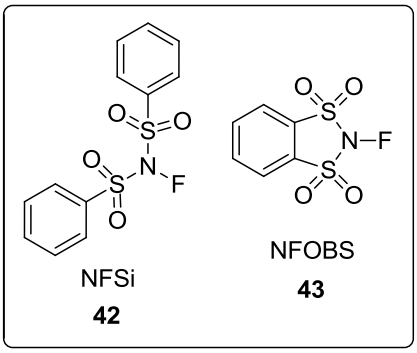
The true scope of this useful transformation has not been determined; however, this small study appears to show that CB/CF exchange is accomplished under mild conditions. It also seems to be limited by the same drawbacks of CH/CF exchange; electron rich *ortho*- or *para*- substituents are required to effect substitution and electron withdrawing substituents are not tolerated. A study of a larger cohort of aryl boron species is required to determine the generality of this novel fluorination.

1.2.3 From aryl-metallic species

The regioselectivity of fluorination is greatly increased when aryl metallic species are quenched with an electrophilic source of fluorine. Snieckus has demonstrated that directed *ortho*- metallation (DoM) to produce aryl lithium species, followed by

fluorination with *N*-fluorobenzenesulfonimide (NFSi) or *N*-fluoro-*O*-benzenedisulfonimide (NFOBS) delivers fluoroarenes in modest yields and complete regioselectivity (Table **8**).[42]

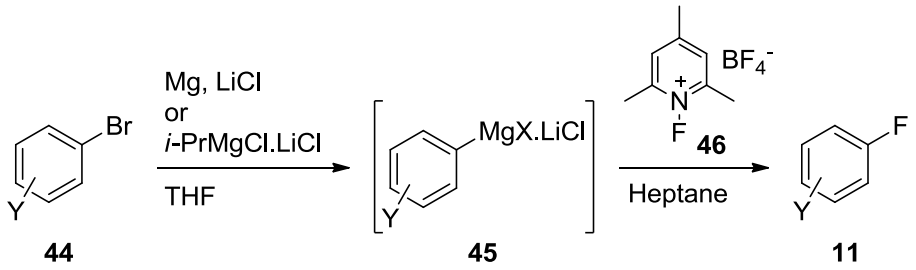




Entry	Y	DMG	DoM conditions	F^+ Source	Yield (%)
1	4-OMe	SO_2NMe_2	*n*-BuLi (1 eq); -40 °C	NFSi	55
2				NFOBS	47
3	H	$SOBu^t$	*n*-BuLi (1 eq); -78 °C	NFSi	74
4				NFOBS	70
5	2-$CONEt_2$	SO_2Bu^t	*n*-BuLi (1 eq); -78 °C	NFSi	58
6				NFOBS	31

Table **8**: Directed *ortho*-lithiation of arenes and subsequent fluorination

The regioselectivity of the lithiations is excellent; however, the organolithium intermediates must be kept at low temperature to avoid degradation and many functional groups are not tolerated. Aryl-magnesium halides have been successfully converted to fluoroarenes by the groups of Beller, using an *N*-fluoropyridinium reagent **46**[43] (Table **9**) and Knochel, using NFSi.[44] The aryl Grignard intermediates require less demanding storage conditions and are less nucleophilic than the lithium species, allowing for more functional group tolerance. Electron rich aryl Grignards were fluorinated in higher yields than electron poor species.



44 **45** **11**

Entry	Y	Yield (%)[a]	Entry	Y	Yield (%)[a]
1	4-OMe	81	7	2-Me-4-OMe	59
2	2-OMe	69	8	4-F	47
3	4-SMe	61	9	4-Cl	48
4	2-SMe	61	10	4-vinyl	60
5	2-Me	70	11	4-CF_3	57[b]
6	3,4-Di-Me	68	12	4-CN	33

a) Determined by GC assay; b) methoxyperfluorobutane ($CH_3OC_4F_9$) used as solvent

Table **9**: Fluoroarene preparation from aryl Grignard reagents

The Grignard intermediates were prepared from aryl bromides by either Mg insertion in the presence of LiCl or by Mg/Br exchange using *i*-PrMgCl.LiCl. This is an excellent method for the preparation of simple fluoroarenes, taking advantage of a readily available catalogue of aryl bromides and using mild metallation techniques. It does not represent a general approach to aromatic fluorine compounds; however, as some functional groups are still sensitive to the Grignard reagents (acyl, esters, OH) and electron poor arenes were not fully investigated.

1.3 Palladium-catalysed fluorination

Palladium-catalysed fluorination of aryl halides has long been investigated as a route for the preparation of fluoroarenes. If the fluorination proceeded along similar reaction pathways to the well established, known palladium coupling cycles then it would overcome several limitations of the fluorination protocols described earlier; there would be excellent regioselectivity, truly mild reaction conditions, activating substituents on the aromatic ring would not be required and a greater range of functional groups would be tolerated.

1.3.1 Coupling using a nucleophilic source of fluorine

Early, extensive efforts to form fluoroarenes by Grushin proved unsuccessful.[45,46] A simple representation of the desired palladium cycle is displayed in Figure **3**.

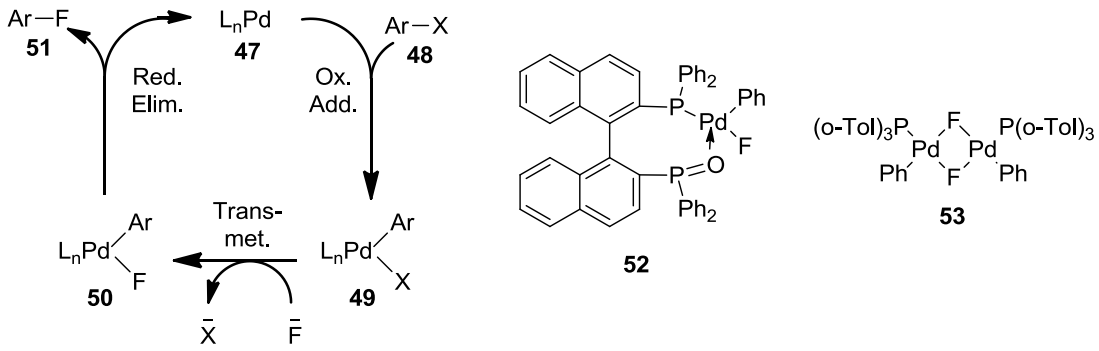
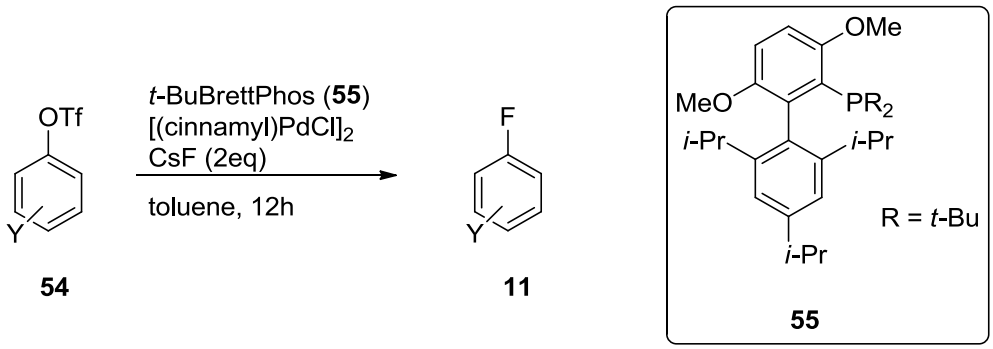


Figure **3**: Palladium-catalysed fluorination cycle and isolated Pd complexes **52** and **53**

Grushin found that oxidative addition of aromatic iodides followed by transmetallation with AgF produced palladium complex **50**. This aggregated into stable dimers like **53**. Thermal decomposition of dimer **53** did not result in C-F union; instead P-C and P-F species were detected. Grushin prepared novel Pd complex **52** to encourage the difficult reductive elimination step by forcing the Ar and F groups *cis* to each other; reductive elimination to form fluoroarenes remained elusive.

Several groups have recently taken up the challenge of delivering effective palladium-catalysed fluorination processes with some success, using both nucleophilic and electrophilic sources of fluorine.

A series of aryl-triflates were successfully fluorinated by Buchwald using CsF as the source of fluorine (Table **10**).[47] Key to the success of the palladium-catalysed fluorination was the use of a bulky phosphine ligand (*t*BuBrettPhos **55**). Buchwald suggests that the ligand promotes reductive elimination and participates in the overall efficiency of the cycle by preventing formation of a palladium dimer such as **53** (Figure **3**).

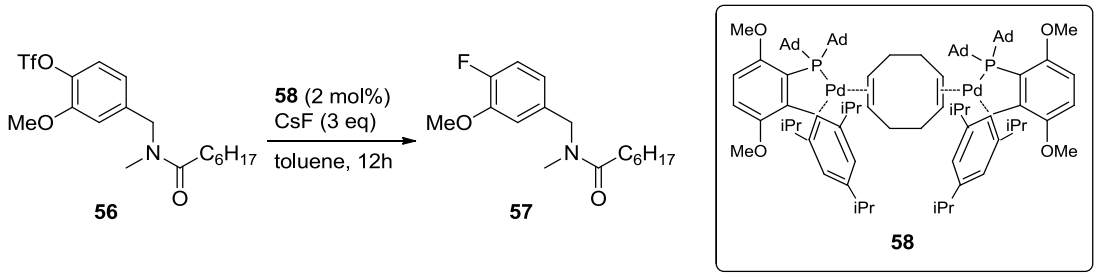


Y	Temperature (°C)	Catalyst (Mol%)[a]	Yield (%)
2-Ph	110	4	82
4-CO_2nBu	80	2	85
3-OBn	130[b]	10	57
3-NO_2-6-Me	110	2	80
4-NO_2-6-Me	110	2	83
3-NMe_2	130[b]	4	84

a) 1:1.5 catalyst:ligand ratio; b) cyclohexane used as solvent

Table **10**: Buchwald's palladium-catalysed fluorination of aryl triflates

Buchwald further improved this fluorination methodology by using a different catalyst/ligand combination (Scheme **7**).[48]

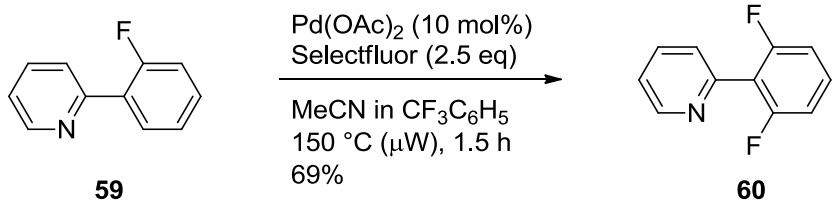


Scheme **7**: Improved nucleophilic palladium-catalysed fluorination

Competitive palladium-catalysed processes (reduction of Ar-OTf and formation of Ar-Cl) were inhibited by using catalyst **58**.

1.3.2 Coupling using an electrophilic source of fluorine

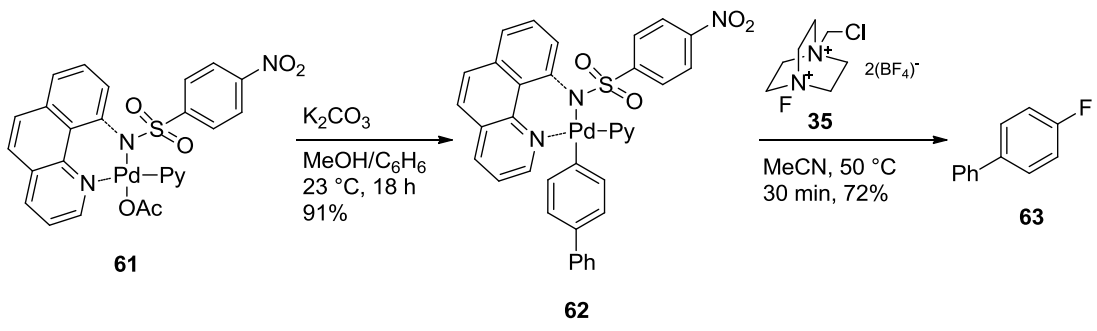
Palladium catalysts in the presence of electrophilic fluorine sources have also been observed to generate fluoroarenes. Sanford described fluorination of Ar-H bonds with simple $Pd(OAc)_2$ and fluoropyridinium salts (Scheme **8**).[49]



Scheme **8**: Directed palladium-catalysed Ar-H fluorination

The requirement for a directing group and strategic blocking of reactive centres imparts a serious limitation on the generality of this methodology.

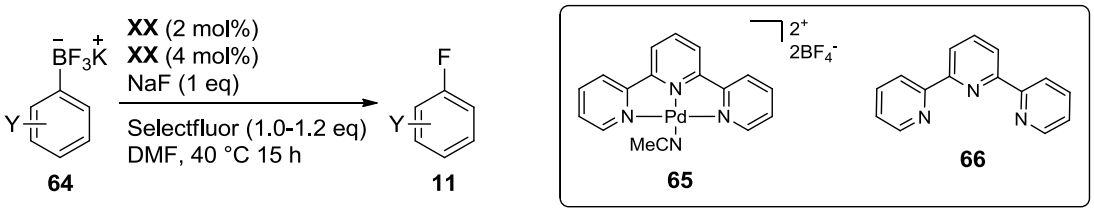
A protocol for the fluorination of aryl boronic acids using Selectfluor™ **35** and a stoichiometric amount of palladium catalyst was developed by Ritter (Scheme **9**).[50]



Scheme **9**: Ritter's palladium-mediated fluorination of boronic acids

Palladium complex **62** is generated by transmetallation of the boronic acid to the Pd(II) catalyst **61**. Exposure of complex **62** to selectfluor generates a fluorinated Pd(IV) complex and subsequent reductive elimination of the aryl and fluoride ligands affords the fluoroarene.[51]

A severe limitation imposed upon this approach is the need for stochiometric amounts of palladium catalyst. Ritter developed a catalytic fluorination using a Pd(III) catalyst to address this issue.[52]



Y	Solvent	Yield (%)
4-*t*-Bu	DMF	98
4-OPh	DMF	99
4-Ph	DMF	73[a]
2-Ph	DMF	85[b]
4-Br	MeCN	96%
4-(2'-pyridyl)	MeCN	86%

a) No NaF used; b) 4% biphenyl

Table **11**: Palladium-catalysed fluorination of boronic acids using selectfluor

A selection of aryl-trifluoroborates were converted to aryl-fluorides in high yield using a Pd(III) catalyst generated *in situ* from **65**, **66** and selectfluor. Ritter proposed an unusual single electron transfer mechanism and has shown that only small

amounts of fluoroarenes (≤5%) are generated in the absence of the palladium catalyst. A trifluoroborate group is necessary for successful fluorinations; however, Ritter demonstrated that these groups can be generated *in situ* from other common boron species such as boronic acids or boronic esters. The scope of the reaction is limited to electron rich or neutral aryl-trifluoroborates and has so far been unable to tolerate heteroaromatic species.

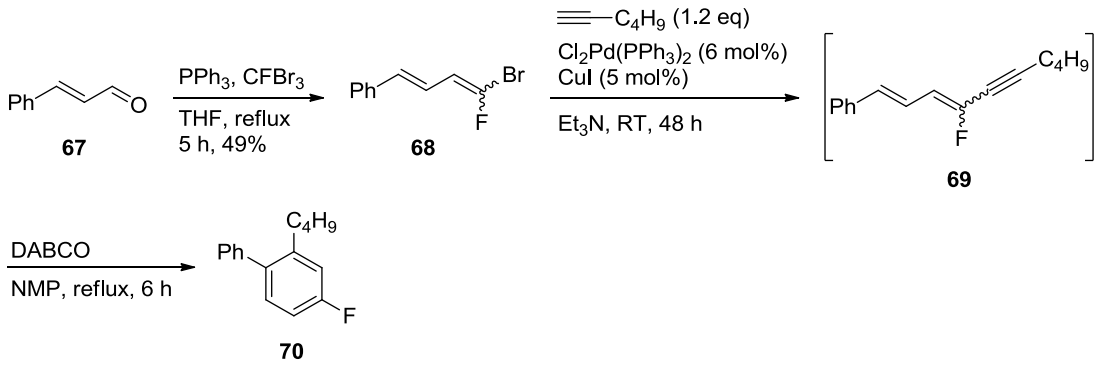
Palladium-catalysed fluorination is an attractive approach to fluoroarene synthesis due to excellent selectivity and mild reaction conditions. The Pd(IV) methodologies developed by Sanford and Ritter, although making a breakthrough in the problematic reductive elimination of fluoride from a palladium complex, were limited by either directing group requirements, poor substrate scope or the use of stochiometric amounts of palladium catalyst. Buchwald's Pd(0) catalysed approach represents an excellent method of fluorination. High temperatures are necessary (110-130 °C) and purification from small amounts of side-products can be difficult but it is a very general procedure with high substrate scope.

1.4 Building block approach

A less common approach to fluoroarene preparation is a building block methodology, with the fluorine atom already present on a smaller non aromatic substrate.

1.4.1 Cyclisation of fluoro-enynes

Burton has prepared some simple fluoroarenes using a building block approach (Scheme **10**).[53] A Wittig reaction was performed on cinnamaldehyde **67** to generate phenyl diene **68** in a *E,E* : *E,Z* ratio of 43:57. Sonogashira coupling then afforded dienyne **69**. The resulting crude mixture of *E,E* and *E,Z* isomers was cyclised under basic conditions (DABCO) in refluxing NMP to afford fluoroarene **70** in 72% yield (based on 57% of *E,Z* diene available from the Wittig reaction).



Scheme **10**: Base catalysed cyclisation of a monofluorodienyne to afford biaryl **70**

Burton used the same methodology to prepare monofluoronaphthalenes from 4-trifluoromethylbenzaldehyde[54] and fluorinated benzofurans and benzothiophenes from heteroaromatic aldehydes (Figure **4**).[55]

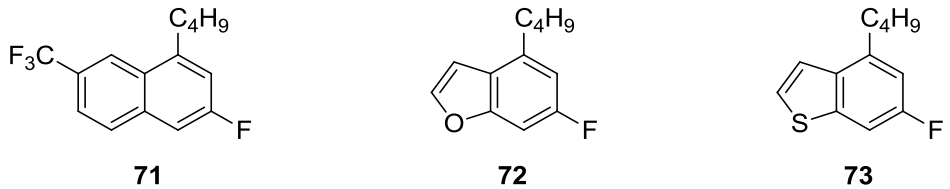


Figure **4**: Fluoroarenes prepared from Burton's building block approach

This approach produces fluoroarenes with complete regioselectivity; however, low reaction yields and extremely low atom efficiency limit its usefulness.

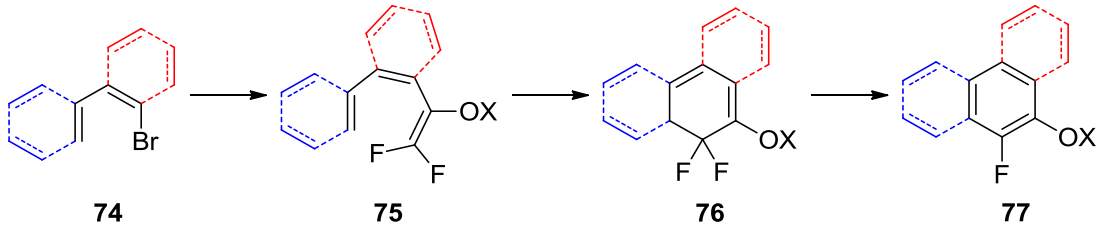
1.5 Summary of fluorination methods

Several simple methods for the fluorination of arenes have been used routinely in the past; both electrophilic and nucleophilic fluorine sources have been used to fluorinate simple arenes but these processes generally require harsh reaction conditions and often make use of toxic fluorinating agents. Fluorinated regioisomers are also often produced which complicates isolation of reaction products. A strong interest in fluorinated aromatic molecules in recent history has stimulated research into improving fluorination protocols, with some success. Most modern methods no longer make use of toxic reagents and try to use mild reaction conditions. Some challenges still remain; however, including lack of generality, regioisomer formation, lack of functional group tolerance and poor atom efficiency. Palladium-catalysed fluorination represents the most significant advance to date, allowing for excellent regioselectivity, mild reaction conditions and late stage fluorination. Coupling using an electrophilic fluorine source, incurring reductive elimination from a fluorinated Pd(IV) complex, produces product under extremely mild reaction conditions but does not tolerate the substrate scope enjoyed by the palladium-catalysed fluorination developed by Buchwald.

Given the keen interest in fluorinated aromatic species and the desire to improve upon known syntheses, a novel building block approach to fluoroarenes was investigated.

1.6 Proposed synthetic strategy

A building block approach to fluoroarenes with 4 key operations is envisaged (Scheme **11**).



74 **75** **76** **77**

X = MEM or DEC

Scheme **11**: Proposed building block strategy for fluoroarene preparation

The key operations are:

- *Z*-Halodiene/halostyrene **74** synthesis.
- Palladium-catalysed assembly of electrocyclisation precursors **75**.
- Electrocyclisation of precursors to generate cyclohexadienes **76**.
- Aromatisation by dehydrofluorination to afford fluoroarenes **77**.

Well established simple chemistry should expediate the synthesis of *Z*-Halodienes/halostyrenes **74**. Similarly, known palladium-catalysed coupling chemistry of difluoroenol species should aid in the delivery of fluorinated

electrocyclisation precursors **75**. Electrocyclisation of the precursors to cyclohexadienes **76** is a novel step; however, should it prove successful, aromatisation to fluoroarenes **77** with the loss of HF should be facile.

1.6.1 Z-Halodiene and Halostyrene synthesis

Four principal methods for the preparation of halodienes and halostyrenes are outlined in Figure **5**. (*Z*)-β-Bromostyrenes **79** can be prepared using a method developed by Kuang (**A**).[56] 2-Bromocinnamic ester **81** can be prepared by performing a Knoevenagel condensation on 2-bromobenzaldehyde **80** followed by an esterification (**B**). 2-Bromostyrenes **83** could be prepared by palladium-catalysed vinylation (**C**). *Z*-Bromodiene **85** can be prepared by performing a Vilsmeier formylation on cyclohexanone **84** followed by a Wittig olefination (**D**).[57]

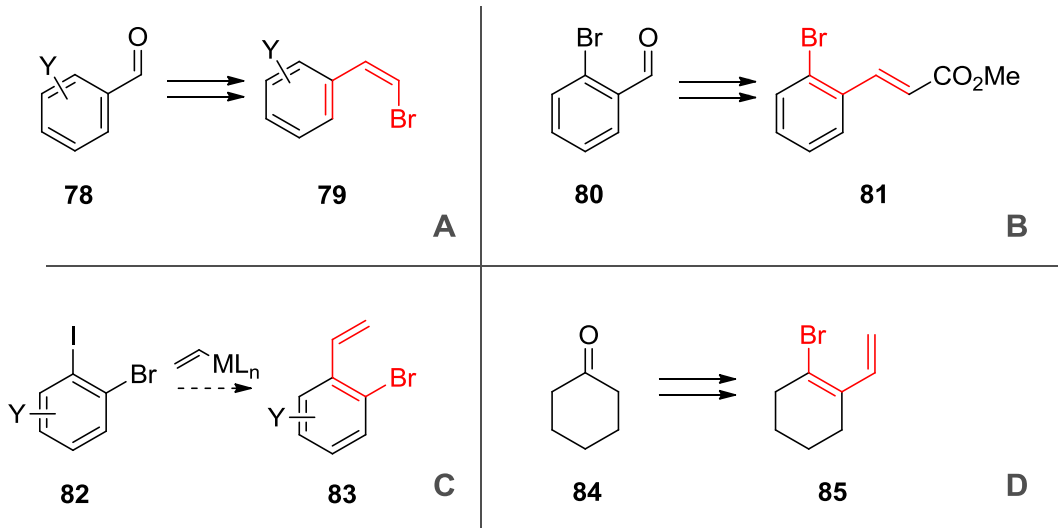


Figure **5**: Strategies for the preparation of *Z*-halodienes and halostyrenes

The proposed preparation of each halodiene and halostyrene is described in more detail in chapter 2.

1.6.2 Palladium-catalysed assembly of fluorinated electrocyclisation precursors

Palladium-catalysed coupling has received enormous attention over the last few decades, particularly since ~1990 (Figure **6**),[58] owing to the wide substrate scope, functional group tolerance and mild reaction conditions enjoyed by the robust C-C bond forming process. The pioneers of the reaction received the Nobel prize for chemistry in 2010,[59,60] indicating the value of palladium coupling to the chemical community.

1.6.2.1 A historical perspective on palladium-catalysed coupling

The first palladium-catalysed coupling reactions as we would recognise them today were performed by Heck in 1968 when he successfully coupled olefins with aryl-mercury species.[61] Mizoroki[62] and Heck[63] later improved the transformation by demonstrating that aryl halides could be used in place of toxic organomercury compounds. Olefination by forming C-C bonds using a Pd catalyst became known as the Mizoroki-Heck coupling reaction (often abbreviated to Heck coupling).

In 1972 Corriu[64] and Kumada[65,66] coupled Grignard reagents with aryl-iodides, -bromides and -chlorides using nickel catalysts. The scope of the Corriu-Kumada coupling was later improved by using palladium;[67] more stable palladium catalysts

allowed for a more robust catalytic cycle; however, organochlorides then became difficult to couple.

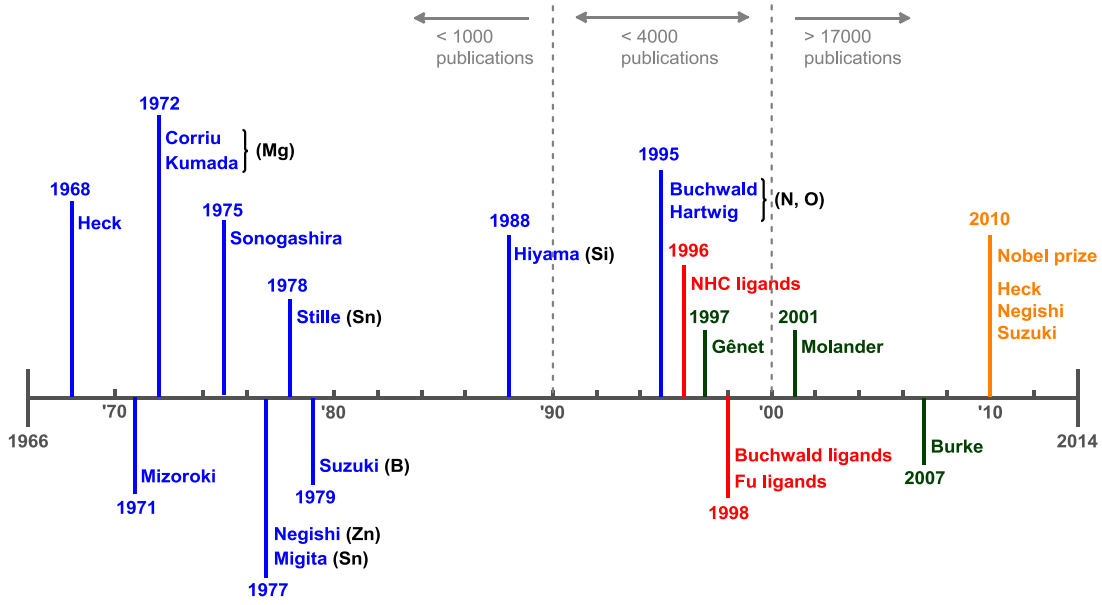


Figure **6**: Timeline of major developments within palladium-catalysed coupling

Shortly after Sonogashira developed a palladium/copper-catalysed protocol for coupling acetylene species with organic halides,[68] work by Negishi,[69,70] Migita,[71] Stille[72,73] and Suzuki and Miyaura[74,75] demonstrated that the excellent selectivity of Corriu-Kumada coupling could be reproduced with organozinc (Negishi coupling), organotin (Migita-Stille coupling) and organoboron (Suzuki-Miyaura coupling) species respectively, while also achieving superior functional group tolerance.

Migita-Stille and Suzuki-Miyaura coupling, often abbreviated to Stille and Suzuki coupling due to the extensive development by these researchers, are extremely versatile, robust reactions that are performed under mild conditions, and as such have been used more than the other coupling methods.[58] Toxic tin residues are

produced as a by-product of the Stille coupling and so limit its use by contemporary chemists.

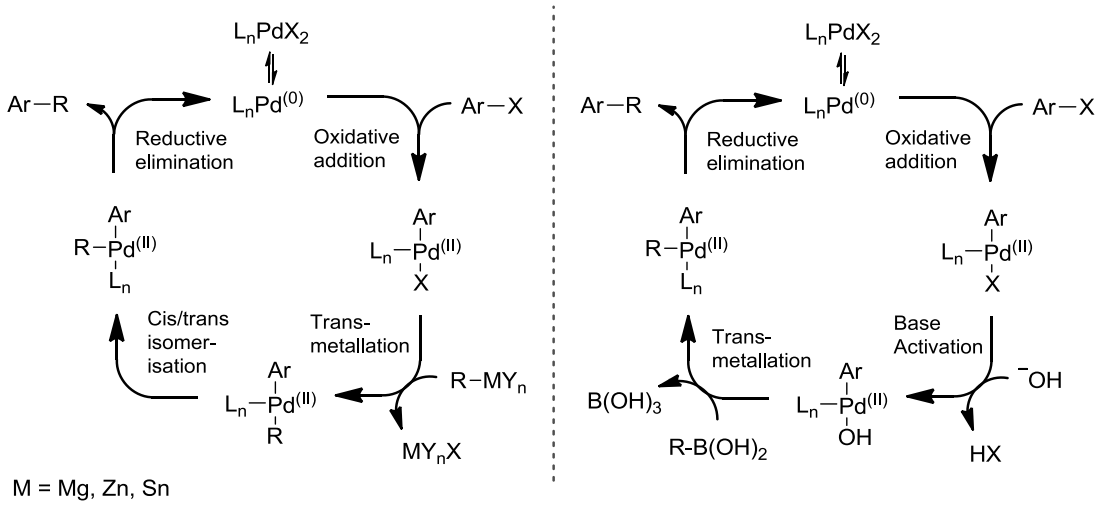


Figure **7**: Catalytic cycles for palladium-catalysed coupling reactions

Organo-iodides and -bromides were routinely used as coupling partners but coupling of less expensive organochlorides continued to pose problems; oxidative addition of organochlorides is slow and is very often the rate-limiting step in palladium-catalysed couplings. There had also been little success enjoyed with challenging coupling partners such as alkyl-halides or alkyl-metals; β-hydride elimination competes with slow transmetallation. Investigations into ligand design began to address these issues and ushered in another flurry of research into palladium catalysed couplings.

Buchwald and Hartwig independently and simultaneously discovered that secondary amines (even those bearing β-hydrogens) could be coupled to aryl-

halides through palladium catalysis using P(*o*-tolyl)$_3$ as a ligand.[76,77] This coupling was termed the Buchwald-Hartwig amination and was improved by the use of chelating phosphine ligands (DPPF and BINAP).[78,79] This methodology was extended to C-O bond forming reactions,[80] demonstrating that slow, problematic steps in palladium-catalysed coupling reactions could be overcome by use of the correct ligand.

Buchwald discovered that amines could be coupled with aryl-chlorides by using a biaryl amino phosphine ligand.[81] This led to the development of an array of similar bulky, biaryl phosphine ligands (such as **86**)[82] that are able to promote formation of mono-ligated Pd(0) catalysts and accelerate the oxidative addition and reductive elimination steps.

Acceleration of the oxidative addition of organochlorides by electron-donating, bulky phosphine ligands was also exploited by Fu.[83] Fu demonstrated that tri-*tert*-butylphosphine (P[*t*-Bu$_3$]) **87** and tri-cyclohexylphosphine (PCy$_3$) **88** ligands could be used in Heck,[84] Stille,[85] Suzuki[86] and Negishi[87] coupling of organochlorides. The value of these ligands was exemplified by their ability to effect palladium-catalysed coupling of alkyl-halides[88] and in particular, alkyl-chlorides.[89]

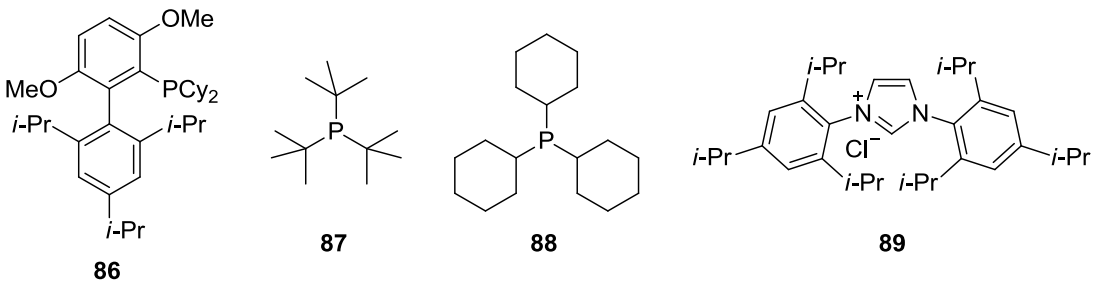
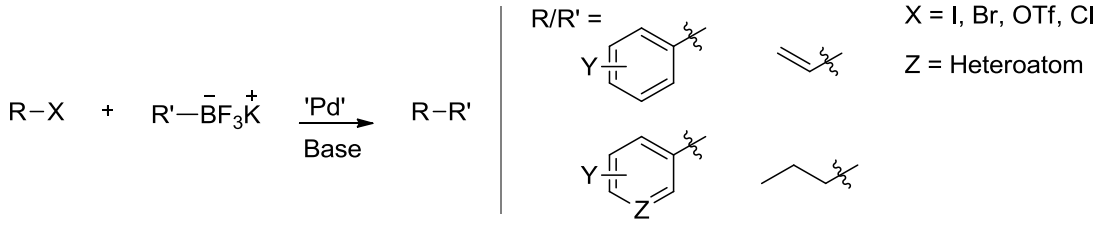


Figure **8**: Some important ligands in the development of palladium-catalysed coupling

N-Heterocyclic carbene (NHC) ligands (such as **89**) have also been used in palladium-catalysed coupling; Herrmann first used these ligands in simple Heck couplings of aryl-halides.[90] The main advantage of the electron rich NHC ligands is strong binding to the metal centre of Pd(0) catalysts, extending their lifetime and promoting oxidative addition of organohalides. NHC ligands have been used in most palladium-catalysed couplings.[91] Organ has recently developed some NHC ligated palladium precatalysts (pyridine enhanced precatalyst preparation, stabilisation, and initiation; PEPPSI) that are capable of coupling difficult substrates,[92] which include sterically hindered aryl-chlorides, alkyl-halides and alkyl-metallic species.[93-95]

A more recent development in palladium-catalysed coupling was the discovery that masked boronic acids could be used as substrates in Suzuki-Miyaura coupling. Suzuki coupling is by far the most used coupling method[58] due to the vast substrate scope and stability of the coupling partners; however, some boronic acids are prone to extensive degradation and stabilisation of these species can lead to higher yielding, more efficient reactions.

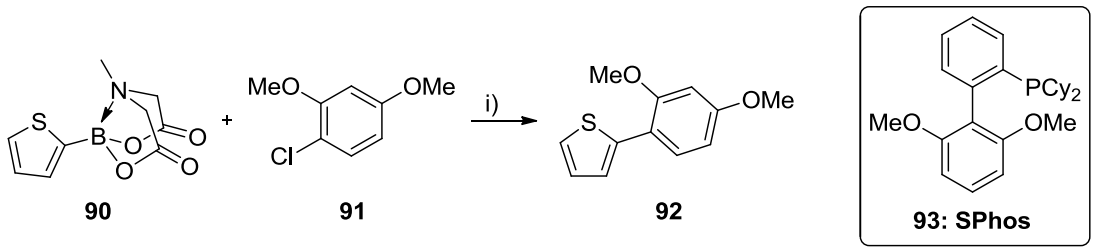
Coupling of a range of arenediazonium-tetrafluoroborates with potassium aryl- and alkenyltrifluoroborates by Gênet[96,97] generally went unnoticed until the scope of the methodology was extended by Molander. Molander demonstrated that the more amenable organohalides could be coupled with an impressive array of potassium organotrifluoroborates (Scheme **12**). The borate salts are generally white solids that are indefinitely stable under ambient storage conditions.



Scheme **12**: Scope of Suzuki-Miyaura coupling of potassium trifluoroborates

The key to the success of the reactions is slow release of the active coupling reagent (boronic acid) under reaction conditions. This means that only a small amount of boron coupling reagent is available at a given time and limits the loss of material through degradation processes.

Some species, particularly potassium heteroaryl-trifluoroborates still proved difficult to couple using the conditions developed by Molander. Burke demonstrated that aryl, heteroaryl, viny, and alkyl *N*-methyliminodiacetic acid (MIDA) boronates could similarly be used as masked boronic acid coupling partners (Scheme **13**).[98,99]



90 **91** **92**

i) $Pd(OAc)_2$ (5 mol%), SPhos **93** (10 mol%), K_3PO_4 (7.5 eq), Dioxane:H_2O (5:1),60 °C, 6 h, 98%

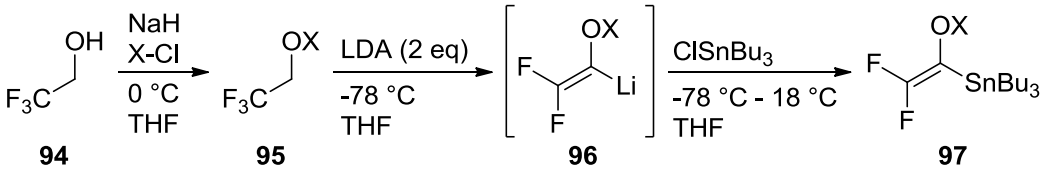
Scheme **13**: Example of Suzuki-Miyaura coupling with a heteroaryl MIDA boronate

Palladium-catalysed C-C and C-X bond formation is an extremely powerful reaction that has become indispensable to the modern synthetic chemist. Some extremely general and efficient coupling methodologies have been delivered after four decades of research, and development continues today. Currently, chemists are striving for a coupling methodology that does not require activation of coupling partners (organohalide or organometallic species). Direct palladium-catalysed cross coupling of arenes has been accomplished through C-H activation.[100] This improves the previous coupling methodology in terms of atom efficiency; however, the scope of the coupling is limited at present as directing groups are necessary to impart regioselectivity.

1.6.2.2 Trifluoroethanol derived building blocks

It is envisaged that palladium-catalysed coupling of difluoroenol coupling partners derived from trifluoroethanol could deliver the electrocyclisation precursors outlined in Scheme **14**. Trifluoroethanol derived vinyl-stannanes **97** have previously

been generated[101,102] and used by Percy in the synthesis of several classes of fluorinated organic compounds.[103-107]



X = MEM [$CH_2O(CH_2)_2OCH_3$] or DEC [$C(O)NEt_2$]

Scheme **14**: Preparation of key difluoroenol coupling reagents

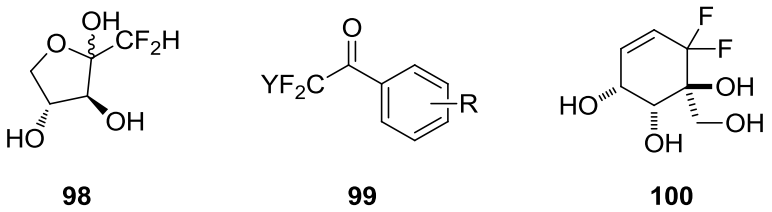
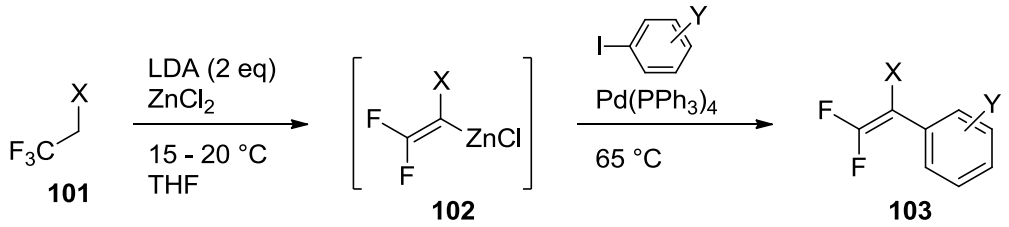


Figure **9**: Fluorinated compounds prepared using stannane **127a**

Preparation of the difluoroenol stannanes requires cryogenic conditions and their use results in release of toxic tin residues. Although the chances of success of delivering electrocyclisation precursors by Stille coupling of **97** are high, investigation into the preparation and reaction of alternative difluoroenol coupling partners of less environmental impact would be of value.

Burton has prepared fluorovinylzinc coupling partners from HFC-134a[108] and HFC-133a[109] at ambient temperature and performed Negishi coupling with a range of aryl-iodides (Table **12**). The key to generating the vinylzinc species at ambient

temperature was slow addition of LDA to a solution of the fluorinated building block and $ZnCl_2$ in THF; the temperature sensitive organolithium intermediates were immediately quenched with $ZnCl_2$. Given the similar, albeit low temperature, LDA preparation of difluoroenol stannanes, Burton's zincation methodology should be applicable to the trifluoroethanol derived building blocks.

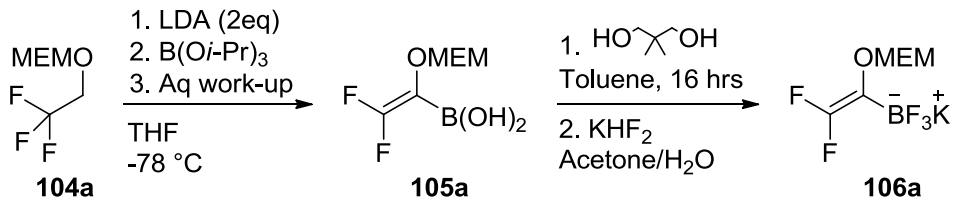


X = F, Cl

X	Y	t (h)	Yield (%)
F	H	3	69
F	4-NO_2	1	37
F	4-CF_3	1.5	66
F	4-OMe	1	82
Cl	H	1	77
Cl	3-NO_2	15	77
Cl	4-Me	12	83
Cl	3-OMe	3	79

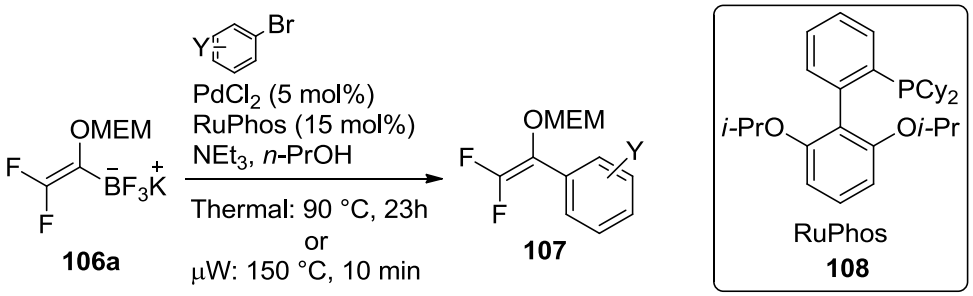
Table **12**: Coupling of vinylzinc species prepared at ambient temperature

Another attractive alternative to Stille coupling is the popular Suzuki coupling. Katz has shown that potassium difluorovinyltrifluoroborate **106a** can be prepared from trifluoroethanol in 50-60% yield (Scheme **15**).[110]



Scheme **15**: Katz preparation of potassium difluorovinyltrifluoroborate **106a**

Katz also demonstrated Suzuki coupling of **106a** with a range of aryl-bromides under regular thermal and microwave conditions using $PdCl_2$ and a bulky phosphine ligand (RuPhos) (Table **13**).



Y	Thermal yield (%)	μW Yield (%)
4-OMe	76	38
3-OMe	85	-[a]
2-OMe	86	83
4-CF_3	82	57
3-NO_2	0	-[a]

a) Coupling not attempted

Table **13**: Katz coupling of potassium trifluoroborate **106a**

1.6.3 Electrocyclisation and rearomatisation

Electrocyclisation reactions are pericyclic reactions that make or break a σ-bond in a ring opening or ring closing process. The reactions can be promoted thermally or photochemically and the outcomes follow strict stereochemical rules;[111] under thermal conditions, systems involving 4n electrons undergo conrotatory cyclisation while systems involving 4n+2 electrons undergo disrotatory cyclisation (Figure **10**). The opposite is true for photochemically promoted electrocyclisations.

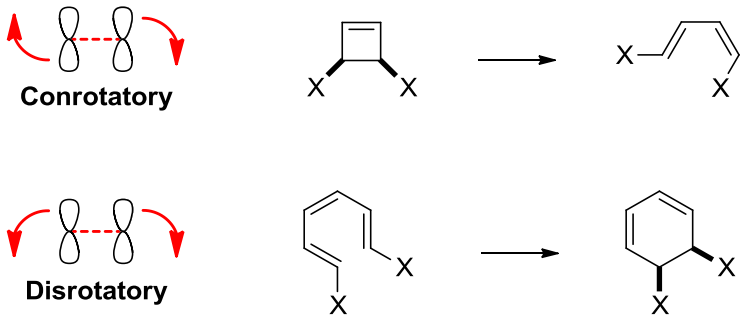
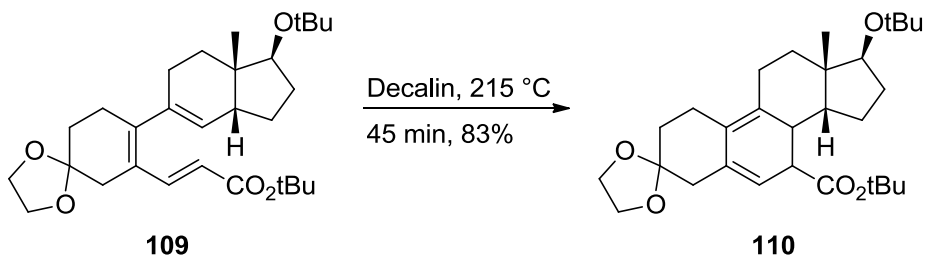


Figure **10**: Thermal electrocyclisation reactions

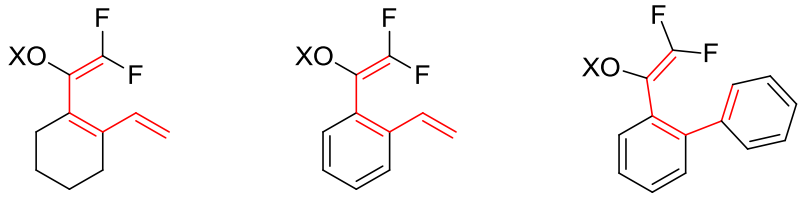
1,3,5-Hexatriene systems are usually associated with a significant activation barrier (see chapter 2; 2.2.4) with temperatures of up to ~200 °C commonly required for electrocyclisation to occur (Scheme **16**).[112]



109 **110**

Scheme **16**: 6π-electrocyclisation of **109** to afford steroid skeleton **110**

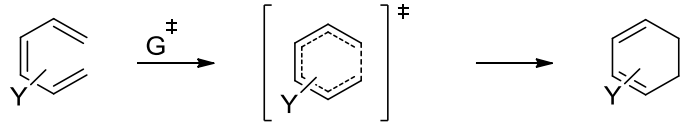
It is hard to predict the level of thermal activation required for electrocyclisation of the proposed 'trienes' in this work (Figure **11**); however, dearomatisation could impose significant activation barriers for systems such as **112** and **113**, leading to high reaction temperatures.



111 **112** **113**

Figure **11**: Hexatriene core of the proposed electrocyclisation precursors

Substitution of the hexatrienes can, in some cases, lower the activation barrier for cyclisation. A series of calculations carried out by Fu[113] revealed that some monosubstituted and in particular some disubstituted trienes had remarkably low activation energies (Table **14**).

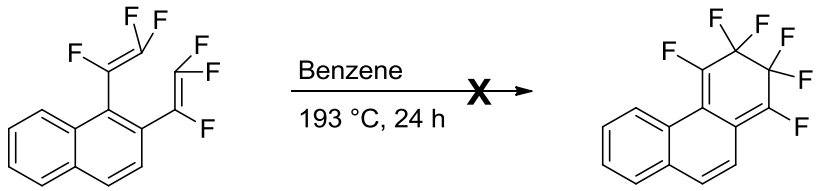


Entry	Y	T (K)	$\Delta G^{‡}$ (kcal/mol)[a]
1	H	298	30.7
2	1-F	298	28.3
3	1,6-F	298	28.2
4	1-F-2-OH	298	27.2
5	2-NO_2-5-NH_2	298	16.7

a) B3LYP/6-31G

Table **14**: Calculated free energy of activation of some substituted hexatrienes

Entries 2-4 suggest that terminal mono-fluorination may have a modest lowering effect on the activation barrier for electrocyclisation. The proposed precursors to the pericyclic step **111**, **112** and **113** all have two terminal fluorines and so may not follow the trend displayed in Table **14**. Indeed, Dolbier has attempted electrocyclisation of hexa-fluorinated precursors without success.[114]



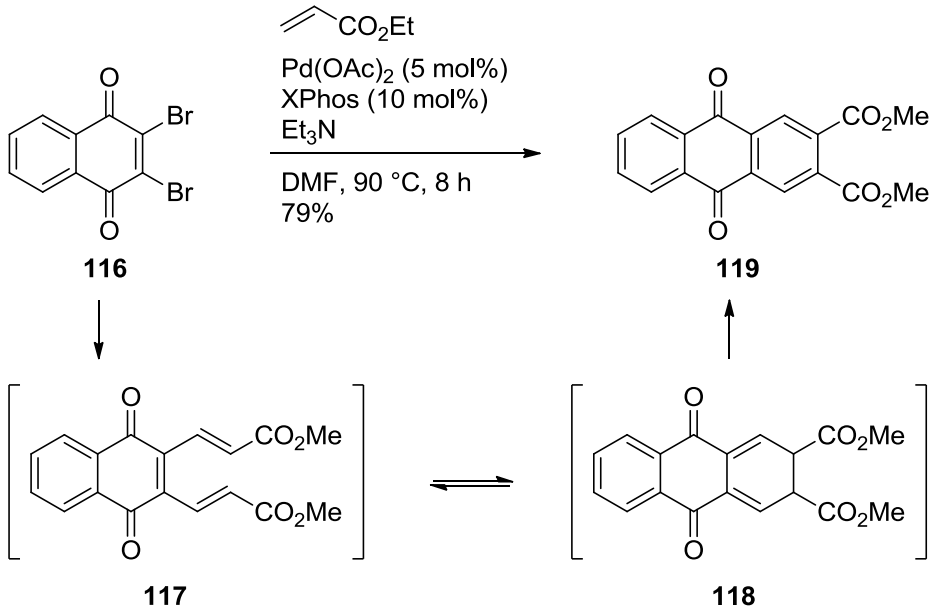
114 **115**

Scheme **17**: Unsuccessful electrocyclisation of hexa-fluorinated **114**

Dolbier suggested that steric repulsion between the terminal fluorines, resulting in destabilisation of the required boat transition state may be the reason for the failure of the cyclisation. Dolbier designed a clever experiment to probe this theory.[115] A tetra-fluorinated compound (terminal position) constrained to undergo Cope rearrangement through a boat transition state was much slower than one able to adopt a chair transition state (see chapter 2; 2.2.4). The proposed electrocyclisation precursors in this work have only two terminal fluorines, and on the same carbon, so similar destabilisation of the chair transition state experienced by Dolbier is not anticipiated.

An iterative coupling strategy towards 'trienes', similar to the proposed method in Figure **5** (C), and subsequent electrocyclisation has been demonstrated by Langer

(Scheme **18**).[116] A two-fold Heck coupling of dibromoquinone **116** with ethyl acrylate in DMF at 90 °C resulted in anthraquinone **119** after 8 h. The same methodology, but at higher temperature (120 °C) was applied to 2,3-dibromoindoles.[117] Langer could not apply the same approach to 2,3-dibromobenzofurans; solvent exchange to Ph_2O was required as a temperature of 200 °C was required for electrocyclisation.[118]



Scheme **18**: Langer's domino Heck coupling/electrocyclisation of naphthoquinone

In the case of the proposed electrocyclisation precursors, rearomatisation will occur with the concomitant release of HF. Care must be taken to trap this highly corrosive acid. KF can be used to trap HF as a potassium salt (KHF_2).

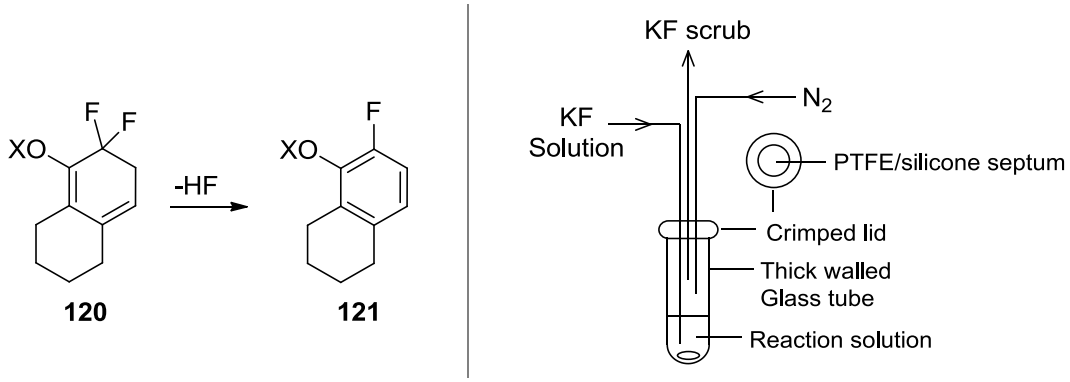


Figure **12**: Proposed trapping of HF released during rearomatisation

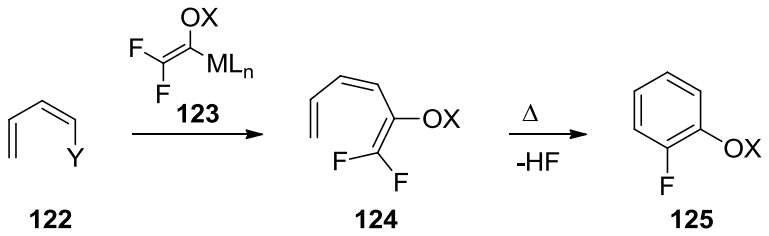
Addition of an aqueous solution of KF on reaction completion would trap any HF dissolved in the reaction medium. A dry KF scrub would also help trap any gaseous HF, with a positive pressure of N_2 forcing any acidic vapours from the reaction vessel headspace through the scrub.

The previous passages have described a proposed novel route for the synthesis of fluorarenes. The strong literature precedence for some of the key steps mean there is scope for some optimism that the proposed palladium-catalysed coupling/electrocyclisation methodology can be successful.

2 Research and Development

2.1 Palladium-Catalysed Coupling

Palladium-catalysed coupling of metallated difluoroenol species was envisaged as a key operation for realising the synthesis of novel fluoroarenes (Scheme **19**).

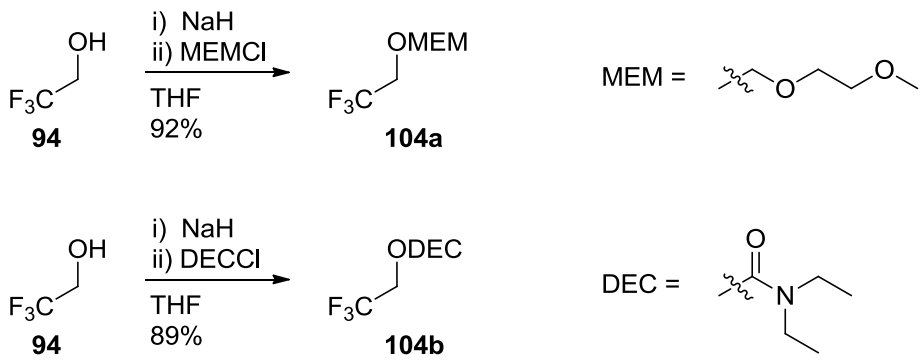


Scheme **19**: Proposed route to fluoroarenes

Investigation of this vital step was essential in order to fulfil the aim of generating fluoroarenes. It also represented an opportunity to improve upon already well-established difluoroenol coupling chemistry. One of the main issues to address was the identification of the most appropriate metal species to be used as the transmetallating reagent, and to try to avoid the cryogenic methods historically employed in their synthesis. With the appropriate difluoroenol coupling partners in hand, the scope of their palladium-catalysed coupling reactions was also assessed.

*2.1.1 Synthesis of trifluoroethanol-derived building blocks **104a** and **104b***

Acetal **104a** and carbamate **104b** were prepared in 0.63 mol and 0.74 mol scale respectively according to previously published procedures (Scheme **20**).[101,102]



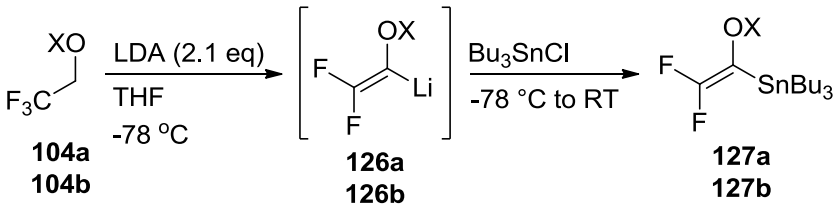
Scheme **20**: Generation of acetal and carbamate building blocks

Trifluoroethanol **94** was added dropwise to a stirring suspension of NaH (60% dispersion in mineral oil) in THF at 0 °C. After hydrogen evolution ceased, methoxyethoxymethyl chloride (MEMCl) or diethylcarbamoyl chloride (DECCl) was added dropwise and the thick suspension was stirred for 18 h. Aqueous work-up and careful distillation afforded acetal **104a** and carbamate **104b** as colourless liquids. These building blocks were stored under N_2 and refrigerated (~5 °C), and were stable for a number of years.

2.1.2 Preparation of Difluoroenol nucleophiles

*2.1.2.1 Stannanes **127a** and **127b***

Stannane **127a** was isolated in 91% yield on an 8 mmol scale using a method developed by Percy (Scheme **21**).[102] Dehydrofluorination/ lithiation of acetal **104a** was effected with dropwise addition of **104a** to a stirring solution of LDA (2.1 eq) in THF at -78 °C. The resulting lithiated species **126a** was quenched by the dropwise addition of tributyltin chloride. Flash chromatography afforded stannane **127a** as a colourless oil.



104a
104b

126a
126b

127a
127b

127a (91%): X = MEM
127b (75%): X = DEC

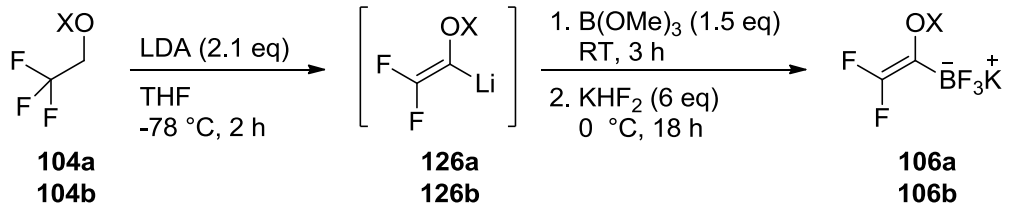
Scheme **21**: Low temperature generation of stannanes **127a** and **127b**

The same method was used to generate stannane **127b** in 75% yield on an 18 mmol scale.[101] These stable stannanes were stored under refrigeration (~ 5 °C) until required for cross coupling.

*2.1.2.2 Potassium trifluoroborates **106a** and **106b***

Potassium trifluoroborate **106a** has previously been synthesised by Katz and co-workers but required the isolation of a boronic ester intermediate.[110] An alternative telescoped procedure was sought to avoid the intermediary isolation in the Katz method.

Trifluoroborates **106a** and **106b** were generated on 0.12 mol and 0.06 mol scales respectively by using an adaptation of a procedure published by Genêt and co-workers (Scheme **22**).[96,97]



104a
104b

126a
126b

106a
106b

106a (55%): X = MEM
106b (47%): X = DEC

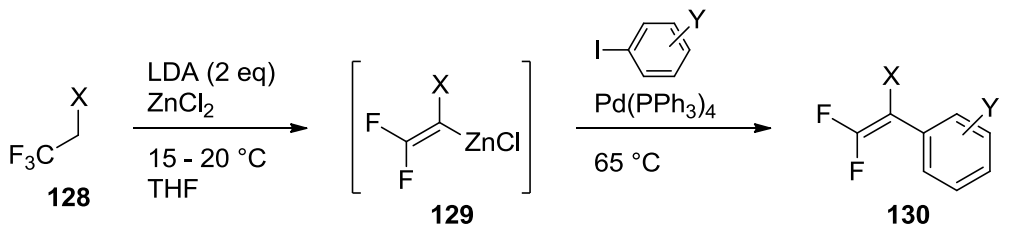
Scheme **22**: Low temperature generation of potassium tifluoroborates **106a** and **106b**

Generation of lithiated species **126a** and **126b** was accomplished as described previously. Trimethyl borate was added to the reaction mixture at -78 °C. After addition of trimethyl borate the reaction mixture was allowed to warm to room temperature and stirred for 3 h; it was then quenched with an aqueous solution of KHF_2 at 0 °C. The trifluoroborates were isolated by extraction into a methanol: acetone mixture (1:4). In the case of **106a**, concentration of the extract and addition of diethyl ether encouraged immediate crystalisation. The crude, concentrated extract of borate **106b** required cooling in the refrigerator for 18 h to bring about crystalisation. The resulting semi-solid was slurried with diethyl ether and the crystals were collected by filtration and dried. The process was repeated twice for the mother liquor to obtain the maximum yield of borate **106b**.

The trifluoroborates were stored at RT under ambient conditions and showed no signs of deterioration in quality after years of storage.

*2.1.2.3 Organozincs **131a** and **131b***

Burton and colleagues have established that a near-ambient zincation of fluorinated building blocks HFC-134a[108] and HFC-133a[109] is possible, using LDA as the base.



X = F, Cl

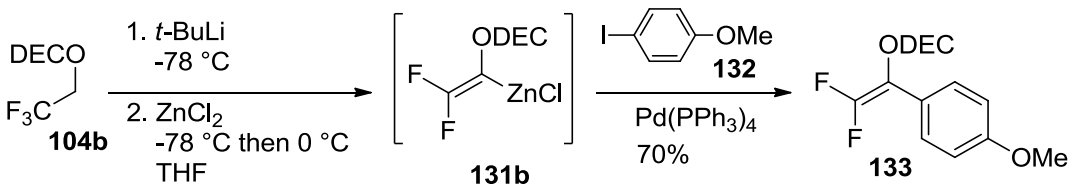
Scheme **23**: Burton's ambient temperature metallation and coupling chemistry

This chemistry lays the foundation for metallation of building blocks **104a** and **104b** at near ambient temperatures, traditionally carried out at low temperature (-78 °C).

*Low temperature zincation of **104b***

Before higher temperature metallation was attempted on building blocks **104a** and **104b**, the dehydrofluorination/metallation of carbamate **104b** was carried out with *t*-BuLi (2 equivalents) in THF at -78 °C. These conditions were chosen to allow the unambiguous (and amine-free) preparation of the organolithium reagent as demonstrated by Arany and co-workers.[119] A solution of freshly-fused zinc chloride (1.1 equivalents) in THF was added and the mixture was held at -78 °C for 2 hours, then allowed to warm to room temperature (RT, 15-18 °C). A palladium coupling assay was performed in order to ascertain if the organozinc species had been

formed. After 30 minutes at RT, the mixture was cannulated onto a mixture of 4-iodoanisole **132** (1.1 equivalents) and *tetrakis*(triphenylphosphino)palladium(0) (5 mol%) [$Pd(PPh_3)_4$], and heated at 65 °C for 16 hours. After work-up and purification, styrene **133** was obtained as the sole fluorinated product in *ca.* 70% yield (Scheme **24**). This result demonstrated that **131b** was both stable at room temperature and available for coupling under palladium-catalysed conditions at higher temperatures.



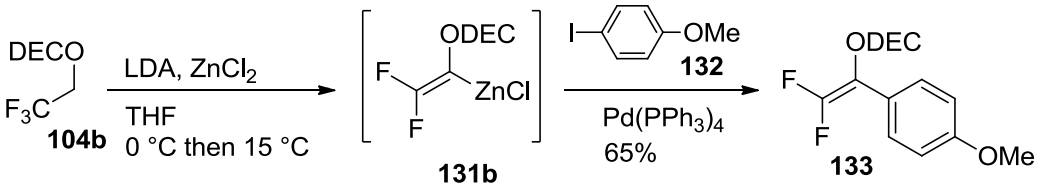
Scheme **24**: Low temperature generation and initial coupling of carbamate **131b**

*Near-ambient zincation of **104b***

A series of simultaneous step changes were then implemented by replacing the alkyllithium base with LDA, raising the dehydrofluorination/metallation reaction temperature to 0 °C and having the zinc(II) salt present from the beginning of the sequence, as described by Burton.[108,120] Although Burton's precedent of near ambient zincation of HFC-134a and subsequent palladium catalysed coupling was a very strong one, the effect of strongly coordinating groups within the alkenylmetal was difficult to predict. Freshly-prepared LDA (2.5 equivalents) was added to a mixture of **104b** and freshly-fused zinc chloride in THF at 0 °C. A yellow solution formed immediately and this colour persisted after a further hour at room

temperature (15-18 °C). After this time had elapsed, a small amount of white precipitate was apparent. This may be lithium fluoride due to the relative insolubility of fluoride salts in organic solvents.[121] No difference in yield was detected when **131b** was used either as a fully homogeneous solution or as a suspension.

Reagent **131b** was cannulated onto a mixture of **132** (1.1 equivalents) and $Pd(PPh_3)_4$ (5 mol%) and heated at 65 °C overnight. Once again, **133** was isolated in good (65%) yield from **104b** (Scheme **25**).



Scheme **25**: Near ambient temperature generation and subsequent coupling of **131b**

The use of excess LDA is worthy of comment. Although it is hard to understand the necessity for a 0.5 eq excess of the amide base, it is clear that it is tolerated by the sensitive difluoroalkene generated by the reaction. An excess of nucleophilic *t*-BuLi would result in an addition/elimination reaction[122-124] and was observed experimentally when chlorotrimethylsilane was used as an electrophile after dehydrofluorination/lithiation of carbamate **104b** with various equivalents of *t*-BuLi (Figure **13**). The generation of **136** and **137** in the presence of 1.9 and 2.0 equivalents of *t*-BuLi could be a result of inaccurate titration of the organolithium base.

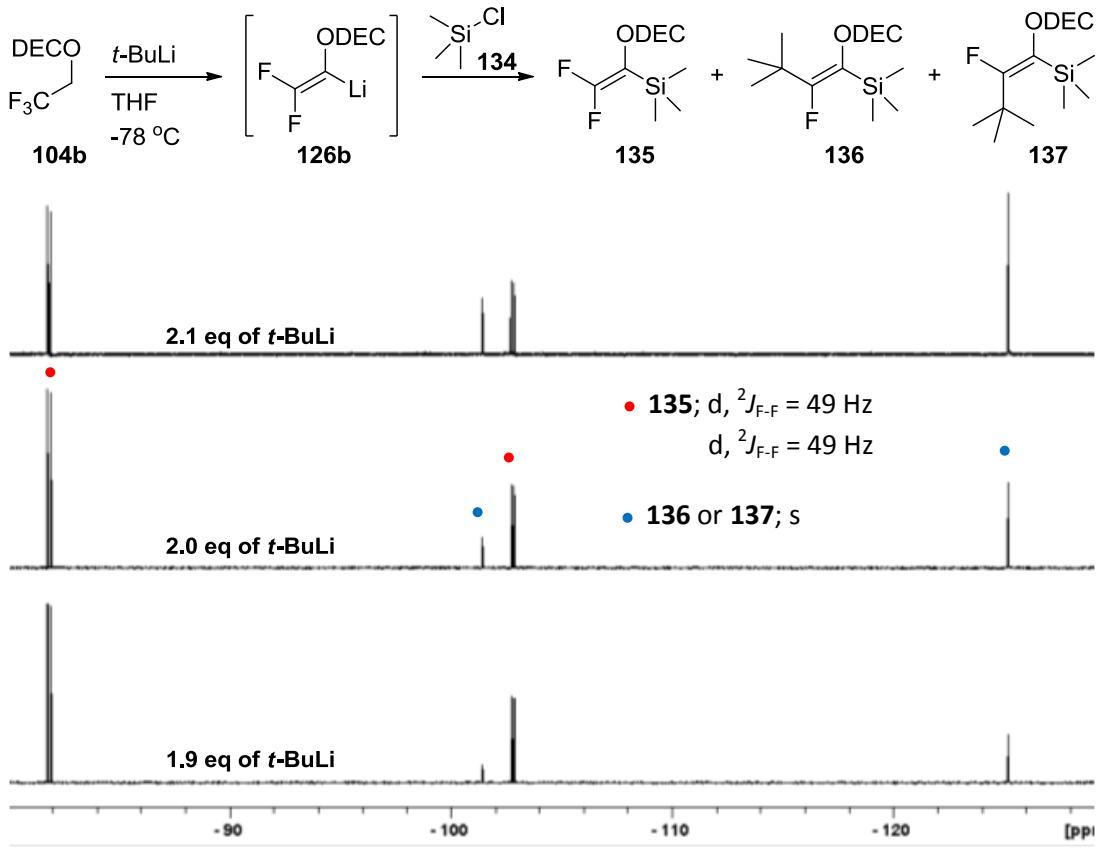
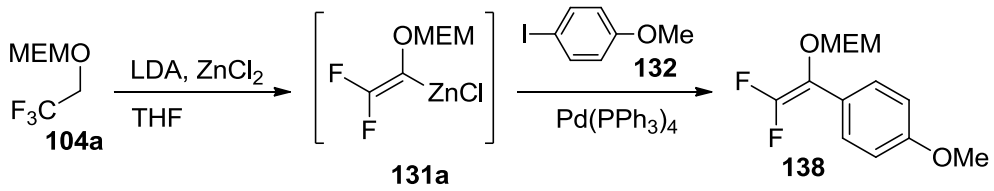


Figure **13**: Crude ^{19}F NMR highlighting addition/ elimination reaction

The near-ambient zincation conditions detailed above for carbamate **104b** were applied to acetal **104a** but the MEM protecting group is cleaved by Zn(II) salts[125] and so reagent and product stability was uncertain.

*Optimisation of near-ambient zincation of **104a***

Low conversions of **104a** were observed under the conditions used for **104b** (as indicated by the ^{19}F NMR spectrum of the crude coupling reaction mixtures [Figure **14**]). Table **15** summarises initial investigations of the reaction of acetal **104a**.



Entry	LDA (eq.)	Zn salt (eq.)	Time at 0 °C (hrs)	Time at 15-18 °C (hrs)	Conversion[a] (%)	Yield[b] (%)
1	2.0	1.0	1	1	27	-
2	2.5	1.1	1	2.5	65	-
3	2.5	1.1	1	4	67	-
4	3.0	1.1	1	4	93	34
5	2.5	1.1	0	4	88	-
6	2.5	1.1[c]	1	3	81	47
7[d]	2.5	1.1	1	1	95	60

[a]Calculated by integration of the ^{19}F NMR spectrum (Pr/SM + Pr); [b]Isolated yield of **138** after chromatography; [c]$ZnCl_2$.TMEDA complex was used; [d]The solvent was 12% v/v DMPU/THF.

Table **15**: Optimisation of near-ambient zincation/coupling of **104a**

Entries 1 and 2 indicate clearly that **104a** and **104b** undergo dehydrofluorination/ metallation at different rates; only a moderate conversion of **104a** was observed after 3.5 hours. There was little to be gained from increasing the reaction time further (entry 3). The use of 3 equivalents of LDA (entry 4), delivered a disappointing yield of product after isolation (34%) despite high conversion (93%); product decomposition was revealed by a low signal-to-noise ratio in the ^{19}F NMR spectrum. Similar results were observed when LDA was added at room temperature (entry 5). We noted that the reaction was slightly exothermic at room temperature; decomposition may be the consequence of failure to control it. The non-

hygroscopic $ZnCl_2$.TMEDA complex synthesised using the protocol of Isobe[126] was investigated as a zinc(II) source (entry 6). The complex was less soluble in THF than the free salt; conversions were comparable to those obtained with zinc chloride, but no better, so there seemed no benefit in an additional preparative step.

As it is known that the DEC group ranks more highly than the methoxymethyl (MOM) group in the DoM hierarchy,[127,128] it was postulated that the carbamate group may be de-aggregating the LDA and increasing the rate of lithiation. *N*,*N*-Dimethylpropylene urea (DMPU) (12% v/v) was added to mimic the carbamate moiety of **104b** and to increase the reactivity of the metal amide base (entry 7).[129-131] The presence of the co-solvent resulted in full conversion of **104a**, a higher isolated yield and a reduced reaction time. A range of co-solvent concentrations (12–65% v/v) were screened; however, it was observed that DMPU concentrations above 12% v/v yielded similar conversions and isolated yields.

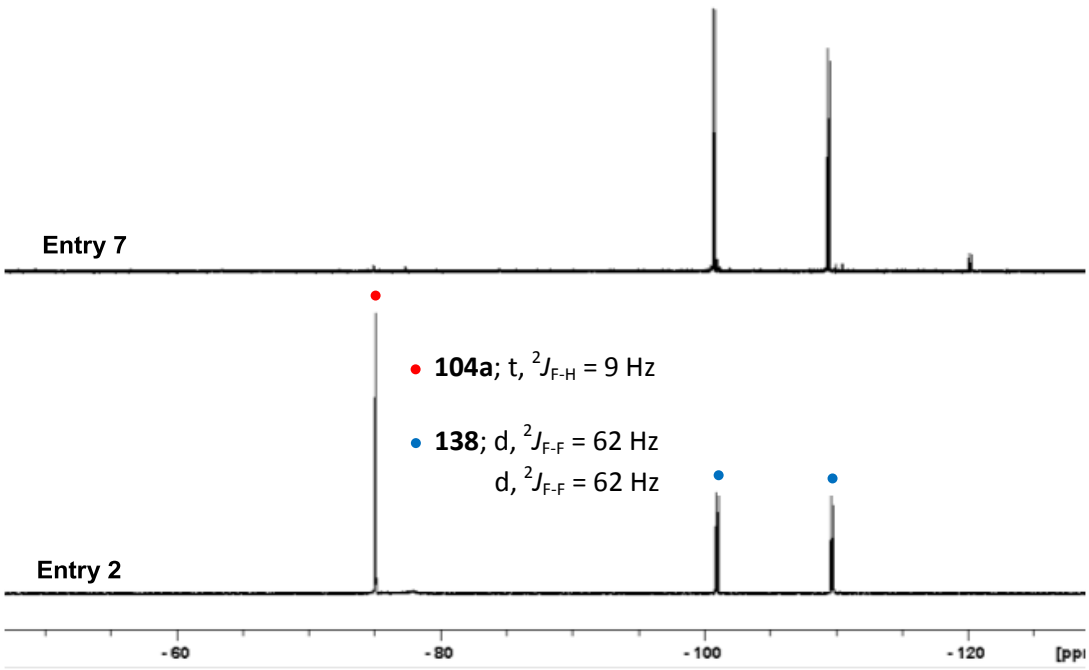


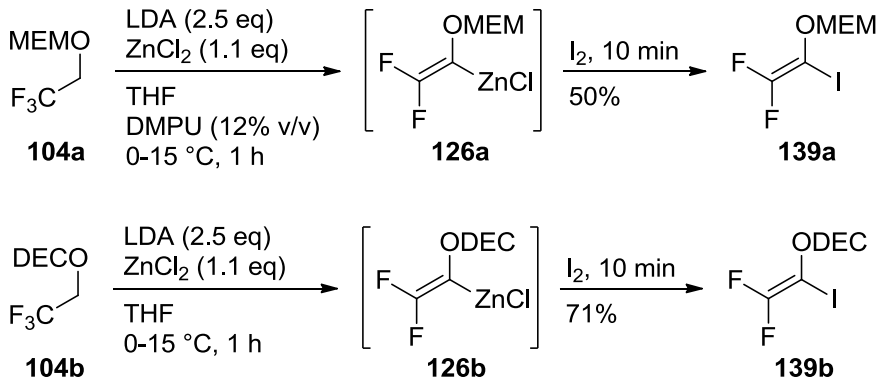
Figure **14**: Crude ^{19}F NMR spectra of selected zincations of **104a**

This much improved procedure was adopted as the standard protocol for generating organozinc species **131a**.

2.1.3 Preparation of difluoroenol electrophiles

*2.1.3.1 Iodides **139a** and **139b***

Generation of iodo(difluoroenol) derivatives **139a** and **139b** was achieved by applying the near ambient zincation conditions, described earlier, to a known literature procedure.[101]



Scheme **26**: Synthesis of iodo(difluoroenol) species **139a** and **139b**

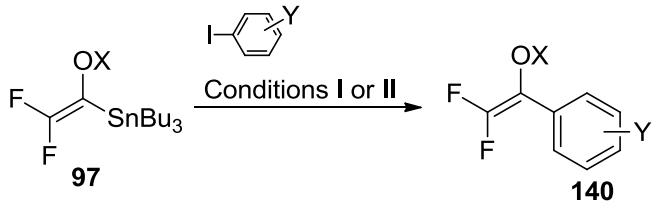
In the case of **139b**, 2.5 equivalents of LDA was added dropwise to a solution of **104b** and $ZnCl_2$ in THF at 0 °C to afford zinc species **131b**. A solution of I_2 in THF was then added via syringe to quench the zinc species; after work-up, the crude iodide was purified by filtration through a plug of silica followed by Kugelrohr distillation, to afford iodide **139b** in 71% yield (0.01 mol scale).

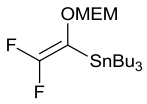
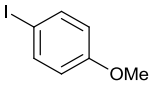
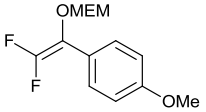
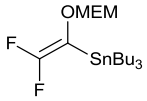
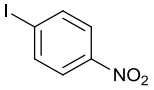
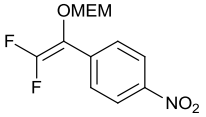
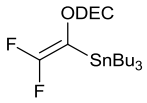
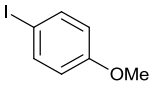
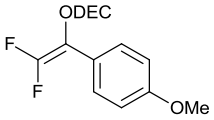
The preparation of iodide **139a** was less efficient, with 50% the highest yield obtained. The same procedure (on a 0.02 mol scale) was followed, but a short contact time between the zinc reagent and iodine was essential for this yield; times of 1 hour and longer significantly reduced the yield of iodide **139a** (*ca*. 25%). Addition of DMPU co-solvent was necessary for an acceptable yield of **139a**; the urea co-solvent ensured full conversion of **104a** to the organozinc intermediate as described previously. Both iodides were found to be stable after purification and could be stored under N_2 in the refrigerator (~5 °C) without decomposition (3 months). Discoloration of the materials was observed when they were stored at room temperature with iodide **139a** being much less stable.

2.1.4 Palladium-catalysed coupling of difluoroenol nucleophiles

*2.1.4.1 Stille coupling of stannanes **127a** and **127b***

Stille coupling of stannanes **127a**[105] and **127b**[104] is already well established with high yields and a broad substrate scope; however, these couplings provided an opportunity to learn the practical aspects of palladium coupling chemistry and test the reproducibility and further scope of the methodology.



Entry	Stannane	Iodide	Conditions	Product (Yield)
1	 **127a**	 **132**	I	 **138** (51%)
2	 **127a**	 **141**	I	 **142** (90%)
3	 **127b**	 **132**	II	 **133** (83%)

I: $Pd(OAc)_2$ (3 mol%), iodide (1.05 eq), PPh_3 (10 mol%), CuI (20 mol%), DMF, 50 °C, 18 h; **II**: Pd_2dba_3 (5 mol%), iodide (1.05 eq), PPh_3 (20 mol%), CuI (10 mol%), DMF, 50 °C, 18 h.

Table **16**: Stille coupling of stannanes **127a** and **127b**

Styrenes **138**, **142** and **133** were generated in moderate to good yield from stannanes **127a** and **127b**. In a typical procedure a mixture of **127a**, iodide **141** (1.1 eq), PPh_3 (10 mol%) and CuI (20 mol%) were taken up in DMF and stirred at 50 °C for 16 h (entry 1). Work-up with a methanolic solution of KF removed most of the toxic organotin by-product Bu_3SnI as solid Bu_3SnF which was filtered off.[132] The remaining tin by-product was removed by flash chromatography to afford styrene **142** in 90% yield. Although stannanes **127a** and **127b** participate in Stille coupling under mild conditions and with a broad scope of electrophiles, toxic tin reagents

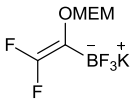
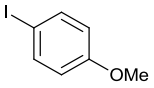
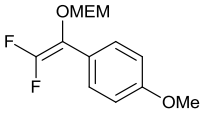
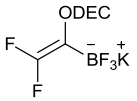
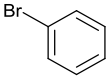
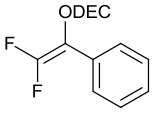
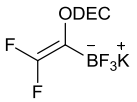
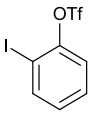
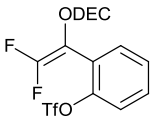
and difficulty of purification and poor atom efficiency are disadvantages that usually persuade chemists to find alternatives to Sn-based nucleophiles.

*2.1.4.2 Suzuki coupling of potassium trifluoroborates **106a** and **106b***

Advantages of Suzuki coupling include functional group tolerance, high atom efficiency with a non-toxic waste stream, and the use of isolable boron coupling reagents that are generally stable to purification and storage.

Trifluoroborates **106a** and **106b** represent extremely stable masked boronic acids that are able to participate in Suzuki coupling with arylhalides (Table **17**). Katz and co-workers have developed conditions for coupling **106a** with a range of aryl bromides.[110] They used RuPhos, a bulky phosphine ligand, to obtain the best yields. Entry 1 demonstrates that these borates can be coupled in the absence of expensive ligands in a slightly lower yield (53% vs 78%).

Styrenes **144** and **146** were generated using an optimised procedure developed when coupling iododifluoroenols **139a** and **139b** (*vide infra*). Interestingly for entry 3, ^{19}F NMR analysis of the crude reaction mixture showed styrene **146** was synthesised with no bis-coupled product or 2-iodostyrene. This suggests that oxidative addition involving the C-I bond is significantly faster than that in the C-OTf bond as would be expected[133] in the absence of bulky phosphine ligands.[86,134]

Entry	Borate	Halide	Conditions	Product (Yield)
1	 **106a**	 **132**	**I**	 **138** (53%)
2	 **106b**	 **143**	**II**	 **144** (54%)
3	 **106b**	 **145**	**II**	 **146** (64%)

I: $Pd(dba)_2$ (5 mol%), Halide (0.9 eq) NEt_3 (3 eq), *n*-PrOH, 90 °C, 18 h; **II**: $(PPh_3)PdCl_2$ (2 mol%), Halide (1 eq), Cs_2CO_3 (3 eq), t-BuOH, 90 °C, 4 h

Table **17**: Suzuki coupling of potassium trifluoroborates **106a** and **106b**

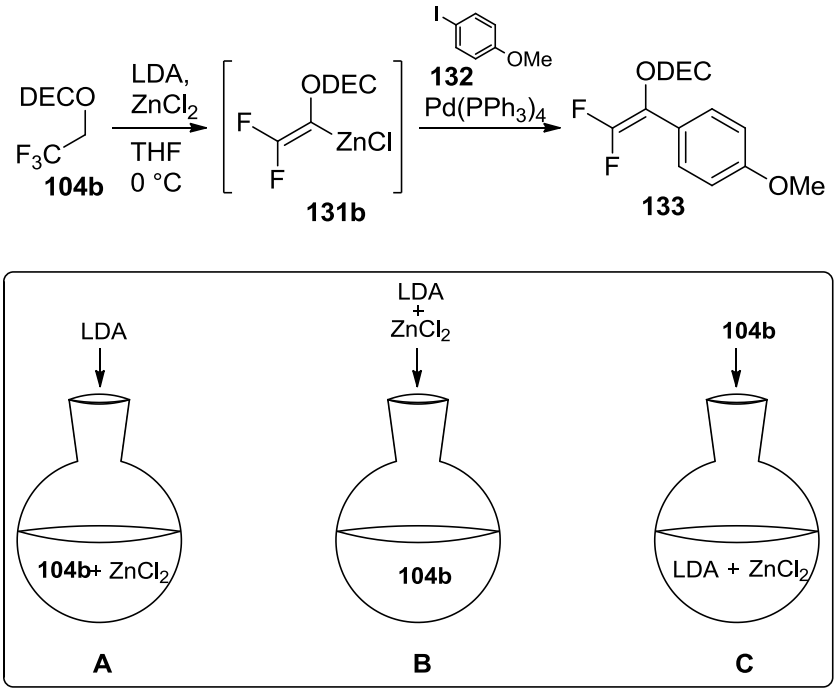
There has been a significant amount of work developing coupling conditions for borate **106a,**[110] and for stannanes **127a**[105] and **127b**[104]. Further work on palladium catalysed coupling of difluoroenol species was therefore focused on the less well developed organozinc (**131a** and **131b**) and iodide (**139a** and **139b**) species.

*2.1.4.3 Negishi coupling of difluoroenolzinc species **131a** and **131b***

Optimisation of the Negishi coupling of **131a** and **131b** was necessary before the scope of the reaction was determined. The protocol was improved immediately by observing that a catalyst loading of 2 mol% was as effective as a 5 mol% loading. Subsequent couplings were performed with the lower loading.

Investigation of order of addition

The order of the addition of the reactants was investigated briefly. Addition of a THF solution of $ZnCl_2$ (1.1 equivalents) and LDA (2.5 equivalents) to a solution of carbamate **104b** (method **B**), followed by coupling with **132** (1.1 equivalents) and $Pd(PPh_3)_4$ (2 mol%) resulted in the same (65%) isolated yield as the earlier procedure (method **A**).

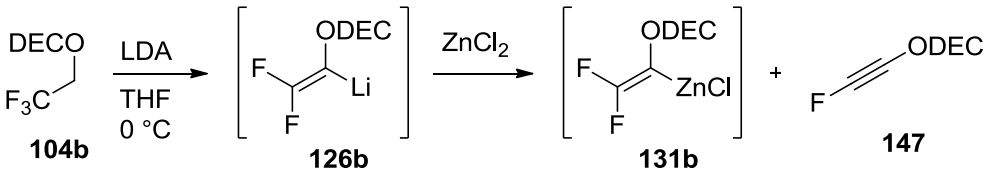


Scheme **27**: Depiction of the order of addition of reagents

Altering the interval between mixing the $ZnCl_2$ solution with LDA and its addition to the carbamate had little effect on the isolated yield of the coupling reaction; yields were similar after 5 minutes (45%), 60 minutes (51%) and 120 minutes (39%). As these are isolated yields after chromatography, it is unlikely that the differences between them are significant (manual deconvolution of column fractions can easily

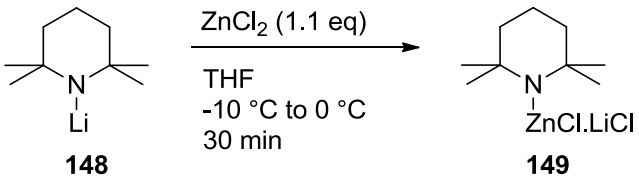
lead to yield variations of this size). A lower (26%) yield of **133** was obtained when **104b** was added dropwise to a solution of LDA (2.5 equivalents) and $ZnCl_2$ (1.1 equivalents) in THF (method **C**), so the order of addition does appear to have an effect.

If LDA is the active base then organolithium **126b** must be zincated extremely rapidly or elimination of lithium fluoride to form acetylene **147** would occur competitively resulting in a decreased yield (Scheme **28**). Such eliminations to form acetylenes has previously been described by Normant.[135,136] The order of addition employed in method **A** (Scheme **27**) would therefore help to ensure rapid zincation by keeping the concentration of lithium amide low with respect to $ZnCl_2$.



Scheme **28**: Proposed competitive elimination under slow zincation conditions

Alternatively, LDA and $ZnCl_2$ may react instantaneously to form an active mixed metal species. Knochel and co-workers reported that TMPZnCl·LiCl was formed within 30 minutes when a solution of $ZnCl_2$ in THF was added to a solution of LTMP in THF at -10 °C (Scheme **29**)[137], but the reaction would have to be much faster than that in our system.



148 **149**

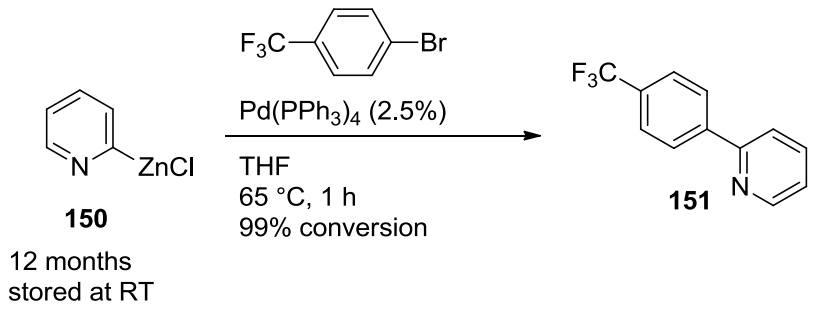
Scheme **29**: Knochel generation of TMPZnCl·LiCl **149**

The yield was also lower when the substrate was added to the LDA/ $ZnCl_2$ mixture (method **C**), conditions under which an active mixed metal species would have time to form fully. Although not fully understood, it is clear that subjecting carbamate **104b** to a high concentration of LDA at these elevated temperatures is detrimental to the yield of the overall reaction.

Method **A** (the addition of LDA to a solution of **104b** and $ZnCl_2$ in THF) was retained as the standard protocol as it was the most straightforward, due to a lower number of reagent transfers.

Stability of difluoroenolzinc species

Coupling reactions were usually performed by preparing a batch of the difluoroenolzinc reagents **131a** or **131b** and transferring the appropriate quantity by syringe to reaction tubes containing a palladium catalyst and the appropriate coupling partner. Organozinc reagents are sometimes avoided because of their sensitivity to moisture and are usually formed *in situ* for immediate consumption; however, Lietner and co-workers discovered that a solution of 2-pyridylzinc bromide could be stored for more than 12 months at room temperature without any significant decomposition (scheme **30**).[138]



Scheme **30**: Stability of 2-pyridylzinc chloride

A solution of reagent **131b** was stored in the refrigerator for 7 days prior to Negishi coupling with **132** using the standard conditions. A 65% yield of styrene **133** was obtained from a coupling carried out at the end of that period, revealing that **131b** is relatively stable in solution, and certainly amenable to batch preparation.

Overcoming an unexpected side reaction

During the course of this investigation it was discovered that the reactions could be carried out smoothly using commercial LDA as a solution in THF/ heptane/ ethylbenzene. This simplified the protocol still further; it became necessary as prominent side products were observed in some cases. GC-MS data from the crude reaction mixtures suggested that an addition/elimination reaction with lithium *n*-butoxide was occurring. Similar side products were also observed by Burton when coupling trifluorovinylzinc species with 4-fluorobenzene iodide.[108] An experiment was devised to ascertain if the *n*-butoxide was introduced from the commercial *n*-BuLi during LDA formation (Figure **15**). *n*-BuLi (0.5 eq) was added to a solution of purified styrene **152** in THF at -78 °C and the reaction stirred for 30 minutes. The solution was then allowed to warm to -30 °C, re-cooled to -78 °C and

stirred for a further 30 minutes. A sample was removed after this time, quenched with water and the organic products were extracted into $CDCl_3$ for analysis by ^{19}F NMR.

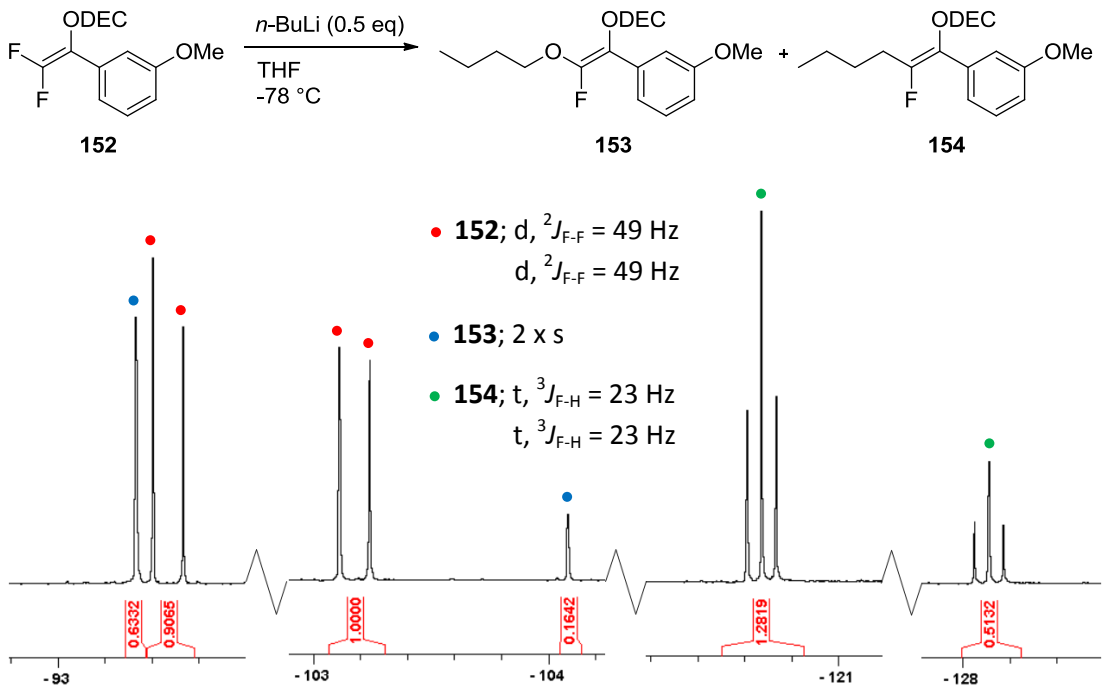


Figure **15**: Identification of butoxide side products using ^{19}F NMR

The ^{19}F NMR spectrum of the reaction mixture revealed some unreacted starting material (2 x d; $^2J_{F\text{-}F}$ 49 Hz) and addition/elimination products (major and minor isomers) from butyllithium (t, $^3J_{F\text{-}H}$ 23 Hz) and lithium butoxide (2 x s) nucleophiles. The butoxide side product was isolated by chromatography (30% diethyl ether in hexane) and the ^1H NMR spectrum obtained (Figure **16**) was consistent with the proposed structure. These results confirmed the presence of a significant amount of lithium butoxide in the commercial source of *n*-BuLi for LDA formation and due care was taken to avoid the use of such contaminated products.

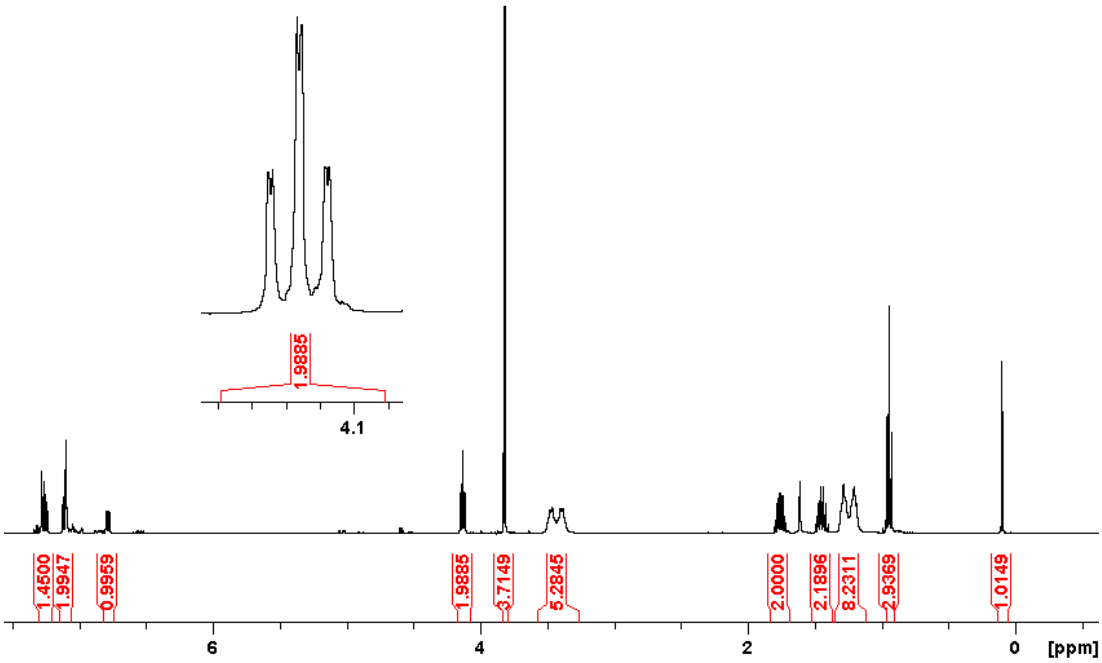
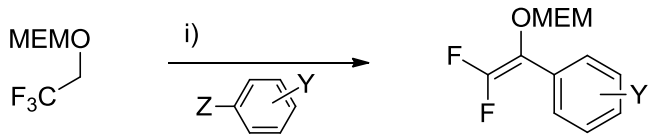


Figure **16**: ^{1}H NMR of purified butoxide side product **153**

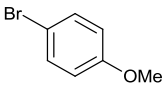
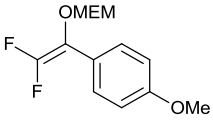
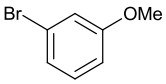
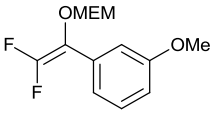
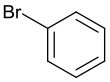
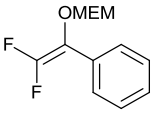
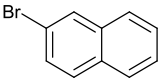
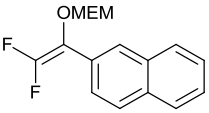
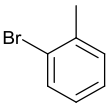
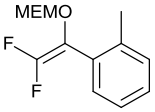
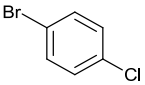
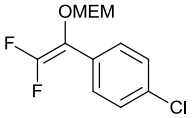
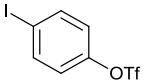
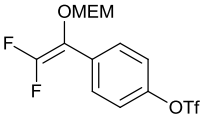
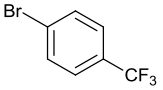
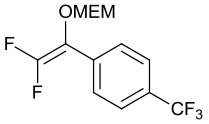
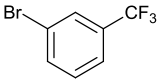
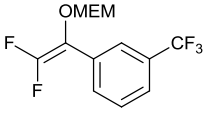
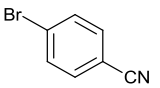
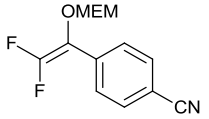
*Scope of Negishi coupling of difluoroenolzinc species **131a** and **131b***

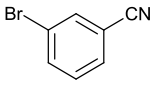
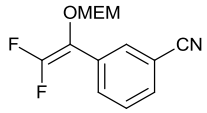
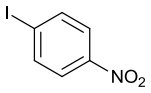
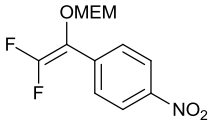
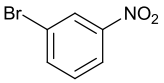
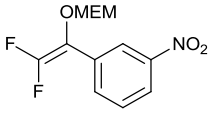
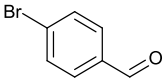
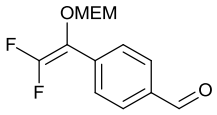
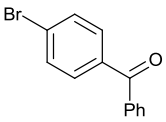
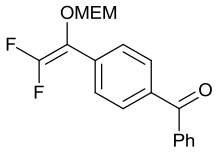
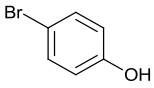
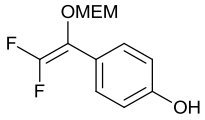
With high conversion conditions in hand for both **131a** and **131b**, the scope of the Negishi coupling could be explored with a palette of aryl bromides and iodides. Table **18** summarises the results for acetal **131a**.



104a

i) LDA (2.5 eq.), $ZnCl_2$ (1.1 eq.), 12% v/v DMPU/THF, 0 °C (1 hour) then 15 °C (1 hour); then aryl halide, $Pd(PPh_3)_4$, 65 °C.

Entry	Halide		Time (h)	Product (yield)	
1	**155**		16		**138** (60%)
2	**156**		16		**169** (73%)
3	**143**		16		**170** (53%)
4	**157**		16		**171** (48%)
5	**158**		16		**172** (40%)
6	**159**		16		**173** (54%)
7[a]	**160**		0.5		**174** (25%)
8[a]	**161**		16		**175** (41%)
9	**162**		0.5		**176** (20%)
10	**163**		0.5		**177** (25%)

11[a]	**164**		0.5		**178** (33%)
12[a]	**141**		16		**142** (41%)
13[a]	**165**		0.5		**179** (31%)
14	**166**		16		**180** (0%)
15	**167**		16		**181** (0%)
16[a]	**168**		16		**182** (0%)

[a]Commercial LDA was used

Table **18**: Scope and limitations of the Negishi coupling protocol with acetal **131a**

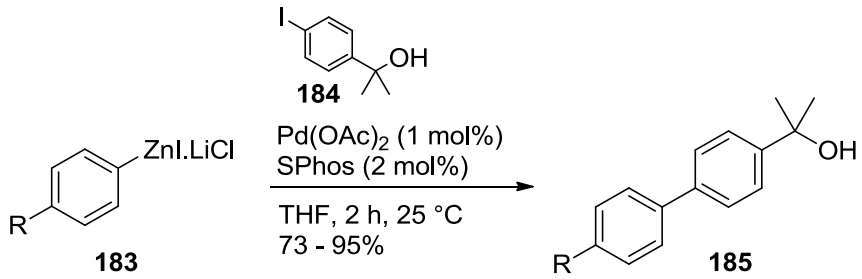
The MEM species **131a** coupled well with π-electron rich and neutral aryl halides (entries 1 - 7). The highest yielding couplings were carried out with 3-(methoxy) (**156**) and 4-(methoxy)bromobenzene (**155**). This suggests that oxidative addition is not the rate-determining step for these Negishi coupling reactions; electron deficient aryl halides would then be expected to undergo faster oxidative addition and perhaps produce higher yields of coupled product.

Steric bulk is also tolerated in the Negishi coupling of MEM vinylzinc **131a** as demonstrated by coupling with 2-bromotoluene (**158**) in 40% yield.

A modest scale-up of the Negishi coupling of **131a** was demonstrated using 1-bromo-4-chlorobenzene **159**. A 54% yield was obtained when coupling 1 mmol of aryl halide **159**. Scaling the reaction to 10 mmol produced a yield of 38%.

Aryl halides containing electron withdrawing groups generally coupled less efficiently (entries 8 - 16) and some required a reduced reaction time to optimise the coupling yields (*vide infra*). Negishi coupling of acyl containing halides 4-bromobenzaldehyde **166** and 4-bromoacetophenone **167** afforded peculiar results. No signals consistent with products **180** or **181** were observed in the ^{19}F NMR spectra of a sample removed from the reaction mixtures. On addition of the aryl halides to a stirring solution of vinylzinc **131a** in THF, an intense blue colour developed almost immediately. This colour dissipated to a dark brown/black colour over 18 h. Investigation of these interesting results was not pursued due to time constraints.

It is clear from entry 16 that acidic protons are not tolerated by this Negishi coupling protocol. ^{19}F NMR of the reaction mixture confirmed that protonated species **205a** was the only product of the reaction. Although there was concern that the vinylzinc reagents **131a** and **131b** would be too basic to tolerate acidic protons, there is literature precedent for Negishi coupling of phenol species. Knochel demonstrated that phenylzinc halides could, with slow addition, be coupled to aryl halides bearing a benzylic alcohol in good yield (Scheme **31**).[139]



R = H, Cn, CO_2Me

Scheme **31**: Negishi coupling of iodobenzyl alcohol **184**

Knochel also demonstrated the difference in rate of protonation between organozinc species (Table **19**).[140] Addition of *i*-PrOH to a solution of the organozinc species at -10 °C revealed their relative basicities; phenylzinc > alkylzinc > benzylzinc.

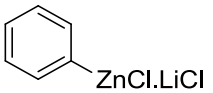
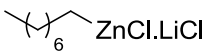
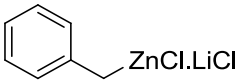
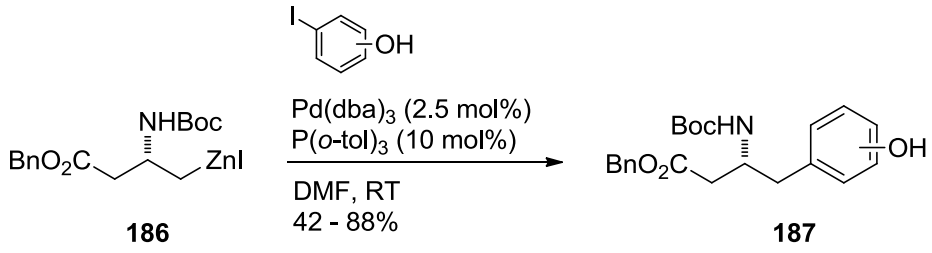
i-PrOH added (eq)	Yield of active zinc reagent (%)		
			
0	100	100	100
1	20	80	>97
2	<3	10	85

Table **19**: Rate of protonation of organozinc species

Jackson demonstrated that alkylzinc species **186** could be coupled with halides bearing a phenolic proton (Scheme **32**).[141]

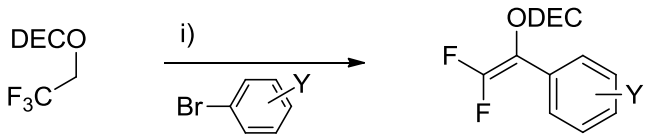


186 **187**

Scheme **32**: Negishi coupling of aryl halides bearing a phenolic proton

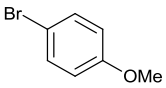
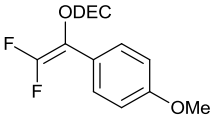
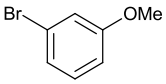
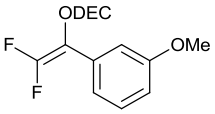
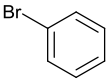
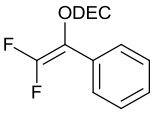
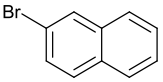
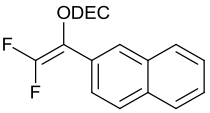
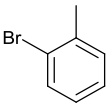
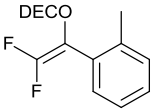
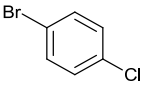
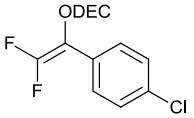
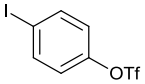
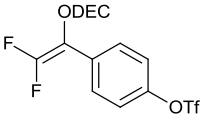
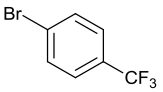
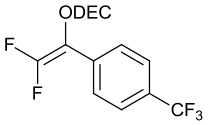
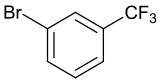
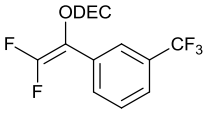
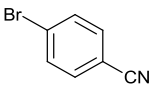
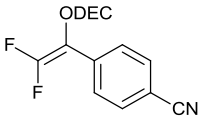
The results of Knochel and Jackson demonstrate that alkylzinc halides are unexpectedly tolerant of acidic protons. The sp^2 hybridised organozinc **131a** would be expected to be of similar reactivity to phenylzinc species, and so the faster rate of protonation of these species demonstrated by Knochel and co-workers would explain its intolerance of phenols.

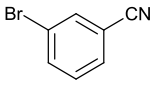
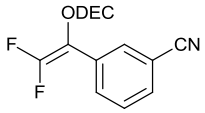
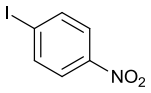
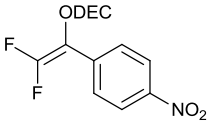
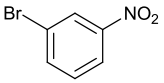
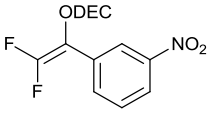
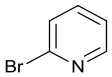
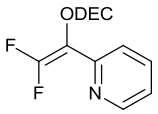
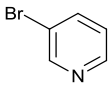
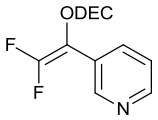
Next, the scope and limitations of Negishi coupling of carbamate **131b** were determined. The results are displayed in Table **20**. As for the coupling of **131a**, the DEC analogue **131b** coupled in better yields with π-electron rich and neutral aryl halides (entries 1 - 7) than with π-electron deficient coupling partners (entries 8 - 15). Investigations into optimising the reactions with electron deficient aryl halides initially focused on 1-iodo-4-nitrobenzene **141**; the lowest coupling yields of Burton's vinylzinc reagents were obtained using this aryl halide.[108,120] The ^{19}F NMR spectrum of the crude reaction mixture from a coupling of halide **141** with vinylzinc **131b** using the standard procedure (16 hours at 65 °C) revealed an array of signals, and styrene **198** was isolated in low yield (13%).



104b

i) LDA (2.5 eq.), $ZnCl_2$ (1.1 eq.), THF, 0 °C (1 hour) then 15 °C (1 hour); then aryl halide, $Pd(PPh_3)_4$, 65 °C.

Entry	Halide		Time (h)	Product (yield)	
1	**155**		16		**133** (65%)
2	**156**		16		**152** (63%)
3	**143**		16		**144** (65%)
4	**157**		16		**190** (57%)
5	**158**		16		**191** (0%)
6	**159**		16		**192** (51%)
7[a]	**160**		0.5		**193** (60%)
8[a]	**161**		16		**194** (53%)
9	**162**		16		**195** (37%)
10	**163**		16		**196** (36%)

11[a]	**164**		16		**197** (29%)
12[a]	**141**		0.25		**198** (42%)
13	**165**		16		**199** (18%)
14	**188**		3		**200** (0%)
15	**189**		3		**201** (0%)

[a]Commercial LDA was used

Table 20: Scope and limitations of the Negishi coupling protocol with carbamate vinylzinc **131b**

A short ^{19}F NMR study to derive a crude reaction profile was undertaken to determine if the low yield was a result of possible side reactions emerging from the catalytic cycle, or from degradation of styrene **198** once it was formed. The reaction was undertaken as normal and an aliquot was removed every 15 minutes for 1 hour. These aliquots were exposed to a crude work-up, then ^{19}F NMR and GC-MS analysis was performed. Not all of the species could be identified after the coupling of halide **141** but unreacted starting materials **104b** and **141**, iodide **139b** and HF addition product **202** were confirmed to be present (Figure **17**). After 15 minutes a significant quantity of styrene **198** was produced along with small amounts of side products.

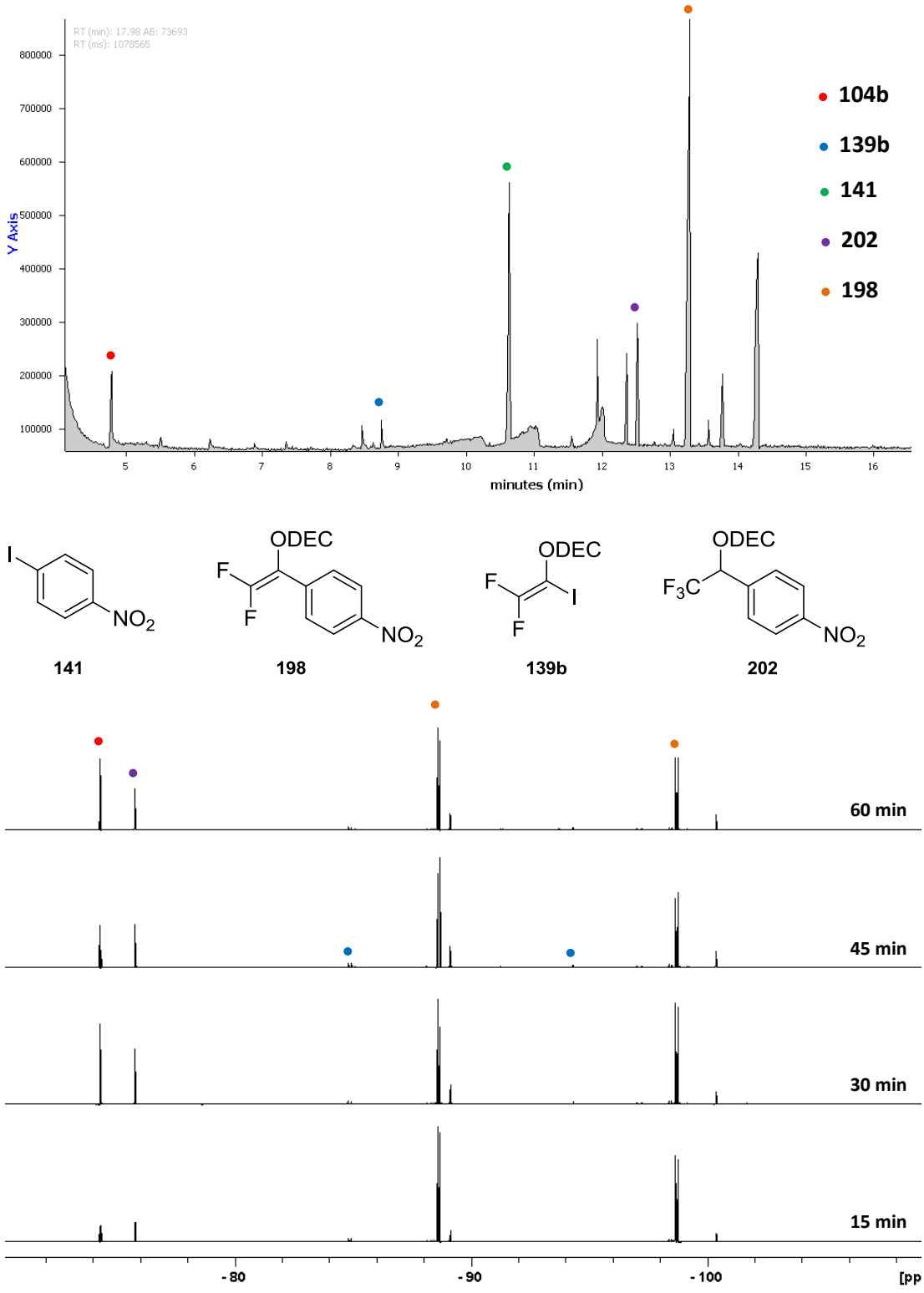
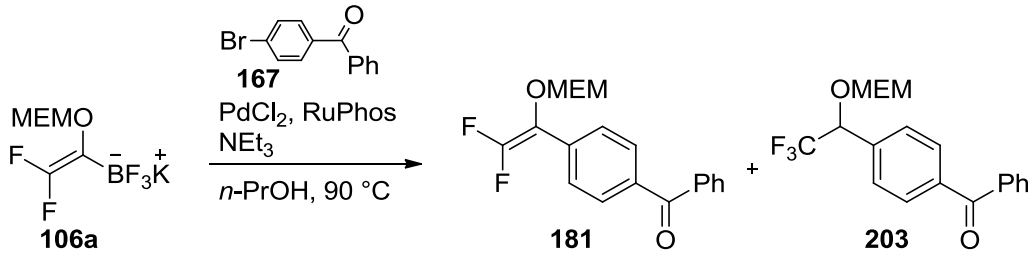


Figure **17**: Crude GC-MS (60 mins) and ^{19}F NMR analysis of Negishi coupling of **131b** with **141** under standard conditions

The presence of trace amounts of iodide **139b** is suggestive of a side reaction of the catalytic cycle but generation of HF addition product **202** in increasing significant quantities over time indicates that low coupling yields are as a result of degradation of styrene **198**. The presence of starting material **104b** is an interesting observation. Although it may be unreacted starting material, an increase in concentration of **104b** over time hints at a more complex regeneration pathway. This observation was not investigated further but would be of significant interest for future work with fluorinated building blocks **104a** and **104b**.

Katz and co-workers also identified HF addition products when generating difluorostyrenes that contained a strong EWG (Scheme **32**).[110] The mechanism of HF addition is clear in the Katz study, as the generated styrenes are exposed to KF in a protic solvent. Presumably, in the case of **198**, the styrene is exposed to fluoride present in the reaction mixture (LiF) and the fluoride adduct is stable until protonation during aqueous work-up.



Scheme **32**: HF addition product observed by Katz and co-workers

A considerably improved isolated yield of styrene **198** (42%) was achieved when the reaction was quenched after just 15 minutes. However, the improvement in yield brought about by shortening the reaction time was not general for all π-electron

deficient aryl halides. It should be noted that 3-nitrostyrene **199** was also isolated in poor yield due to a significant amount of HF addition product, but due to time constraints a coupling reaction with a reduced reaction time was not attempted. Reduced exposure to the LiF and the Negishi coupling conditions would be expected to result in a higher yield. Yields of triflates **174** and **193** were also improved when the reaction time was reduced to 30 minutes.

A notable difference between Negishi coupling of acetal **131a** and carbamate **131b** is the latter's intolerance of steric bulk. Styrene **172** was generated in a 40% yield from 2-bromotoluene **158**; however, attempts to couple carbamate **131b** with **158** were unsuccessful. Only protonated species **205** was observed by ^{19}F NMR when the reaction mixture was quenched. This limitation was overcome by interchanging the transmetalating and oxidative addition species (*vide infra*) suggesting that transmetalation from **131b** to an (*o*-tolyl)palladium phosphine complex may be slow.

Entries 14 and 15 of Table **20** suggest that heteroaromatic halides are unsuitable substrates for this Negishi coupling approach. In the case of entry 15, a ^{19}F NMR spectrum of the reaction mixture revealed only a small amount of product **201**, unreacted starting material **104b**, protonated species **205b** and homodimer **204** (Figure **18**).

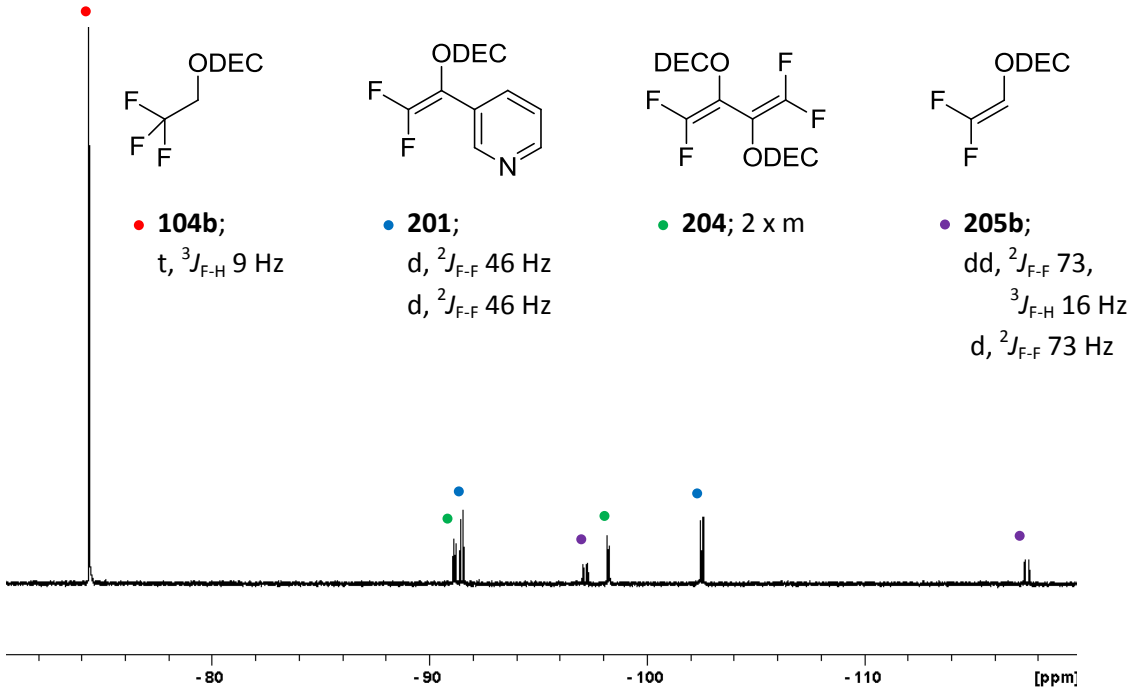
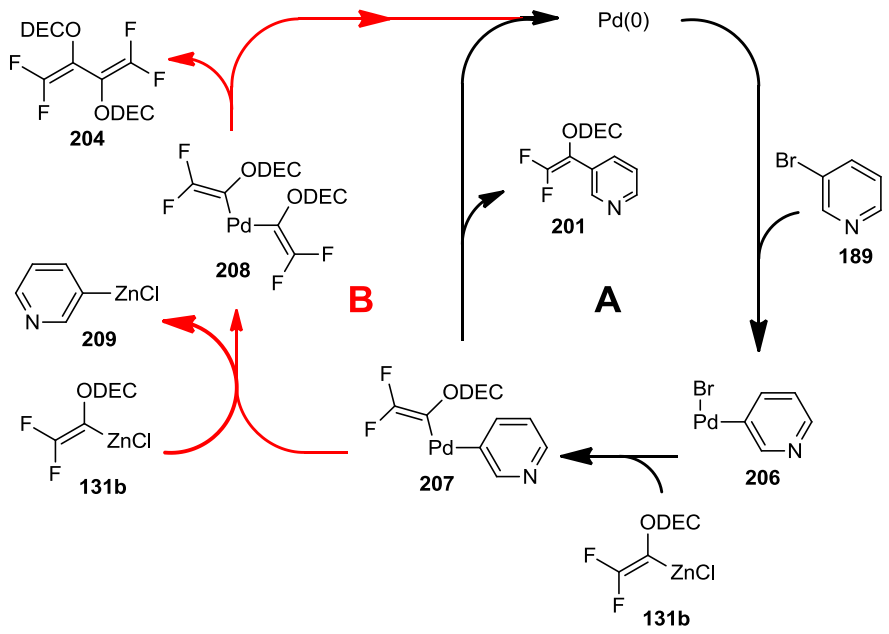


Figure **18**: ^{19}F NMR of reaction mixture of Negishi coupling between **131b** and **189**

A significant amount of starting material is present (only 22% conversion of **104b**) and may be as a result of poor conversion to vinylzinc species **131b**. Poor coupling selectivity is also apparent from the ^{19}F NMR spectrum as **201** and **204** were observed in a 2: 1 ratio. Formation of the homodimer may be the result of competition between a second transmetallation and reductive elimination, a mechanism proposed by Casares[142] and also by Lei.[143] Scheme **33** represents a possible catalytic cycle that would result in the generation of homodimer **204**.



Scheme **33**: Proposed catalytic cycle for generation of homodimer **204**

Cycle **A** represents a simple, conventional Negishi coupling of pyridyl bromide **189** with vinylzinc **131b**. Oxidative addition yields palladium complex **206** with subsequent transmetallation yielding complex **207**. The Negishi coupling cycle is completed by reductive elimination to form styrene **201** and regenerate Pd(0). However, if reductive elimination is slow from complex **207**, then a competitive second transmetallation (cycle **B**) may occur to generate complex **208**. Reductive elimination from this species would yield homocoupled product and regenerate Pd(0) to propagate the coupling cycle. No further optimisation of the coupling of vinylzinc **131b** with heteroaromatic halides was attempted; however, a judicious choice of ligand may have increased the rate of reductive elimination and inhibited the proposed double transmetallation.

The general trends observed in the Negishi coupling of **131a** and **131b** are similar to those obtained by Burton and co-workers[108,109] for trifluorostyrene synthesis from

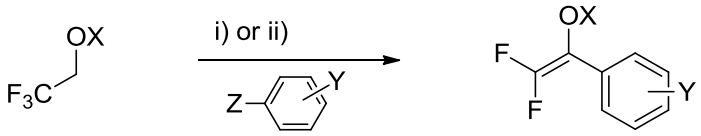
HFC-134a, HFC-133a and aryl iodides. The highest yields were obtained using π-electron rich aryl iodides and lower yields obtained when the arene was π-electron deficient.

Effect of halide on coupling efficiency

The Negishi couplings of aryl iodides were compared with those of the analogous bromide coupling partners to probe the efficiency of the more reactive halide and determine if highest yields depended on the use of the more costly and less available iodides (Table **21**).

The use of iodides offered no advantages over the reactions of the bromides; essentially the same product yields were obtained for each halide derivative. The results lend further evidence to the theory that oxidative addition is not the rate determining step in the catalytic cycle of species **131a** and **131b** as aryl iodides would be expected to undergo oxidative addition significantly faster than the analogous bromides.

A single attempt at coupling 4-(methoxy)chlorobenzene with vinylzinc **131a** was unsuccessful under the standard Negishi conditions, suggesting that oxidative addition had become rate limiting. This was not unexpected as it is known that organochloride coupling partners usually require activation in order to participate in oxidative addition.[87] Due to time constraints a ligand study was not undertaken and so coupling with a range of aryl chlorides was not attempted.



104a; X = MEM
104b; X = DEC

Method i) LDA (2.5 eq.), $ZnCl_2$ (1.1 eq.), 25% v/v DMPU/THF, 0 °C (1 hour) then 15 °C (1 hour); then aryl halide, $Pd(PPh_3)_4$, 65 °C.
Method ii) LDA (2.5 eq.), $ZnCl_2$ (1.1 eq.), THF, 0 °C (1 hour) then 15 °C (1 hour); then aryl halide, $Pd(PPh_3)_4$, 65 °C.

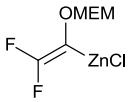
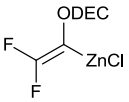
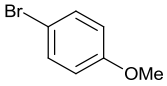
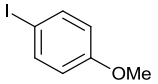
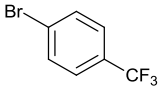
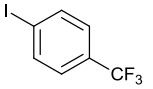
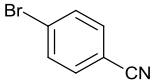
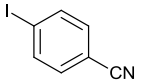
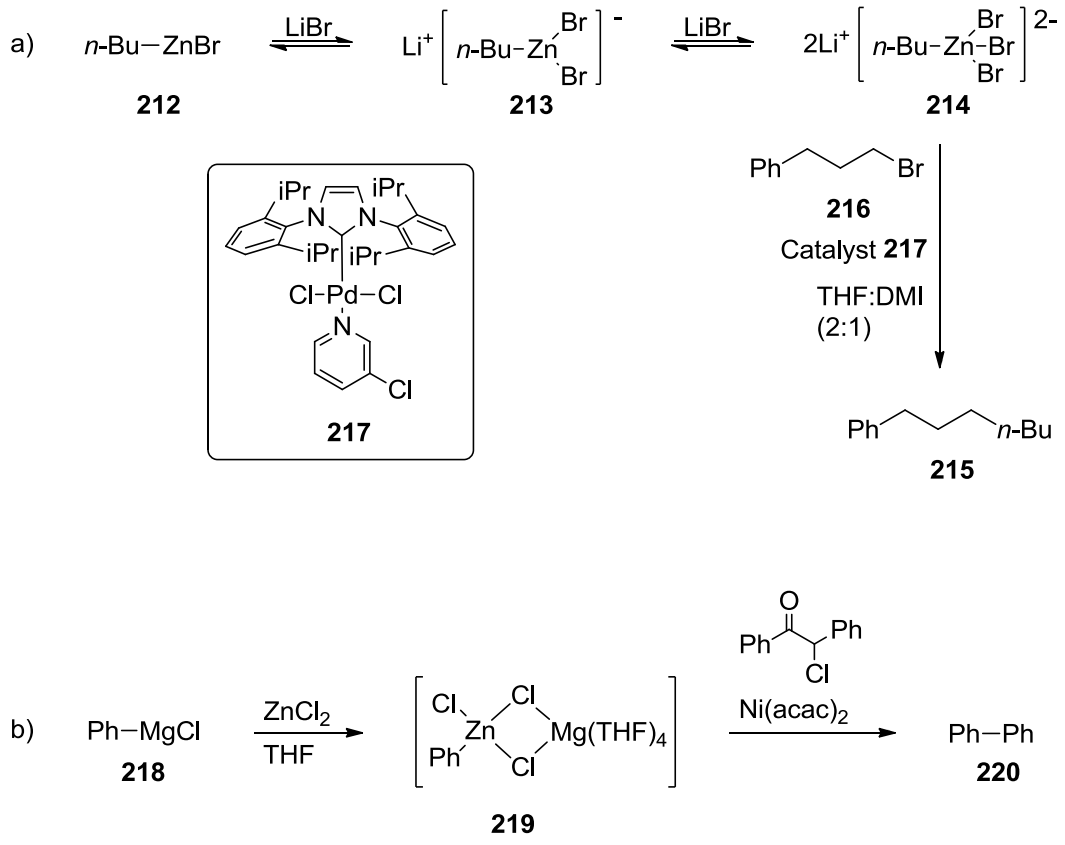
Entry	Aryl halide		Product (Yield %)	
				
1	**155**		**138** (60)	**133** (65)
2	**132**		**138** (58)	**133** (65)
3	**161**		**175** (41)	**194** (53)
4	**210**		**175** (29)	**194** (53)
5	**163**		**177** (22)	**196** (36)
6	**211**		**177** (22)	**196** (32)

Table **21:** Comparison of coupling efficiencies of aryl iodides and bromides

Effect of additives on coupling efficiency

The nature of the organozinc species can play a pivotal role in the level of success of the Negishi coupling reaction. Organozincate species donate a ligand more rapidly than diorganozinc species which in turn donate a ligand faster than organozinc halides. Organ has proposed that sp^3-sp^3 Negishi coupling can be promoted in the presence of LiBr or LiCl (1 – 2 eq) by forming an alkylzincate (Scheme **34**; a).[95] Lei

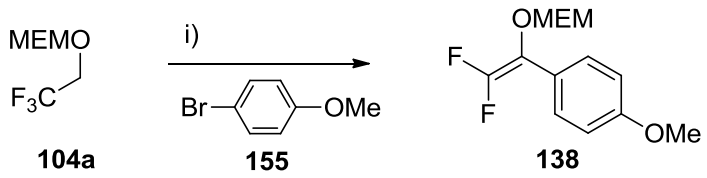
and co-workers observed a rapid increase in reaction rate when $MgCl_2$ was present as an additive in the Ni catalysed homocoupling of phenylzinc chloride (Scheme **34**; b).[144] Although the observations by Organ and Lei are of an increased reaction rate, it was important to perform Negishi couplings on the difluorozinc species with these additives to determine their effect on the yields of the couplings.



Scheme **34**: Organ and Lei's acceleration of Negishi couplings using alkali salts

The usual zincation of **104a** was performed in the presence of 1 or 2 equivalents of LiCl, added before the coupling step to generate styrene **138** (scheme **35**). Added LiCl appeared to have no effect on the yield of the coupling; the yield of **138** was 63% with 1 added equivalent of LiCl and 59% with 2 added equivalents. However, 2

equivalents of lithium salt (LiCl and LiF) are already present in the reaction mixture as a result of the dehydrofluorination/metallation step and may already be assisting the Negishi couplings.

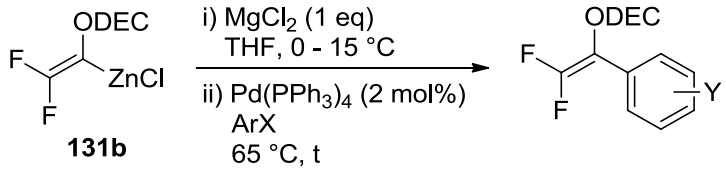


104a **155** **138**

Method: i) LDA (2.5 eq.), $ZnCl_2$ (1.1 eq.), LiCl, 12% v/v DMPU/THF, 0 °C (1 hour) then 15 °C (1 hour); then aryl halide, $Pd(PPh_3)_4$, 65 °C.

Scheme **35**: Negishi coupling of **131a** in the presence of excess LiCl

There also appeared to be no positive effect on the Negishi couplings of **131b** when $MgCl_2$ was used as an additive (Table **22**). Difluorovinylzinc species **131b** was generated in the usual manner before being added to a flask containing a suspension of $MgCl_2$ in THF at 0 °C. This suspension was allowed to warm to RT before a solution of aryl halide and $Pd(PPh_3)_4$ in THF was added and the reaction mixture was stirred at 65 °C.



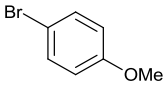
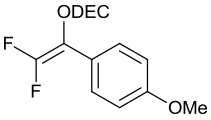
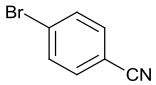
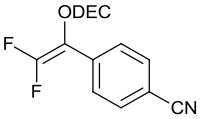
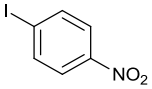
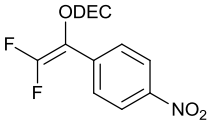
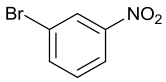
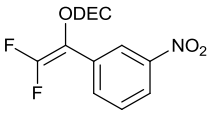
Entry		Aryl halide	Time (h)	Product (Yield %)	
1	**155**		16		**133** (39%)
2	**163**		16		**196** (48%)
3	**141**		0.3		**198** (50%)
4	**165**		0.5		**199** (10%)

Table **22**: Negishi coupling of **131b** in the presence of $MgCl_2$

These results demonstrate that the yields of the Negishi couplings remain unaffected by LiCl and $MgCl_2$ additives; however, their effect on the rate of the reaction is unknown and would require kinetic studies to gain a complete understanding.

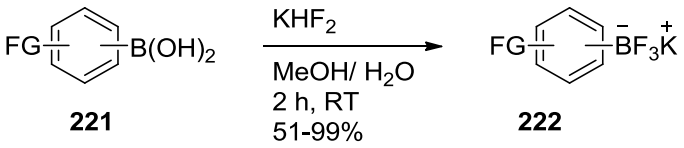
2.1.5 Palladium-catalysed coupling of difluoroenol electrophiles

*2.1.5.1 Suzuki coupling of iodo(difluoroenol) derivatives **139a** and **139b***

The main limitations with palladium-catalysed coupling of difluoroenol nucleophiles were poor yields when a strong EWG is present on the aryl halide, failure to tolerate

heteroaryl halides and steric sensitivity. The Suzuki-Miyaura coupling of iodides **139a** and **139b** was investigated to try to overcome some of these limitations.

Potassium trifluoroborate coupling partners were used to probe the scope of the iodo(difluoroenol) species in Suzuki-Miyaura coupling. Trifluoroborates are reported to have better stability and efficacy than the more traditional boronic acids, exemplified by the wide range of couplings performed by Molander and co-workers.[145-149] These stable salts were generated in moderate to excellent (51-99%) yields from the boronic acids following literature procedures of Vedejs and Molander (Scheme **36**).[150,151] A solution of KHF_2 in H_2O was added to a stirring solution of boronic acid in methanol. The resulting mixture was stirred at RT for 2 h then concentrated under reduced pressure to afford a white solid. The trifluoroborates were then extracted from the solid with a methanol:acetone mixture (1:4) and precipitation was encouraged by addition of diethyl ether. The salts were then collected by filtration and were all stored at RT.



221 **222**

Scheme **36**: generation of aryl trifluoroborates

Optimisation of the Suzuki coupling reaction

The coupling conditions were based initially on those reported by Molander.[148] These are: Boron reagent; $(Ph_3P)_2PdCl_2$ (2 mol%) pre-catalyst and Cs_2CO_3 in a toluene: water mixture (2.7: 1 v/v). Initial investigations indicated that the more stable Pd(II) catalyst $(Ph_3P)_2PdCl_2$ was more effective than $Pd(PPh_3)_4$ and that toluene was a more effective solvent than THF as indicated by the ^{19}F NMR analysis of the coupling between **139b** and **223** (Figure **19**).

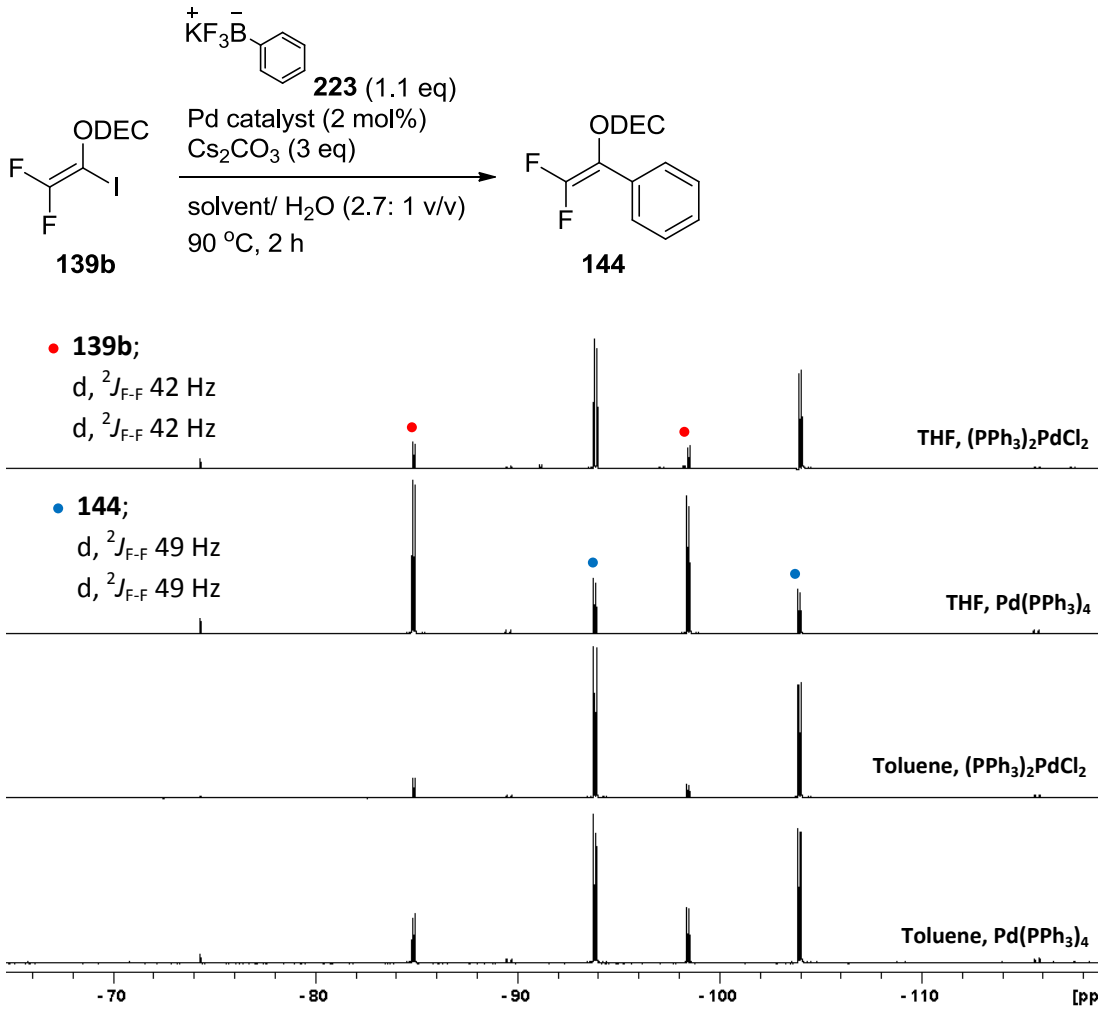


Figure **19**: ^{19}F NMR of the crude RM's of initial Suzuki couplings of **139b**

It was observed that 1.1 eq of borate coupling partner was not sufficient to completely consume iodide **139b** (Figure **19**). Due to difficulty separating unreacted iodide from the coupled products a modest excess of boron reagent (1.2 eq) was required to fully convert the iodides **139a** and **139b**.

Iodide **139b** was used to optimise the Suzuki coupling. Full conversion of the iodide occurred over 2 hours at 90 ^{o}C with a number of electron-rich potassium aryltrifluoroborates, producing products in good to excellent yields (Table **24**). Not all borates coupled successfully under these conditions, with solubility appearing to be limiting in some cases, prompting a search for more general conditions. To improve borate solubility, more polar solvents were investigated; alcohols were chosen as relatively sustainable candidates.[152] The (3-nitro)phenyl borate **224** was chosen to optimise the reaction conditions as products **179** and **199** are difficult compounds to generate in good yield as observed by the efforts of Burton[108] and Katz.[110] Borate **224** (1.2 eq), iodide **139b**, Cs_2CO_3 (3 eq) and $(Ph_3P)_2PdCl_2$ (2 mol%) dissolved fully in an alcohol (*n*-PrOH, *i*-PrOH or *t*-BuOH) : water (2.7:1) mixture and the solutions were stirred at 90 °C. Iodide **139b** was consumed completely in all alcoholic solvent systems but different ratios of side products were observed in each case. When *n*-PrOH was used addition, addition/elimination and reduced species **225**, **227** and **205b** were generated in a 4:1:10 ratio (**Figure 20**). Changing to *i*-PrOH removed addition and addition/elimination products **225** and **227** but **205b** was now the major product. Only a small reduction in the amount of **205b** produced was observed when the *i*-PrOH was degassed by using the freeze-pump-thaw method. The use of *t*-BuOH as solvent completely inhibited the formation of **205b**

but HF addition product **226** was then a major constituent of the reaction mixture. A reduction in reaction time from 18 h to 4 h limited the amount of **226** formed. Figure **20** maps the optimisation of the Suzuki coupling reaction of **139b** with **224**.

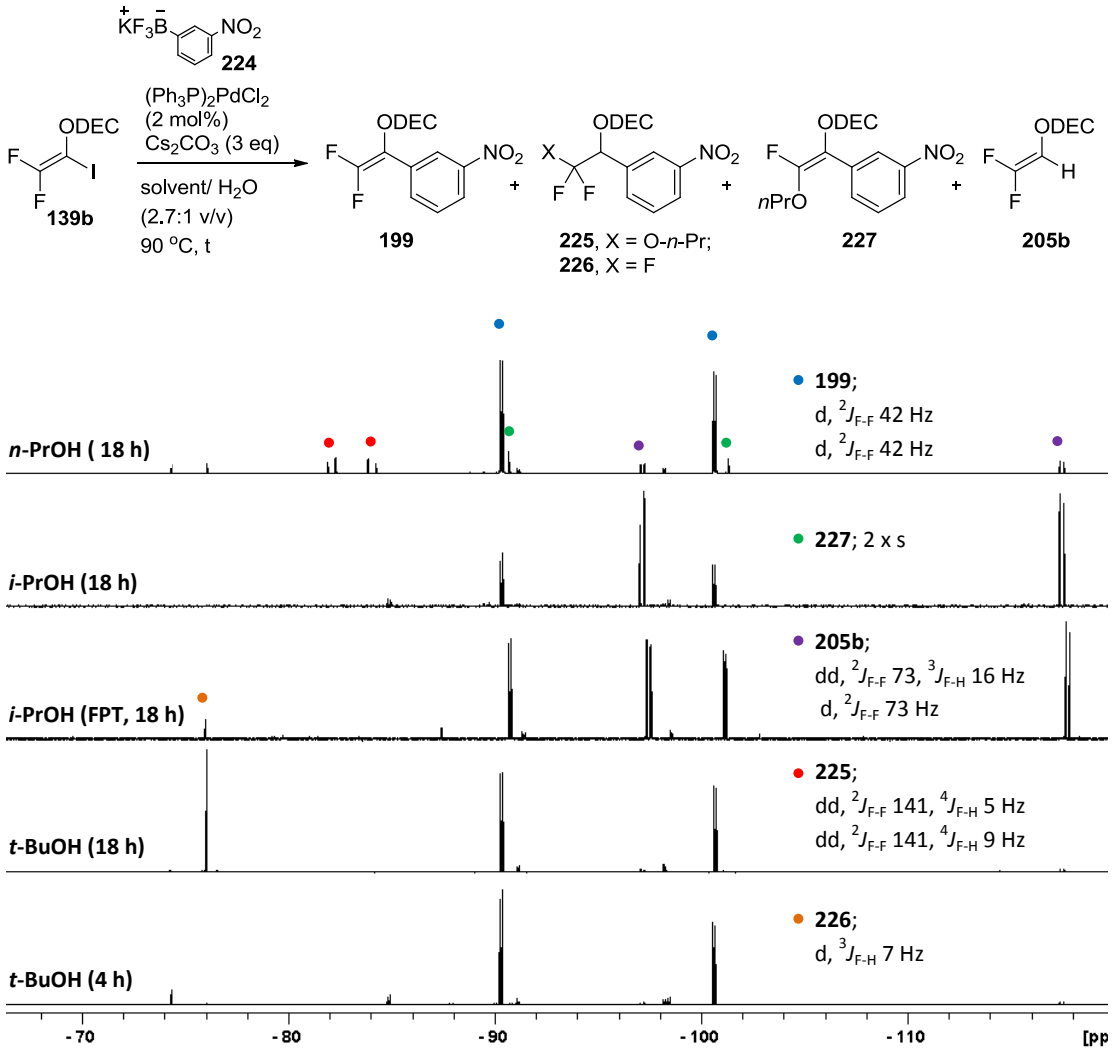
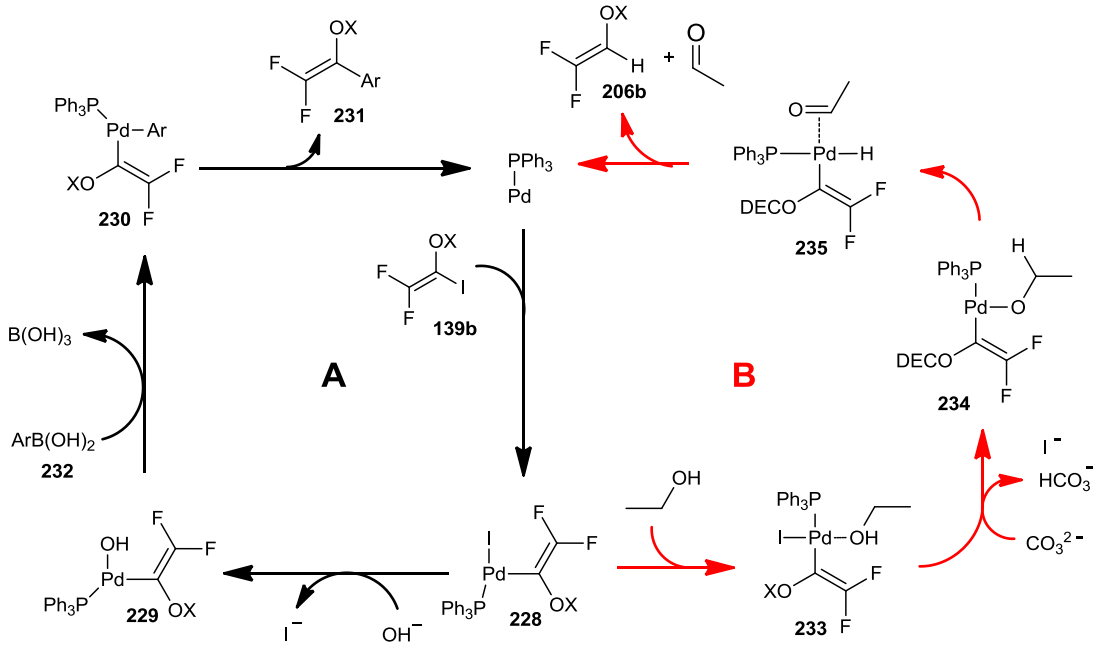


Figure **20**: Optimisation of the Suzuki coupling of **139b** with **224**

*Investigation into the generation of deiodinated **205b***

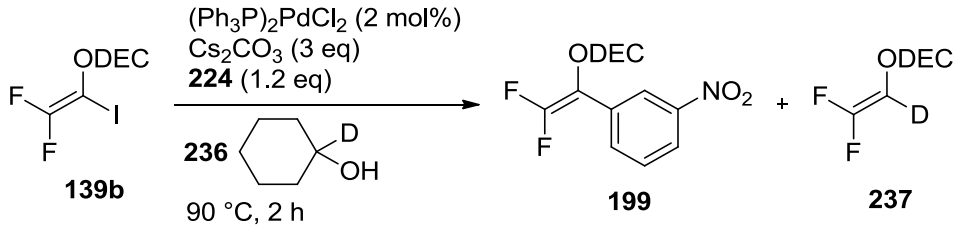
The observation that *t*-BuOH completely suppressed the formation of deiodinated species **205b** was key to understanding its origin. It was clear that **205b** was being

generated when oxidisable alcohols were used as solvent. The formation of **205b** could arise from reductive elimination from a palladium hydride complex such as **235**, itself produced from β-hydride elimination of palladium alkoxide **234** (Scheme **37**). The key intermediate **228** is shown, which partitions between the Suzuki-Miyaura coupling pathway and the reductive pathway. In the former, iodide is displaced by generic boronic acid **232**, formed *in situ* from the trifluoroborate[153] before transmetallation in a monophosphine cycle.[154] In the latter, alcohol coordination is followed by elimination[155] of HI followed by β-hydride elimination[156] to form an hydridopalladium complex; reductive elimination then releases **205b**. Similar reactions were reported by Helquist during the palladium-catalysed dehalogenation of arenes,[157] and Buchwald and co-workers[158] in palladium-catalysed ether formation.



Scheme **37**: Proposed Catalytic Cycle for Generation of **206b**

The β–hydride pathway to **205b** was confirmed by carrying out the coupling of **139b** and borate **224** in 1-deuterio-1-cyclohexanol **236** (Scheme **38**). The deuterated alcohol was prepared by reducing cyclohexanone with $LiAlD_4$ using the procedure of Olah.[159]



Scheme **38**: Probing the origin of product **205b**

Product **199** and deuterated species **237** were produced in a ~3:1 ratio; the ^{19}F NMR chemical shifts of **237** were distinct from those of **205b**, and one of the fluorine nuclei showed a splitting pattern consistent with the spin quantum number of deuterium (I = 1) (Figure **21**). The same reaction performed in cyclohexanol produced **199** and reduced species **205b** in a ~4:1 ratio. Neither β–hydride elimination nor reductive elimination is likely to be the rate-determining step for the side reaction. The different proportions of **205b** and **237** may arise from the partitioning of **228** between the two ligand exchange steps in **Scheme 37**.

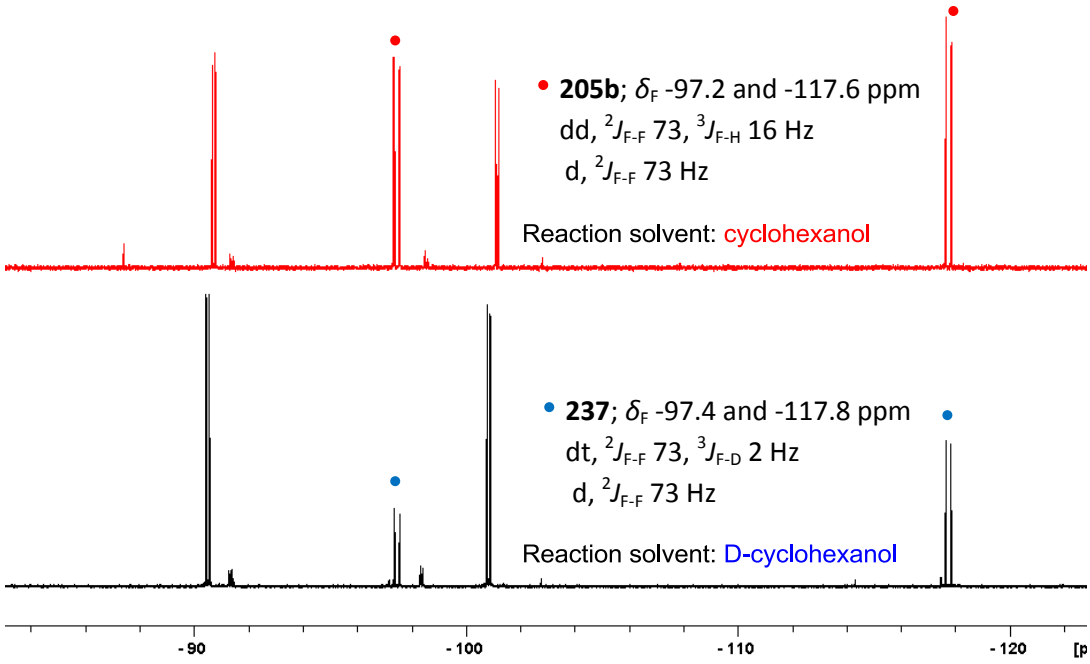


Figure **21**: ^{19}F NMR of reaction mixture containing **205b** and **237**

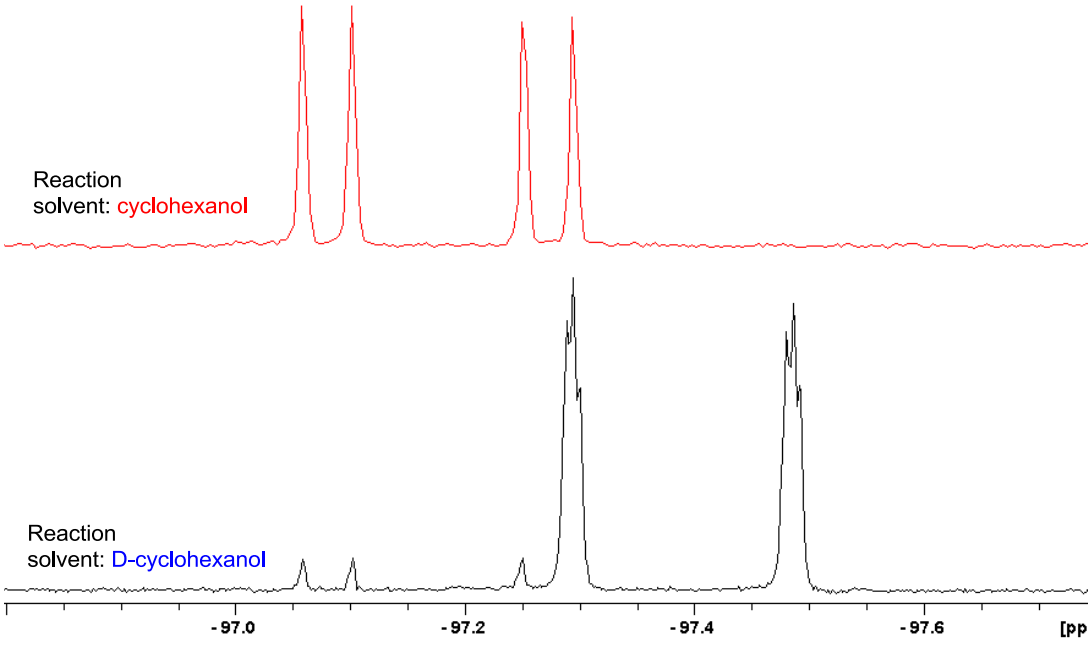
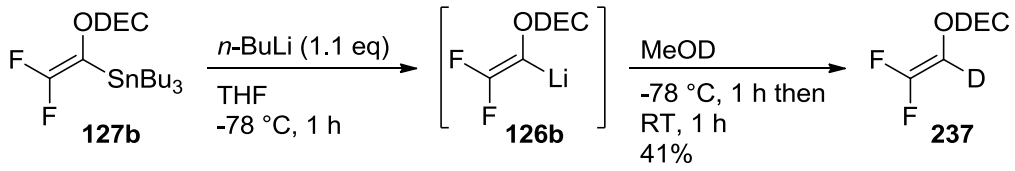


Figure **22**: Expanded ^{19}F NMR of reaction mixture containing **205b** and **237**

Finally, in order to confirm the identity of deuterated species **237**, it was synthesised and isolated independently (Scheme **39**).

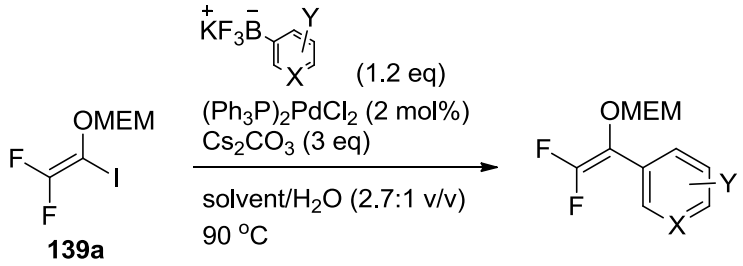


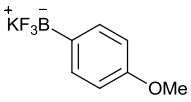
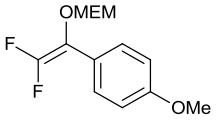
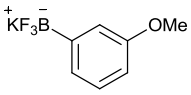
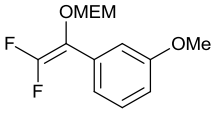
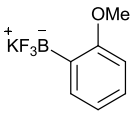
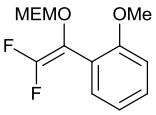
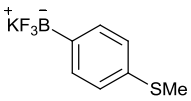
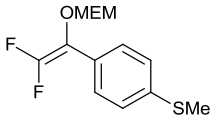
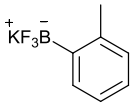
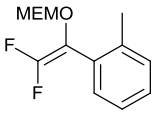
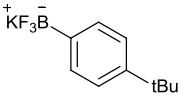
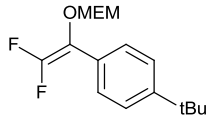
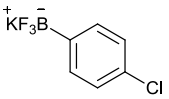
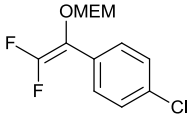
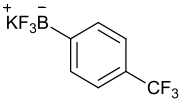
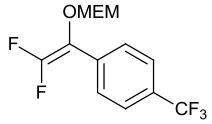
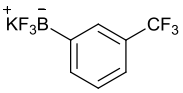
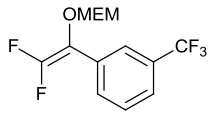
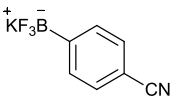
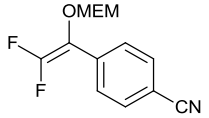
Scheme **39**: Generation of deuterated species **237**

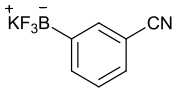
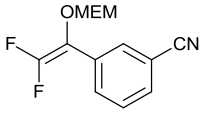
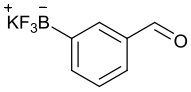
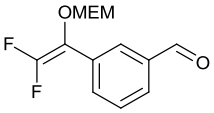
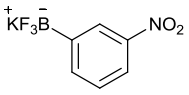
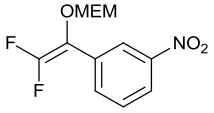
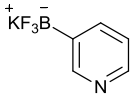
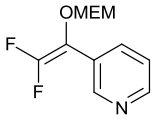
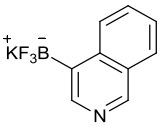
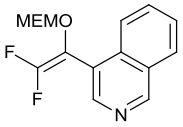
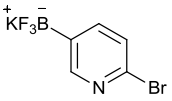
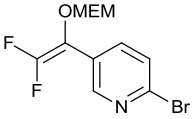
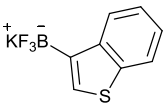
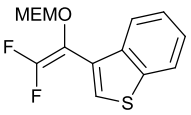
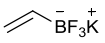
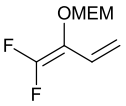
n-BuLi was added dropwise to a stirring solution of stannane **127b** in THF at -78 °C to form lithium species **126b**. This was quenched with deuterated methanol to afford **237**. The deuterated species was isolated by careful distillation so as to leave the tin residues behind. NMR and mass spectrometric analysis confirmed the identity of **237** and thus its formation in the Suzuki coupling reactions as previously described.

*Scope of Suzuki coupling of iodo(difluoroenol) derivatives **139a** and **139b***

With the optimisation of the Suzuki coupling of **139a** and **139b** complete, the scope of the coupling was investigated, beginning with **139a** (Table **23**).



Entry		Borate	Method	Time (h)	Product (yield)	
1	238		3	18		**138** (87%)
2	239		3	18		**169** (95%)
3	240		1	2		**254** (93%)
4	241		3	18		**255** (62%)
5	242		3	18		**172** (95%)
6	243		3	18		**256** (99%)
7	244		1	2		**173** (72%)
8	245		1	18		**175** (88%)
9	246		3	18		**176** (78%)
10	247		3	18		**177** (59%)

11	**247**		3	18		**178** (55%)
12	**248**		2	2		**257** (67%)
13	**224**		3	4		**179** (61%)
14	**249**		3	18		**258** (54%)
15	**250**		3	18		**259** (32%)
16	**251**		3	18		**260** (32%)
17	**252**		3	18		**261** (57%)
18	**253**		3	18		**262** (27%)

1: $(Ph_3P)_2PdCl_2$ (2 mol%), Cs_2CO_3 (3 eq), potassium trifluoroborate (1.2 eq), toluene/H_2O (2.7 : 1), 90 °C; **2**: $(Ph_3P)_2PdCl_2$ (2 mol%), Cs_2CO_3 (3 eq), potassium trifluoroborate (1.2 eq), *i*PrOH/H_2O (freeze-pump-thaw) (2.7 : 1) 90 °C; **3**: $(Ph_3P)_2PdCl_2$ (2 mol%), Cs_2CO_3 (3 eq), potassium trifluoroborate (1.2 eq), *t*BuOH/H_2O (2.7 : 1), 90 °C.

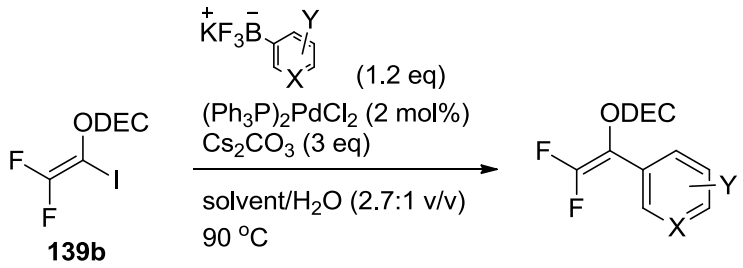
[a]Estimated yield: product contaminated with ~ 1% of **205a** and ~ 1% of **139a**

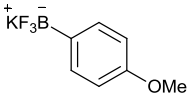
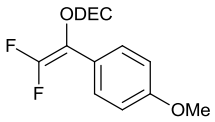
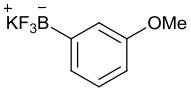
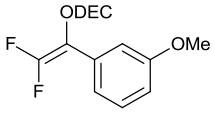
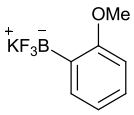
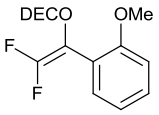
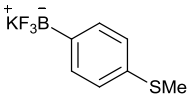
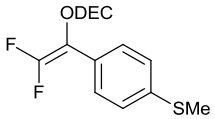
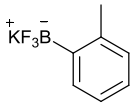
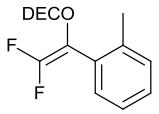
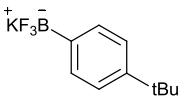
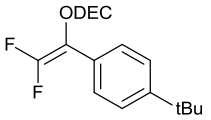
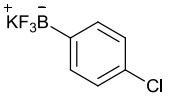
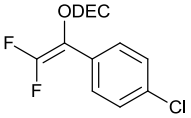
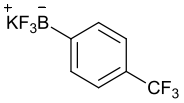
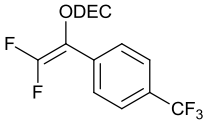
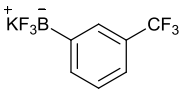
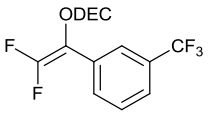
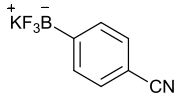
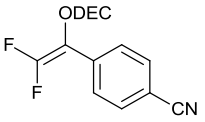
Table **23**: Scope and limitations of the Suzuki coupling of iodo(difluoroenol) **139a**

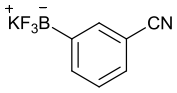
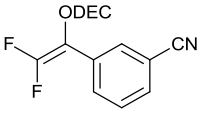
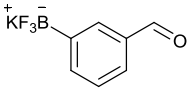
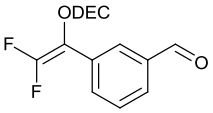
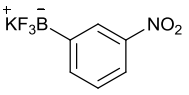
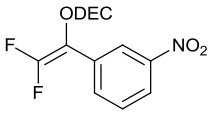
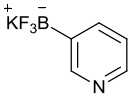
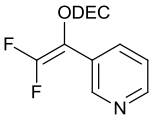
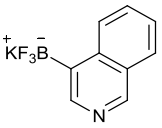
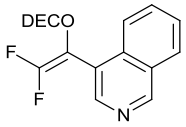
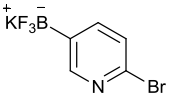
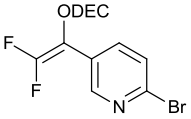
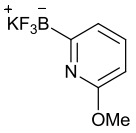
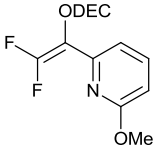
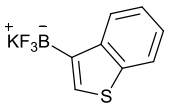
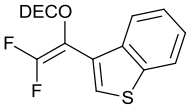
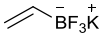
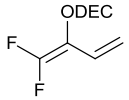
As in the case for Negishi coupling, styrenes bearing an EDG were formed in higher yield than those bearing an EWG. In the case of the Negishi coupling protocol, the variable reagent was undergoing oxidative addition whereas here they are undergoing transmetallation. The borates bearing a strong EWG, being less nucleophilic would undergo slower transmetallation. The lower yields in this case

would be more likely to arise from degradation of the styrenes as the reaction time was extended to allow the reactions of the electron deficient borate coupling partners to reach completion. Styrene **257** was generated in 67% yield; this is a good result as no formyl bearing styrenes could be generated using the Negishi protocol. Another successful outcome arose from the coupling of **139a** with electron deficient borates; the problematic nitro styrene **179** was obtained in 61% yield.

Next, the Suzuki coupling of iodo(difluoroenol) **139b** was performed with a range of trifluoroborates (Table **24**).



Entry		Halide	Method	Time (h)	Product (yield)	
1	238		1	1		**133** (80%)
2	239		2	2		**152** (59%)
3	240		2	2		**264** (59%)
4	241		1	2		**265** (93%)
5	242		1	2		**191** (93%)
6	243		1	2		**266** (66%)
7	244		1	2		**192** (88%)
8	245		1	18		**194** (88%)
9	246		2	2		**195** (60%)
10	247		1	18		**196** (62%)

11	**247**		1	2		**197** (61%)
12	**248**		2	2		**267** (90%)
13	**224**		3	4		**199** (75%)
14	**249**		2	3		**201** (61%)
15	**250**		2	2		**268** (44%)
16	**251**		3	3		**269** (52%)
17	**263**		3	18		**270** (70%)
18	**252**		1	2		**271** (57%)
19	**253**		3	18		**272** (30%)[a]

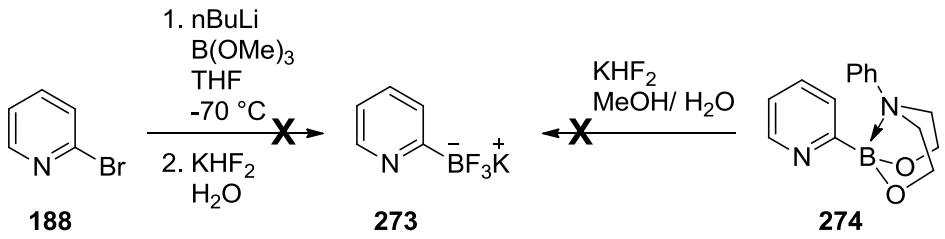
1: $(Ph_3P)_2PdCl_2$ (2 mol%), Cs_2CO_3 (3 eq), potassium trifluoroborate (1.2 eq), toluene/H_2O (2.7 : 1), 90 °C; **2**: $(Ph_3P)_2PdCl_2$ (2 mol%), Cs_2CO_3 (3 eq), potassium trifluoroborate (1.2 eq), *i*PrOH/H_2O (freeze-pump-thaw) (2.7 : 1) 90 °C; **3**: $(Ph_3P)_2PdCl_2$ (2 mol%), Cs_2CO_3 (3 eq), potassium trifluoroborate (1.2 eq), *t*BuOH/H_2O (2.7 : 1), 90 °C. [a]Estimated yield: product contaminated with ~ 5% of **205b** and ~ 4% of **139b**

Table **24**: Scope and limitations of the Suzuki coupling of iodo(difluoroenol) **139b**

The general coupling trends for carbamate coupling partner **139b** were similar to those observed for **139a**. Borates with a strong EWG generally coupled less efficiently than those with an EDG. Some tolerance of steric bulk was observed

(entries 3 and 5). In contrast, the carbamate coupling partner **131b** used in the Negishi protocol described earlier could not couple with 2-tolylbromide. Coupling of Iodide **139b** afforded styrenes **191** and **264** in moderate to excellent yield.

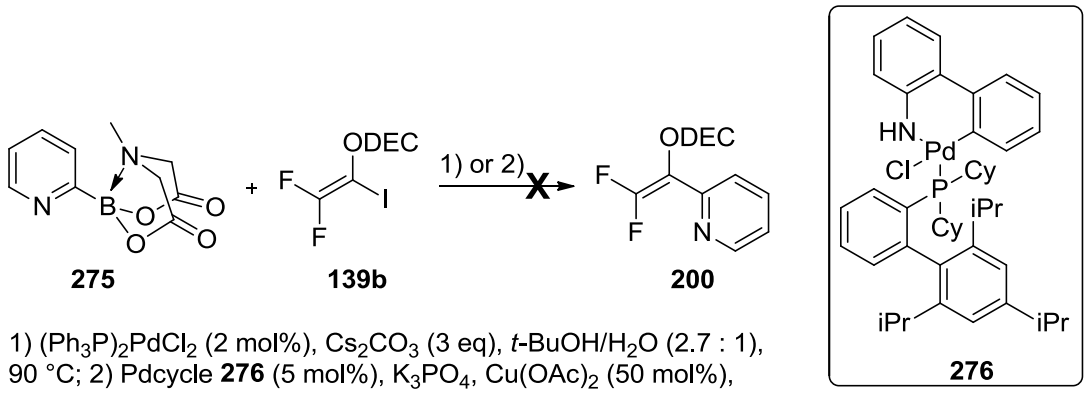
Heteroaromatic species were also coupled in moderate yields using the Suzuki coupling strategy (Entries 14-17); no heteroaromatic coupling partners were utilised effectively using the Negishi protocol. Entry 17 is an interesting case as generally 2-pyridyl boron coupling partners are prone to rapid deborylation and couple in poor yields.[160,161] 6-Substituted 2-pyridylborates like **263** have been shown to participate efficiently in Suzuki coupling reactions by Zou and co-workers,[162] and styrene **270** was generated in 70% yield when **263** was coupled with **139b**. Attempts to generate potassium 2-pyridyltrifluoroborate **273** from 2-bromopyridine[161,162] and trimethylborate proved unsuccessful (Scheme **40**), demonstrating the sensitive nature of borate **273** as previously highlighted by Molander.[160]



Scheme **40**: Attempted syntheses of potassium 2-pyridyltrifluoroborate **273**

An alternative coupling partner is Burke's 2-pyridyl *N*-methyliminodiacetic acid (MIDA) boronate **275**.[161,163] It has been shown to have long term stability in storage, and to participate in Suzuki coupling reactions under highly optimised conditions.[163] Synthesis of 2-pyridyl MIDA boronate using the literature method was unsuccessful;

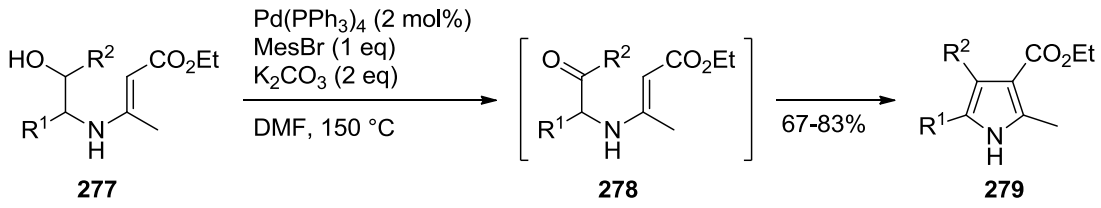
however, a small amount of commercially available material was procured in order to attempt Suzuki coupling with iodide **139b** (Scheme **41**).



Scheme **41**: Attempted Suzuki coupling of **275** with iodide **139b**

Both the Burke optimised coupling conditions (2) and the standard Suzuki coupling conditions of this work (1) failed to generate any styrene **200**. ^{19}F NMR analysis of the coupling reaction under the standard Suzuki conditions revealed unreacted iodide **139b** and some de-iodinated species **205b** after 4 h, but no styrene. The same analysis of the reaction under Burke's conditions revealed complete consumption of iodide **139b**, but only de-iodinated species **205b** was observed. This was a surprising result and indicated that iodide **239b** was not stable under Burke's conditions. It is possible that **239b** had undergone oxidative addition to a Cu(I) or Cu(0) species in the reaction mixture analogous to an Ullmann reaction. The subsequent aqueous quench of a sample for NMR analysis would release de-iodinated species **205b**. No homodimer **204** was observed in the reaction mixture as would be expected from a successful Cu(0) promoted Ullmann reaction, suggesting that the active metal species for this reaction pathway would be Cu(I). It is also

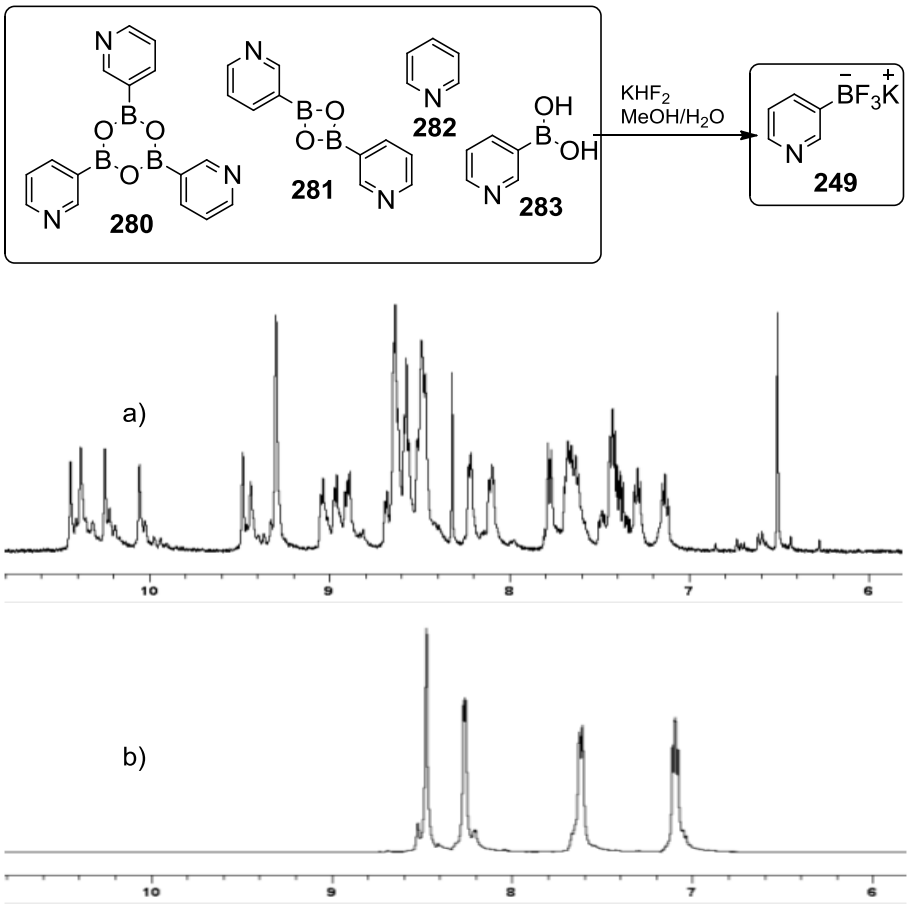
possible that DEA behaves like the ethanol molecules in Scheme **37** and generates de-iodinated **205b** as previously described. Ohta has used this methodology to prepare a series of pyrroles from hydroxy-enamines (Scheme **42**).[164]



R^1 = H, Me, Bn, Ph, *i*-Pr
R^2 = H, Me, Ph

Scheme **42**: Palladium-catalysed oxidation of hydroxyl-enamines in the preparation of pyrroles

The focus of the boron coupling species has been centred on trifluoroborates as they have been shown to have advantages over their parent boronic acids;[149] they are generally more stable compounds, both in storage and under coupling reaction conditions. As supplied, the acids can be complex mixtures of monomers, dimers and trimers and some species are prone to deborylation on prolonged storage. An example of this was observed when generating 3-pyridyl borate **249** from commercial boronic acid that had been stored for *ca.* 12 months (Scheme **43**).

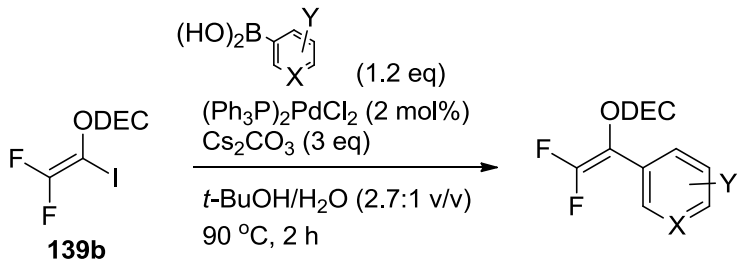


Scheme **43**: Expanded ^{1}H NMR of (a) commercial 3-pyridyl boronic acid **283** and (b) 3-pyridyltrifluoroborate **249**

3-Pyridylborate **249** was prepared from the commercial boronic acid using the standard procedure described previously with KHF_2 (Scheme **36**). A single species was isolated in 76% yield making determination of reaction stoichiometry considerably less challenging and demonstrating the worth of borate formation as a method of 'cleaning-up' boronic acids, particularly if they are of higher than usual value.

Suzuki-Miyaura coupling of iododifluoroenol **139b** was performed with a range of freshly-purchased boronic acids under the standard conditions (Table **25**). Entries 1-

5 demonstrate that boronic acids are effective coupling partners. Styrene **199** could be made in the same yield from the boronic acid or from the trifluoroborate salt (entry 5). The absence of fluoride from this reaction mixture confirms that the HF addition product observed when coupling borate **224** was completely suppressed with a shorter reaction time. As expected, the heteroaromatic boronic acids coupled less efficiently than their borate counterparts. 3-Pyridyl species **283** did not couple at all and only unreacted iodide **139b** was observed by ^{19}F NMR analysis of the reaction mixture after 2 h. Isoquinolyl boronic acid **289** only produced **268** in 10% yield and 6-bromo-3-pyridyl boronic acid only generated **269** in 25% yield.



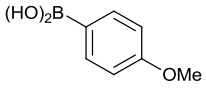
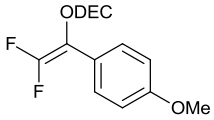
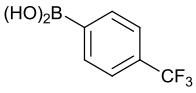
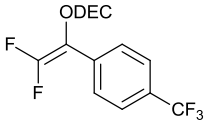
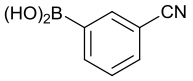
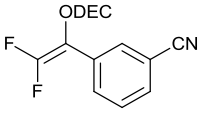
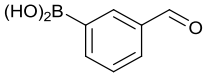
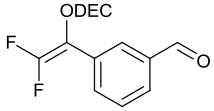
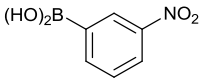
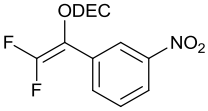
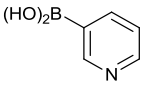
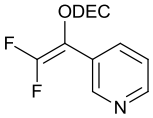
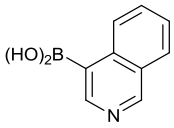
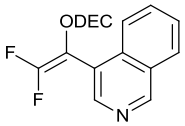
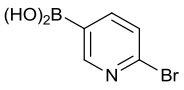
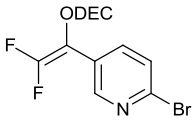
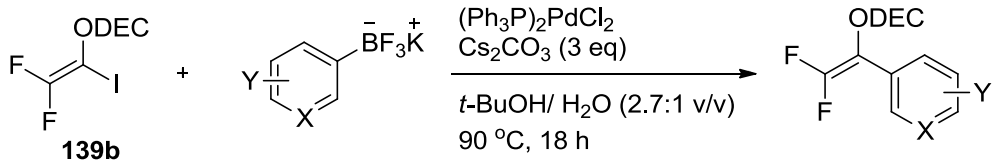
Entry	Halide	Product (yield)
1 **284**		 **133** (83%)
2 **285**		 **194** (92%)
3 **286**		 **197** (74%)
4 **287**		 **267** (60%)
5 **288**		 **199** (75%)
6 **283**		 **201** (0%)
7 **289**		 **268** (10%)
8 **290**		 **269**(25%)

Table **25**: Suzuki-Miyaura coupling of **139b** with a range of boronic acids

Catalyst loading study

Catalyst loading is of great importance to any reaction but it is of particular importance when the catalyst is expensive. On the scale typically used to perform the Suzuki couplings described here (50 mg, 0.17 mmol), 2 mol% of palladium catalyst (2 - 3 mg) is an acceptable amount of catalyst. Extrapolating for a moderate scaling of the reaction to generate 5 Kg of styrene **133** for example, would require 238 - 357 g of $(PPh_3)_2PdCl_2$. At the time of writing the cost for this amount of $(PPh_3)_2PdCl_2$ from a commercial supplier is ~£3000.



Concentration of $(Ph_3P)_2PdCl_2$ (mol%)	Volume of stock solution[a] (µL)	Conversion[b] (%)		
		192	**195**	**201**
0.0	0	0	0	0
0.01	11.5 (A)	6	-	-
0.025	29 (A)	40	-	-
0.05	58 (A)	100	76	0
0.1	115 (A)	100	100	0
0.5	575 (A)	-	-	0
1.0	500 (B)	-	-	100
2.0	1000 (B)	100	100	100

a) Stock solution A: 1.42 mM solution of $(PPh_3)_2PdCl_2$ in *t*-BuOH; Stock solution B: 3.3 mM solution of $(PPh_3)_2PdCl_2$ in *t*-BuOH; b)eg [**192**/(**192** + **139b**)]

Table **26**: $(PPh_3)_2PdCl_2$ loading study on the effect of Suzuki coupling of **139b** with borates **244**, **246** and **249**

A short study was performed, probing the scope for reducing the loading of palladium catalyst in the coupling of iodide **139b** with potassium aryltrifluoroborates. The study was performed by adding a volume of a stock solution of $(PPh_3)_2PdCl_2$ (table **26**) to a mixture of potassium trifluoroborate e.g. **192** (43 mg, 0.2 mmol), iodide **139b** (50 mg, 0.17 mmol) and caesium carbonate (161 mg, 0.5 mmol). A volume of *t*-BuOH (to bring total volume of alcohol to 1.15 mL) and H_2O (0.425 mL) were added and the reaction mixture was stirred at 90 °C for 18 hours. After this time the reaction mixture was cooled to room temperature and partitioned between DCM (5 mL) and H_2O (5 mL). The organic phase was separated and dried by passing through a hydrophobic frit. The reaction conversion was then calculated from ^{19}F NMR spectroscopy of the crude samples (Table **26**).

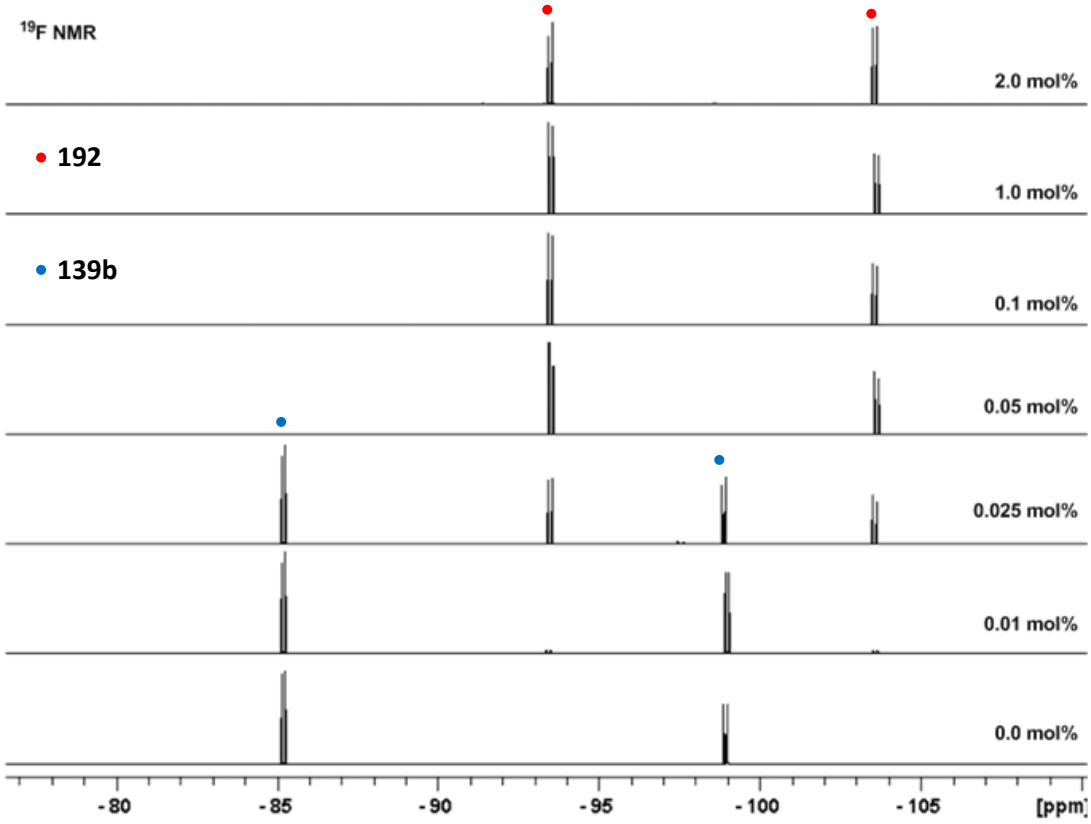


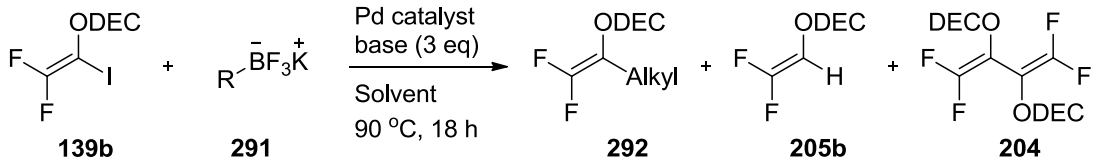
Figure **23**: Results of the $(PPh_3)_2PdCl_2$ loading study visualised by ^{19}F NMR

Figure **23** illustrates the spectral results obtained by ^{19}F NMR for the coupling of borate **244**. A catalyst loading as low as 0.05 mol% is tolerated in the Suzuki coupling of iodide **139b** with borate **244** before catalyst turnover becomes slow at 0.025 mol% and effectively stops at 0.01 mol%. Reducing the catalyst loading from 2 mol% to 0.05 mol% would represent a 40-fold saving on the cost of the expensive transition metal catalyst.

The results from the loading study of the coupling of **195** and **201** demonstrate that minimum catalyst loadings are borate specific; 3-CF_3 borate **195** required 0.1 mol% of catalyst for complete conversion of iodide **139b** while pyridyl borate **201** required 1 mol%. This may be as a result of slow turnover of the catalyst. If transmetallation of the boron coupling partner is slow then accumulation of the boronic acids generated *in situ* could occur. Pyridyl species **201** could undergo facile deborylation leading to incomplete conversion of iodide **139b**.

Coupling of potassium alkyltrifluoroborates

Alkyl coupling partners are amongst the most challenging partners in palladium catalysed coupling reactions;[165] β-hydride elimination from an alkyl-Pd complex can severely reduce the yield of coupling. Attempts to couple potassium alkyltrifluoroborates to iodide **139b** are detailed in Table **27**.



139b **291** **292** **205b** **204**

	R	Catalyst	Solvent	Base	Products[a]
1	*n*-Butyl	$(PPh_3)_2PdCl_2$ (2 mol%)	*t*-BuOH/H_2O	Cs_2CO_3	**139b**, **205b**
2	Isobutyl	$(PPh_3)_2PdCl_2$ (2 mol%)	*t*-BuOH/H_2O	Cs_2CO_3	**139b, 205b**, **204**
3	Isobutyl	$Pd(OAc)_2$ (5 mol%)/DPPP	toluene/H_2O	Cs_2CO_3	**139b**, **205b**
4	Isobutyl	$Pd(OAc)_2$ (5 mol%)/DPPF	toluene/H_2O	Cs_2CO_3	**139b**, **205b**
5	Cyclopropyl	$(PPh_3)_2PdCl_2$ (2 mol%)	*t*-BuOH/H_2O	Cs_2CO_3	**139b**
6	Cyclopropyl	PEPPSI-*i*Pr (2 mol%)	*i*-PrOH/H_2O	Cs_2CO_3	**139b**, **205b**
7	Cyclopropyl	PEPPSI-*i*Pr (2 mol%)	*t*-BuOH/H_2O	Cs_2CO_3	**139b**
8	Cyclopropyl	$Pd(PPh_3)_4$ (2 mol%)	toluene/H_2O	K_3PO_4	**139b**, **292**, **205b**, **204**

a) Analysis by ^{19}F NMR of reaction mixture

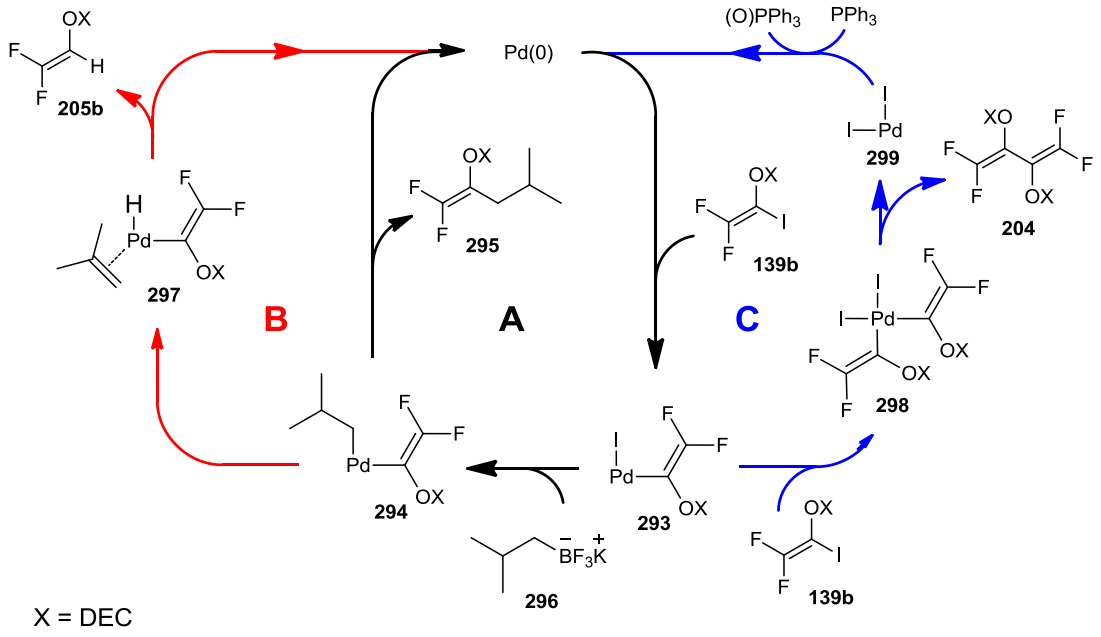
Table **27**: Suzuki coupling of potassium alkyltrifluoroborates with iodide **139b**

Initially Suzuki coupling of iodide **139b** was attempted with *n*-butyl trifluoroborate. This coupling partner was generated by quenching *n*-BuLi with tri-*iso*propylborate. The boron ester intermediate was then hydrolysed and the salt was formed by addition of KHF_2 solution. The standard coupling conditions (entry 1) were unsuccessful. The only fluorinated species present after stirring at 90 °C for 18 h were unreacted iodide **139b** and de-iodinated species **205b** in a 1: 0.1 ratio.

NMR analysis of the reaction of *iso*butyl borate under the standard coupling conditions (entry 2) reveals unreacted iodide **139b**, de-iodinated species **205b** and homodimer **204** in a ratio of 1: 0.2: 0.1.

The proposed mechanism for the generation of **205b** and **204** is detailed in Scheme **44**. The recovery of a substantial amount of unreacted starting material **139b**, and

the formation of de-iodinated species **205b** suggests that Suzuki coupling of alkyltrifluoroborates is slow, and that the known competitive β-hydride elimination[156] from an alkyl-Pd complex **294** is probably occurring (Scheme **44**, path **B**). Coupling with *iso*butyltrifluoroborate **296** also generates an appreciable amount of homodimer **204**. It is possible that a second oxidative addition to Pd complex **293** could occur generating Pd(IV) complex **298**.[166,167] Subsequent reductive elimination would afford homodimer **204** and palladium iodide **299**. Regeneration of Pd(0) could then be effected by reaction with PPh_3 present from the precatalyst (path **C**).



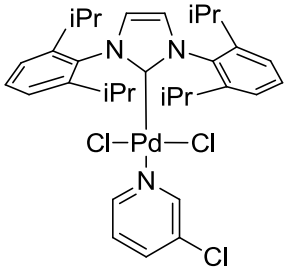
Scheme **44**: Proposed catalytic cycles for the generation of **205b** and **204**

In some cases, retardation of β-hydride elimination pathway **B** has been accomplished using chelating phosphine ligands.[168,169] 1,3-Bis(diphenylphosphino)propane **301** (dppp) and 1,1'-*bis*(diphenylphosphino) ferrocene **302** (dppf) ligands were utilised in conjunction with $Pd(OAc)_2$ to try to

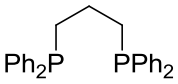
inhibit the formation of **205b**and encourage the desired catalytic cycle to form **292** (entries 3 & 4). Both catalyst/ ligand systems failed to generate any desired product and ^{19}F NMR analysis of the reaction mixture revealed iodide **139b** and de-iodinated **205b** as the only fluorinated species present in a 1: 0.2 ratio. Formation of homodimer **204** may have been inhibited by the chelating ligands forming a coordinatively saturated Pd-complex after the first oxidative addition. The second oxidative addition to complex **293** would then be difficult.

Coupling between potassium cyclopropyltrifluoroborate and **139b** was then attempted as the β-hydride elimination pathway to de-iodinated **205b** should be significantly retarded[170] as a result of the greater sp^2 character.[171] The standard Suzuki conditions (entry 5) did not yield any coupled product; only unreacted iodide was present in the reaction mixture after 18 h. An alternative Pd-N-heterocyclic carbene (Pd-NHC) catalyst (PEPPSI-*i*Pr **300**) was used in an effort to generate desired coupled product; strong binding of the bulky, electron rich NHC to the metal centre helps to keep the Pd ligated and extend the catalyst lifetime.[92] This catalyst has been used successfully in a range of C-C bond forming reactions and has been used effectively by Organ and co-workers in the Negishi[92] and Suzuki[94] coupling of alkyl species. A reaction under the conditions employed by Organ[93] failed to generate any desired product (entry 6). Complete consumption of iodide **139b** occurred and exclusive formation of de-iodinated **205b** resulted due to use of *i*-PrOH as solvent; the alcohol is oxidised to acetone in the formation of a hydridopalladium complex which undergoes reductive elimination to generate **205b** as described earlier (Scheme **37**). Exchanging the solvent to *t*-BuOH completely

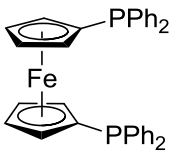
suppressed the de-iodination side reaction as expected but only iodide **139b** was present on analysis of the reaction mixture after 18 h (entry 7).



300



301



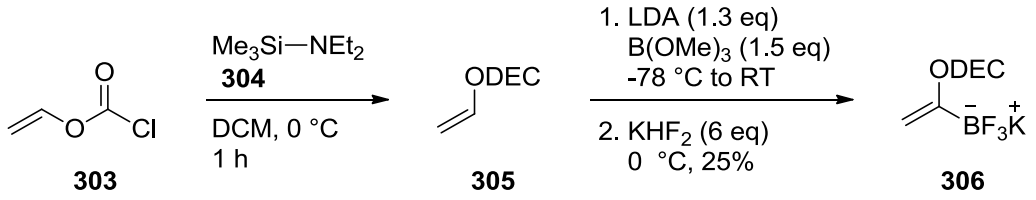
302

Deng and co-workers were able to perform Suzuki coupling on a range of potassium cyclopropyltrifluoroborates with aryl halides using $Pd(PPh_3)_4$ as catalyst, $K_3PO_4.3H_2O$ as base and toluene as solvent.[172] Applying these conditions to the coupling of **139b** with cyclopropyl trifluoroborate afforded a range of fluorinated species as observed by ^{19}F NMR of the reaction mixture (entry 8). Iodide **139b**, product, homodimer **204** and de-iodinated **205b** were all observed in a 1: 0.5: 0.4: 0.1 ratio. Presumably homodimer was generated via a Pd(IV) complex as described earlier (Scheme **44**). De-iodinated **205b** was generated in a small quantity under these coupling conditions, demonstrating that β-hydride elimination from a Pd-cyclopropyl complex is not inhibited completely. The identity of product was confirmed by GC-MS analysis of the reaction mixture and entry 8 represents the first set of conditions able to produce any desired coupling between **139b** and an alkyl coupling partner. No attempt to isolate the product was undertaken due to the complex reaction mixture and small quantity of material produced.

Palladium catalysed coupling of alkyltrifluoroborates with iodide **139b** represents a particularly challenging problem. The attempted couplings described in Table **27** do not represent an exhaustive screening of conditions but do represent a robust initial foray into sp^2-sp^3 coupling of iodide **139b**.

2.1.6 Effect of β-fluorination on palladium coupling efficiency

A competition reaction between trifluoroborates **306** and **106b** was attempted in an effort to determine the effect of terminal fluorination on the coupling reaction. Borate **306** was generated using a procedure adapted from that of Bowser,[173] followed by the standard low temperature metalation and trifluoroborate salt formation (Scheme **45**).

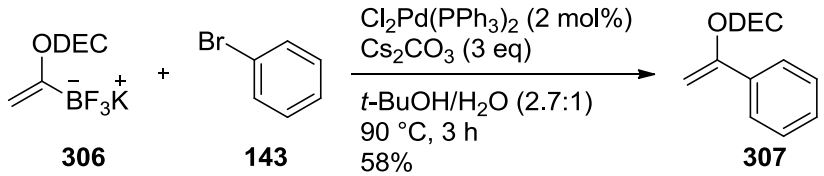


Scheme **45**: generation of enoltrifluoroborate **306**

Silylamine **304** was added to a stirring solution of vinylchloroformate **303** in DCM at 0 °C. The reaction was complete after 1 hour and the crude oil isolated after work-up was taken through to trifluoroborate **306** in 25% yield (0.04 mol scale) from **305** using the same procedure described for **106b**.

A competition reaction between **306** and **106b** could determine which substrate underwent palladium catalysed coupling more readily. The Suzuki coupling protocol was chosen for the investigation as it was envisaged that handling and monitoring discrete difluoroenol substrates would be easier than using coupling partners generated *in situ* (which would be the case with the zinc based coupling methodology discussed previously).

Suzuki coupling of **306** was attempted in order to confirm its competence in the palladium catalysed coupling reaction (Scheme **46**).



Scheme **46**: Suzuki coupling of trifluoroborate **306**

Non-fluorinated styrene **307** was isolated in 58% yield. This compares well with the Suzuki coupling of **106b** with **143** (54%) and confirms the suitability of the trifluoroborates for participation in the study.

The competition reaction was performed using the standard optimised Suzuki coupling conditions with 1 eq of each of the trifluoroborates **106b** and **306**, 1 eq of bromobenzene **143**, 3 eq of Cs_2CO_3 and 2 mol% $Cl_2Pd(PPh_3)_2$ at 90 °C in a *tert*-butanol:water (2.7:1) solvent system. The reaction was monitored by GC-MS analysis of samples removed at different time points. The spectra revealed a complex mixture of starting materials, products and side products. (Figure **24**).

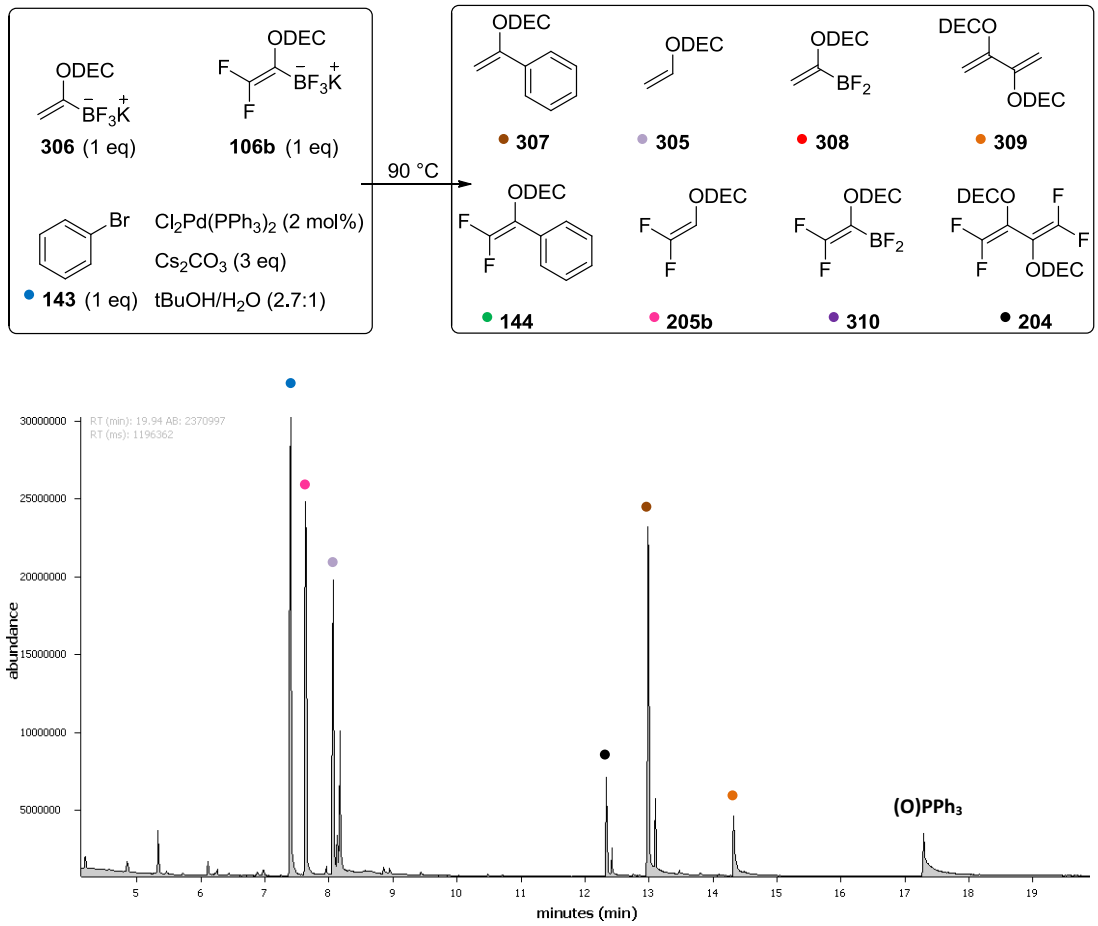
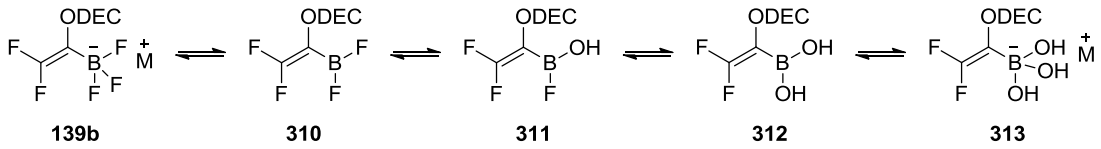


Figure **24**: Typical GC-MS trace observed for competition reaction between **106b** and **306** (90 mins)

Most of the species identified by the GC-MS analysis had been observed previously by ^{19}F NMR but it was surprising to see difluoroborate species **308** and **310**. These borate species exist in equilibrium with the trifluoroborates and the active boronic acids (Scheme **47**).[153,174]



Scheme **47**: Equilibrium between trifluoroborate **106b** and trihydroxyborate **313**

The results of the GC-MS study suggest that transmetallation of **106b** is considerably slower than that of **306**. A selection of the data is plotted in Figure **25**; the profiles for the consumption of **143** and generation of **144** and **307,** demonstrates that formation of **144** does not occur until formation of **307** has stopped. This would indicate that the terminal fluorines do not have a positive effect on the rate of coupling of difluoroenol nucleophiles. It also provides further circumstantial evidence that transmetallation is the rate determining step in the palladium catalysed coupling of nucleophilic difluoroenol coupling partners.

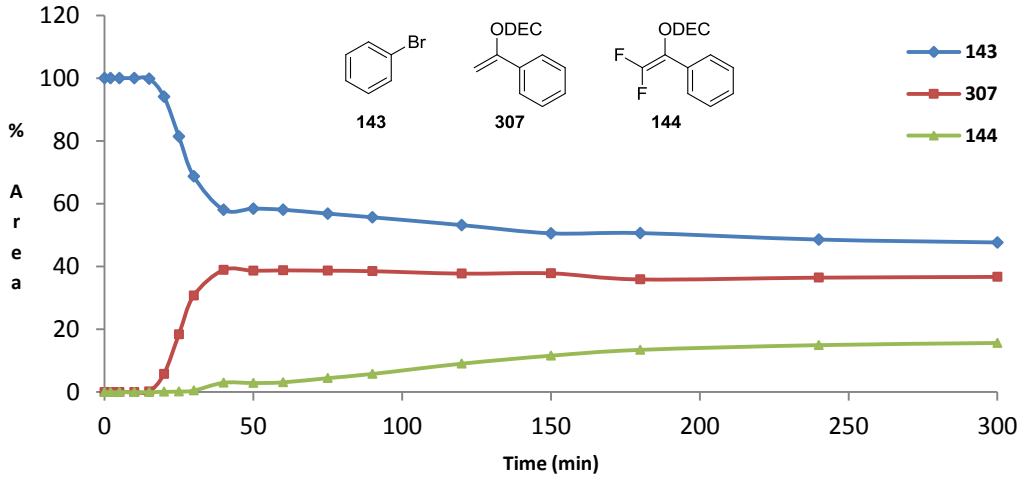


Figure **25**: Plot of % area vs time for competition reaction between **106b** and **306**

Further observations from the GC-MS study reveal a picture of competing catalytic and degradation pathways. The advantages accrued from the Suzuki coupling of organotrifluoroborates is attributed to a low level of deborylation due to slow release of boronic acid. Observation of difluoroboron species **308** and **310** (Figure **26**) exposes a potentially rapid equilibration between borates **106b** and **306** with the active boronic acid species. Competitive base catalysed deborylation[175] could

then occur and may be the cause of the poor conversion of bromide **143**. The presence of a significant quantity of deborylated **205b** at the first data point in Figure **26** suggests that hydrolysis of fluorinated alkenyl borate **106b** and subsequent deborylation is considerably faster than for the analogous **306**.

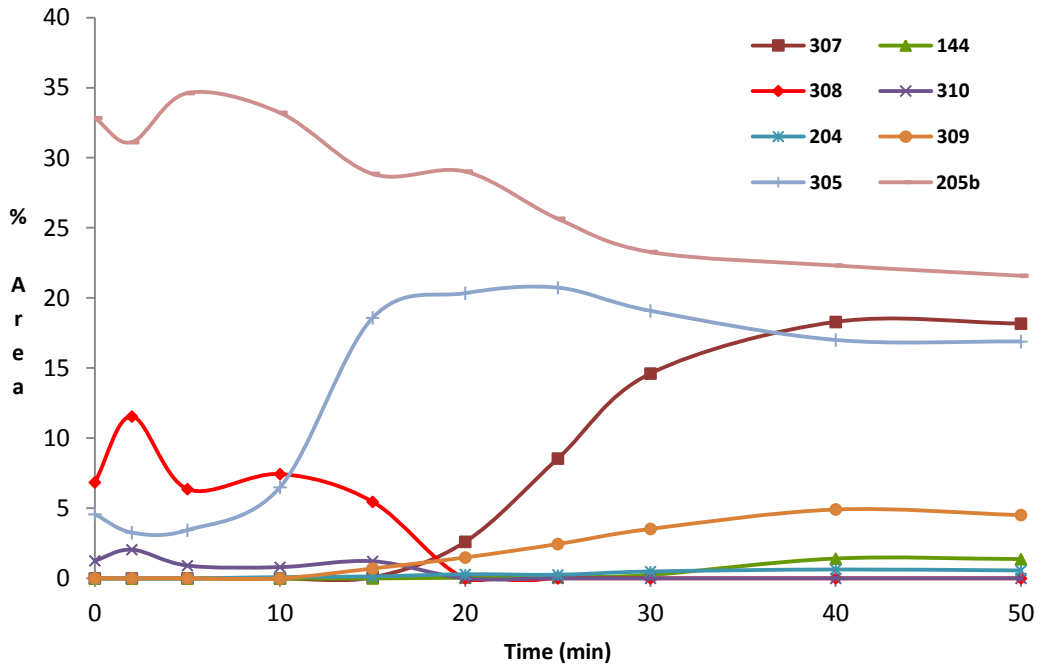
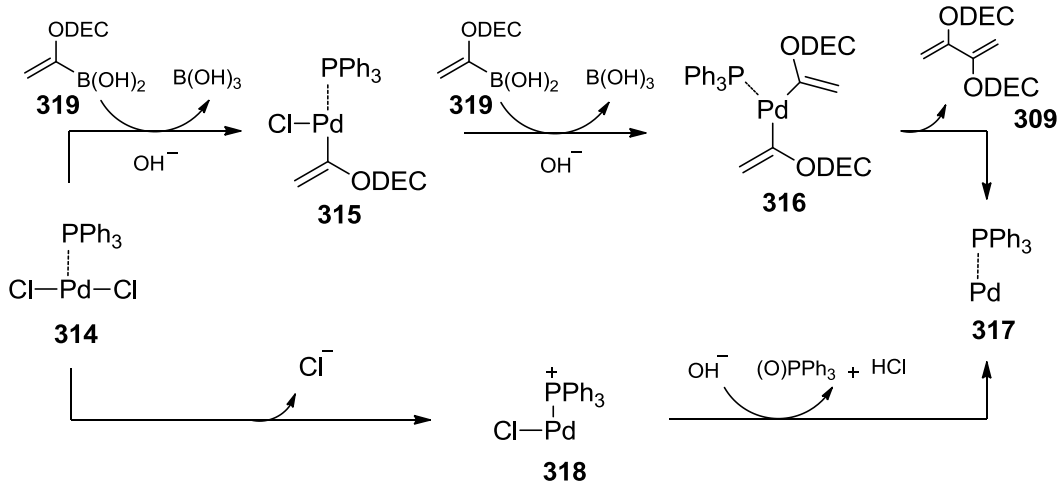


Figure **26**: Plot of % area vs time of select species from the competition reaction between **106b** and **306**

GC-MS analysis (Figure **24**) also revealed formation of homodimers **309** and **204**. This suggests that borates **306** and **106b** are involved in a sacrificial double transmetallation and reductive elimination cycle to reduce the Pd(II) precatalyst to an active Pd(0) species (Scheme **48**).[175] The formation of dimer **309** before any formation of coupled **307** is consistent with this proposal. Triphenylphosphine oxide

($OPPh_3$) was also observed by GC-MS and suggests a competitive PPh_3 reduction of the precatalyst.



Scheme **48**: Proposed mechanism for generation of active catalyst

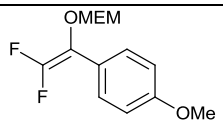
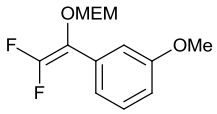
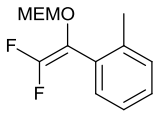
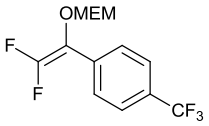
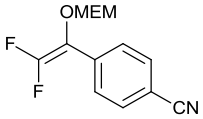
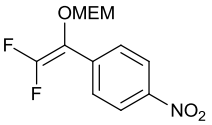
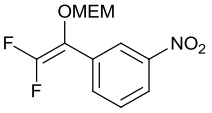
A significant amount of difluoroboron species **308** was formed immediately. Consumption of this species coincides with the generation of a significant amount of deborylated **305**, all before Suzuki coupling to form **307** occurs. This would explain the moderate yield (58%) for the coupling reaction described previously. A similar trend is observed for the difluoroenol analogue **106b**; a significant quantity of deborylated product **205b** is observed after only 2 minutes.

Supressing the rate of formation of the difluoroboron species **308** and **310** may reduce the rate of deborylation and formation of **305** and **205b**, ultimately leading to a better yield.

A fuller picture of the effect of the fluorine atom substituents on the coupling reaction would be obtained if a similar competition reaction was performed with (iodo)difluoroenol species **139b**.

2.1.7 Summary of palladium coupling of difluoroenol derivatives

Preparations of difluoroenol derivatives have been performed and their subsequent palladium-catalysed coupling investigated. The work has built upon a solid foundation of coupling chemistries both from within the group and also from the wider chemical literature. The main developments have been the near-ambient preparations of difluoroenolzinc species **131a** and **131b** and their subsequent *in situ* Negishi coupling, avoiding isolation and costly cryogenic preparation conditions. (Iodo)difluoroenols **139a** and **139b** were also prepared utilising the near-ambient methodology. Suzuki coupling of these species circumvented the substrate scope limitation of the Negishi coupling. A comparison of the various coupling methodologies performed on fluorinated building block **104a** is detailed in Table **28**.

Product	Coupling method (% isolated overall yield from 104a)			
	Negishi	Suzuki[a]	Stille	Suzuki[b]
 **138**	60	50	50	44
 **169**	73	55	(-)[c]	48
 **172**	40	48	(-)[c]	48
 **175**	41	53	(-)[c]	36
 **177**	25	(-)[c]	46	30
 **142**	41	(-)[c]	61	(-)[C]
 **179**	31	0	(-)[c]	31

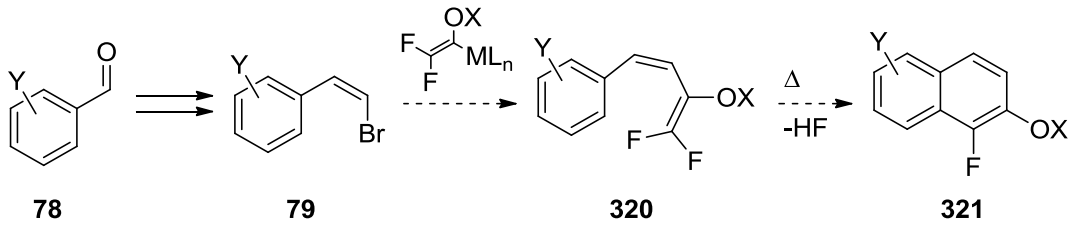
[a]Ref. 27;[b]From iodide **139a**; [c]Reaction not carried out

Table **28**: Selected comparisons of coupling strategies

Armed with an array of difluoroenol substrates and palladium-catalysed coupling conditions, and underpinned by a knowledge of their limitations, the preparation of fluoroarenes could be addressed.

2.2 Preparation of Fluoroarenes

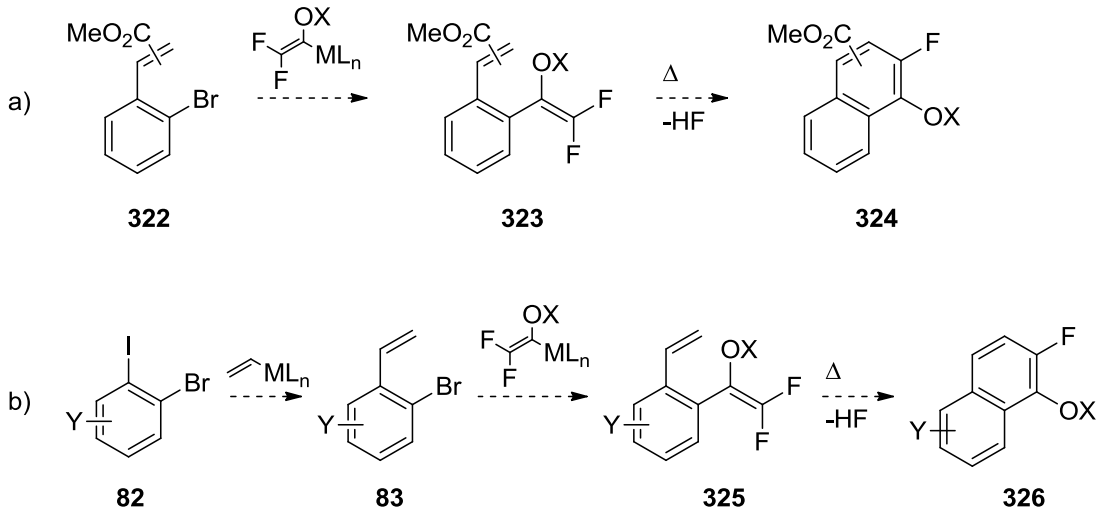
Three strategies to generate electrocyclisation precursors using the palladium-catalysed coupling chemistry described earlier were envisaged.



Scheme **49**: Strategy 1: phenyl-1,3-diene approach

Strategy 1 (Scheme **49**) would take advantage of simple, established chemistry to generate (*Z*)-β-bromostyrenes rapidly.[56] Palladium-catalysed coupling to form phenyldienes **320** and subsequent electrocyclisation could then be explored.

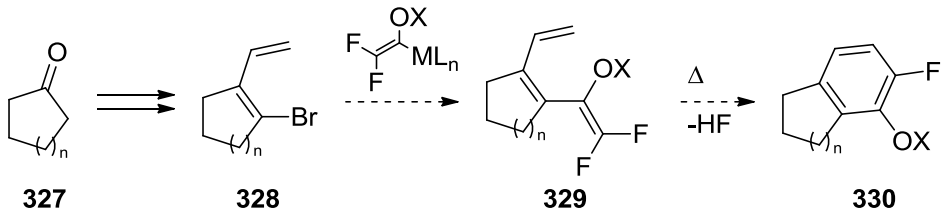
Alternative strategies with the internal π-bond of the electrocyclic triene locked in a *Z*-configuration were also envisaged.



Scheme **50**: Strategy 2: Divinylbenzene approach

Strategy 2a) (Scheme **50**) would require preparation of phenylacrylates **322** using known literature methods.[176] Palladium-catalysed coupling would deliver divinylbenzenes **323** and electrocyclisation would then afford fluoroarenes **324**.

Alternatively, an iterative coupling approach (2b) would afford divinylbenzenes **325** before palladium-catalysed coupling and subsequent electrocyclisation could be probed. Due care should be taken using this approach as there is potential for symmetrical bis-coupled side products to form after the first coupling step (*vide infra*).



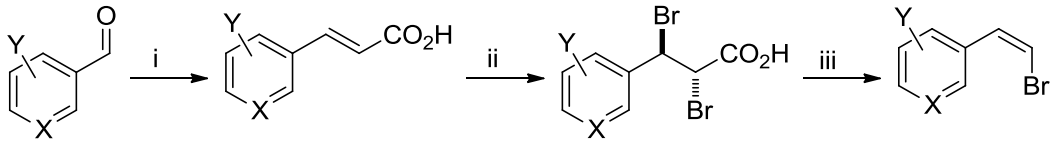
Scheme **51**: Strategy 3: 1,2-divinylcyclohexene approach

Strategy 3 (Scheme **51**) would once again make use of known chemistry to form bromodienes **328**.[57] The key coupling and electrocyclisation steps could then be explored.

2.2.1 Strategy 1: phenyldiene approach

2.2.1.1 Preparation of (Z)-β-bromostyrenes

The generation of (*Z)*-β-bromostyrenes (**79a-d**) was achieved using literature procedures.[56,177] Small adjustments to the literature methods were necessary to obtain satisfactory results.



78a-d **331a-d** **332a-d** **79a-d**

i) Malonic acid, Pyridine, Piperidine, 100 °C, 3 h; ii) Br_2, chloroform, 0 °C, 1-3 h; iii) μW, DMF, TEA, 140 °C, 3mins

	78	**331**	**332**	**79**
a	Benzaldehyde	70%	84%	88%
b	4-Methoxybenzaldehyde	68%	81%[a]	83%[d]
c	4-Nitrobenzaldehyde	96%	60%[b]	93%
d	3-Pyridinecarboxaldehyde	87%	74%[c]	41%

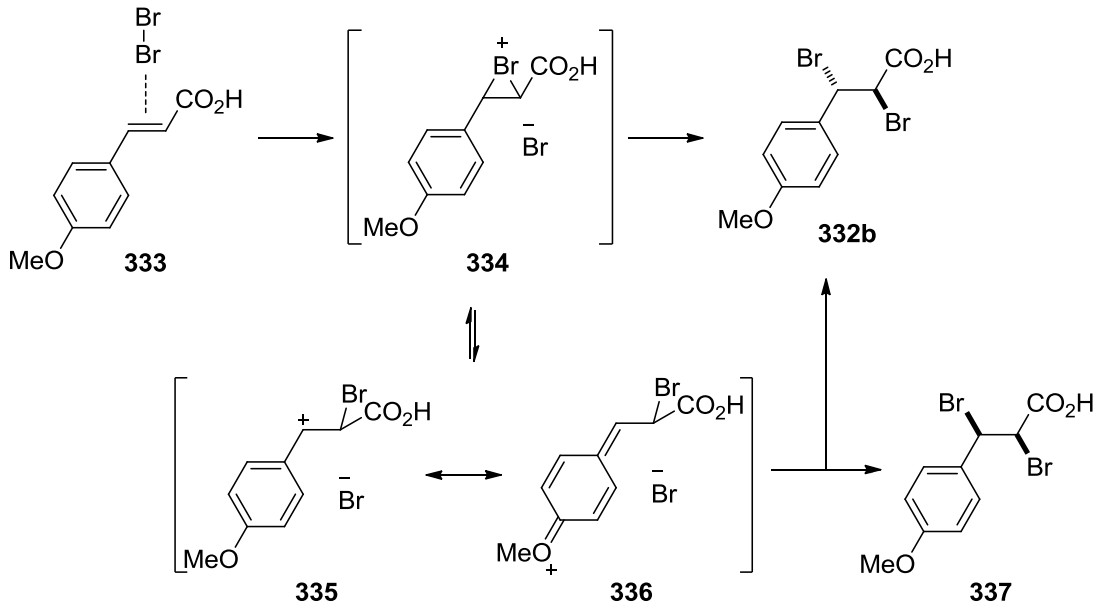
a) 5: 1 ratio of anti: syn; b) Conditions: Br_2, AcOH, reflux; c) heated to 60 °C; d) 89: 11 ratio of *Z*:*E*

Table **29**: Generation of (*Z*)-β-bromostyrenes

Cinnamic acids **331a-d** were generated in good yield using the Knoevenagel condensation with the Doebner modification (refluxing in pyridine to effect decarboxylation *in situ*). The acids were isolated from the reaction solution by precipitation upon the addition of aqueous HCl and subsequent filtration. Re-crystallisation from ethanol was necessary to isolate **331a-d** as pure, dry crystalline solids. Precipitation from acidic media was ineffective in isolating pyridylcinnamic acid **131d** as protonation occurred, trapping the product in the aqueous layer. Instead, the reaction solvent was removed under reduced pressure and the resulting sticky solid was washed with water and isolated by filtration and air dried to afford a white powder.

Cinnamic acids **331a**, **331b** and **331d** were brominated by adding a solution of Br_2 in $CHCl_3$ to a suspension of the acids in $CHCl_3$ at 0 °C. The acids usually dissolved within ~5 mins after complete addition of the Br_2 solution. The reaction solutions were stirred at RT (60 °C for pyridyl **331d**) and after 1 h a precipitate had formed. The precipitate was collected by filtration and air dried to afford **332a**, **332b** and **332d** in good yield. An alternative method was sought for the nitro analogue **332c** as no bromination occurred due to its insolubility in $CHCl_3$. The reaction procedure remained the same for **332c** but acetic acid was used as the solvent instead of chloroform. The reaction mixture was stirred at reflux for 3 h and then allowed to cool to RT. The resulting precipitate was collected by filtration and air dried to afford **332c** as a yellow powder. The extra reaction time needed for bromination presumably resulted from the electron deficiency of the alkene due to the strongly electron withdrawing nitro group.

Dibromocinnamic acids **332a**, **332c** and **332d** were produced as the *anti*-adducts with no *syn*-adducts observed. Methoxy analogue **332b** was produced in a 5:1 *anti*:*syn* ratio, possibly as a result of stabilisation of a benzylic carbocation (Scheme **52**).[178] Bromide trapping of **335** would erode the stereochemical *anti*-preference.



Scheme **52**: Proposed generation of syn addition product **337**

Microwave-mediated decarboxylation/dehydrobromination was then performed using the method of Kuang.[56] This involved irradiation of the dibromoacids in DMF containing TEA at 200 W for 30-60 seconds. Initially the reaction was performed on dibromoacid **332a** in a sealed microwave vessel but low conversion and poor *E*/*Z* selectivity resulted. Irradiating under the same conditions but in an open vessel resulted in full conversion and complete selectivity for (*Z*)-β-bromostyrene **79a** (Figure **27**). The isomers could be identified by the coupling constants of the vicinal protons. The *E* isomer has a significantly larger coupling constant (*J* = 16.1 Hz) than the *Z* isomer (*J* = 8.1 Hz) as predicted by the Karplus equation.[179,180]

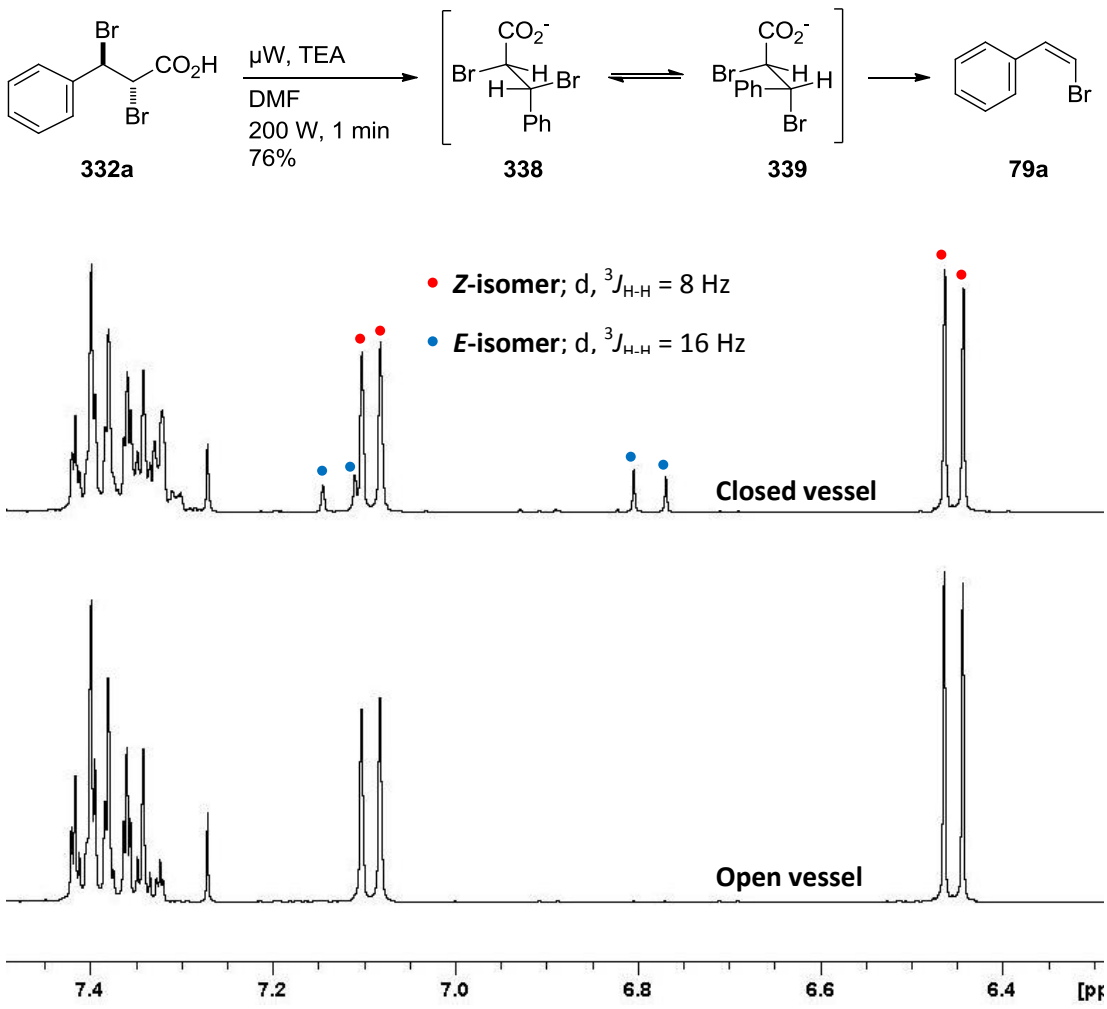


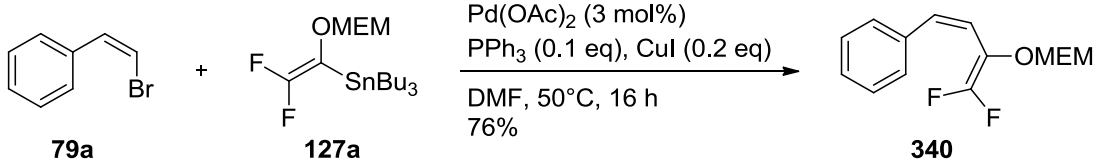
Figure **27**: ^{1}H NMR of open and closed vessel microwave-induced generation of **79a**

The yield of **79a** was improved further (88%) by irradiating at 140 °C for three minutes while stirring; the DMF solvent discoloured and refluxed violently when controlling the reaction by maximum power (200 W). Styrenes **79b**, **79c** and **79d** were obtained in good yield using this method. It should also be noted that **79b** was generated in 80% yield by stirring a solution of dibromoacid **332b** and TEA in DMF at RT for 96 h. This method would be of considerable value if scale-up was required; the amount of **79b** produced by microwave irradiation is limited by the size of the reactor cavity.

With (*Z*)-β-bromostyrenes in hand the developed palladium-catalysed coupling methodology could be applied to generate electrocyclisation precursors.

2.2.1.2 Preparation of 1,3-phenyldienes

Key to the success of this strategy was the ability of the palladium-catalysed coupling to generate phenyldienes with retention of the internal *Z*-alkene configuration, which was essential for the subsequent electrocyclisation step. Stille coupling of stannane **127a** with bromostyrene **79a** using the Stille conditions described earlier, afforded phenyldiene **340** in 76% yield after chromatography (Scheme **53**).



79a **127a** **340**

Scheme **53**: Stille coupling to afford phenyldiene **340**

In order to gain confidence that the generated diene was of *Z*-configuration, some commercial *E*-(β)-bromostyrene was purchased and coupled with stannane **127a** and the resulting ^{1}H NMR was compared with that of **340** (Figure **28**). The purchased *E*-(β)-bromostyrene was supplied as a 85:15 (*E*:*Z*) isomeric ratio (confirmed by ^{1}H NMR). Stille coupling with **127a** under the standard conditions afforded a mixture of **340** and **341** in a 88:12 ratio.

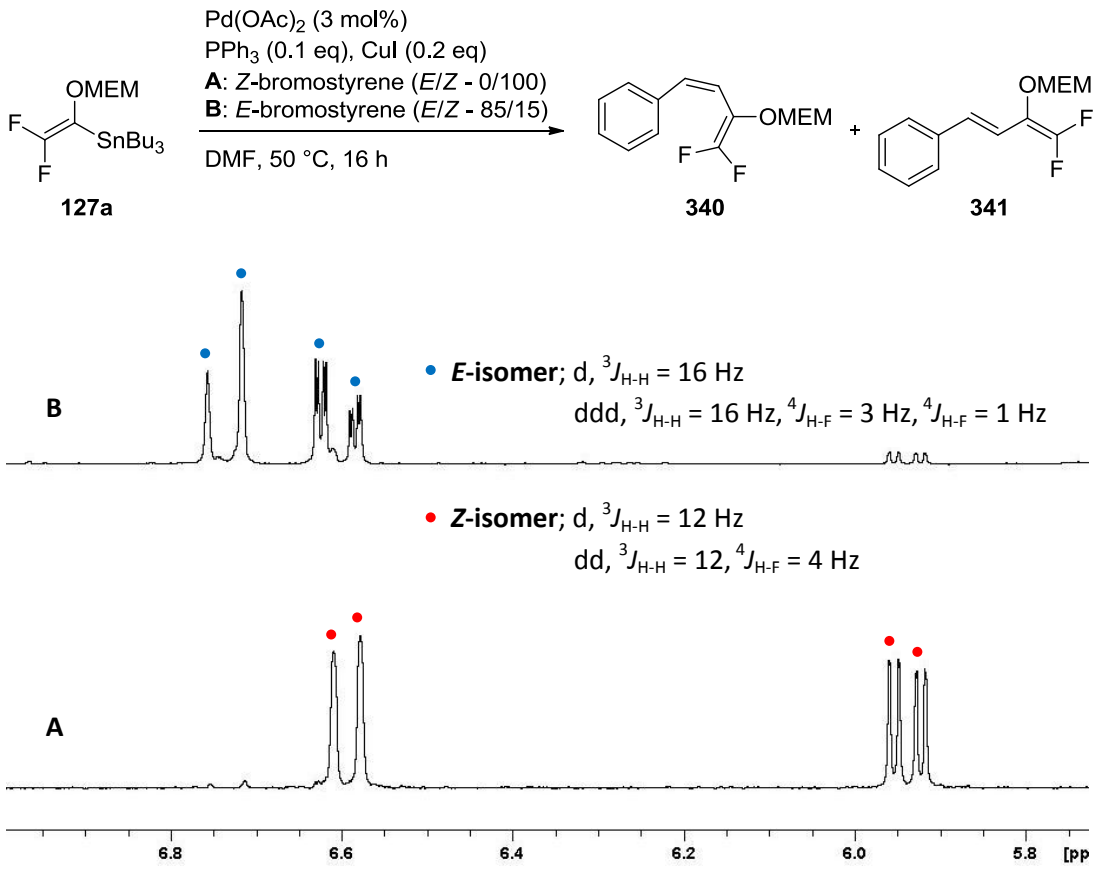
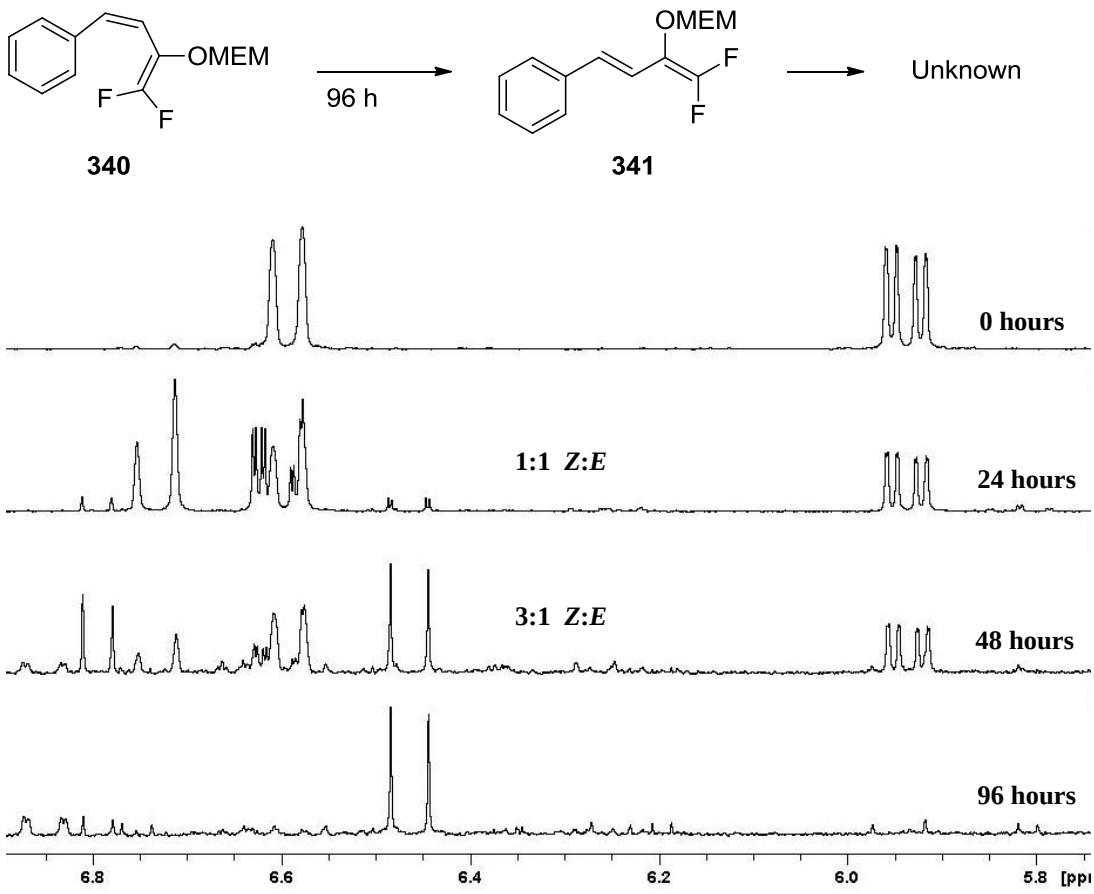


Figure **28**: Expanded ^{1}H NMR after coupling of **127a** with *Z*-bromostyrene (**A**) and *E*-bromostyrene (**B**)

The alkene coupling constant (*J*) observed for phenyldiene **340** (generated under conditions **A**) was 12.4 Hz while the coupling constant observed for phenyldiene **341** (generated under conditions **B**) was found to be 16.1 Hz. The observed coupling constants, in conjunction with the retained isomeric ratio of starting materials and products using conditions **B**, confirmed that coupling of **127a** and *Z*-(β)-bromostyrenes occurs with fidelity.

It became quickly apparent that phenyldiene **340** was not stable either as a solution in $CDCl_3$ or stored neat under refrigeration (~5 °C). Within hours in both cases a

significant quantity of *E*-isomer was observed (^{1}H NMR; Figure **29**). Rapid degradation of the *E*-isomer was also observed.

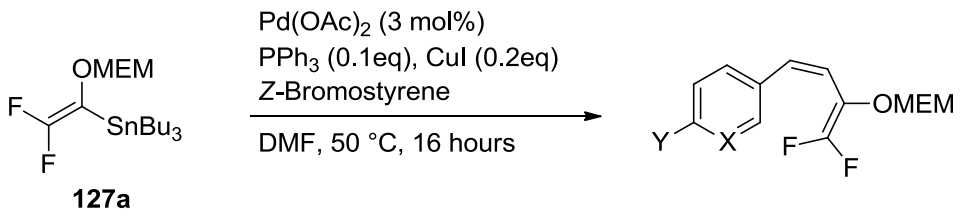


340 **341**

Figure **29**: Expanded ^{1}H NMR spectra showing the degradation of phenyldiene **340**

Grubbs[181] and Pine[182] have prepared similar (*Z*)-phenyl dienes by olefination of cinnamic esters with retention of stereochemistry. Neither described the lifetime of the dienes or the isomeric ratios over time.

The isomerisation/degradation behaviour was repeated for other (*Z*)-phenyldienes (Table **30**).



Structure	Y	X	Yield
340	H	CH	76%
342	OMe	CH	-[a]
343	NO_2	CH	82%
344	H	N	52%

a) Not recorded

Table **30**: Summary of the preparation of (*Z*)-phenyl dienes

The 4-methoxy analogue **342** was not isolated but a mixture of the *Z*- and *E*-isomers was observed by ^{1}H and ^{19}F NMR of the crude reaction mixture. The nitro and pyridyl analogues **343** and **344** were isolated but also isomerised and degraded rapidly.

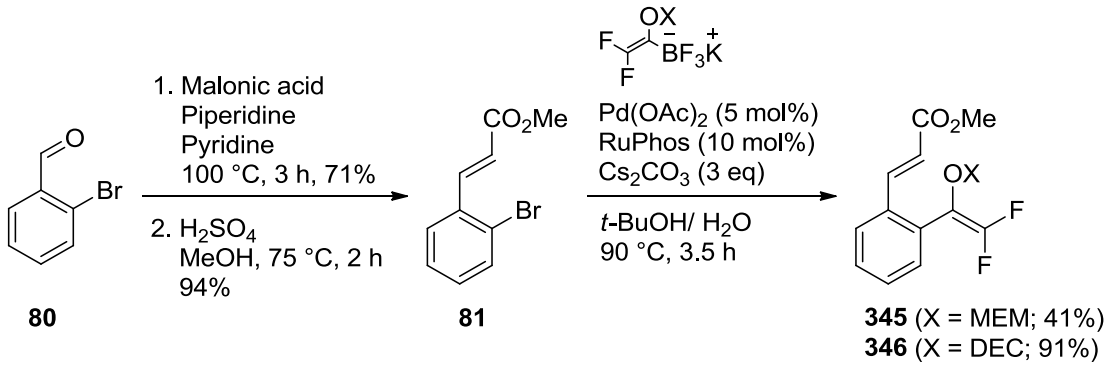
The degradation products were not identified but the rapid isomerisation and degradation of these phenyl dienes meant they were unsuitable as electrocyclisation precursors. An alternative electrocylisation approach was investigated.

2.2.2 Strategy 2: Divinylbenzene approach

2.2.2.1 3-Phenylacrylate species

The divinylbenzene approach appeared to be a more robust option as there was no opportunity for isomerisation of a double bond to occur. The first divinylbenzene

motif was generated by a Knoevenagel condensation on bromobenzaldehyde **80**. The resulting cinnamic acid was converted to the methyl ester which was then coupled with trifluoroborate **106a** (Scheme **54**). The previously developed Suzuki conditions (*vida supra*) resulted in only traces of **345** (observed by GC-MS); it is possible that greater steric demand imposed by the *ortho*-substituent resulted in poor conversion to **345**. Using the same base and reaction solvents but exchanging the catalyst for $Pd(OAc)_2$/RuPhos catalyst/ligand system afforded **345** and **346** in 41% and 91% isolated yields respectively.

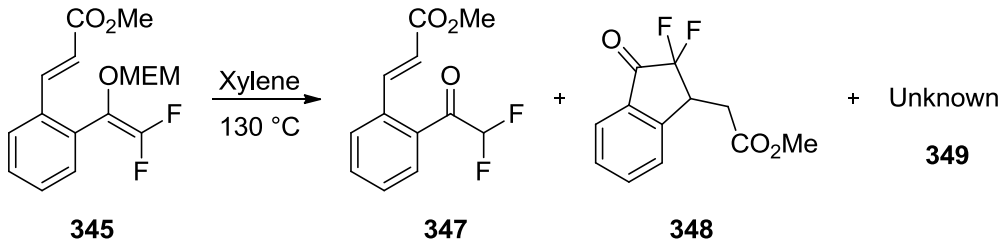


Scheme **54**: Preparation of divinylbenzenes **345** and **346**

It is unclear why the yield of **345** was lower than that of the DEC analogue **346**; however, electrocyclisation precursors were in hand for the first time and electrocyclisation was attempted.

The first electrocyclisation was attempted on divinylbenzene **345** (Scheme **55**). A solution of **345** in xylene was stirred at 130 °C in a sealed tube for 18 h. The starting material had been completely consumed by this time (^{19}F NMR) and signals for three major fluorinated compounds were observed (Figure **30**). The different

species were isolated by chromatography and NMR and GC-MS analysis was performed to identify the compounds.



345 **347** **348** **349**

Scheme **55**: First electrocylisation attempt of **345**

The relatively labile MEM group was cleaved under the conditions used to afford difluoroketone **347**, which has a characteristic doublet in the ^{19}F NMR spectrum, and a corresponding triplet in the ^{1}H NMR spectrum. Difluoroindanone **348** was identified by a characteristic geminal fluorine coupling in the ^{19}F NMR spectrum consistent with the presence of non-equivalent fluorines on an sp^3 centre; the GC-MS analysis was also consistent with the structure of **348**. The third major species observed in the crude ^{19}F NMR spectrum could not be identified. The data accrued suggested that the MEM group was intact and that the alkenyl protons were still present. A new signal in the ^{1}H NMR (t, J = 12 Hz) corresponding to the triplet in the ^{19}F NMR (J = 17 Hz) appeared to be the only significant difference in the spectroscopic data from that of starting material **345**. The three species were generated in a 1:1:1 ratio.

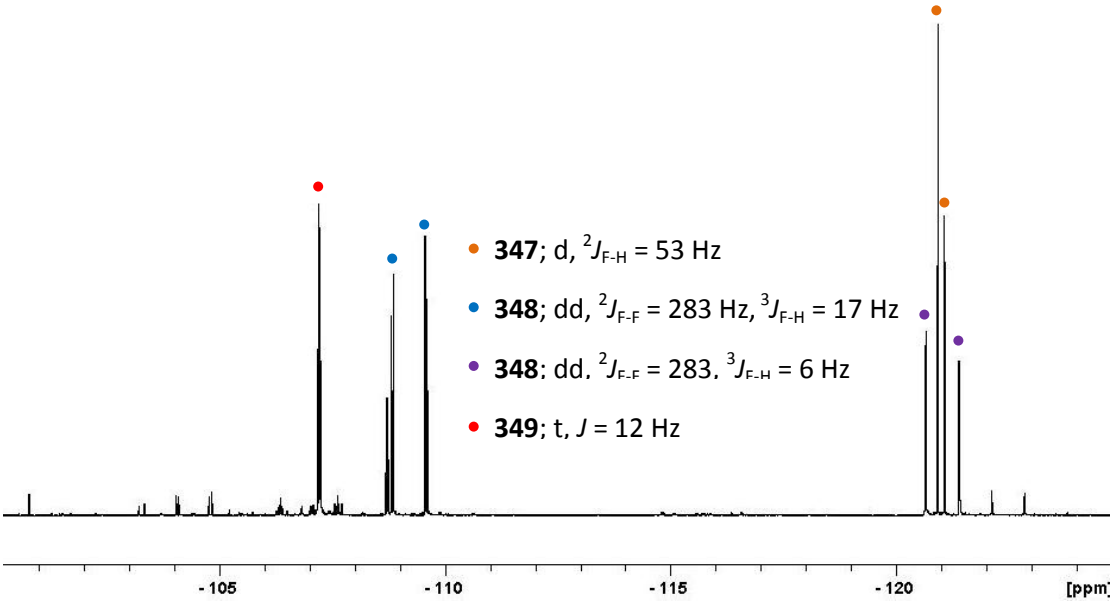
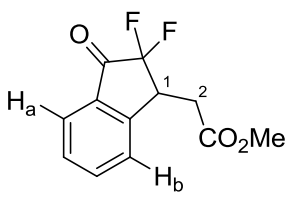
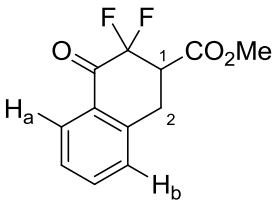


Figure **30**: ^{19}F NMR of the crude RM of the electrocyclisation of **345**

Identification of intramolecular conjugate addition product difluoroindanone **348** required some investigation as the observed NMR spectra and GC-MS data were also consistent with the *endo*-cyclised species **350**, which would be generated via electrocyclisation.



348



350

HMBC NMR analysis revealed correlations consistent with species **348**, but not with **350**. It was expected that proton H_b would correlate with C_1 of **348** but not with C_1 of **350**.

The ^{13}C NMR signal for C_1 was identified easily, as it had a larger C-F coupling constant than C_2, due to being closer to the difluorinated carbon (Figure **31**).

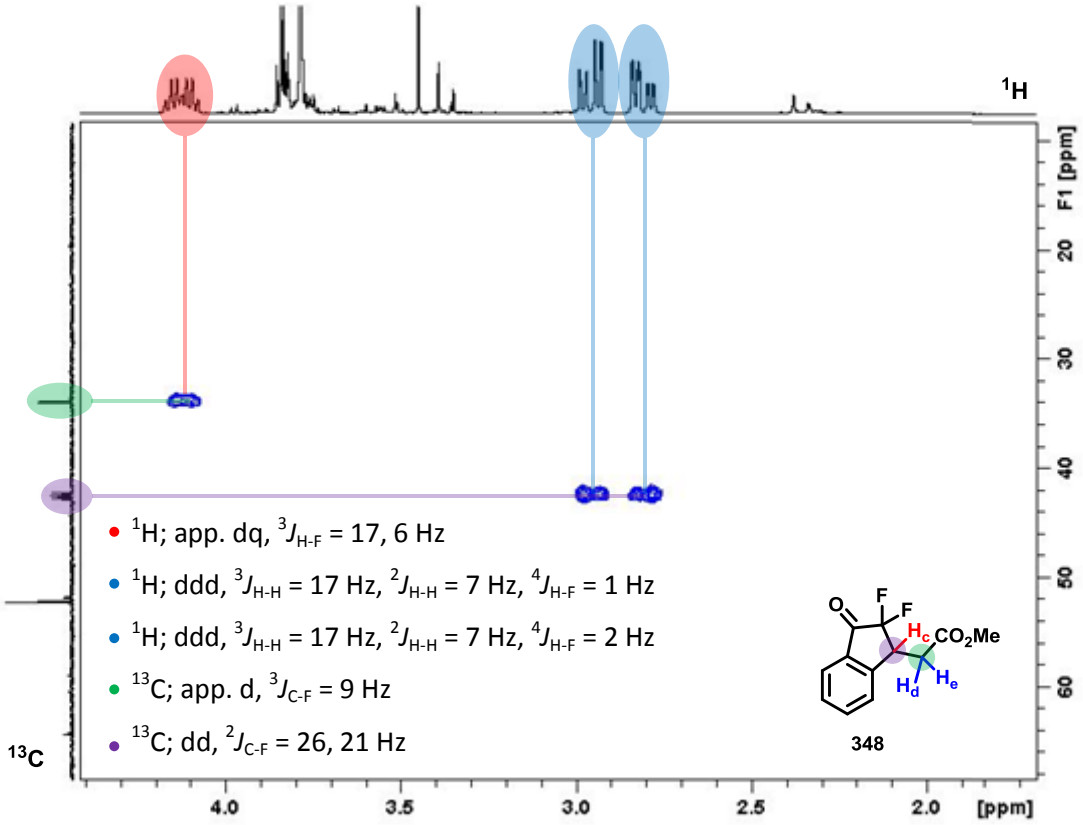


Figure **31**: Expanded HMBC of indanone **348** showing ^1H-^{13}C correlations of H_c ,H_d and H_e

As expected, protons H_a and H_b appear as a pair of doublets by ^1H NMR. H_a was identified easily as it correlated with the distinctive carbonyl carbon while H_b did not (Figure **32**).

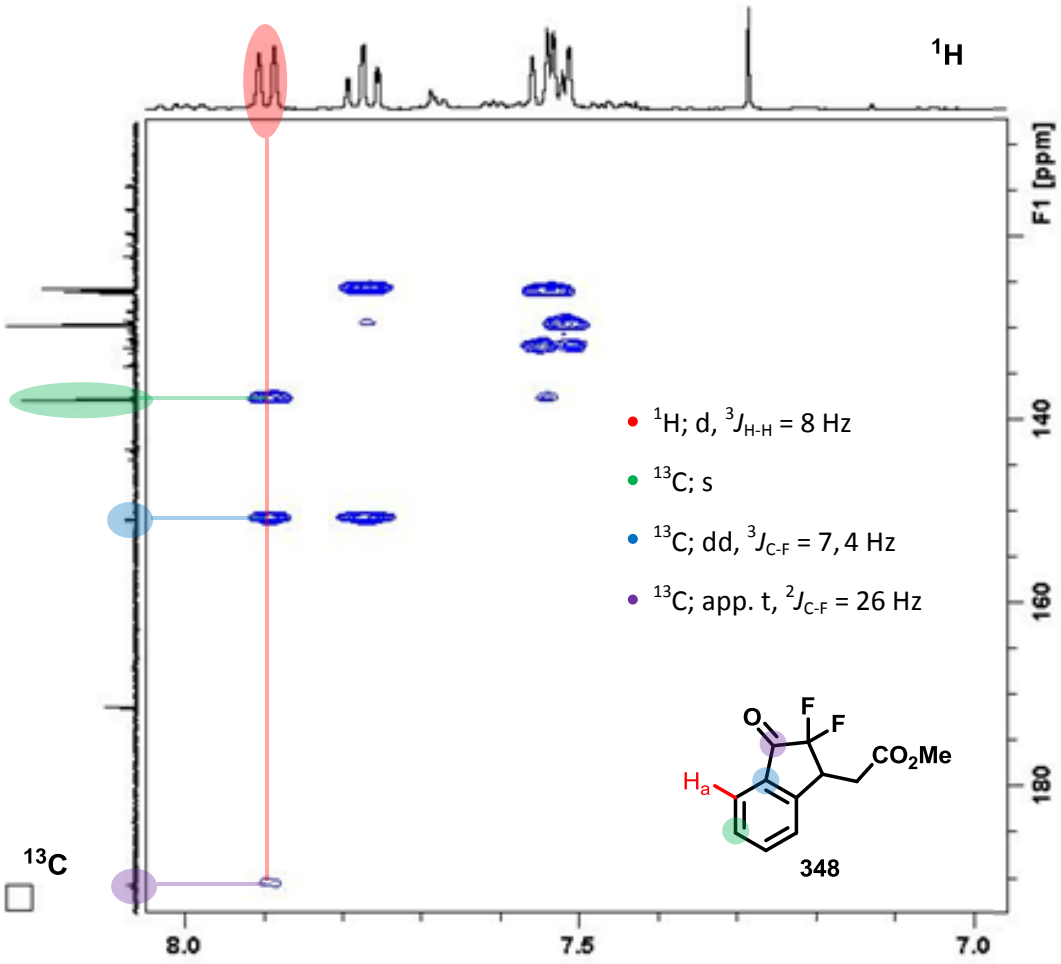


Figure **32**: Expanded HMBC of indanone **348** showing ^{1}H-^{13}C correlations of H_a

Once the ^{13}C and ^{1}H NMR signals for C_1 and H_b were identified, it was a simple task to search for a correlation between the two signals. Such a correlation was observed (Figure **33**) proving the formation of indanone **348**.

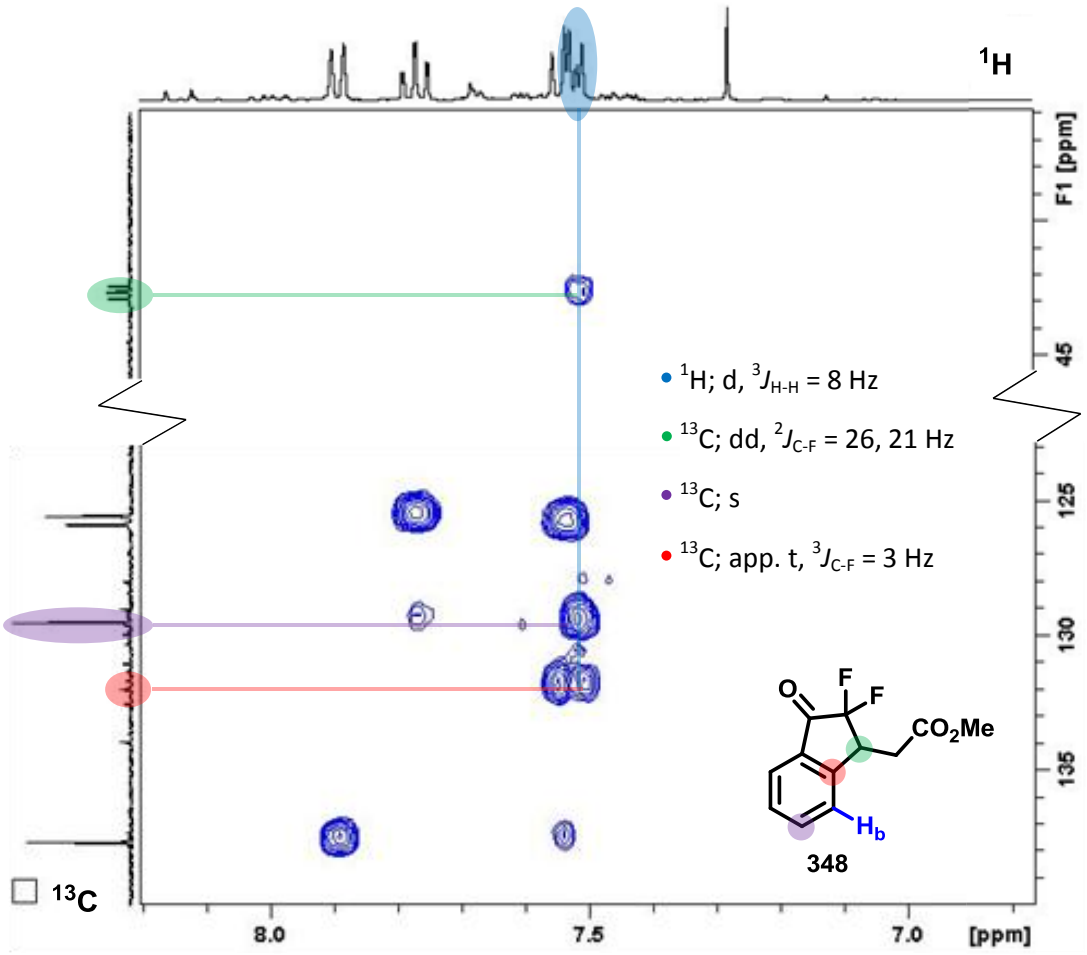
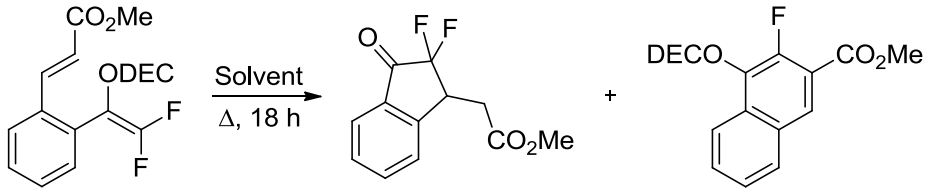


Figure **33**: Expanded HMBC of indanone **348** showing ^{1}H - ^{13}C correlations of H_b

Electrocyclisation of DEC divinylbenzene **346** was attempted using the conditions described for **345**, but no conversion was observed. Conversion of starting material was observed only above 170 °C (Table **31**). At 180 °C in diphenylether, indanone **348** and electrocyclisation product **351** were identified by ^{19}F NMR analysis of the crude reaction mixture (entry 3). Formation of indanone **348** was surprising as the DEC group is considerably less labile than the MEM protecting group; however, fluoroarene **351** was generated for the first time indicating that electrocyclisation of

divinylbenzene motifs is possible. The ratio of **348**:**351** remained virtually unchanged when the reaction temperature was increased (entries 4 and 5).



346 **348** **351**

Entry	Solvent	T (°C)	Conversion[a]	XX:XX
1	Xylene	130	0%	-
2	Xylene	170	0%	-
3	Ph_2O	180	85%	2:3
4	Ph_2O	200	100%	1:1
5	Ph_2O	220	100%	1:1[b]

a) ([**348**+**351**]/[**346**+**348**+**351**]) x 100; b) 9 mg (38%) isolated by chromatography as a 3:2 ratio

Table **31**: Development of the electrocyclisation of **346**

Electrocyclisation of **346** by UV irradiation was performed in an attempt to increase the selectivity for either indanone **348** or fluoroarene **351**. In the first instance a solution of **346** in heptane in a sealed vessel was irradiated continuously for 48 h with a full spectrum lamp (220-700 nM). LC-MS analysis of the crude reaction mixture revealed complete conversion of **346**, and generation of fluoroarene **351** and a new species. The new compound was isolated by chromatography as the major species in a 3:2 mixture with **351** and analysed by NMR (Figure **34**). The ^{19}F NMR signals contained a geminal coupling constant of 148.7 Hz, suggestive of non-

equivalent fluorine atoms on an sp^3 hybridised carbon. ^{1}H NMR analysis also revealed that the DEC group had remained intact.

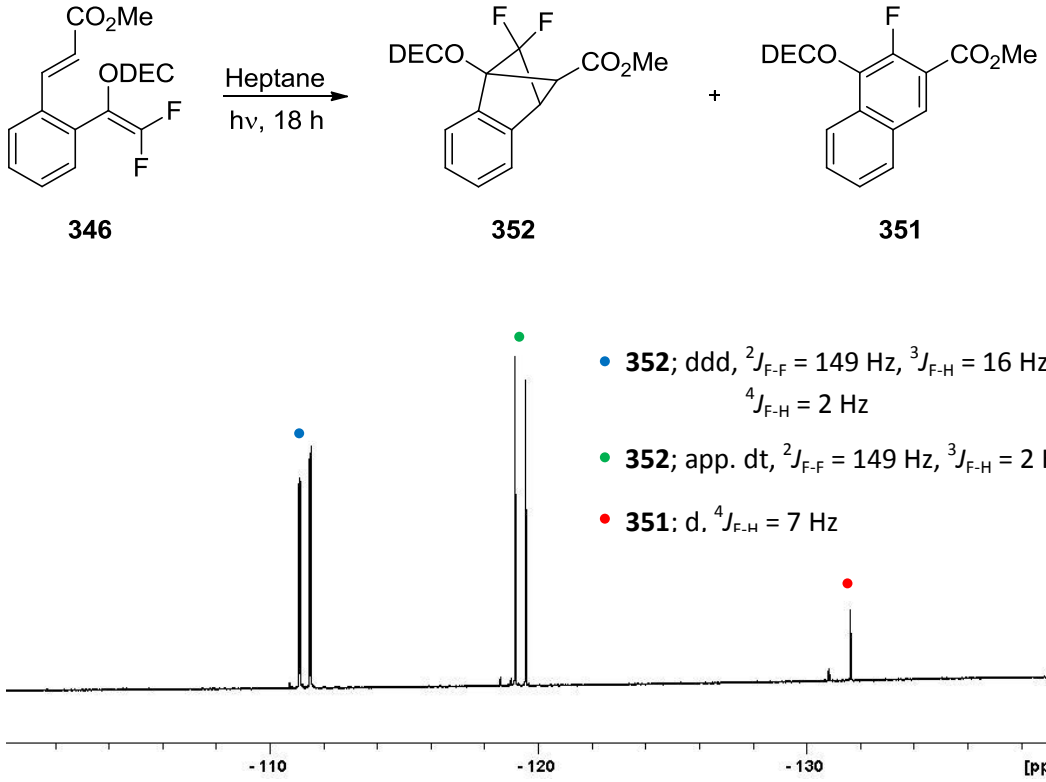


Figure **34**: ^{19}F NMR of a mixture of fluoroarene **351** and suspected species **352**

A significant amount of heat was generated by the lamp which may have contributed to the formation of the fluoroarene. Irradiation of **346** under flow conditions was performed in an attempt to generate suspected bridged species **352** selectively; flow chemistry would minimise any reaction by thermal activation.

Using flow conditions established by Booker-Milburn[183] and developed by Harrowven,[184] a solution of **346** in acetonitrile was irradiated with a 9 W UV (254 nM) bulb. After a reaction time of 1 h, ^{19}F NMR analysis revealed suspected bridged species **352** and fluoroarene **351** in a 5:2 ratio. Preparative HPLC of the crude oil

isolated after work-up afforded 12 mg (35%) of **352** and 5 mg of **351**. The ^{1}H and ^{13}C NMR spectra of the purified compound revealed signals that were consistent with **352** (Figure **35**).

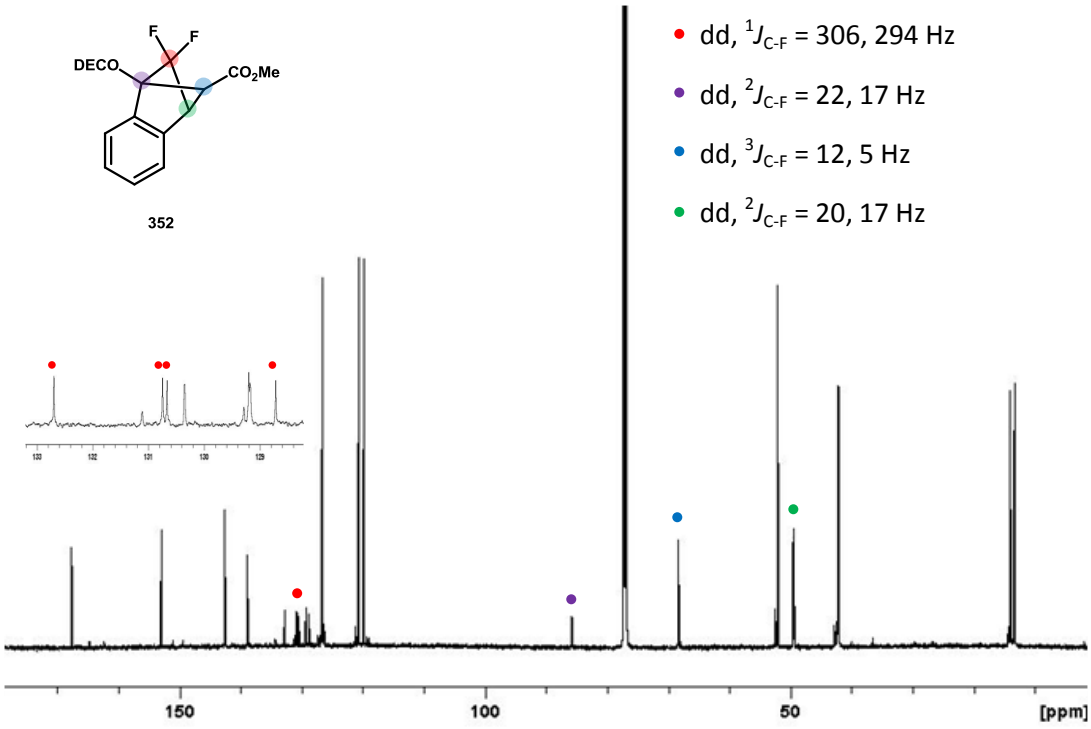
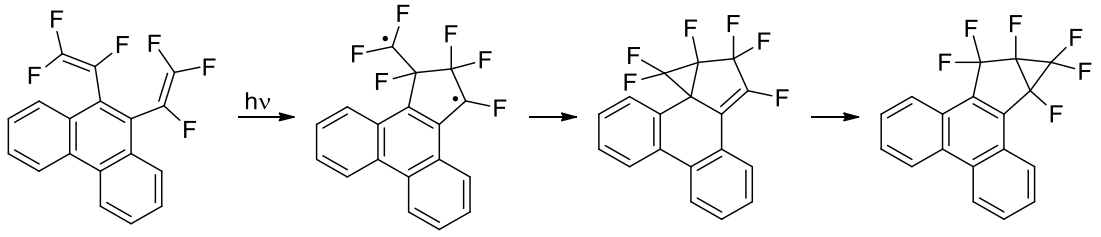


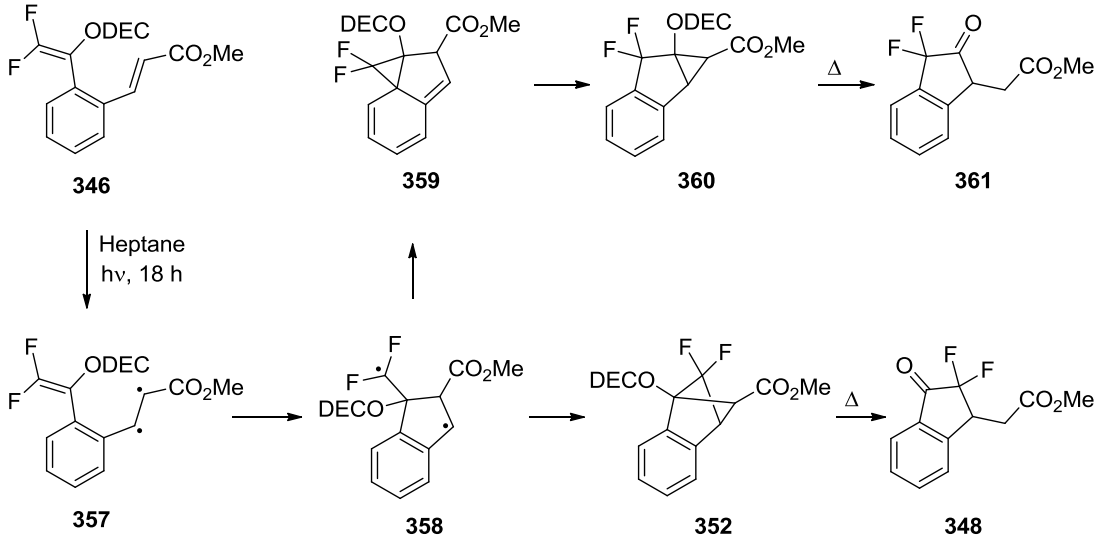
Figure **35**: ^{13}C NMR spectrum of bridged species **352** after preparative HPLC

Dolbier and co-workers have previously performed electrocyclisations of similar fluorinated divinylphenanthrenes **353** to form biaryl species **356** (Scheme **56**).[114] A radical cyclisation was suggested as the mechanism of the reaction. The main species observed by Dolbier was rationalised by suggesting a radical isomerisation from **355** to **356**.



Scheme **56**: Suggested radical cyclisation of divinylphenanthrene **353**

Applying Dolbier's mechanism to the cyclisation of divinylbenzene **346** would give rise to two possible species, the bridged species **352** and a new bridged species **359** (Scheme **57**). Both compounds would be very difficult to differentiate by spectral analysis.



Scheme **57**: Possible radical cyclisation mechanism for the formation of **352** and **359**

The isolated product of the photochemical electrocyclisation was heated at 200 °C in diphenylether in a sealed vessel to simulate the electrocyclisation conditions, and resulted in exclusive formation of difluoroindanone **348**. The signals in the ^{19}F NMR

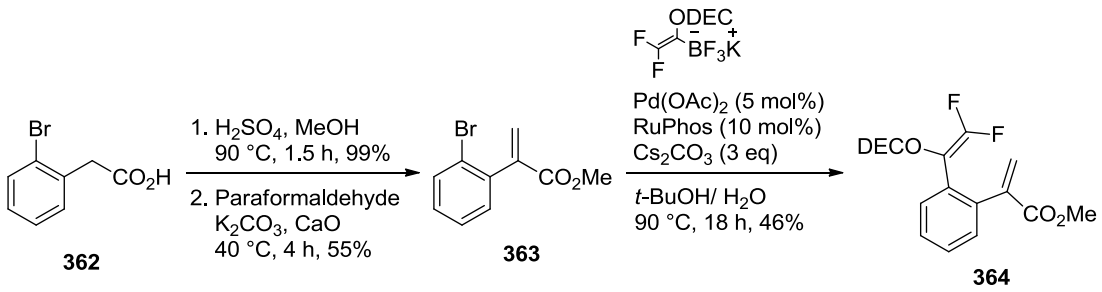
spectrum of the crude reaction mixture matched those of the previously isolated difluoroindanone exactly, ruling out the formation of the isomeric difluoroindanone **361** and therefore also ruling out the isomerisation mechanism suggested by Dolbier.

To rule out the possibility of ambient light triggering a photocyclisation, **346** was subjected to the thermal electrocyclisation conditions (Xylene, 200 °C) in darkness (tin foil covered vessel). The same ratio of indanone **348** and fluoroarene **351** was observed by analysis of the crude reaction mixture by ^{19}F NMR.

A small amount of fluoroarene was observed after attempted electrocyclisation of 3-phenylacrylate **346**; however, formation of difluoroindanone side-products suggest that species with a methoxycarbonyl group at the β-position are unsuitable for this transformation.

2.2.2.2 2-Phenylacrylate species

In order to determine if the methoxycarbonyl group at the β-position was inhibiting the electrocyclisation reaction, divinylbenzene **364** was generated (Scheme **58**) and electrocyclisation attempted.



Scheme **58**: Preparation of divinylbenzene **364**

Acid **362** was esterified under acidic conditions on a 52 mmol scale to afford the methyl ester in 99% yield. The ester was then olefinated using paraformaldehyde to afford 2-(2'-bromophenyl)-acrylate **363** in 58% yield. Suzuki coupling of **363** with **106b** generated divinylbenzene **364** in 46% yield after chromatography. The coupling yield was significantly lower than for the corresponding coupling of 3-phenylacrylate **346** with **106b** (91%). The low yield may be due to the steric bulk of the electrophile; slow oxidative addition of **363** would result in an increased amount of deborylation side product **205b** and hence a lower conversion of acrylate **363** (incomplete conversion of **363** was observed by GC-MS). Since the rate of oxidative addition has already been enhanced by the use of the RuPhos ligand, control of the rate of trifluoroborate **106b** hydrolysis may improve the reaction yield by decreasing the deborylation side product. Lloyd-Jones and co-workers suggest that one of the key factors governing the rate of release of the active boronic acids from trifluoroborate salts is control of the pH.[153,174] An induction period (substrate specific) with slow release of boronic acid precedes a rapid decrease in pH and release of boronic acid. The solvent system used by Lloyd-Jones is a THF:H_2O (10:1) mix that results in a biphase when Cs_2CO_3 (3 eq) is used as base, with a lower pH recorded in the bulk organic phase than the aqueous phase. The induction period before acid catalysed hydrolysis was prolonged by adequate stirring of the phases and by addition of more base. Two phases are not present in the Suzuki conditions used to prepare **364** and so an effort was made to attenuate the rapid hydrolysis of **106b** by increasing the concentration of Cs_2CO_3. Mixtures of **106b** with 2, 3, 4 and

10 equivalents of Cs_2CO_3 in *t*-BuOH/H_2O (2.7:1) were stirred at 90 °C for 18 h. A sample of each reaction mixture was removed and analysed by ^{19}F NMR (Figure **36**).

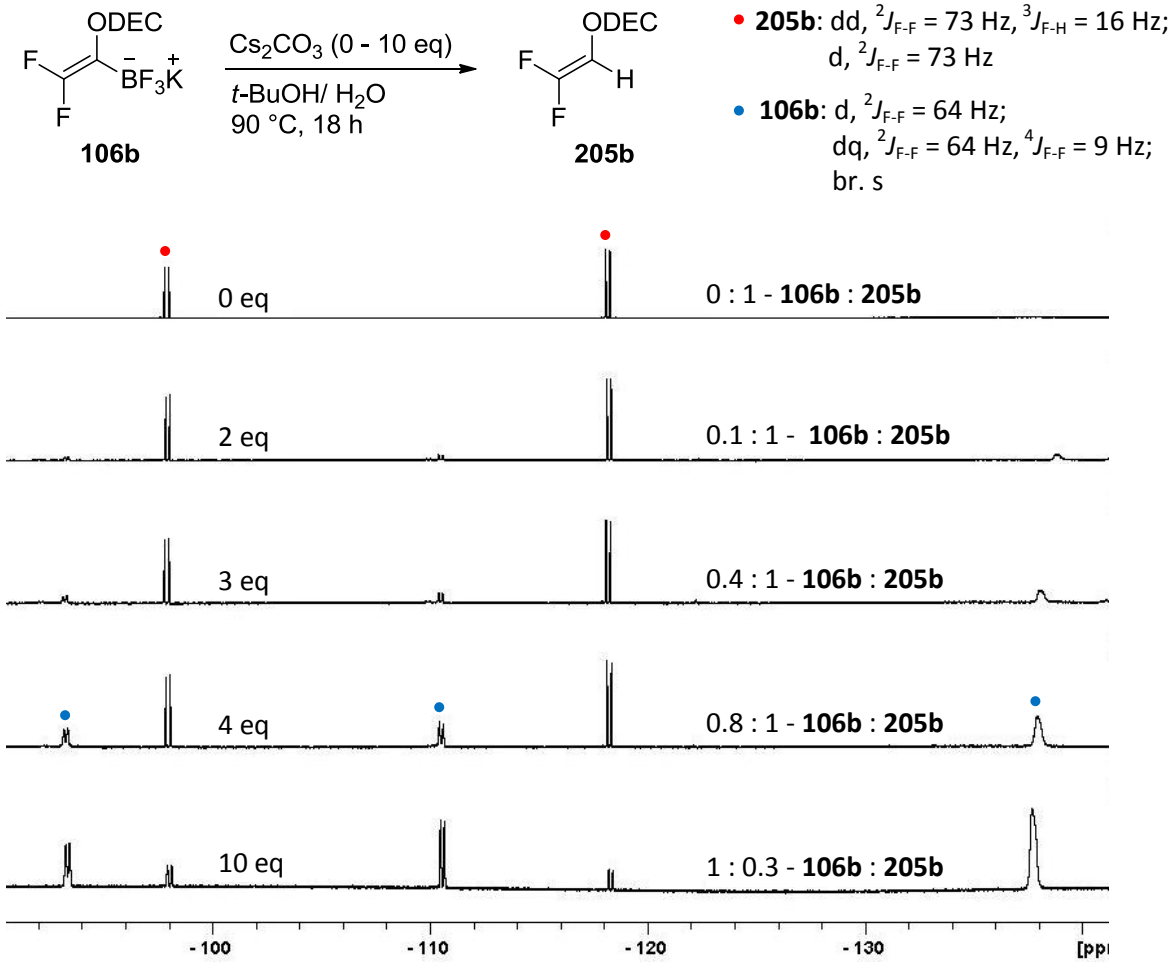


Figure **36**: ^{19}F NMR analysis of crude reaction mixtures from base study (0 – 10 eq)

A significant amount of trifluoroborate **106b** was present after 18 h when 10 eq of base was used. Borate was still present after 48 h (Figure **37**), demonstrating that increased Cs_2CO_3 concentrations significantly retarded the rate of hydrolysis of **106b** ($t_{1/2}$ = ~48 h).

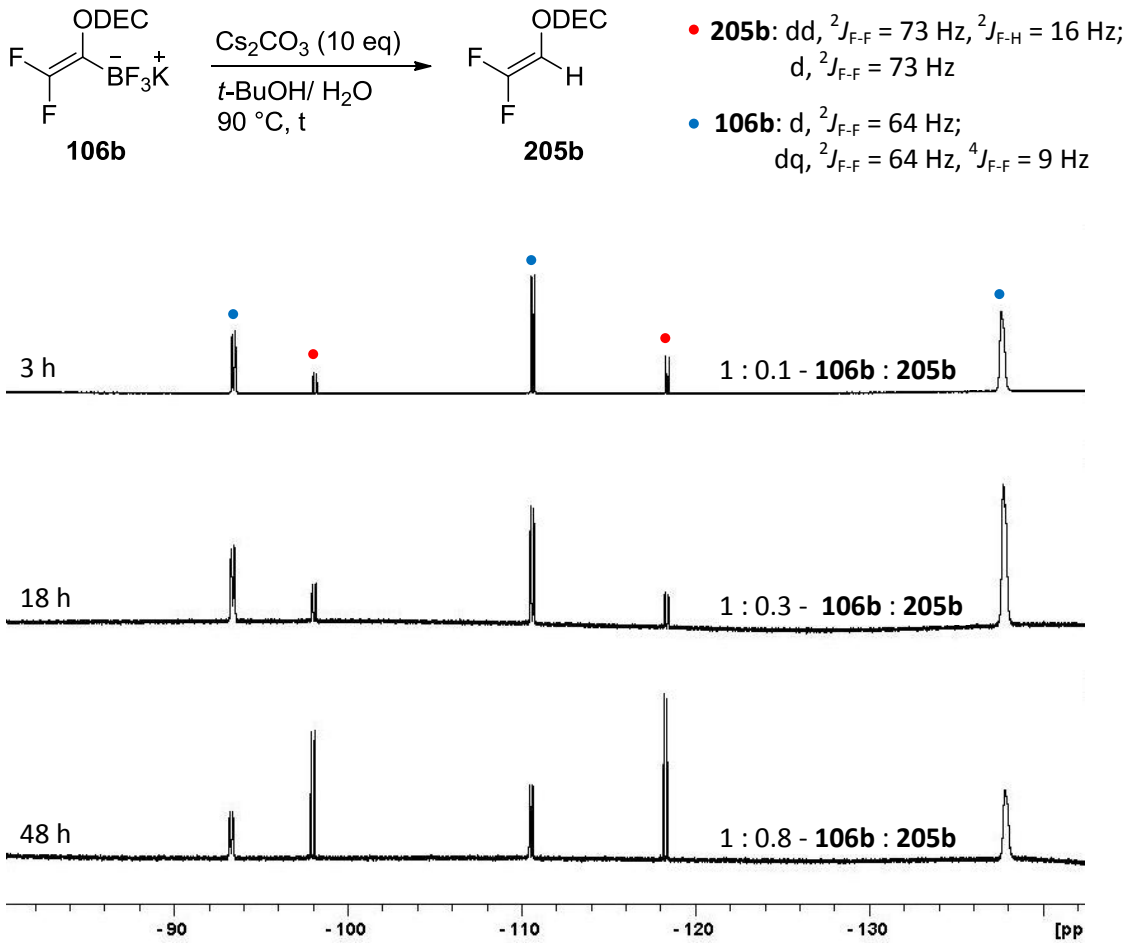
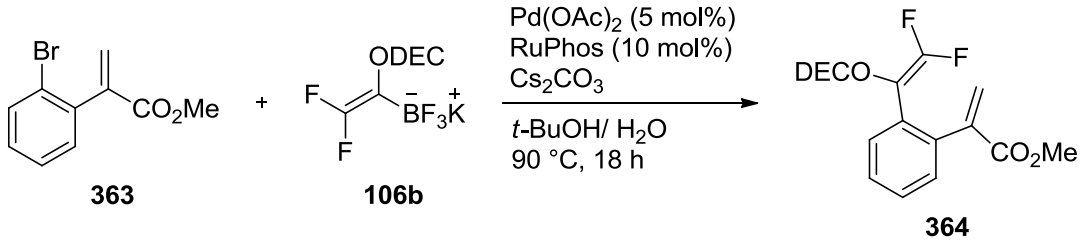


Figure **37**: ^{19}F NMR analysis of crude reaction mixtures from base study (10 eq)

Suzuki coupling of trifluoroborate **106b** and acrylate **363** was attempted with an increased concentration of Cs_2CO_3 to try to take advantage of the slower rate of hydrolysis of **106b**. Suzuki couplings with various concentrations of Cs_2CO_3 were run in parallel (Table **32**).



363 **106b** **364**

Entry	Cs_2CO_3 (eq)	106b : 205b[a]	Yield of 364[b]
1	0.2	1 : 0.39	39%
2	0.3	1 : 0.30	46%
3	0.4	1 : 0.33	44%
4	10	1 : 0.30	49%

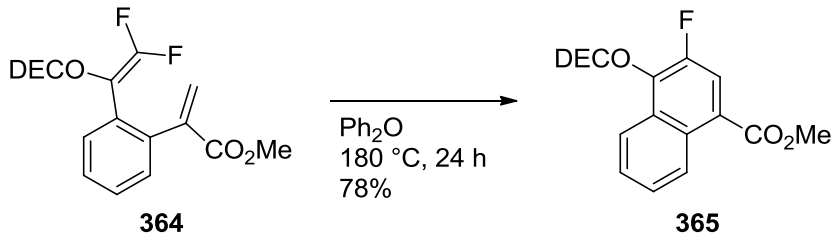
a) ^{19}F NMR analysis of RM after 18 h; b) After chromatography

Table **32**: Suzuki coupling of **106b** with **363** using various concentrations of Cs_2CO_3

Increasing the base concentration made little difference to the isolated yield of divinylbenzene **364**. A modest reduction in deborylated species **205b** resulted in a marginal gain in yield.

With some divinylbenzene **364** in hand, electrocyclisation was attempted; a solution of **364** in diphenylether was stirred at 180 °C in a sealed vessel for 24 h. ^{19}F NMR analysis of the reaction mixture revealed complete conversion to a single fluorinated product. The new fluorinated compound had a distinctive ^{19}F NMR signal (δ 130.8, d, *J* = 11 Hz) indicative of fluoroarene formation. Flash chromatography (20% diethyl ether in cyclohexane) afforded fluoroarene **365** in 78% yield.

Exclusive formation of fluoroarene **365** from divinylbenzene **364** with loss of HF represents the first successful electrocyclisation reaction of this type. The scope of the methodology was then investigated.



364 **365**

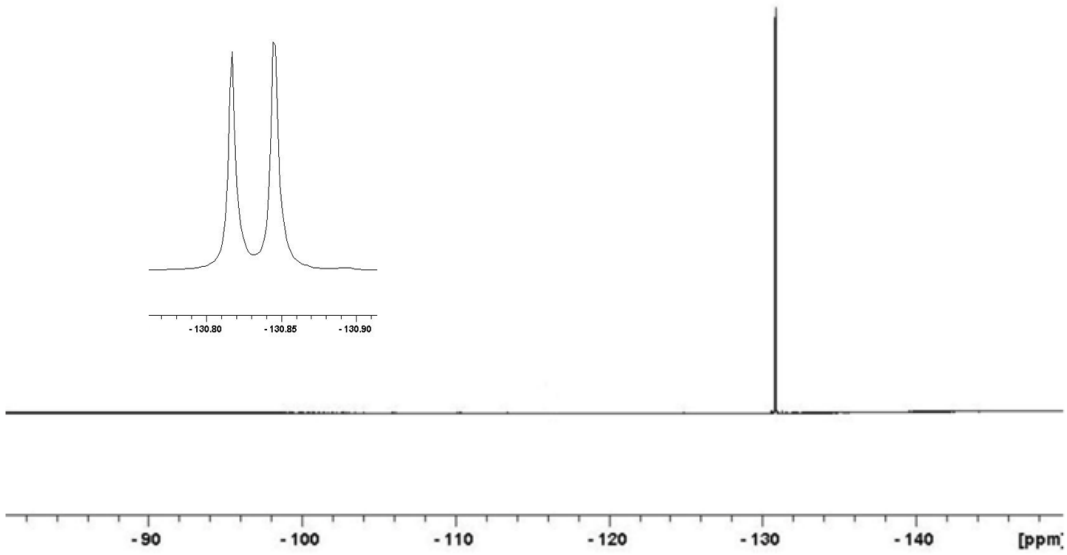
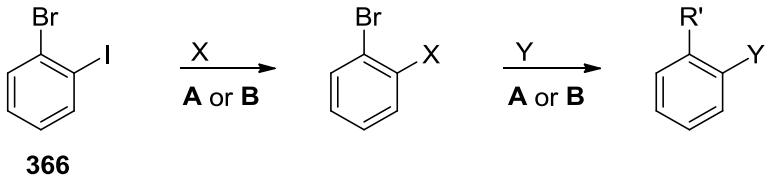


Figure **38**: ^{19}F NMR spectrum of fluoroarene **365**

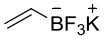
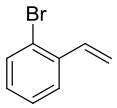
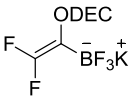
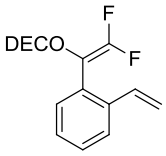
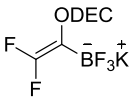
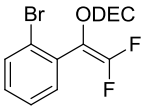
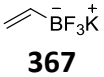
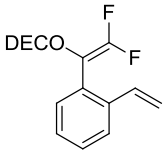
2.2.2.3 Iterative coupling approach

Order of coupling

To increase the scope of the electrocyclisation strategy a double palladium-catalysed coupling approach was undertaken using 1-iodo-2-bromobenzene **366**. To determine the most efficient preparation of electrocyclisation precursors, the order of vinyl coupling was investigated (Table **33**). Divinylbenzene **369** was used as the test substrate as it is the simplest divinylbenzene species available by this route.



366

Entry	Coupling Partner 1	Conditions	Product (yield)	Coupling Partner 2	Conditions	Product (yield)
1	 **367**	**A**	 **368**:(94%)	 **106b**	**B**	 **369**:(59%)
2	 **106b**	**B**	 **370**:(46%)	 **367**	**B**	 **369**:(84%)

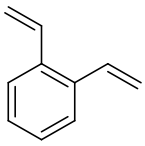
A: $(PPh_3)_2PdCl_2$ (5 mol%), Cs_2CO_3 (3 eq), *t*-BuOH/H_2O (2.7:1); **B**: $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (3 eq), RuPhos (10 mol%), *t*-BuOH/H_2O (2.7:1).

Table **33**: Order of coupling in preparation of divinylbenzene **369**

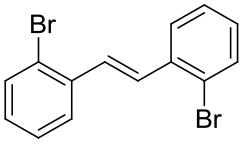
'Ligand-free' Suzuki coupling of vinyltrifluoroborate **367** with **366** afforded 2-bromostyrene **368** in high yield (94%) after chromatography (entry 1). No *bis*-coupled side product **371** was observed by GC-MS analysis of the reaction mixture. However, traces of a stillbene-type species **372** were observed. Side product **372**, generated by Heck coupling of styrene **368** and **366**, is a common product when generating species with a free vinyl moiety under palladium-catalysed conditions.[146,185,186] The second Suzuki coupling with **106b** afforded divinylbenzene **369** in 59% yield after chromatography and 55% overall yield from **366**.

The alternative coupling order (entry 2) generated **369** in an inferior 39% overall yield. The first Suzuki coupling of **106b** and **366** resulted in a significant quantity of

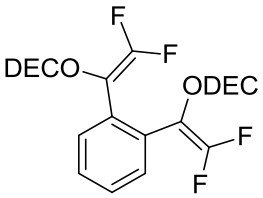
bis-coupled side product **373**. Presumably the electron withdrawing difluorovinyl moiety on **370** results in activation of the C-Br bond for a second oxidative addition.



371

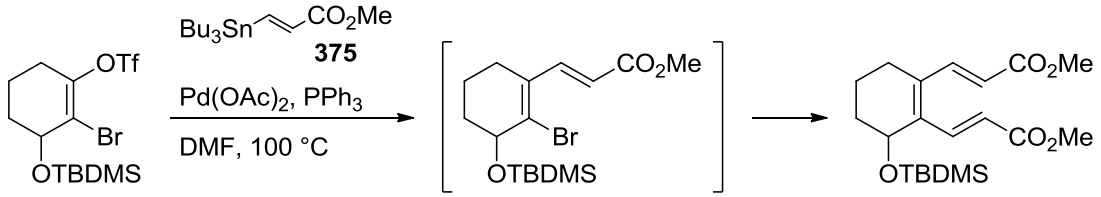


372



373

This *bis*-coupling issue was observed by Meijere and co-workers when coupling 1-trifloxy-2-bromocyclohexene with tributylstannyl acrylate (Scheme 59).[187] The C-Br bond of the first-formed butadiene was activated by the strong electron withdrawing nature of the acrylate and coupling of another unit of stannyl acrylate to form a symmetrical triene could not be suppressed.



374 **376** **377**

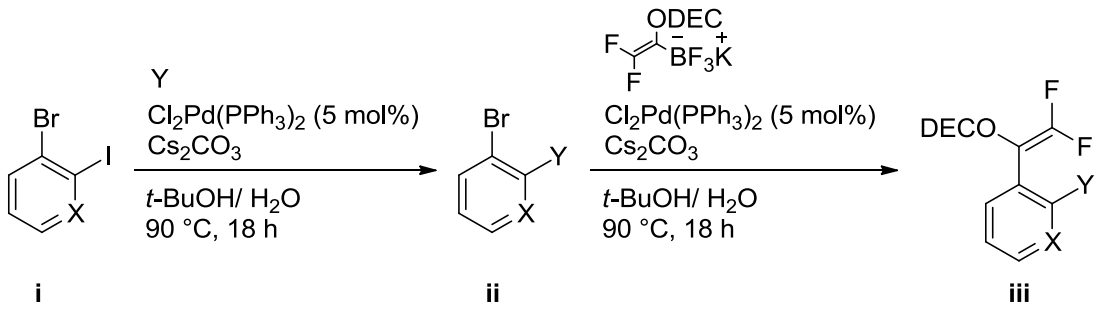
Scheme **59**: Meijere's uncontrolled *bis*-coupling of trifloxy-2-bromocyclohexene **374** with stannane **375**

The second Suzuki coupling of **370** with vinyltrifluoroborate **367** afforded the desired divinylbenzene **369** in good (84%) yield after chromatography.

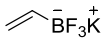
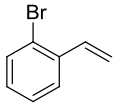
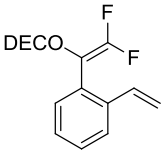
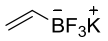
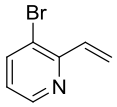
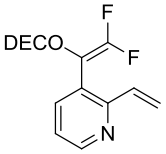
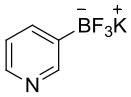
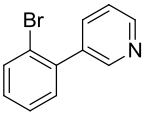
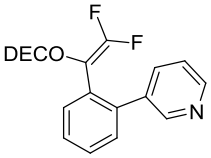
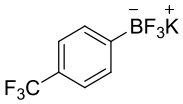
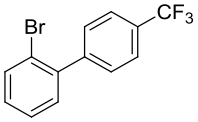
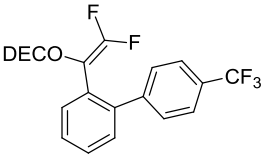
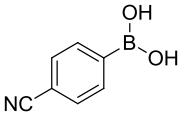
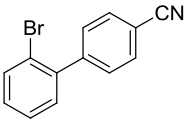
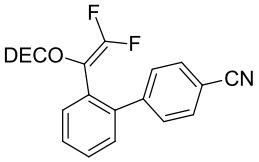
The order of palladium-catalysed coupling outlined in entry 1 (Table **33**) was adopted as the standard method for preparation of electrocyclisation precursors under the iterative coupling methodology.

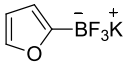
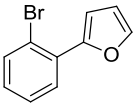
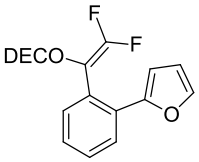
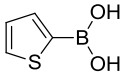
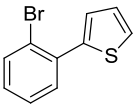
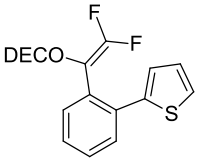
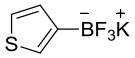
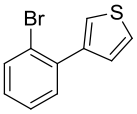
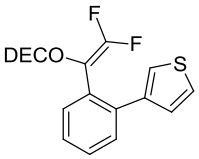
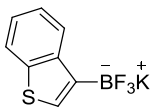
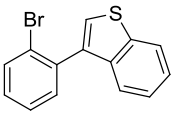
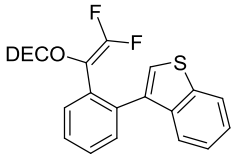
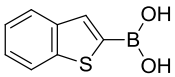
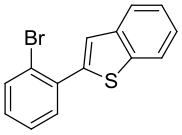
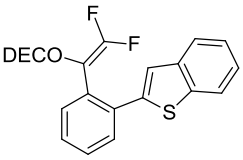
Electrocyclisation: scope and limitations

Due to time constraints the iterative coupling methodology was not optimised further, although it was observed that coupling of **106b** with styrenes generated from the first coupling did not require the Ruphos ligand to afford product in moderate yield. The un-optimised Suzuki couplings to afford electrocyclisation precursors are summarised in Table **34**. Boronic acids as well as trifluoroborates were used in the Suzuki couplings to good effect (entries 5, 7 and 10).



i **ii** **iii**

Entry	Y	Product ii (yield)	Product iii (yield)
1	 **367**	 **368**:(94%)	 **369**:(59%)[a]
2	 **367**	 **384**:(26%)	 **393**:(18%)
3	 **249**	 **385**:(38%)	 **394**:(60%)
4	 **245**	 **386**:(23%)	 **395**:(48%)
5	 **378**[b]	 **387**:(51%)	 **396**:(60%)

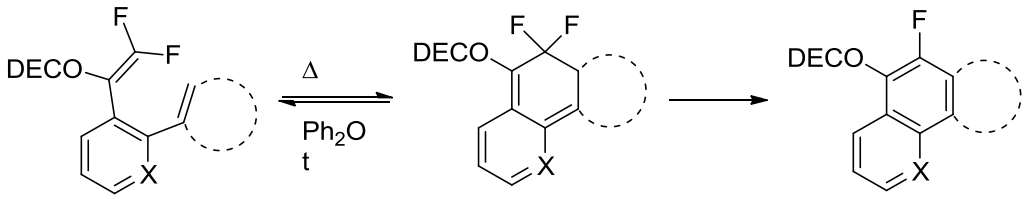
6			
	379	**388**:(16%)	**397**:(44%)
7			
	380	**389**:(28%)	**398**:(26%)
8			
	381	**390**:(53%)	**399**:(28%)
9			
	382[c]	**391**:(79%)	**400**:(24%)
10			
	383	**392**:(27%)	**401**:(66%)

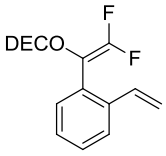
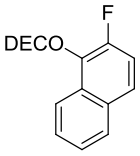
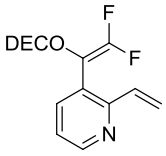
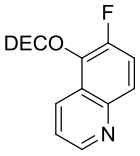
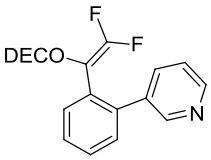
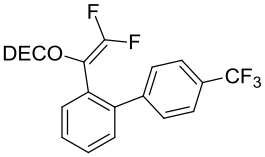
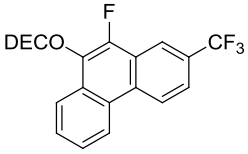
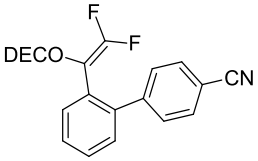
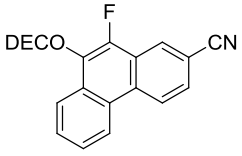
a) Coupling conditions: $(PPh_3)_2PdCl_2$ (5 mol%), Cs_2CO_3 (3 eq), RuPhos (10 mol%), *t*-BuOH/H_2O (2.7:1); b) 36% yield when trifluoroborate used; c) 68% yield when boronic acid used.

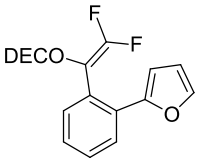
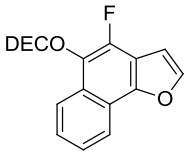
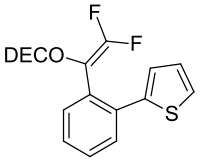
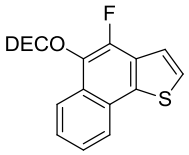
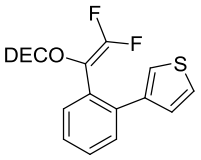
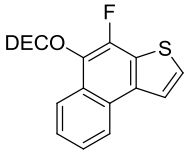
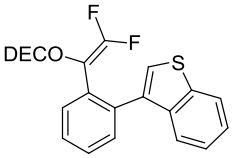
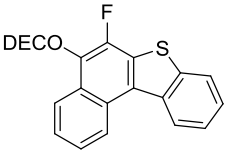
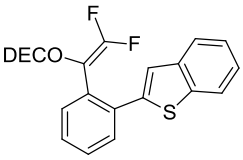
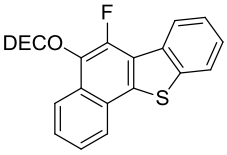
Table **34**: Scope of the iterative coupling methodology

With several bis-coupled species in hand, electrocyclisation was attempted (Table **35**) using the same procedure as for divinylbenzene **364**. There was a marked difference in temperature required to effect electrocyclisation of divinylbenzene **369** and the biaryl species (entries 3-10), presumably due to the cost of disruption

of the aromaticity of the second aromatic ring. Biaryl species containing no heteroatoms (entries 4 & 5) in the rings were considerably more difficult to cyclise than the heteroaromatic species (entries 6-10).



Entry	Starting material	T (°C)	t (h)	Product (yield)
1	 **369**	180	24	 **402**:(84%)
2	 **393**	240	48	 **403**:(54%)
3	 **394**	240	72	-[a]
4	 **395**	240	72	 **404**:(4%)
5	 **396**	240	144	 **405**:(5%)

6	 **397**	240	48	 **406**:(31%)
7	 **398**	240	48	 **407**:(28%)
8	 **399**	240	48	 **408**:(59%)
9	 **400**	240	72	 **409**:(42%)
10	 **401**	240	48	 **410**:(63%)

a) Not isolated due to low conversion and regioisomers.

Table **35**: Electrocyclisation of products generated from the iterative coupling methodology

A quantitative measure of the aromaticity of particular rings could help to rationalise the ease of electrocyclisation of the species displayed in Table **35**. There have previously been several attempts to establish general scales of aromaticity.[188-190] The most common methods include calculation of aromatic stabilisation energies

(ASE) through heats of reaction (combustion and hydrogenation)[189] and calculations of changes to the magnetic parameters of a compound; magnetic susceptibility (Λ)[191] and nucleus independent chemical shifts (NICS).[192,193] Some values obtained for each of these methods are displayed in Table **36**. Although the values from each method cannot be compared directly, a trend in the measured aromaticities of some selected compounds can be made.

	$\Delta H_{combustion}$ (Kcal/ mol)	$\Delta H_{hydrogenation}$ (Kcal/ mol)	NICS(I)[a] (ppm)	Λ ($10^{-6}cm^3mol^{-1}$)
Benzene	36-37	36	-10.8	-14.5
Pyridine	23-43	-	-11.1	-13.5
Thiophene	24-31	29	-10.3	-13.0
Furan	16-23	22	-9.2	-8.9

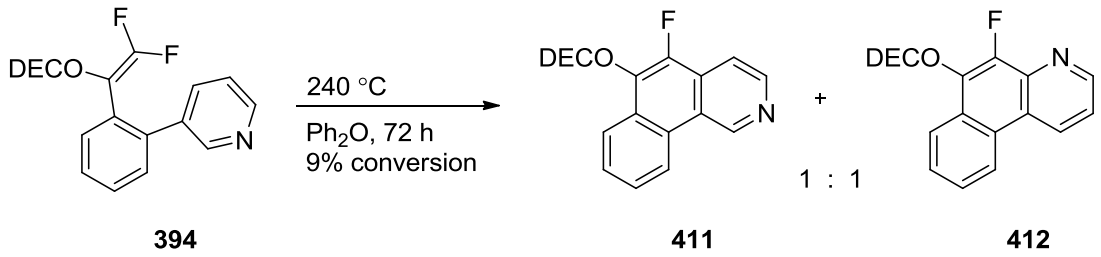
a) GIAO-HF/ 6-311+G*

Table **36**: Literature values for aromaticity using different methods of measurement

The greater the heat of combustion or hydrogenation then the greater the stabilisation energy that must be overcome, suggesting a greater extent of aromaticity. The heat of combustion results displayed predict the order of aromaticity to be: benzene>thiophene>furan. This aromaticity ranking is replicated for the heat of hydrogenation reactions. The error associated with the heat of combustion of pyridine is high and so it is unclear where pyridine ranks on the aromaticity scale.

The two methods probing the magnetic parameters of the aromatic species in table **36** cannot be used to compare aromaticities of compounds of different ring size.[189] Both NICS and Λ predict that thiophene is more aromatic than furan, consistent with the heat of reaction results. The strength of aromaticity of benzene and pyridine is predicted to be similar by NICS and Λ; however, pyridine is more aromatic in the former and *vice versa* in the latter.

These strength of aromaticity trends help rationalise the reaction conditions required for the electrocyclisation of the species in table **35**. The temperature for the cyclisation of divinylbenzenes **346**, **364** and **369** (180 °C) is lower than that required for the cyclisation of the biaryl species (240 °C). This can be attributed to the need for the ASE of only one ring to be overcome. The higher temperature required for cyclisation of divinylpyridine **393**, and the poor conversion and long reaction time required for pyridine-containing biaryl **394** suggests that pyridine has a greater ASE than benzene. After heating pyridyl **394** at 240 °C for 72 h, only a small amount of fluoroarene was generated. ^{19}F NMR analysis of the crude reaction mixture revealed ~9% conversion of the starting material. Two aromatic fluorine signals were present in the NMR spectrum in a 1:1 ratio indicating that there was no regioselectivity in the reaction (Scheme **60**). No further investigation into the electrocyclisation of **394** was undertaken because of this disappointing result.



394 **411** **412**

Scheme **60**: Attempted electrocyclisation of pyridyl biaryl **394**

Low yields were obtained for fluorophenanthrenes **404** and **405**. Electrocyclisation of cyano species **396** was monitored by ^{19}F NMR analysis of the reaction mixture (Figure **39**). A small amount of phenanthrene **405** was generated after 18 h at 240 °C, as indicated by the emergence of a singlet at ~140 ppm. The reaction was stirred at 240 °C for a further 54 h resulting in 90% conversion of the starting material. Some interesting new signals in the ^{19}F NMR spectrum were observed; these were a doublet ($^{2}J_{F\text{-}H}$ = 54 Hz), assumed to have arisen from difluoroketone **414** formed by cleavage of the DEC group *via* an acylium ion aided by nascent HF, and a set of doublet of doublets ([$^{2}J_{F\text{-}F}$ = 259 Hz, $^{4}J_{F\text{-}H}$ = 5 Hz] and [$^{2}J_{F\text{-}F}$ = 259 Hz, $^{4}J_{F\text{-}H}$ = 14 Hz]) similar to those observed for indanone species **348** (*vide supra*), assumed in this case to be from difluoro- intermediate **413**. This species was not expected to be observed as it was thought that re-aromatisation by dehydrofluorination would be too rapid. Nevertheless, the signal observed is consistent with **413**. Generation of **413** by fluoride addition via an S_NAr type reaction to form an equilibrium with **405** was discarded as a possibility, because none of the intermediate was observed in the reaction mixture after 144 h. This strongly suggests that the intermediate is consumed to form phenanthrene **405**. The low yield of **405** may be due to loss of

material during purification and isolation (chromatography and recrystallisation) as the ^{19}F NMR spectrum suggests that the product is almost exclusively desired material after a reaction time of 144 h.

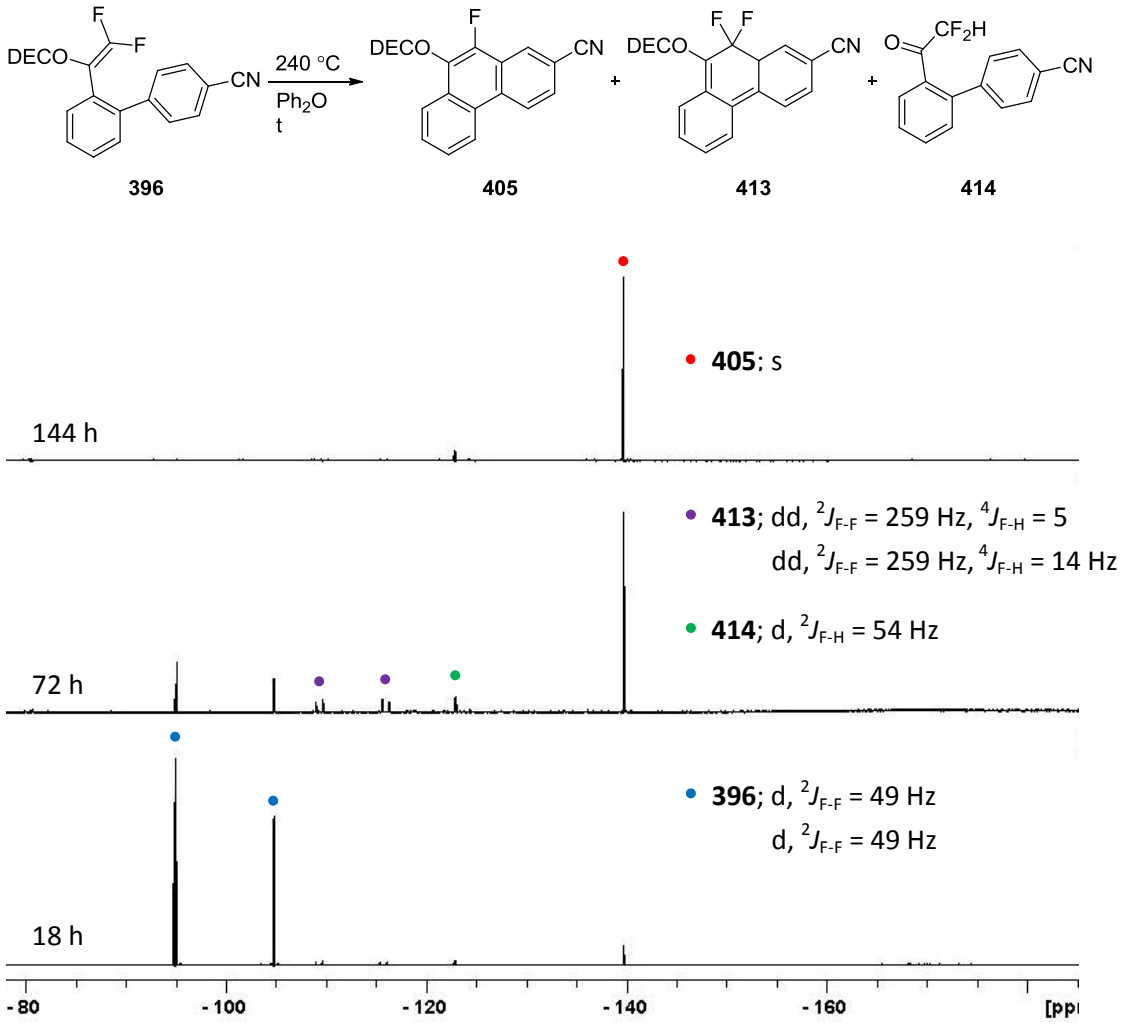


Figure **39**: ^{19}F NMR analysis of the generation of phenanthrene **405**

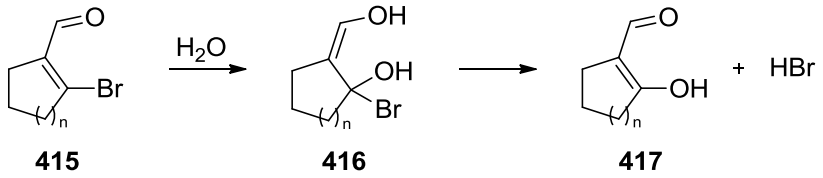
The lower reaction times and moderate yields obtained for heteroaromatic species (entries 6-10) suggest that they undergo electrocyclisation more easily than the biaryl species **404** and **405**; these results correlate well with the strength of aromaticity scale inferred from Table **36**.

Table **35** represents the first, unoptimised attempts at electrocyclisation of the species and so the moderate to low yields obtained may not be a true representation of the utility of the reaction. A range of species have, however, undergone electrocyclisation with various 'aromatisation penalties' overcome (divinylbenzene vs biaryl). Next, preparation and electrocyclisation of non-aromatic precursors was investigated.

2.2.3 Strategy 3: triene approach

2.2.3.1 Preparation of cyclic bromodienes

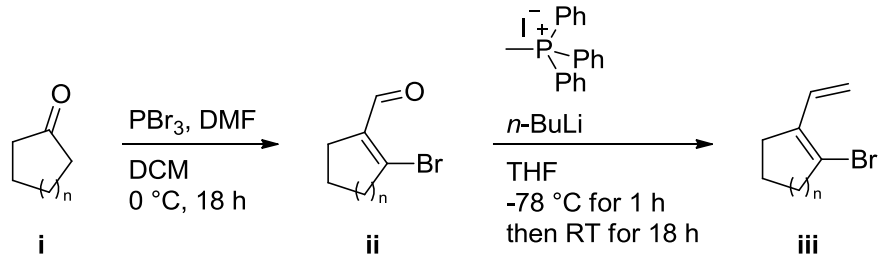
Cyclic bromodienes bearing a 5-, 6- and 7-membered ring were prepared in good yield using the procedure of Larock and co-workers (Table **37**). A Vilsmeier formylation generated bromo-aldehydes **418**, **84** and **419**. Neutralisation of HBr released during the reaction was essential as degradation of the aldehydes occurred when the crude reaction mixtures were concentrated under vacuum. Better yields of the subsequent Wittig olefination were obtained when the aldehydes were purified by chromatography. Rapid discolouration and degradation of the aldehydes and bromodienes occurred in storage, even on refrigeration (~5 °C, 3 months), and were accompanied by a lowering of the pH. The proposed degradation pathway (Scheme **61**) is consistent with these observations.



415 **416** **417**

Scheme **61**: Proposed degradation pathway of Vilsmeier formylation products

Immediate consumption of the intermediates in the preparation of the electrocyclisation precursors was essential in order to minimise material loss.



i **ii** **iii**

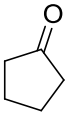
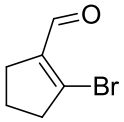
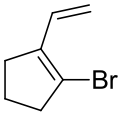
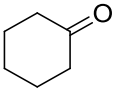
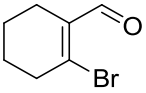
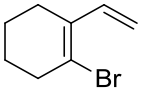
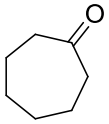
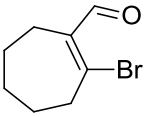
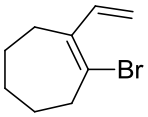
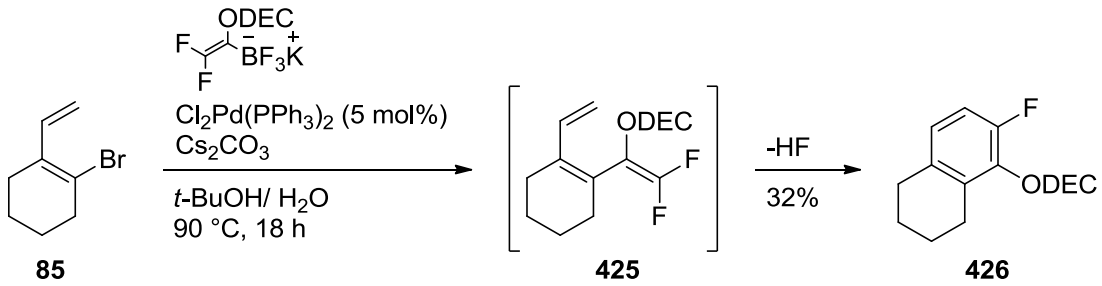
Entry	Starting material i	Product ii (yield)	Product iii (yield)
1	 **418**	 **420**:(55%)	 **423**:(72%)
2	 **84**	 **421**:(75%)	 **85**:(70%)
3	 **419**	 **422**:(28%)	 **424**:(63%)

Table **37**: preparation of cyclic bromodienes of various ring size

2.2.3.2 Preparation of trienes

The usual Suzuki coupling conditions generated fluoroarene **426** instead of the expected triene **425** (Scheme **62**). The arene was isolated in 32% yield after chromatography.



Scheme **62**: Unexpected generation of fluoroarene **426** under Suzuki coupling conditions

This result demonstrates that triene species **425** has a considerably lower activation barrier to electrocyclisation than the divinylbenzene and biaryl species investigated earlier, as no penalty for the disturbance of aromaticity was incurred.

The coupling reaction of bromodiene **85** with borate **106b** was performed at a lower temperature and monitored by LC-MS to try to observe the predicted triene **425** *in situ* (Figure **40**). After a reaction time of 18 h at 70 °C a significant quantity of bromodiene **85** remained. A peak with a mass consistent with triene **425** was observed, as was a trace amount of fluoroarene **426**. Stirring the reaction mixture for another 24 h at 70 °C resulted in consumption of triene and an increase in the amount of fluoroarene **426**. The reaction temperature was then increased to 90 °C

and a sample was removed for analysis after 3 h; further consumption of **425** and generation of **426** was observed. After a further 18 h at 90 °C complete consumption of triene **425** was observed.

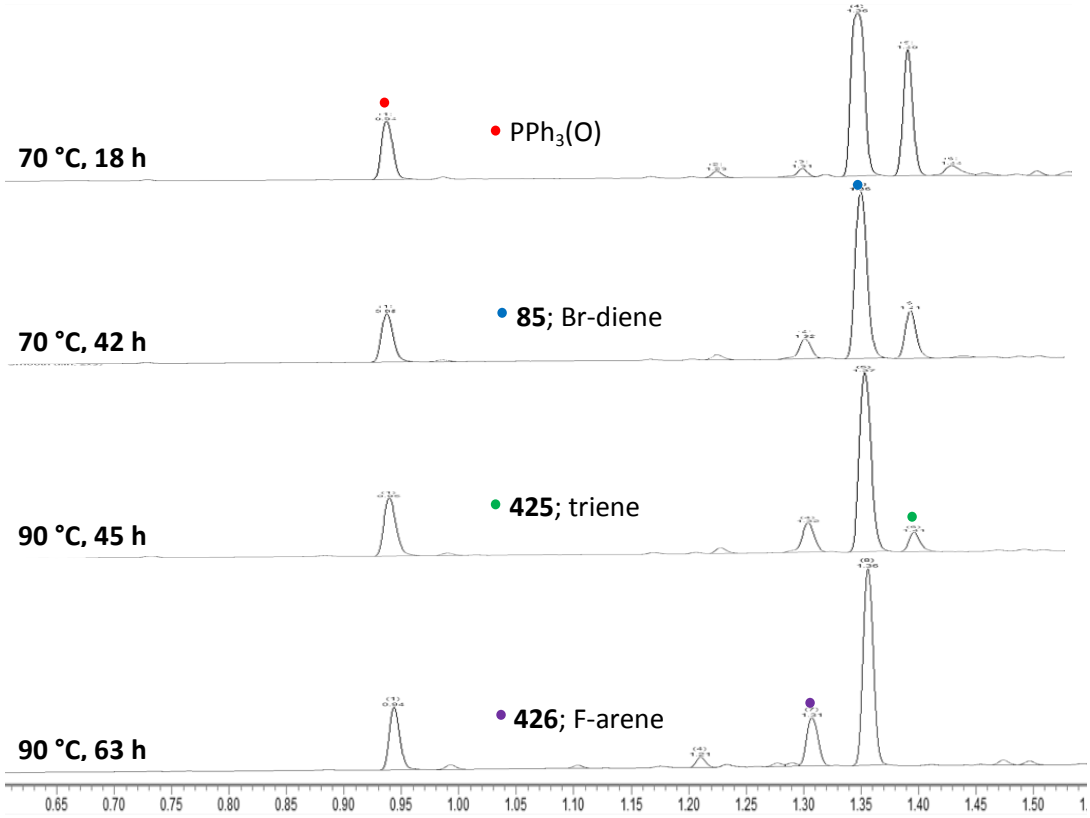
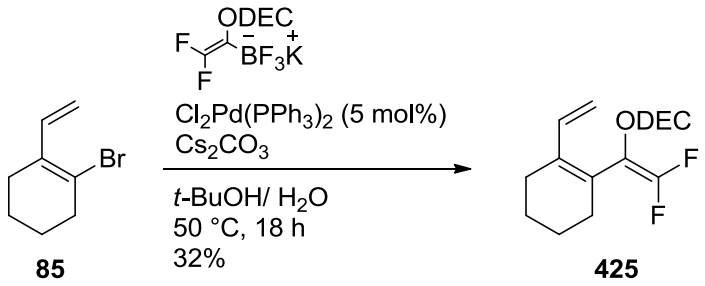


Figure **40**: LC-MS study of the Suzuki coupling of br-diene **85** with borate **106b**

A considerable amount of bromodiene was still present after this time, indicating that the coupling reaction to form triene **425** was inefficient and was responsible for limiting the yield of fluoroarene **426**.

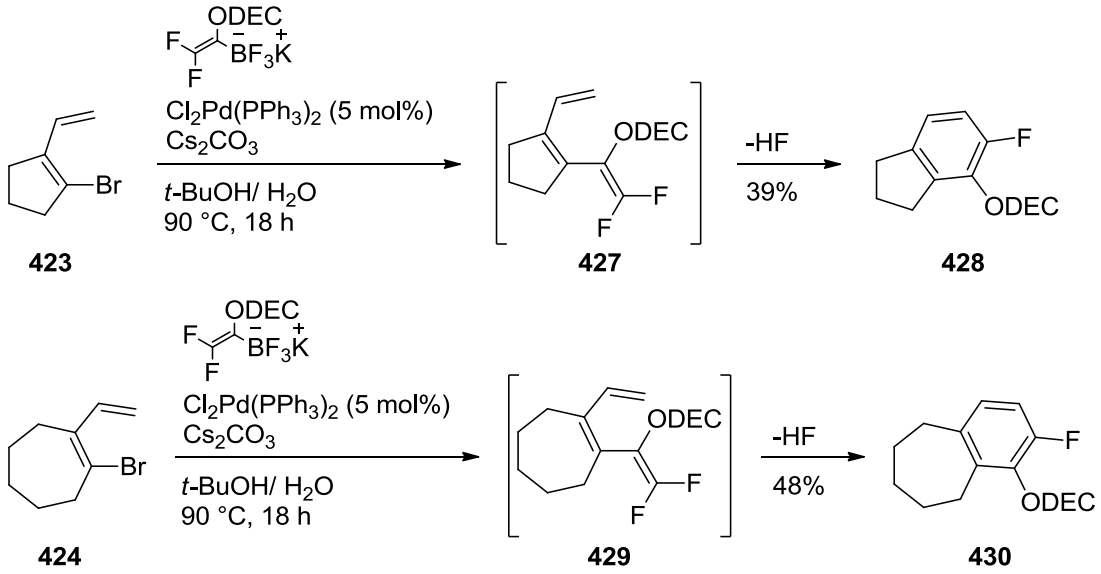
An attempt to isolate triene **425** by performing the Suzuki coupling at a still lower temperature was successful (Scheme **63**). Triene **425** was isolated in 32% yield after chromatography.



85 **425**

Scheme **63**: Preparation of triene **425** at lower temperature

Fluoroarenes **428** and **430** were generated from their bromodienes in 39% and 48% yield respectively, without isolation of the trienes, by performing the Suzuki coupling at 90 °C (Scheme **64**).



423 **427** **428**

424 **429** **430**

Scheme **64**: Preparation of fluoroarenes **428** and **430**.

A series of fluoroarenes have been prepared with a developed palladium-catalysed coupling step at the heart of the methodology. The range in temperatures required to prepare the fluoroarenes suggests significant differences in activation energies associated with each electrocyclisation. A better understanding of the requirements

for facile electrocyclisation was sought; the reactions were therefore investigated computationally.

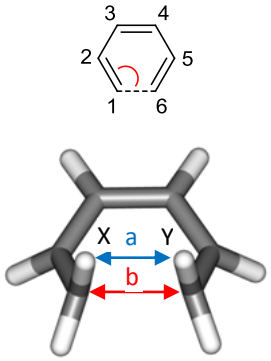
2.2.4 Computational investigation

2.2.4.1 Energies of activation of electrocyclisation

The energy of activation for the electrocyclisation process of some of the generated species was calculated with Spartan software[194] at the B3LYP/6-31G**[195,196] and M06-2X/6-31+G*[197] levels of theory (Table **38**). Geometry optimisation was performed on the lowest energy conformer for each of the electrocyclisation precursors. The energies of the respective transition states (TS) were calculated from optimisation of a boat-like geometry.[198]

A previous calculation of the energy of activation of 1,3,5-hexatriene by Rodríguez-Otero[199] using the B3LYP/6-31G** level of theory ($\Delta E^{\ddagger}$ = 29.8 Kcal/mol at 400 K) was in good correlation with the experimentally determined value of Steiner[200] (E_a = 29.9 Kcal/mol at 390-434 K). To determine if this value could be reproduced the calculation was performed using the method of Rodríguez-Otero and also using a different method with a higher level of theory (M06-2X/6-31+G*). Both methods produced energies of activation (30.2 and 29.6 Kcal/mol) that correlate well with the theoretical and experimental values previously determined. The 1,3,5-hexatriene electrocyclisation TS generated by M06-2X/6-31+G* was compared with the TS previously generated by Otero[199] (B3LYP/6-31G**) and Houk[198,201] (MP2/6-

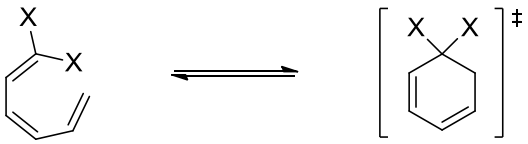
31G*) (Figure **41**). A boat-like geometry was predicted by all three levels of theory. The M06-2X generated C_1-C_6 interatomic distance of 2.15 Å compares well with the previously reported figures of 2.28 Å and 2.24 Å respectively. The C_2-C_1-C_6 angle of 104.2° also compares well with the 104.6° reported by Houk.

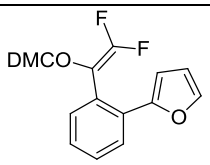
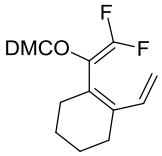
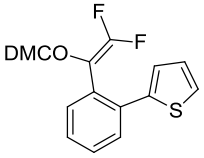
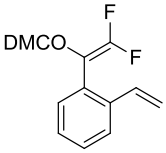
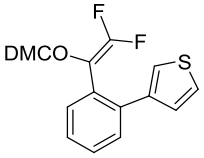
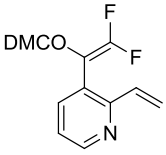
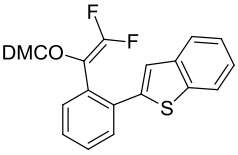
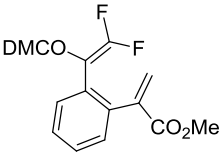
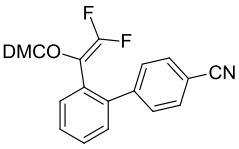


	This work[a]	Otero[b]	Houk[c]
$\Delta E^{\ddagger}$ (Kcal/mol)	29.6	29.8	26.1
X-Y (a) (Å)	1.87	-[d]	1.86
C_1-C_6 (b) (Å)	2.15	2.28	2.24
C_2-C_1-C_6 Angle (°)	104.2	-[d]	104.6
ν_i (cm^{-1})	579	573	909

Figure **41**: Comparison of M06-2X/6-31+G* generated 1,3,5-hexatriene TS with literature data

The closely related energies of electrocyclisation of 1,3,5-hexatriene calculated at the M06-2X/6-31+G* and B3LYP/6-31G** levels of theory with those published in the literature, and the favourable comparison of the TS, validated the method to investigate energies of electrocyclisation. A dimethylcarbamoyloxy group was used in place of the diethylcarbamoxloxy group as it is conformationally less complicated and therefore simplified the calculations.



Electrocyclisation[a] precursor	ΔE‡ (Kcal/mol) B3LYP/ 6-31G**	ΔE‡ (Kcal/mol) M06-2X/ 6-31+G*	Electrocyclisation[a] precursor	ΔE‡ (Kcal/mol) B3LYP/ 6-31G**	ΔE‡ (Kcal/mol) M06-2X/ 6-31+G*
 **431**	30.2 (578)	29.6 (579)	 **397**	37.4 (428)	41.4 (508)
 **425**	25.1 (509)	27.2 (539)	 **398**	36.8 (426)	40.6 (508)
 **369**	31.6 (552)	35.3 (600)	 **399**	47.3 (312)	53.3 (406)
 **393**	33.0 (549)	36.4 (600)	 **401**	34.4 (417)	37.7 (489)
 **364**	30.4 (509)	33.4 (586)	 **396**	40.3 (423)	46.8 (491)

a) DMCO = Dimethylcarbamoyloxy [$C(O)NMe_2$]; imaginary frequencies in parentheses (cm^{-1})

Table **38**: Calculated energies of activation of electrocyclisation

The M06-2X/6-31+G* calculations delivered activation energies that were higher than the corresponding B3LYP/6-31 G** calculations in every case, with the exception of 1,3,5-hexatriene. The trends in energies between each precursor were

reliably reproduced by both methods (Figure **42**) and for the purposes of this discussion only the values calculated by the M06-2X method will be used.

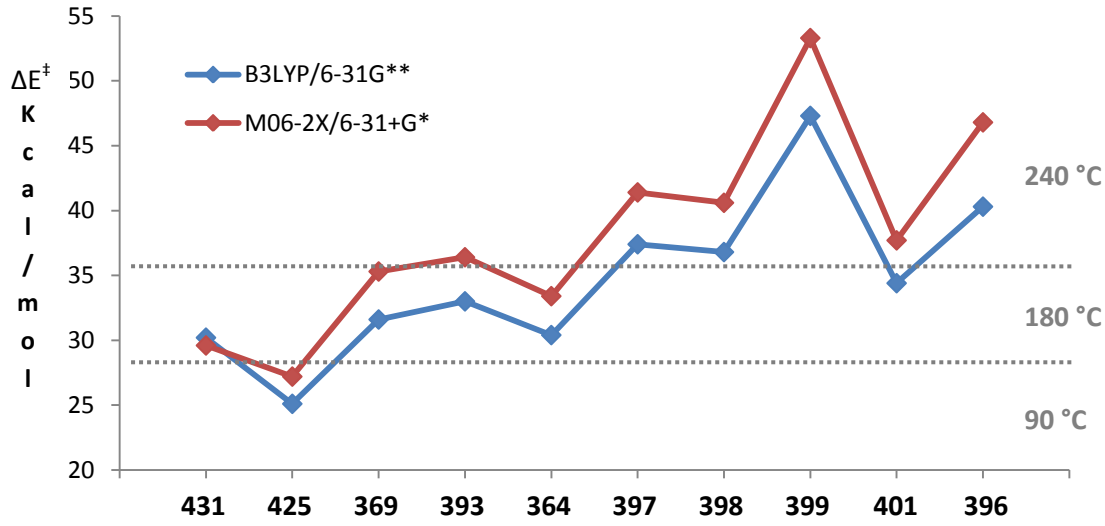


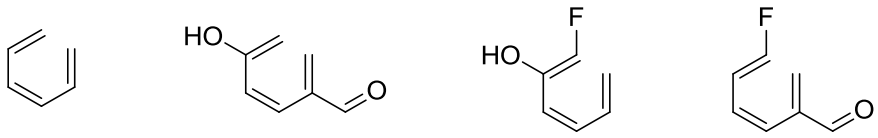
Figure **42**: Line plot of the energies of activation of species in Table **38**

The trends observed in practice were reproduced by the calculations. Triene **425**, cyclised under the Suzuki coupling conditions at the lowest temperature (90 °C), had the lowest activation energy of any species (27.2 Kcal/mol) as there was no need for loss of aromaticity. The increased reaction temperature (180 °C) required for the divinylbenzene species **369** and **364** was translated into activation energies of 35.3 and 33.4 Kcal/mol. The still higher reaction temperature (240 °C) required for the biaryl systems was predicted by the calculations; larger activation energies of 37.7-53.3 Kcal/mol were produced. Biaryl **396** ($\Delta E^{\ddagger}$ = 46.8 Kcal/mol) required a reaction time of 144 h at 240 °C to effect full consumption of starting material. Thiophene species **399** had the largest activation energy of 53.3 Kcal/mol. This is a surprising result as **399** only required a reaction time of 48 h at 240 °C to convert all

of the starting material to fluoroarene, the same reaction conditions as the thiophene isomer **398**, which had an activation energy of 40.6 Kcal/mol. The calculations appear to show that species with $\Delta E^{\ddagger} \leq 27.2$ Kcal/mol are electrocyclised at T ≤90 °C, species with $\Delta E^{\ddagger} \leq 35.3$ Kcal/mol are electrocyclised at T ≤180 °C and species with $\Delta E^{\ddagger} \geq 36.4$ Kcal/mol are electrocyclised at T ≥240 °C. The calculated energies of activation correlated well with the temperature of reaction and the number of aromatic rings in the electrocyclisation precursor; 0 rings = 90 °C, 1 ring = 180 °C, 2-3 rings = 240 °C. These data represent a foundation for predicting temperatures of reaction for novel electrocyclisation precursors.

2.2.4.2 Effect of ring substitution on electrocyclisation

Ring substituents have been calculated to have an accelerating effect on electrocyclisation when captodative substitution patterns (synergistic participation of electron-withdrawing and electron-donating groups) are present.[113] Calculations carried out by Fu and co-workers at the B3LYP/6-31G level of theory suggest that some disubstituted trienes could undergo rapid electrocyclisation.[113] A lowering of the free energy of activation of 2,5-disubstituted triene **432** by 10 Kcal/mol from that of 1,3,5-hexatriene was predicted; smaller differences were calculated for 1,2- and 1,5-disubstituted species such as **433** and **434**.



431	**432**	**433**	**434**
30.7 Kcal/mol	20.8 Kcal/mol	27.2 Kcal/mol	24.4 Kcal/mol

Despite the 2,5- substitution pattern of acrylate **364** (Table **38**), only a modest lowering of the activation energy was calculated (33.4 Kcal/mol) with respect to divinylbenzene **369** (35.3 Kcal/mol).

In an effort to understand the effect of the carbamoyloxy and fluorine substituents on the electrocyclisations, energies of activation of some test structures were calculated (Table **40**).

Mono-fluorination (**439**) resulted in lowering the energy of activation of 1,3,5-hexatriene by 3 Kcal/mol. *Bis*-fluorination does not seem to affect the activation energy; the apparent positive effect of one fluorine may have been cancelled out by the steric effect of the second fluorine atom. Dolbier and co-workers demonstrated that the Cope rearrangement of **438**, constrained to react through a boat transition state, was significantly slower than that of the analogous **436**, which was able to adopt a chair transition state (Scheme **65**).[115]

435: X = H, $\Delta H^{\ddagger}$ = 28.0 ± 1.1 kcal/mol
436: X = F, $\Delta H^{\ddagger}$ = 22.4 ± 0.2 kcal/mol

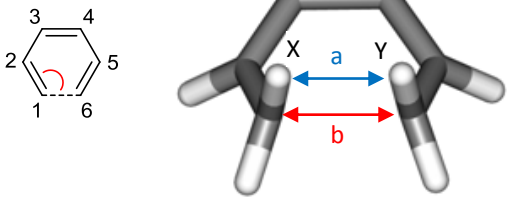
Chair transition state

437: X = H, $\Delta H^{\ddagger}$ = 41.6 ± 0.5 kcal/mol
438: X = F, $\Delta H^{\ddagger}$ = 49.5 ± 1.0 kcal/mol

Boat transition state

Scheme **65**: Cope rearrangements of terminally fluorinated chair and boat transition states

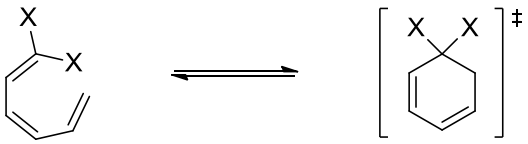
Dolbier attributed these results to destabilisation of the boat transition state by steric repulsion of the terminal fluorines. Interatomic measurements of the M06-2X generated electrocyclisation precursor transition states (Table **39**) show small increases in distance between the terminal atoms (H-H or H-F) when more fluorines are introduced. In comparison with Dolbier's species **438**, less steric repulsion would be expected in these cases as fewer fluorines crowd the reaction centre (2 vs 4); these small steric effects may have manifested themselves as small increases in activation energies of electrocyclisation.

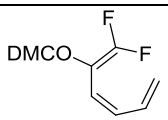
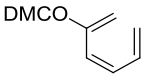
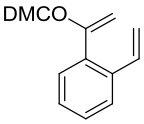
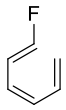
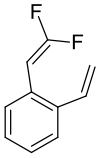
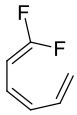
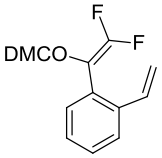


Electrocyclisation[a] precursor	Interatomic distance (Å)	Electrocyclisation[a] precursor	Interatomic distance (Å)
431	H-H (a) = 1.87 C_1-C_6 (b) = 2.15	**441**	H-F (a) = 1.93 C_1-C_6 (b) = 2.32
439	H-H (a) = 1.91 C_1-C_6 (b) = 2.32	**425**	H-F (a) = 1.93 C_1-C_6 (b) = 2.29
440	H-F (a) = 1.93 C_1-C_6 (b) = 2.32	**369**	H-F (a) = 1.95 C_1-C_6 (b) = 2.14

Table **39**: Measured interatomic distances of selected electrocyclisation transition states

The carbamoyloxy substituent also has a positive effect on the energy of activation. Triene **442** has a calculated activation energy of 27.4 Kcal/mol, 2 Kcal/mol lower than the unsubstituted triene **431**. The effects of the carbamoyl and fluorine substituents combine in triene **441** to produce an activation energy of 26.6 Kcal/mol.



Electrocyclisation[a] precursor	ΔE‡ (Kcal/mol) B3LYP/ 6-31G**	ΔE‡ (Kcal/mol) M06-2X/ 6-31+G*	Electrocyclisation[a] precursor	ΔE‡ (Kcal/mol) B3LYP/ 6-31G**	ΔE‡ (Kcal/mol) M06-2X/ 6-31+G*
 **431**	30.2 (578)	29.6 (579)	 **441**	25.7 (464)	26.6 (493)
 **442**	26.8 (510)	27.4 (517)	 **443**	34.6 (577)	39.0 (604)
 **439**	27.5 (483)	26.8 (502)	 **444**	36.5 (661)	38.1 (722)
 **440**	30.6 (565)	30.1 (608)	 **369**	31.6 (552)	35.3 (600)

a) DMCO = Dimethylcarbamoyloxy [$C(O)NMe_2$]; imaginary frequencies in parentheses (cm^{-1})

Table **40**: Probing substituent effects on calculated electrocyclisation activation energies

Similar trends were observed for divinylbenzene species **443**, **444** and **369**. Little difference in the activation energies of carbamoyloxy substituted **443** and fluorinated **444** was observed but the combined effect of the substituents was to significantly lower the energy to 35.3 Kcal/mol.

The calculations in table **38** provide theoretical confirmation of the reactivity trends observed through experiment; the reaction temperatures and times for each class of electrocyclisation precursor (triene, divinylbenzene, biaryl) correlated well with the calculated energies of activation. The MO6-2X functional, although slightly overestimating the activation energies in comparison to the B3LYP functional, faithfully reproduced the trends produced by the B3LYP calculations, indicating its suitability in probing these pericyclic reactions. Table **40** represents an attempt to probe the effects of substitution on the electrocyclisation reactions; the results suggest that the carbamoyloxy and terminal fluorine atoms combine to significantly lower the activation energy of electrocyclisation.

The groundwork has been laid to use this methodology as a predictive tool to further probe the scope and limitations of the electrocyclisation of difluorinated building blocks.

3 Conclusions and Future Work

A near ambient preparation of difluoroenolzinc and (iodo)difluoroenol species from trifluoroethanol has been developed. Previously, difluoroenol coupling partners were generated at -78 °C and although performing cryogenic synthesis on a laboratory scale is no great hardship, scale-up of the reaction would be costly. Negishi and Suzuki coupling of difluoroenols with a range of aryl-iodides and aryl-bromides has been performed with the Suzuki methodology showing greater scope; heteroaromatic species and carbonyl containing substituents were tolerated when coupling (iodo)difluoroenol using the Suzuki-Miyaura coupling conditions.

Side reactions of both coupling methodologies were observed and overcome. An addition/elimination side-reaction of fluorinated styrene products with lithium butoxide (present as a significant impurity in commercial *n*-BuLi) was circumvented by performing the zincation of **104a** and **104b** using commercial LDA. Also, using *t*-BuOH/H_2O as the reaction solvent in the Suzuki-Miyaura couplings, led to significantly improved yields by halting a palladium-catalysed dehalogenation of aryl-halide starting materials.

Extending the coupling methodology to the use of aryl chlorides would be useful. It would be necessary to screen an array of ligands and pre-catalysts to effect oxidative addition.

The effect of the fluorines on the coupling step was briefly investigated by mapping the reaction profile via GC-MS. The study suggests that terminal fluorines of borate

106b increases the rate of equilibration to the active boronic acid coupling partner. The study also suggests that the fluorines slow the rate of transmetallation.

Although qualitative data was gathered, quantitative data was limited due to a small number of data points and a crude sampling method. A full kinetic investigation would yield greater understanding of substituent effects on the coupling reaction as well as identifying the rate determining step.

The palladium-catalysed coupling methodology, developed in chapter 2, was applied to the synthesis of trienes, divinylbenzenes and biaryl species. Potassium difluorovinyltrifluoroborate **106b** was found to be the most effective coupling partner for generation of the electrocyclisation precursors. Low temperature coupling (50 °C) was required to intercept triene **425** as electrocyclisation occurred at $\leq$90 °C. The iterative coupling strategy proved the most effective method to introduce diversity to the products. Attaching the difluorvinyl trifluoroborate coupling partner **106b** second was the preferred order of coupling as it afforded product in greater yields. Telescoping the synthesis is a real possibility as the same catalyst was used for each C-C union.

A range of temperatures and reaction times were necessary to overcome differing de-aromatisation penalties and effect electrocyclisation. Cyclisation precursors with a greater number of arenes required higher temperatures, leading to a crude banding: arenes = 0, T = ~90 °C; arenes = 1; T = ~180 °C; arenes = 2; T = $\geq$180 °C. Acceleration of the electrocyclisation using Lewis acids may be a possibility and should be investigated.[202]

Activation energies of electrocyclisation were calculated using DFT (B3LYP and M06-2X functionals) level of theory for each electrocyclisation precursor. The values produced by the calculations compared well with the experimental parameters observed in the laboratory (temperature banding). A greater number of aromatic rings resulted in a greater activation energy.

This computational power could be used to predict the activation free energies of electrocyclisation for species yet to be generated in the lab. This data could then be used to synthesise a library of diverse fluoroarenes with confidence of a successful outcome.

4 Experimental

General experimental

NMR spectra were recorded on Bruker DPX-400 or AV-600 spectrometers. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded using the deuterated solvent as the lock and the residual solvent as the internal reference. The multiplicities of the spectroscopic data are presented in the following manner: s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Homocouplings (H–H, F–F) are given in Hertz and specified by *J*; the nuclei involved in known heteronuclear couplings are defined with the observed nucleus given first.

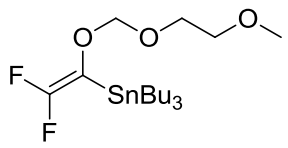
HRMS measurements were recorded on a Micromass Autospec 500 OAT spectrometer (ESI) or a Thermofisher LTQ Orbitrap XL (APCI and NSI). LRMS (LC) measurements were recorded on a Waters Ultra Performance LC spectrometer fitted with an Acquity UPLC BEH C18 column (50 mm x 2.1 mm i.d. 1.7 µm packing diameter) running at 40 °C. LRMS (GC) measurements were recorded on an Agilent Technologies 5975C (CI) mass spectrometer fitted with an Agilent Technologies DB5MS UI column (30 m x 0.25 µm) running a 70 – 320 °C temperature programme, ramp rate 20 °C min^{-1} with Helium carrier gas flow at 1 mL $minute^{-1}$.

Column chromatography was performed on silica gel (40-63 µm or 33-70 µm) using a Combiflash companion^{TM} sem-automated system or a Büchi Sepacore system. Reverse phase column chromatography was performed on a Combiflash

companion™ sem-automated system using a Redi*Sep* C18 cartridge. Thin layer chromatography was performed on pre-coated polyester-backed silica gel plates (Polygram® Sil G/UV, Macherey-Nagel, Düren, Germany) or precoated aluminium backed silica gel plates (Merck, silica gel 60 F_{254}) and visualisation was achieved using potassium permanganate staining and UV detection at 254 nm.

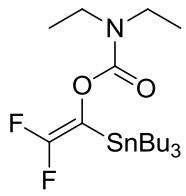
IR spectra were recorded on a Perkin Elmer ATR IR spectrometer or a Perkin Elmer 1 FT-IR spectrometer as KBr disks, or as films between NaCl plates. Microwave reactions were performed in a CEM Discover (open vessel) or a Biotage Initiator™ Eight (closed vessel) microwave reactor. Melting points were recorded on a Stuart SMP40® automatic melting point apparatus or a Reichert hot stage melting point apparatus and are uncorrected. Phase separation was accomplished with Whatman FT 5.0 µ PTFE fritted phase separators.

Alkyllithium reagents were titrated using the procedure recorded by Duhamel and Plaquevent.[203] Anhydrous solvents were obtained from a Puresolv purification system (Innovative Technologies Inc.), purchased from Aldrich or distilled using standard laboratory procedure. Hexane was distilled before chromatography. 1-(*N,N*-Diethylcarbamoyloxy)-2,2,2-trifluoroethane was prepared according to the method of Howarth[101] and 1-(2'-methoxy-ethoxymethoxy)-2,2,2-trifluoroethane was prepared according to the method of Patel.[102] All trifluoroborates were generated from the commercial boronic acids using the methods of Vedejs[150] and Molander[151] All other materials were used as received unless otherwise stated.



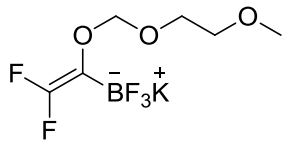
2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(tributylstannyl) ethene 127a

n-Butyllithium (7.9 mL of a 2.4 M solution in hexanes, 19 mmol) was added dropwise to a solution of dry di*iso*propylamine (2.76 mL, 20 mmol) in dry THF (9 mL) at -78 °C and the mixture was stirred for 20 minutes. The solution was allowed to warm to -30 °C over 10 minutes before the solution was again cooled to -78 °C and 2,2,2-trifluoro-1-(2'-methoxy-ethoxymethoxy)ethane **104a** (1.44 mL, 9 mmol) was added dropwise over a period of 15 minutes. The solution was stirred for 40 minutes at -78 °C before the addition of tributyltin chloride (2.18 mL, 8 mmol) in one portion. The reaction mixture was stirred for 2 h, gradually allowing the temperature to reach -30 °C, resulting in a thick brown mixture. This was quenched with saturated NH_4Cl (25 mL) and extracted with diethyl ether (2 x 25 mL). The organic extracts were combined, washed with brine (25 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude residue was purified by column chromatography on silica (10% diethyl ether in petroleum ether) to afford stannane **127a** (2.98 g, 80%) as a colourless oil; R_f (10% diethyl ether in petroleum ether) 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.77 (d, *J* 0.8, 2 H), 3.79-3.76 (m, 2 H), 3.58-3.55 (m, 2 H), 3.40 (s, 3 H), 1.62-0.84 (m, 27 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -85.0 (d, *J* 66.6, 1 F), -109.5 (d, *J* 66.6, 1 F). These data were in agreement with those reported previously.[102]



2,2-Difluoro-1-(*N*,*N*-diethylcarbamoyloxy)-1-(tributylstannyl) ethene 127b

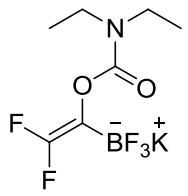
Stannane **127b** was prepared as for **127a** using *n*-butyllithium (13.7 mL of a 2.3 M solution in hexanes, 31.5 mmol), di*iso*propylamine (4.45 mL, 31.5 mmol), 2,2,2-trifluoro-1-(*N*,*N*-diethylcarbamoyloxy)ethane **104b** (2.99 g, 15 mmol) and THF (30 mL). The crude residue was purified by passing through a short plug of alumina (Brockman 1) (l = 3 cm, d = 3 cm) with toluene (100 mL). The solvent was removed under reduced pressure and **127b** was isolated as a colourless oil (5.33 g, 76%); R_f (10% diethyl ether in petroleum ether) 0.27; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.31 (q, *J* 7.1, 4 H), 1.57-0.87 (m, 27 H), 1.20-1.12 (m, 6 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -83.7 (d, *J* 64.3, 1 F), -110.3 (d, *J* 64.3, 1 F). These data were in agreement with those reported previously.[101]



Potassium 2,2-difluoro-1-(2'-methoxy-ethoxymethoxy)ethenyl trifluoroborate 106a

n-Butyllithium (100 mL of a 2.5 M solution in hexanes, 0.25 mol) was added dropwise to a solution of di*iso*propylamine (35.27 mL, 0.25 mol) in THF (135 mL) at -78 °C. The colourless solution was allowed to warm to -30 °C for 10 min and then re-cooled to -78 °C. Acetal **104a** (22.4 g, 0.12 mol) was added dropwise over 30 min

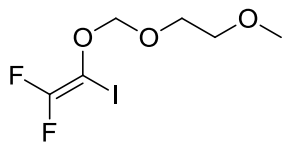
via a dropping funnel and the brown reaction mixture was stirred at -78 °C for 2 h. Trimethylborate (42 mL, 0.38 mol) was added in one portion and left to stir and warm to room temperature over 3 h. The now orange reaction solution was cooled to 0 °C and a solution of KHF_2 (117 g in 300 mL of water, 1.5 mol) was added dropwise *via* a dropping funnel. The reaction mixture was stirred at room temperature overnight then the solvent and water were removed under reduced pressure to reveal a white solid. The crude product was extracted into hot acetone (5 x 100 mL) and hot filtered. Removal of acetone under reduced pressure afforded an orange solid that was recrystallised from acetone and collected by filtration to afford trifluoroborate **106a** (17.79 g, 55%) as fine colourless needles; mp 131–132 °C, ^{1}H NMR (400 MHz, D_2O) δ (ppm); 4.79 (s, 2 H), 3.78-3.74 (m, 2 H), 3.55-3.51 (m, 2 H), 3.26 (s, 3 H); ^{13}C NMR (100 MHz, D_2O) δ (ppm) 159.3 (br. dd, $J_{C\text{-}F}$ 296.3, 277.5), 114.8 (br. s), 94.7, 70.5, 67.1, 57.6; ^{19}F NMR (376 MHz, D_2O) δ (ppm) -93.3 (d, *J* 69.0, 1 F), -110.2 (dq, *J* 69.0, *J* 10.8, 1 F), (-138.7)–(-139.3) (m, 3 F); LRMS *m/z* (EI) 235 [M - K]$^-$; HRMS (NSI) m/z calcd for $C_6H_9BF_5O_3$ [M - K]$^-$ 235.0565, found 235.0564. The data reported by Katz and co-workers did not include C–F coupling constants.[110]



Potassium 2,2-Difluoro-1-(*N*,*N*-diethylcarbamoyloxy)ethenyl trifluoroborate 106b

n-Butyllithium (67.6 mL of a 2.2 M solution in hexanes, 0.149 mol) was added dropwise to a solution of di*iso*propylamine (21 mL, 0.149 mol) in dry THF (50 mL) at

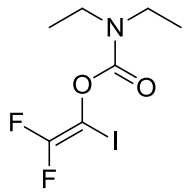
-78 °C and stirred for 30 minutes. The colourless solution was allowed to warm to -30 °C over 15 minutes and then re-cooled to -78 °C. The colourless LDA solution was then added dropwise *via* cannula to a solution of carbamate **104b** (11.85 g, 59.5 mmol) in dry THF (10 mL) at -78 °C over a period of 20 minutes. A purple colour developed during addition of LDA and changed to a deep blue after 30 minutes of stirring at -78 °C. After stirring for 1 h -78 °C, trimethylborate (9.95 mL, 89.3 mmol) was added *via* syringe in one portion and the reaction solution was stirred for 1 h at -78 °C. The solution was left to stir at room temperature for 2 h; during this time an orange/brown colour developed. The reaction solution was cooled to 0 °C, a solution of potassium hydrogen difluoride (27.9 g, 0.357 mol) in H_2O (50 mL) was added in 3 portions, and the reaction mixture was left to stir at RT overnight. The solvent was removed under reduced pressure to reveal a mixture of white solid and a viscous brown oil. The brown oil was then extracted with an acetone/methanol (4:1) mixture (3 x 100 mL). The extracts were then concentrated until a small amount of precipitate was apparent; full precipitation was achieved by adding diethyl ether (30 mL). The precipitate was collected and washed by vacuum filtration to afford trifluoroborate **106b** as a white solid (8.03 g, 47%); mp 152-154 °C, ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm); 3.23 (q, *J* 7.1, 4 H), 1.05 (t, *J* 7.1, 6 H); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm) 157.7 (dd, *J* 298.3, 277.0), 153.8, 115.8 (br. s), 41.2, 13.4; ^{19}F NMR (376 MHz, DMSO-d6) δ (ppm) -91.6 (d, *J* 63.8, 1 F), -109.2 (dq, *J* 63.8, *J* 8.6, 1 F), (-140.9) – (-141.7) (m, 3 F); LRMS *m/z* (EI) 246 $[M - K]^-$; HRMS (NSI) m/z calcd for $C_7H_{10}BF_5NO_2$ $[M - K]^-$ 246.0725, found 246.0724.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-iodoethene 139a

n-Butyllithium (26.09 mL, 2.3 M, 60 mmol) was added dropwise to a solution of di*iso*propylamine (8.43 mL, 60 mmol) in THF (20 mL) at 0 °C and the reaction stirred for 30 minutes at this temperature. The freshly prepared LDA was added dropwise via cannula to a solution of acetal **104a** (3.76 g, 20 mmol), $ZnCl_2$ (3.0 g, 22 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (10 mL) in THF (40 mL) at 0 °C. The yellow solution was stirred at 0 °C for 1 h, then 1 h further at room temperature. A solution of iodine (5.08 g) in THF (25 mL) was added via syringe (a slight exotherm to ca. 10 °C was observed) and the orange solution was stirred for 10 minutes. The solution was quenched with aqueous ammonium chloride (60 mL) and extracted with diethyl ether (2 x 100 mL). The organic extracts were combined, washed with saturated sodium sulfite solution (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The brown residue was washed through a pad of silica (10% diethyl ether in hexane), concentrated under reduced pressure and distilled (Kugelrohr, 70 °C/2 mbar) to afford iodide **139a** (2.96 g, 50%) as a colourless oil; R_f (40% diethyl ether in hexane) 0.39; ν_{max}(film)/cm^{-1} 2937, 2894, 2829, 1774, 1735, 1457, 1285, 1181, 1155, 1101, 1075, 1026, 963, 911, 847; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.88 (s, 2 H), 3.85-3.82 (m, 2 H), 3.61-3.58 (m, 2 H), 3.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 152.2 (dd, $J_{C\text{-}F}$ 296.4, 278.8), 96.0 (t, $J_{C\text{-}F}$ 3.1), 71.8 (dd, $J_{C\text{-}F}$ 53.8, 27.8), 71.0, 68.6, 58.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm) -89.7 (d, *J* 49.2, 1 F), -100.6 (d, *J* 49.2, 1 F); LRMS (CI) *m/z* 262 $[M - CH_3O]^+$; GC (98%)

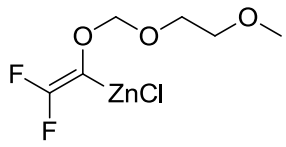
t_R 8.01 mins.. The compound decomposed before accurate mass spectrometric measurements could be carried out off-site.



1-(*N*,*N*-Diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene 139b

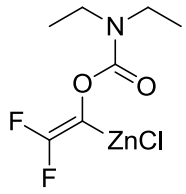
Lithium di*iso*propylamide (17.9 mL of a 1.4 M solution in THF, 25 mmol) was added dropwise to a solution of 2,2,2-trifluoroethyl carbamate **104b** (1.99 g, 10 mmol, 1.63 mL) and freshly-fused zinc chloride (1.5 g, 11 mmol) in dry THF (20 mL) at 0 °C over a period of 10 min. The resulting yellow solution was stirred at 0 °C for 1 h, then for 1 h at room temperature, to afford alkenylzinc reagent **131b** (assumed to be a 0.25 M solution in THF). A solution of iodine (2.54 g, 10 mmol in 10 mL of THF) was added dropwise to **131b** (40 mL of a 0.25 M solution in THF, 10 mmol) at 15 °C. The reaction mixture was stirred at this temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (30 mL) and extracted with diethyl ether (2 x 40 mL). The organic extracts were combined, washed with saturated sodium sulfite solution (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure and distilled (Kugelrohr, 70 °C/2 mbar) to afford iodide **139b** (2.17 g, 71%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.39-3.25 (m, 4 H), 1.19 (br. t, *J* 6.9, 6 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 153.8 (dd, $J_{C\text{-}F}$ 280.0, 297.7), 151.3, 60.7 (dd, $J_{C\text{-}F}$ 58.2, 27.4), 42.9, 42.0, 14.2, 13.2;

^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) -84.9 (d, *J* 42.3, 1 F), -98.5 (d, *J* 42.3, 1 F). These data are consistent with those reported by Percy and co-workers.[101]



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)ethenylzinc chloride 131a

Lithium di*iso*propylamide (17.9 mL of a 1.4 M solution in THF, 25 mmol) was added dropwise over a period of 10 mins to a solution of 2,2,2-trifluoroethyl acetal **104a** (1.88 g, 1.55 mL, 10 mmol), freshly fused zinc chloride (1.5 g, 11 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)- pyrimidinone (DMPU) (5 mL) in dry THF (20 mL) at 0 °C. The resulting yellow solution was stirred at 0 °C for 1 h, then for 1 h at room temperature, to afford **131a** (assumed to be a 0.22 M solution in DMPU/THF). The appropriate volume was then used for each Negishi coupling reaction.



2,2-Difluoro-1-(*N*,*N*-diethylcarbamoyloxy)ethenylzinc chloride 131b

Lithium diisopropylamide (17.9 mL of a 1.4 M solution in THF, 25 mmol) was added dropwise to a solution of 2,2,2-trifluoroethyl carbamate **104b** (1.99 g, 1.63 mL) , 10 mmol, freshly fused zinc chloride (1.5 g, 11 mmol) in dry THF (20 mL) at 0 °C over a period of 10 min. The resulting yellow solution was stirred at 0 °C for 1 h, then for 1

h at room temperature, to afford **131b** (assumed to be a 0.25 M solution in THF). The appropriate volume was then used for each Negishi coupling reaction.

General Stille coupling procedure 1

Stannane **127a** or **127b** (0.5 mmol) was added to a stirring solution of aryl halide (0.52 mmol), copper(I) iodide (21 mg, 0.110 mmol), triphenylphosphine (13 mg, 0.05 mmol) and palladium(II) acetate (3 mg, 0.014 mmol) in dry, degassed DMF (5 mL). The reaction solution was stirred at 50 °C for 18 hours then cooled to room temperature and partitioned between diethyl ether (30 mL) and water (40 mL). The layers were filtered through a pad of Kieselgur then the organic layer was separated, dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (30% ethyl acetate in petroleum ether) afforded coupled product.

General Negishi coupling procedure 1

Alkenylzinc reagent **131a** (4.45 mL of a 0.22 M solution in THF/DMPU, 1.0 mmol) was added in one portion to a flask containing aryl halide (1.1 mmol) and *tetrakis*(triphenylphosphino)palladium(0) (23 mg, 0.02 mmol) and the mixture was heated at 65 °C overnight. The mixture was cooled to room temperature, diluted with DCM (30 mL) and water (40 mL) then filtered through a short pad of Celite. The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (30% diethyl ether in light petroleum ether) to afford coupled product.

General Negishi coupling procedure 2

Alkenylzinc reagent **131b** (4.0 mL of a 0.25 M solution in THF, 1.0 mmol) was added in one portion to a flask containing aryl halide (1.1 mmol) and *tetrakis*(triphenylphosphino)palladium(0) (23 mg, 0.02 mmol) and the mixture was heated at 65 °C overnight. The mixture was cooled to room temperature, diluted with DCM (30 mL) and water (40 mL) then filtered through a short pad of Celite. The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (30% diethyl ether in light petroleum ether) to afford coupled product.

General Negishi coupling procedure 3

Alkenylzinc species **131b** (4.0 mL of a 0.25 M solution, 1.0 mmol) was added to a suspension of $MgCl_2$ (95 mg, 1.0 mmol) (dried under vacuum until free flowing) in THF (1 mL) at 0 °C. This mixture was stirred at 0 °C for 1 hour. A solution of aryl halide (1.1 mmol, 1.1 eq) and *tetrakis*(triphenylphosphino)palladium (23 mg, 2 mol%) in THF (3 mL) was added in one portion and the reaction mixture stirred at 65 °C for the times indicated. The mixture was cooled to room temperature, diluted with DCM (30 mL) and water (40 mL) then filtered through a short pad of Celite. The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (30% diethyl ether in light petroleum ether) to afford coupled product.

General Suzuki coupling procedure 1

A mixture of potassium trifluoroborate (0.41 mmol), iodide **139a** or **139b** (0.34 mmol), caesium carbonate (332 mg, 1.0 mmol) and *bis*(triphenylphosphino)palladium dichloride (4.8 mg, 0.0068 mmol) was taken up in a mixture of toluene (0.75 mL) and H_2O (0.275 mL). The reaction mixture was stirred at 90 °C for 2 hours. The reaction mixture was then cooled to room temperature and partitioned between DCM (10 mL) and H_2O (10 mL). The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (10% diethyl ether in hexane) to afford coupled product.

General Suzuki coupling procedure 2

A mixture of potassium trifluoroborate (0.2 mmol), iodide **139a** or **139b** (0.17 mmol), caesium carbonate (166 mg, 0.51 mmol) and *bis*(triphenylphosphino)palladium dichloride (2.4 mg, 0.0034 mmol) was taken up in a (2.7 : 1) mixture of degassed (3 x freeze-pump-thaw cycle) *iso*-propanol and H_2O (1 mL). The reaction mixture was stirred at 90 °C for 2 hours. The reaction mixture was then cooled to room temperature and partitioned between DCM (5 mL) and H_2O (5 mL). The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (10% diethyl ether in hexane) to afford coupled product.

General Suzuki coupling procedure 3

A mixture of potassium trifluoroborate (0.13 mmol), iodide **139a** or **139b** (0.11 mmol), caesium carbonate (103 mg, 0.32 mmol) and *bis*(triphenylphosphino)palladium dichloride (1.5 mg, 0.0021 mmol) was taken up in a (2.7 : 1) solution of *tert*-butanol and H_2O (1 mL). The reaction mixture was stirred at 90 °C for 18 hours, then cooled to room temperature and partitioned between DCM (5 mL) and H_2O (5 mL). The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (10% diethyl ether in hexane) to afford coupled product.

General Suzuki coupling procedure 4

A mixture of trifluoroborate **106a** (0.50 mmol), aryl halide (0.46 mmol), triethylamine (0.21 mL, 1.50 mmol) and $Pd(dba)_2$ (14 mg, 0.025 mmol) was taken up in *n*-propanol (2.5 mL). The reaction mixture was stirred at 90 °C for 18 hours, then cooled to room temperature and partitioned between diethyl ether (30 mL) and H_2O (30 mL). The organic phase was separated, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica (10% diethyl ether in hexane) to afford coupled product.

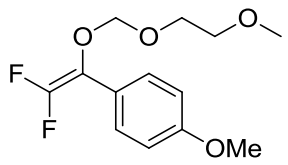
General Suzuki coupling procedure 5

A mixture of trifluoroborate **106b** (1.0 mmol), aryl halide (1.0 mmol), caesium carbonate (978 mg, 3.0 mmol) and *bis*(triphenylphosphino)palladium dichloride (14

mg, 0.02 mmol) was taken up in a (2.7 : 1) solution of *tert*-butanol and H_2O (6.5 mL). The reaction mixture was stirred at 90 °C for 18 hours, then cooled to room temperature and partitioned between DCM (30 mL) and H_2O (30 mL). The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (10% diethyl ether in hexane) to afford coupled product.

General Suzuki coupling procedure 6

A mixture of boronic acid (0.13 mmol), iodide **139b** (0.11 mmol), caesium carbonate (103 mg, 0.32 mmol) and *bis*(triphenylphosphino)palladium dichloride (1.5 mg, 0.0021 mmol) was taken up in a (2.7 : 1) mixture of *tert*-butanol and H_2O (1 mL). The reaction mixture was stirred at 90 °C for 18 hours, then cooled to room temperature and partitioned between DCM (5 mL) and H_2O (5 mL). The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (10% diethyl ether in hexane) to afford coupled product.



2,2-Difluoro-1-(2′-methoxy-ethoxymethoxy)-1-(4′′-methoxyphenyl) ethene 138

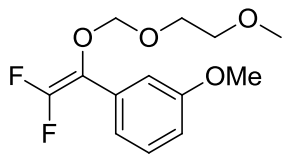
Prepared from **131a** (4.45 mL of a 0.22 M solution) and **155** (206 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford styrene **138** (170 mg, 60%) as a

yellow oil; R_f (40% diethyl ether in light petroleum ether) 0.30; ν_{max}(film)/cm^{-1} 2936, 1737, 1611, 1515, 1465, 1257, 1179, 1151, 1035, 979, 950, 836; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43-7.38 (m, 2 H), 6.96-6.90 (m, 2 H), 4.87 (s, 2 H), 3.90-3.85 (m, 2 H), 3.84 (s, 3 H), 3.60-3.56 (m, 2 H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.1, 154.6 (app. t, $J_{C\text{-}F}$ 287.4), 127.9 (dd, $J_{C\text{-}F}$ 5.3, 3.8), 121.5 (br. d, $J_{C\text{-}F}$ 5.8), 114.8 (dd, $J_{C\text{-}F}$ 36.1, 18.7), 113.5, 94.6 (t, $J_{C\text{-}F}$ 2.8), 71.1, 67.9, 58.5, 54.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -99.9 (d, *J* 61.5, 1 F), -108.5 (d, *J* 61.5, 1 F); LRMS (CI) *m/z* 292 [M + NH_4]$^+$; HRMS (NSI) m/z calcd for $C_{13}H_{16}F_2NaO_4$ [M + Na]$^+$ 297.0909, found 297.0901; GC (98%) t_R 13.81 mins..

Styrene **138** (70 mg, 51%) was also prepared from **132** (122 mg, 0.52 mmol) and stannane **127a** (229 mg, 0.50 mmol) using general Stille coupling procedure 1. The data were consistent with those reported above.

Styrene **138** (30 mg, 87%) was also prepared from trifluoroborate **238** (27 mg, 0.13 mmol) and iodide **139a** (31 mg, 0.11 mmol) using general Suzuki coupling procedure 3. The data were consistent with those reported above.

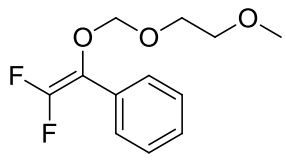
Styrene **138** (72 mg, 53%) was also prepared from trifluoroborate **106a** (137 mg, 0.50 mmol) and **155** (106 mg, 0.46 mmol) using general Suzuki coupling procedure 4. The data were consistent with those reported above.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(3''-methoxyphenyl) ethene 169

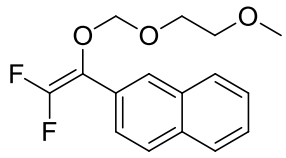
Prepared from **131a** (4.45 mL of a 0.22 M solution) and **156** (206 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford **169** (199 mg, 73%) as a yellow oil; R_f (40% diethyl ether in light petroleum ether) 0.17; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 (t, *J* 8.0, 1 H), 7.08 (dq, *J* 7.8, 1.3, 1 H), 7.04-7.02 (m, 1 H), 6.88 (br. dd, *J* 8.3, 2.5, 1 H), 4.90 (s, 2 H), 3.90-3.86 (m, 2 H), 3.83 (s, 3 H), 3.60-3.56 (m, 2 H), 3.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.2, 155.1 (app. t, $J_{C\text{-}F}$ 289.7), 130.8 (br. d, $J_{C\text{-}F}$ 6.0), 129.1, 118.8 (dd, $J_{C\text{-}F}$ 5.6, 3.6), 115.0 (dd, $J_{C\text{-}F}$ 35.4, 18.4), 113.5, 111.8 (dd, $J_{C\text{-}F}$ 5.6, 3.6), 94.9 (t, $J_{C\text{-}F}$ 3.1), 71.1, 68.0, 58.5, 54.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -97.6 (d, *J* 55.3, 1 F), -105.7 (d, *J* 55.3, 1 F). These data were consistent with those reported previously.[110]

Styrene **169** (53 mg, 95%) was also prepared from trifluoroborate **239** (44 mg, 0.20 mmol) and iodide **139a** (50 mg, 0.17 mmol) using general Suzuki coupling procedure 3. The data were consistent with those reported above.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-phenyl ethene 170

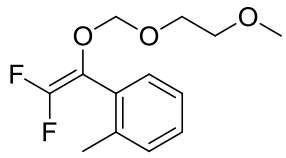
Prepared from **131a** (4.45 mL of a 0.22 M solution, 1.0 mmol) and **143** (172 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford **170** (130 mg, 53%) as a yellow oil; Rf (40% diethyl ether in light petroleum ether) 0.33; ν_{max}(film)/cm^{-1} 2929, 2884, 1735, 1449, 1265, 1201, 1177, 1153, 1103, 1070, 1032, 980, 948, 767, 715, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.51-7.46 (m, 2 H), 7.42-7.37 (m, 2 H), 7.35-7.30 (m, 1 H), 4.90 (s, 2 H), 3.90-3.86 (m, 2 H), 3.60-3.56 (m, 2 H), 3.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.0 (app. t, $J_{C\text{-}F}$ 289.3), 129.4 (br. d, $J_{C\text{-}F}$ 6.1), 128.0, 127.8, 126.3 (dd, $J_{C\text{-}F}$ 5.7, 3.2), 115.2 (dd, $J_{C\text{-}F}$ 35.2, 18.3), 94.8 (t, $J_{C\text{-}F}$ 3.0), 71.1, 68.0, 58.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -98.0 (d, *J* 56.0, 1 F), -106.5 (d, *J* 56.0, 1 F); LRMS (CI) *m/z* 245 $[M + H]^+$; GC (98%) t_R 10.48 mins.; HRMS (ES-TOF) m/z calcd for $C_{12}H_{14}F_2NaO_3$ $[M + Na]^+$ 267.0809, found 267.0814.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-naphthyl ethene 171

Prepared from **131a** (4.45 mL of a 0.22 M solution, 1.0 mmol) and **157** (228 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford **171** (142 mg, 48%) as a yellow oil; R_f (40% diethyl ether in light petroleum ether) 0.30; ν_{max}(film)/cm^{-1} 2929, 2884, 2813, 1728, 1451, 1267, 1232, 1193, 1122, 1023, 954, 858, 840, 818, 749,

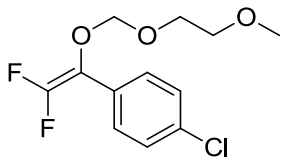
475; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.97 (br. s, 1 H), 7.89-7.83 (m, 3 H), 7.60 (dt, *J* 8.7, 1.7, 1 H), 7.54-7.51 (m, 2 H), 4.96 (s, 2 H), 3.94-3.90 (m, 2 H), 3.61-3.58 (m, 2 H), 3.41 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.2 (app. t, $J_{C\text{-}F}$ 291.1), 132.6, 132.5, 127.8, 127.7, 127.1, 126.8 (br. d, $J_{C\text{-}F}$ 6.0), 126.1, 126.0, 125.9 (app. t, $J_{C\text{-}F}$ 5.0), 123.6 (dd, $J_{C\text{-}F}$ 6.3, 2.7), 115.3 (dd, $J_{C\text{-}F}$ 35.2, 18.4), 95.0 (t, $J_{C\text{-}F}$ 3.0), 71.1, 68.1, 58.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -97.3 (d, *J* 55.1, 1 F), -106.1 (d, *J* 55.1, 1 F); LRMS (CI) *m/z* 295 $[M + H]^+$; GC (98%) t_R 13.52 mins.; HRMS (NSI) m/z calcd for $C_{16}H_{20}F_2NO_3$ $[M + NH_4]^+$ 312.1411, found 312.1409.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(2''-methylphenyl) ethene 172

Prepared from **131a** (4.45 mL of a 0.22 M solution, 1.0 mmol) and **158** (188 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford **172** (103 mg, 40%) as a yellow oil; R_f (20% diethyl ether in light petroleum ether) 0.23; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37-7.19 (m, 4 H), 4.73 (d, *J* 0.67, 2 H), 3.83-3.79 (m, 2 H), 3.58-3.54 (m, 2 H), 3.40 (s, 3 H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.2 (dd, $J_{C\text{-}F}$ 290.2, 280.3), 138.4 (br. d, $J_{C\text{-}F}$ 2.3), 130.7 (br. t, $J_{C\text{-}F}$ 2.8), 130.4, 129.5, 128.0, 125.7, 114.3 (dd, $J_{C\text{-}F}$ 42.0, 17.9), 93.3, 71.6, 67.8, 59.0, 19.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -102.2 (d, *J* 64.1, 1 F), -109.2 (d, *J* 64.1, 1 F); LRMS (CI) *m/z* 259 $[M + H]^+$; GC (98%) t_R 10.57 mins. These data were consistent with those reported previously.[110]

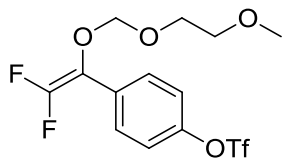
Styrene **172** (40 mg, 91%) was also prepared from trifluoroborate **242** (50 mg, 0.17 mmol) and iodide **139a** (40 mg, 0.20 mmol) using general Suzuki coupling procedure 3. The data were consistent with those reported above.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(4''-chlorophenyl) ethene 173

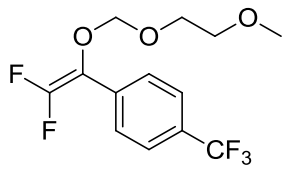
Prepared from **131a** (4.45 mL of a 0.22 M solution, 1.0 mmol) and **159** (192 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford **173** (151 mg, 54%) as a yellow oil; Rf (40% diethyl ether in light petroleum ether) 0.49; ν_{max}(film)/cm^{-1} 2929, 2882, 2821, 1729, 1493, 1263, 1151, 1092, 1027, 979, 939, 832, 832; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44-7.36 (m, 4 H), 4.88 (s, 2 H), 3.89-3.85 (m, 2 H), 3.59-3.56 (m, 2 H), 3.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 155.0 (app. t, $J_{C\text{-}F}$ 290.3), 133.6, 128.3, 128.0 (br. d, $J_{C\text{-}F}$ 5.8), 127.5 (dd, $J_{C\text{-}F}$ 6.0, 3.4), 114.5 (dd, $J_{C\text{-}F}$ 35.3, 19.2), 95.0 (t, $J_{C\text{-}F}$ 3.0), 71.1, 68.1, 58.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ(ppm) -97.0 (d, *J* 54.5, 1 F), -105.4 (d, *J* 54.5, 1 F); LRMS (CI) *m/z* 279 $[M + H]^+$; GC (98%) t_R 11.55 mins.; HRMS (EI) m/z calcd for $C_{12}ClH_{13}F_2O_3$ $[M]^+$ 278.0521, found 278.0520.

Styrene **173** (68 mg, 72%) was also prepared from trifluoroborate **244** (89 mg, 0.41 mmol) and iodide **139a** (100 mg, 0.34 mmol) using general Suzuki coupling procedure 1. The data were consistent with those reported above.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-[4''-(trifluoromethanesulfonyloxy) phenyl] ethene 174

Prepared from **131a** (4.45 mL of a 0.22 M solution, 1.0 mmol) and **160** (387 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford **174** (97 mg, 25%) as a yellow oil; R_f (40% diethyl ether in hexane) 0.32; ν_{max}(film)/cm^{-1} 1731, 1504, 1428, 1271, 1251, 1215, 1179, 1142, 1103, 984, 941, 889, 847; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (br. d, *J* 8.9, 2 H), 7.32 (br. d, *J* 8.9, 2 H), 4.91 (s, 2 H), 3.89-3.85 (m, 2 H), 3.58-3.55 (m, 2 H), 3.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.3 (app. t, $J_{C\text{-}F}$ 291.7), 148.4, 130.3 (br. d, $J_{C\text{-}F}$ 6.3), 128.0 (dd, $J_{C\text{-}F}$ 6.3, 3.4), 121.1, 118.2 (q, $J_{C\text{-}F}$ 320.1), 114.1 (dd, $J_{C\text{-}F}$ 35.1, 19.8), 95.3 (t, $J_{C\text{-}F}$ 3.1), 71.0, 68.2, 58.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -72.8 (s, 3 F), -95.6 (d, *J* 51.8, 1 F), -104.4 (d, *J* 51.8, 1 F); LRMS (CI) *m/z* 393 $[M + H]^+$; GC (98%) t_R 11.87 mins.; HRMS (ES-TOF) m/z calcd for $C_{13}H_{13}F_5O_6S$ $[M + Na]^+$ 415.0251, found 415.0247.

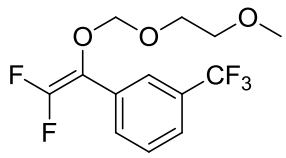


2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(4'-trifluoromethylphenyl) ethene 175

Prepared from **131a** (4.45 mL of a 0.22 M solution, 1.0 mmol) and **161** (248 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford **175** (118 mg, 41%) as a

yellow oil; R_f (20% diethyl ether in light petroleum ether) 0.15; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (br. d, *J* 8.6, 2 H), 7.61 (br. d, *J* 8.6, 2 H), 4.90 (s, 2 H), 3.89-3.85 (m, 2 H), 3.58-3.54 (m, 2 H), 3.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.0 (app. t, $J_{C\text{-}F}$ 291.9), 133.4 (br. d, $J_{C\text{-}F}$ 6.4), 129.7 (q, $J_{C\text{-}F}$ 32.5), 126.3 (dd, $J_{C\text{-}F}$ 6.5, 3.5), 125.0 (q, $J_{C\text{-}F}$ 3.0), 123.4 (q, $J_{C\text{-}F}$ 271.8), 114.5 (dd, $J_{C\text{-}F}$ 34.2, 19.3), 95.4 (t, $J_{C\text{-}F}$ 3.0), 71.0, 68.2, 58.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -62.8 (s, 3 F), -94.9 (d, *J* 50.0, 1 F), -103.6 (d, *J* 50.0, 1 F); LRMS (CI) *m/z* 313 $[M + H]^+$; GC (98%) t_R 10.28 mins. These data were consistent with those reported previously.[110]

Styrene **175** (47 mg, 88%) was also prepared from trifluoroborate **245** (51 mg, 0.20 mmol) and iodide **139a** (50 mg, 0.17 mmol) using general Suzuki coupling procedure 1. The data were consistent with those reported above.

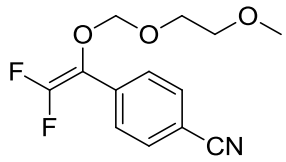


2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(3''-trifluoromethylphenyl) ethene 176

Prepared from **131a** (4.45 mL of a 0.22 M solution, 1.0 mmol) and **162** (248 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford **176** (63 mg, 20%) as a yellow oil; R_f (40% diethyl ether in hexane) 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.76 (br. s, 1 H), 7.68 (br. d, *J* 7.8, 1 H), 7.59 (br. d, *J* 7.8, 1 H), 7.53 (t, *J* 7.8, 1 H), 4.92 (s, 2 H), 3.90-3.86 (m, 2 H), 3.58-3.55 (m, 2 H), 3.40 (s, 3 H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ (ppm) 155.0 (app. t, $J_{C\text{-}F}$ 291.3), 130.7 (br. d, $J_{C\text{-}F}$ 6.4), 130.6 (q, $J_{C\text{-}F}$ 32.6), 129.3 (br. d, $J_{C\text{-}F}$ 4.0), 128.6, 124.4 (d, $J_{C\text{-}F}$ 3.5), 123.4 (q, $J_{C\text{-}F}$ 272.6), 123.1 – 122.8 (m), 114.4 (dd, $J_{C\text{-}F}$ 34.6, 19.3), 95.4 (t, $J_{C\text{-}F}$ 3.2), 71.0, 68.2, 58.5; NMR ^{19}F (376 MHz, $CDCl_3$) δ (ppm) -62.8 (s, 3 F) -95.7 (d, *J* 51.9, 1 F), -104.5 (d, *J* 51.9, 1 F); LRMS (CI) *m/z* 313 $[M + H]^+$; GC (97%) t_R 10.17 mins.; HRMS (APCI) m/z calcd for $C_{13}H_{17}F_5NO_3$ $[M + NH_4]^+$ 330.1129, found 330.1133.

Styrene **176** (40 mg, 78%) was also prepared from trifluoroborate **246** (51 mg, 0.20 mmol) and iodide **139a** (50 mg, 0.17 mmol) using general Suzuki coupling procedure 3. The data were consistent with those reported above.

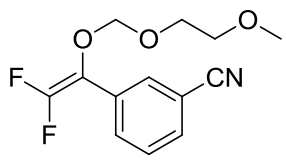


2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(4''-cyanophenyl) ethene 177

Prepared from **131a** (4.45 mL of a 0.22 M solution, 1.0 mmol) and **163** (200 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford **177** (68 mg, 25%) as a yellow oil; R_f (40% diethyl ether in hexane) 0.11; ν_{max}(film)/cm^{-1} 2885, 2822, 2229, 1717, 1608, 1267, 1153, 1099, 1074, 980, 932, 844; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (d, *J* 8.5, 2 H), 7.60 (d, *J* 8.5, 2 H), 4.91 (s, 2 H), 3.89-3.86 (m, 2 H), 3.58-3.55 (m, 2 H), 3.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.6 (app. t, $J_{C\text{-}F}$ 293.8), 134.6 (br. d, $J_{C\text{-}F}$ 6.8), 131.8, 126.4 (dd, $J_{C\text{-}F}$ 7.0, 3.4), 117.9, 114.4 (dd, $J_{C\text{-}F}$ 33.7, 19.5), 111.2, 95.6, 71.0, 68.3, 58.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -93.1 (d,

J 45.5, 1 F), -101.5 (d, *J* 45.5, 1 F); LRMS (CI) *m/z* 298 $[M + C_2H_5]^+$; GC (98%) t_R 12.26 mins.; HRMS (ES-TOF) m/z calcd for $C_{13}H_{17}F_2N_2O_3$ $[M + NH_4]^+$ 287.1202, found 287.1205.

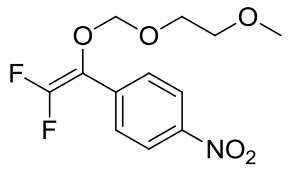
Styrene **177** (27 mg, 59%) was prepared from trifluoroborate **247** (43 mg, 0.20 mmol) and iodide **139a** (50 mg, 0.17 mmol) using general Suzuki coupling procedure 3. The data were consistent with those reported above.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(3''-cyanophenyl) ethene 178

Prepared from **131a** (4.45 mL of a 0.22 M solution, 1.0 mmol) and **164** (200 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford **178** (89 mg, 33%) as a yellow oil; Rf (40% diethyl ether in light petroleum ether) 0.13; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.80-7.79 (m, 1 H), 7.74 – 7.71 (m, 1 H), 7.61 (dt, J 7.8, *J* 1.3, 1 H), 7.52 (t, *J* 7.8, 1 H), 4.91 (s, 2 H), 3.90-3.86 (m, 2 H), 3.59-3.55 (m, 2 H), 3.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.4 (app. t, $J_{C\text{-}F}$ 292.0), 131.4 (dd, $J_{C\text{-}F}$ 6.3, 2.2), 131.1, 130.2 (dd, $J_{C\text{-}F}$ 6.8, 3.3), 129.6 (dd, $J_{C\text{-}F}$ 6.2, 3.9), 129.0, 117.8, 113.9 (dd, $J_{C\text{-}F}$ 34.5, 19.8), 112.6, 95.5 (t, $J_{C\text{-}F}$ 3.1), 71.0, 68.3, 58.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -94.5 (d, *J* 50.2, 1 F), -103.5 (d, *J* 50.2, 1 F); LRMS (CI) *m/z* 270 $[M + H]^+$; GC (97%) t_R 12.12 mins.; HRMS (APCI) m/z calcd for $C_{13}H_{17}F_2N_2O_3$ $[M + NH_4]^+$ 287.1202, found 287.1201.

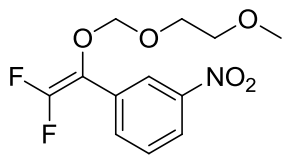
Styrene **178** (25 mg, 55%) was also prepared from trifluoroborate **247** (43 mg, 0.20 mmol) and iodide **139a** (50 mg, 0.17 mmol) using general Suzuki coupling procedure 3. The data were consistent with those reported above.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(4''-nitrophenyl) ethene 142

Prepared from **131a** (4.45 mL of a 0.22 M solution, 1.0 mmol) and **141** (274 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford **142** (119 mg, 41%) as orange needles; mp 35-38 °C; (Found: C, 60.9; H, 6.0; N, 5.3; $C_{13}H_{15}F_2NO_2$ requires C, 61.2; H, 5.9; N, 5.5 %); Rf (40% diethyl ether in light petroleum ether) 0.13; ν_{max}(film)/cm^{-1} 2920, 2891, 2818, 1709, 1594, 1505, 1457, 1346, 1331, 1266, 1180, 1159, 1100, 1081, 1032, 980, 914, 851, 757, 729, 698, 672; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.27-8.23 (m, 2 H), 7.69-7.64 (m, 2 H), 4.92 (s, 2 H), 3.90-3.86 (m, 2 H), 3.58-3.54 (m, 2 H), 3.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.8 (app. t, $J_{C\text{-}F}$ 294.6), 146.7, 136.5 (br. d, $J_{C\text{-}F}$ 6.7), 126.5 (dd, $J_{C\text{-}F}$ 7.0, 3.6), 123.3, 114.4 (dd, $J_{C\text{-}F}$ 33.5, 19.7), 95.7 (t, $J_{C\text{-}F}$ 3.1), 71.0, 68.4, 58.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -92.3 (d, *J* 43.6, 1 F), -100.8 (d, *J* 43.6, 1 F); HRMS (CI) m/z calcd for $C_{12}H_{17}F_2N_2O_5$ [M + NH_4]$^+$ 307.1100, found 307.1101.

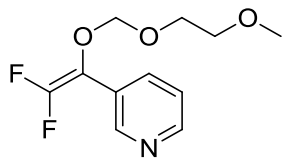
Styrene **142** (130 mg, 90%) was also prepared from **141** (129 mg, 0.52 mmol) and stannane **127a** (229 mg, 0.50 mmol) using general Stille coupling procedure 1. The data were consistent with those reported above.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(3''-nitrophenyl) ethene 179

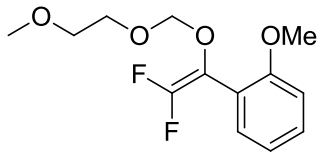
Prepared from **131a** (4.45 mL of a 0.22 M solution, 1.0 mmol) and **165** (222 mg, 1.1 mmol) using general Negishi coupling procedure 1 to afford **179** (91 mg, 31%) as a yellow oil; Rf (40% diethyl ether in hexane) 0.13; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.37 (app. t, *J* 2.0, 1 H), 8.18 (dd, *J* 8.0, *J* 2.0, 1 H), 7.82 (m, including app. d, *J* 8.0, 1 H), 7.59 (app. t, *J* 8.0, 1 H), 4.95 (s, 2 H), 3.92-3.88 (m, 2 H), 3.59-3.55 (m, 2 H), 3.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.5 (app. t, $J_{C\text{-}F}$ 292.6), 148.1, 131.9 (dd, $J_{C\text{-}F}$ 6.5, 2.1), 131.7 (dd, $J_{C\text{-}F}$ 6.9, 3.2), 129.1, 122.4, 120.9 (dd, $J_{C\text{-}F}$ 6.0, 3.7), 114.1 (dd, $J_{C\text{-}F}$ 34.1, 19.5), 95.7 (t, $J_{C\text{-}F}$ 3.0), 71.0, 68.3, 58.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -94.1 (d, *J* 49.0, 1 F), -103.0 (d, *J* 49.0, 1 F); LRMS (CI) *m/z* 318 $[M + C_2H_5]^+$; GC (98%) t_R 12.66 mins. These data are consistent with those reported previously.[110]

Styrene **179** (30 mg, 61%) was also prepared from trifluoroborate **224** (47 mg, 0.20 mmol) and iodide **139a** (50 mg, 0.17 mmol) using general Suzuki coupling procedure 3. The data were consistent with those reported above.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(3-pyridyl) ethene 258

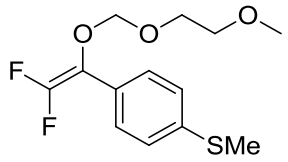
Prepared from iodide **139a** (50 mg, 0.17 mmol) and trifluoroborate **249** (38 mg, 0.20 mmol) using general Suzuki coupling procedure 3 to afford **258** (27 mg, 54%) as a yellow oil; R_f (70% diethyl ether in hexane) 0.19; ν_{max}(film)/cm^{-1} 2934, 2885, 1731, 1567, 1418, 1267, 1153, 1125, 1099, 1077, 978, 937, 849, 812, 711; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.73 (br. s, 1 H), 8.55 (br. d, *J* 4.8, 1 H), 7.79-7.75 (m, 1 H), 7.32 (dd, *J* 8.1, 4.8, 1 H), 4.90 (s, 2 H), 3.87-3.84 (m, 2 H), 3.56-3.53 (m, 2 H), 3.38 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.7 (app. t, $J_{C\text{-}F}$ 291.8), 149.2, 147.9 (dd, $J_{C\text{-}F}$ 6.7, 3.5), 134.0 (dd, $J_{C\text{-}F}$ 6.2, 3.3), 126.4 (d, $J_{C\text{-}F}$ 6.8), 123.3, 113.6 (dd, $J_{C\text{-}F}$ 36.3, 19.7), 95.8 (t, $J_{C\text{-}F}$ 3.1), 71.5, 68.7, 59.0; ^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) -95.3 (d, *J* 52.8, 1 F), -105.0 (d, *J* 52.8, 1 F); LRMS *m/z* (CI) 274 $[M + C_2H_5]^+$; GC (98%) t_R 10.77 mins.; HRMS (NSI) *m/z* calcd for $C_{11}H_{13}F_2NO_3$ $[M]^+$ 245.0858, Found 245.0854.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(2''-methoxyphenyl) ethene 254

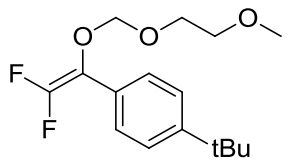
Prepared from iodide **139a** (50 mg, 0.17 mmol) and trifluoroborate **240** (44 mg, 0.20 mmol) using general Suzuki procedure 3 to afford **254** (52 mg, 93%) as a pale yellow oil. R_f (40% diethyl ether in hexane) 0.28; ν_{max}(film)/cm^{-1} 2977, 2939, 2842, 1724, 1497, 1422, 1264, 1142, 982, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41-7.32 (m, 2

H), 6.99 (dt, *J* 7.5, *J* 0.8, 1 H), 6.95 (d, *J* 8.2, 1 H), 4.80 (s, 2 H), 3.87 (s, 3 H), 3.83-3.79 (m, 2 H), 3.57-3.53 (m, 2 H), 3.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.4, 154.0 (dd, $J_{C\text{-}F}$ 289.4, 281.5), 131.2, 130.4, 119.9, 117.5 (br. s), 111.7 (dd, $J_{C\text{-}F}$ 42.0, 19.8), 110.7, 93.6, 71.1, 67.4, 58.5, 55.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -100.1 (d, *J* 60.1, 1 F), -107.7 (d, *J* 60.1, 1 F); LRMS *m/z* (CI) 275 $[M + H]^+$; GC (98%) t_R 11.32 mins.; HRMS (NSI) *m/z* calcd for $C_{13}H_{20}F_2NO_4$ $[M+NH_4]^+$ 292.1355, Found 292.1358.



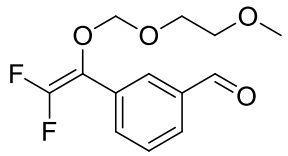
2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(4''-thioanisoyl) ethene 255

Prepared from iodide **139a** (50 mg, 0.17 mmol) and trifluoroborate **241** (47 mg, 0.20 mmol) using general Suzuki coupling procedure 3 to afford **255** (37 mg, 62%) as a pale yellow oil. R_f (40% diethyl ether in hexane) 0.28; ν_{max}(film)/cm^{-1} 2887, 2820, 1730, 1495, 1262, 1178, 1096, 1077, 980, 945, 824; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41-7.37 (m, 2 H), 7.29-7.25 (m, 2 H), 4.89 (s, 2 H), 3.89-3.86 (m, 2 H), 3.60-3.56 (m, 2 H), 3.40 (s, 3 H), 2.51 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.9 (app. t, $J_{C\text{-}F}$ 289.1), 138.6, 126.6 (dd, $J_{C\text{-}F}$ 5.7, 3.4), 126.0 (br. d, $J_{C\text{-}F}$ 6.6), 125.8, 114.8 (dd, $J_{C\text{-}F}$ 35.0, 18.5), 94.9 (t, $J_{C\text{-}F}$ 3.0), 71.1, 68.0, 58.5, 15.0; ^{19}F NMR (400 MHz, $CDCl_3$) δ (ppm) -98.0 (d, *J* 56.9, 1 F), -106.4 (d, *J* 56.9, 1 F); LRMS *m/z* (CI) 319 $[M + C_2H_5]^+$; GC (98%) t_R 12.94 mins.; HRMS (NSI) *m/z* calcd for $C_{13}H_{20}F_2NO_3S$ $[M+NH_4]^+$ 308.1127, found 308.1128.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(4''-*t*-butylphenyl) ethene 256

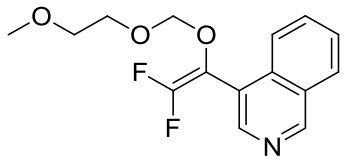
Prepared from iodide **139a** (50 mg, 0.17 mmol) and trifluoroborate **243** (49 mg, 0.20 mmol) using general Suzuki coupling procedure 3 to afford **256** (61 mg, 99%) as a colourless oil. R_f (40% diethyl ether in hexane) 0.47; ν_{max}(film)/cm^{-1} 2960, 2882, 1722, 1465, 1260, 1154, 1109, 975, 945, 837, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42 (br. s, 4 H), 4.89 (s, 2 H), 3.90-3.87 (m, 2 H), 3.60-3.56 (m, 2 H), 3.40 (s, 3 H), 1.35 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.9 (app. t, $J_{C\text{-}F}$ 288.4), 150.9, 126.4 (br. d, $J_{C\text{-}F}$ 6.1), 126.0 (dd, $J_{C\text{-}F}$ 5.5, 3.5), 125.0, 115.1 (dd, $J_{C\text{-}F}$ 35.5, 18.3), 94.8 (t, $J_{C\text{-}F}$ 3.0), 71.1, 68.0, 58.5, 34.1, 30.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -98.7 (d, *J* 58.0, 1 F), -107.1 (d, *J* 58.0, 1 F); LRMS *m/z* (CI) 301 $[M + H]^+$; GC (98%) t_R 12.25 mins.; HRMS (NSI) m/z calcd for $C_{16}H_{26}F_2NO_3$ $[M+NH_4]^+$ 318.1875, found 318.1880.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(3''-formylphenyl) ethene 257

Prepared from iodide **139a** (50 mg, 0.17 mmol) and trifluoroborate **248** (43 mg, 0.2 mmol) using general Suzuki coupling procedure 2 to afford styrene **257** (31 mg, 67%) as a colourless oil; R_f (40% diethyl ether in hexane) 0.13; ν_{max}(film)/cm^{-1} 2924, 2893, 2738, 1698, 1293, 1146, 1070, 1021, 1008, 850, 799, 734, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.05 (s, 1 H), 8.00 (br. s, 1 H), 7.85 (dd, *J* 7.7, 1.23, 1 H), 7.78 -

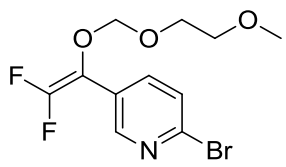
7.73 (m, 1 H), 7.58 (t, *J* 7.7, 1 H), 4.92 (br. s, 2 H), 3.9 – 3.87 (m, 2 H), 3.59 – 3.55 (m, 2 H), 3.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 191.3, 155.3 (app. t, $J_{C\text{-}F}$ 291.5), 136.2, 131.8 (dd, $J_{C\text{-}F}$ 6.3, 3.2), 130.9 (br. d, $J_{C\text{-}F}$ 6.5), 128.8, 128.7, 127.5 (dd, $J_{C\text{-}F}$ 6.0, 3.8), 114.4 (dd, $J_{C\text{-}F}$ 34.8, 19.2), 95.3 (t, $J_{C\text{-}F}$ 3.0), 71.0, 68.2, 58.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -95.7 (d, *J* 52.6, 1 F), -104.6 (d, *J* 52.6, 1 F); LRMS (CI) *m/z* 301 $[M + C_2H_5]^+$; GC (98%) t_R 12.02 mins.; HRMS (NSI) *m/z* calcd for $C_{13}H_{18}F_2NO_4$ $[M+NH_4]^+$ 290.1204, Found 290.1202.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(4-isoquinolyl) ethene 259

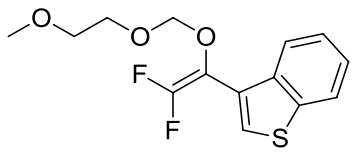
Prepared from iodide **139a** (50 mg, 0.17 mmol) and trifluoroborate **250** (48 mg, 0.20 mmol) using general Suzuki coupling procedure 3 to afford **259** (19 mg, 32%) as a pale yellow oil; R_f (70% diethyl ether in hexane) 0.22; ν_{max}(film)/cm^{-1} 2932, 2895, 2822, 1752, 1504, 1279, 1193, 1166, 1150, 960, 761, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.30 (s, 1 H), 8.60 (s, 1 H), 8.12 (br. d, *J* 8.4, 1 H), 8.04 (br. d, *J* 8.4, 1 H), 7.81-7.77 (m, 1 H), 7.71-7.66 (m, 1 H), 4.80 (d, $J_{H\text{-}F}$ 0.7, 2 H), 3.82-3.79 (m, 2 H), 3.53-3.50 (m, 2 H), 3.38 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.0 (dd, $J_{C\text{-}F}$ 292.1, 283.5), 153.7, 144.5 (t, $J_{C\text{-}F}$ 3.1), 133.9 (d, $J_{C\text{-}F}$ 3.1), 130.7, 127.9, 127.6, 127.2, 123.8, 119.7, 111.3 (dd, $J_{C\text{-}F}$ 40.8, 21.5), 93.6, 71.0, 67.6, 58.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -98.4 (d, *J* 57.3, 1 F), -107.1 (d, *J* 57.3, 1 F); LRMS *m/z* (CI) 324 $[M + C_2H_5]^+$;

GC (98%) t_R 13.19 mins.; HRMS (NSI) *m/z* calcd for $C_{15}H_{16}F_2NO_3$ $[M+H]^+$ 296.1093, found 296.1096.



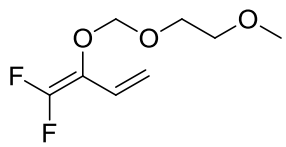
2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(6''-bromo-3-pyridyl) ethene 260

Prepared from iodide **139a** (50 mg, 0.17 mmol) and trifluoroborate **251** (54 mg, 0.20 mmol) using general Suzuki coupling procedure 1 to afford **260** (21 mg, 32%) as a yellow oil; R_f (40% diethyl ether in hexane) 0.23; ν_{max}(film)/cm^{-1} 2930, 2885, 2820, 1724, 1457, 1271, 1155, 1088, 975, 936, 837; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.49 (d, *J* 2.5, 1 H), 7.65 (ddd, *J* 8.4, *J* 2.5, J_{H-F} 0.9, 1 H), 7.52 (d, *J* 8.4, 1 H), 4.92 (s, 2 H), 3.88-3.85 (m, 2 H), 3.58-3.54 (m, 2 H), 3.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.3 (app. t, J_{C-F} 292.5), 147.7 (dd, J_{C-F} 6.8, 3.5), 141.2, 135.8 (dd, J_{C-F} 6.5, 3.2), 127.5, 125.6 (br. d, J_{C-F} 6.6), 112.6 (dd, J_{C-F} 35.8, 20.3), 95.7 (t, J_{C-F} 3.1), 71.1, 68.4, 58.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -94.0 (d, *J* 50.2, 1 F), -103.6 (d, *J* 50.2, 1 F); LRMS *m/z* (CI) 352 $[M + C_2H_5]^+$; GC (98%) t_R 12.34 mins.; HRMS (NSI) *m/z* calcd for $C_{11}H_{13}BrF_2NO_3$ $[M+H]^+$ 324.0041, found 324.0049.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(3-benzothiophenyl) ethene 261

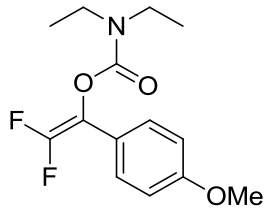
Prepared from iodide **139a** (50 mg, 0.17 mmol) and trifluoroborate **252** (49 mg, 0.20 mmol) using general Suzuki coupling procedure 3 to afford **261** (35 mg, 57%) as a yellow oil; R_f (40% diethyl ether in hexane) 0.36; ν_{max}(film)/cm^{-1} 3103, 2926, 2889, 2822, 1745, 1457, 1429, 1284, 1224, 1114, 1096, 1079, 958, 913, 831, 760, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.98-7.94 (m, 1 H), 7.91-7.87 (m, 1 H), 7.59 (s, 1 H), 7.46-7.38 (m, 2 H), 4.82 (d, J_{H-F} 0.8, 2 H), 3.86-3.83 (m, 2 H), 3.57-3.53 (m, 2 H), 3.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.9 (dd, J_{C-F} 290.5, 284.5), 139.4, 137.0 (d, J_{C-F} 3.2), 127.6 (t, J_{C-F} 3.9), 124.3, 124.2, 123.9 (dd, J_{C-F} 5.3), 122.7, 122.2, 110.8 (dd, J_{C-F} 39.9, 19.3), 93.9 (t, J_{C-F} 2.6), 71.1, 67.7, 58.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -99.5 (d, J 57.3, 1 F), -107.2 (d, J 57.3, 1 F); LRMS *m/z* (CI) 329 $[M + C_2H_5]^+$; GC (98%) t_R 12.98 mins.; HRMS (NSI) *m/z* calcd for $C_{14}H_{18}F_2NO_3S$ $[M+H]^+$ 318.0970, found 318.0974.



2,2-Difluoro-1-(2'-methoxy-ethoxymethoxy)-1-(vinyl) ethene 262

Prepared from iodide **139a** (549 mg, 1.87 mmol) and trifluoroborate **253** (300 mg, 2.24 mmol) using general Suzuki coupling procedure 3 to afford **262** (97 mg, 27%) as a colourless oil after Kugelrohr distillation (100 mbar, 95 °C); R_f (40% diethyl ether in

hexane) 0.31; ν_{max}(film)/cm^{-1} 2975, 2935, 2889, 1744, 1455, 1366, 1244, 1192, 1162, 1086, 1045, 1024, 983, 896, 849; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.25 (dddd, *J* 17.3, 11.1, $J_{H\text{-}F}$ 3.7, 1.6, 1 H), 5.43 (br. d, *J* 17.3, 1 H), 5.16 (dq, *J* 11.2, 1.4, 1 H), 4.95 (s, 2 H), 3.90-3.87 (m, 2 H), 3.61-3.58 (m, 2 H), 3.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.7 (app. t, $J_{C\text{-}F}$ 293.5), 123.9 (d, $J_{C\text{-}F}$ 4.7), 115.2 (dd, $J_{C\text{-}F}$ 35.8, 17.3), 113.3 (dd, $J_{C\text{-}F}$ 11.9, 4.4), 95.7 (t, $J_{C\text{-}F}$ 3.0), 71.1, 68.1, 58.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -98.1 (d, *J* 54.5, 1 F), -106.6 (dd, *J* 54.5, $J_{F\text{-}H}$ 2.7, 1 F); LRMS *m/z* (CI) 195 $[M + H]^+$; GC (98%) t_R 10.48 mins.; HRMS (APCI) m/z calcd for $C_8H_{16}F_2NO_3$ $[M+NH_4]^+$ 212.1093, found 212.1092.



1-(*N*,*N*-Diethylcarbamoyloxy)-2,2-difluoro-1-(4'-methoxyphenyl) ethene 133

Prepared from **131b** (3.95 mL of a 0.25 M solution, 1.0 mmol) and **155** (206 mg, 1.1 mmol) using general Negishi coupling procedure 2 to afford styrene **133** (185 mg, 65%) as a yellow oil; R_f (40% diethyl ether in light petroleum ether) 0.35; ν_{max}(film)/cm^{-1} 1729, 1611, 1515, 1425, 1269, 1147, 1035, 983, 838, 824, 786, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39-7.35 (m, 2 H), 6.95-6.91 (m, 2 H), 3.83 (s, 3 H), 3.46 (q, *J* 7.1, 2 H), 3.38 (q, *J* 7.1, 2 H), 1.27 (t, *J* 7.1, 3 H), 1.20 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.9, 154.1 (app. t, $J_{C\text{-}F}$ 288.1), 152.5, 126.6 (dd, $J_{C\text{-}F}$ 6.0, 3.3), 122.1 (br. d, $J_{C\text{-}F}$ 6.3), 113.6, 111.7 (dd, $J_{C\text{-}F}$ 38.9, 19.5), 54.8, 42.0, 41.4, 13.7, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -95.9 (d, *J* 54.4, 1 F), -106.0 (d, *J* 54.4,

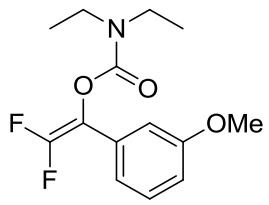
1 F); LRMS (CI) *m/z* 286 $[M + H]^+$; GC (98%) t_R 12.50 mins.; HRMS (EI) m/z calcd for $C_{14}H_{17}F_2NO_3$ $[M]^+$ 285.1177, found 285.1188.

Styrene **133** (110 mg, 39%) was also prepared from **131b** (4 mL of a 2.5 M solution, 1.0 mmol) and aryl iodide **132** (257 mg, 1.1 mmol) using general Negishi coupling procedure 3. The data were consistent with those reported above.

Styrene **133** (260 mg, 83%) was also prepared from **132** (283 mg, 1.21 mmol) and stannane **127b** (515 mg, 1.1 mmol) using general Stille coupling procedure 1. The data were consistent with those reported above.

Styrene **133** (103 mg, 80%) was also prepared from trifluoroborate **238** (107 mg, 0.5 mmol) and iodide **139b** (137 mg, 0.45 mmol) using general Suzuki coupling procedure 1. The data were consistent with those reported above.

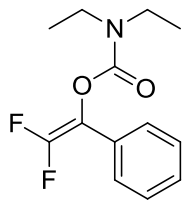
Styrene **133** (39 mg, 84%) was also prepared from boronic acid **284** (28 mg, 0.18 mmol) and iodide **139b** (50 mg, 0.16 mmol) using general Suzuki coupling procedure 6. The data were consistent with those reported above.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(3'-methoxyphenyl) ethene 152

Prepared from **131b** (3.95 mL of a 0.25 M solution, 1.0 mmol) and **156** (206 mg, 1.1 mmol) using general Negishi coupling procedure 2 to afford **152** (179 mg, 63%) as a pale yellow oil; Rf (40% diethyl ether in light petroleum ether) 0.31; ν_{max}(film)/cm^{-1} 2977, 2939, 1733, 1602, 1581, 1422, 1382, 1270, 1219, 1142, 1096, 1043, 1007, 952, 931, 843, 782, 755, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 (app. t, *J* 8.1, 1 H), 7.06-7.03 (m, 1 H), 6.98 (br. s, 1 H), 6.87 (dd, *J* 8.1, *J* 2.5, 1 H), 3.82 (s, 3 H), 3.47 (q, *J* 7.1, 2 H), 3.40 (q, *J* 7.1, 2 H), 1.29 (t, *J* 7.1, 3 H), 1.20 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.1, 154.5 (app. t, $J_{C\text{-}F}$ 290.3), 152.4, 131.1 (d, $J_{C\text{-}F}$ 6.6), 129.1, 117.4 (dd, $J_{C\text{-}F}$ 6.7, 3.5), 113.2, 111.8 (dd, $J_{C\text{-}F}$ 37.8, 19.1), 110.8 (dd, $J_{C\text{-}F}$ 6.7, 3.6), 54.7, 42.1, 41.5, 13.7, 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -93.4 (d, *J* 48.3, 1 F), -103.1 (d, *J* 48.3, 1 F); LRMS (CI) *m/z* 303 $[M + C_2H_5]^+$, 286 $[m + H]^+$; GC (98%) t_R 12.43 mins.; HRMS (ES-TOF) m/z calcd for $C_{14}H_{17}F_2NO_3Na$ $[M + Na]^+$ 308.1069, found 308.1059.

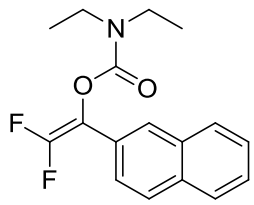
Styrene **152** (33 mg, 59%) was also prepared from trifluoroborate **239** (42 mg, 0.2 mmol) and iodide **139b** (50 mg, 0.17 mmol) using general Suzuki coupling procedure 2. The data were consistent with those reported above.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-phenyl ethene 144

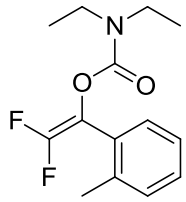
Was prepared from **131b** (3.95 mL of a 0.25 M solution, 1.0 mmol) and **143** (172 mg, 1.1 mmol) using general Negishi coupling procedure 2 to afford **144** (165 mg, 65%) as a yellow oil; Rf (40% diethyl ether in light petroleum ether) 0.31; ν_{max}(film)/cm^{-1} 1732, 1424, 1382, 1269, 1224, 1148, 984, 759, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46-7.38 (m, 4 H), 7.34-7.29 (m, 1 H), 3.47 (q, *J* 7.1, 2 H), 3.38 (q, *J* 7.1, 2 H), 1.29 (t, *J* 7.1, 3 H), 1.20 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.4 (app. t, $J_{C\text{-}F}$ 289.8), 152.4, 129.7 (br. d, $J_{C\text{-}F}$ 6.6), 128.0, 127.6, 125.0 (dd, $J_{C\text{-}F}$ 6.5, 3.5), 111.9 (dd, $J_{C\text{-}F}$ 38.40, 19.1), 42.1, 41.5, 13.7, 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -93.7 (d, *J* 49.1, 1 F), -103.7 (d, *J* 49.1, 1 F); LRMS (CI) *m/z* 284 $[M + C_2H_5]^+$, 256 $[m + H]^+$; GC (98%) t_R 11.15 mins.; HRMS (EI) m/z calcd for $C_{13}H_{15}F_2NO_2$ $[M]^+$ 255.1071, found 255.1068.

Styrene **144** (138 mg, 54%) was also prepared from trifluoroborate **106b** (157 mg, 1.0 mmol) and **143** (285 mg, 1.0 mmol) using general Suzuki coupling procedure 5. The data were consistent with those reported above.



1,1-Difluoro-2-(*N,N*-diethylcarbamoyloxy)-2-(2'-naphthyl) ethene 190

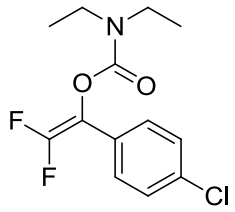
Prepared from **131b** (3.95 mL of a 0.25 M solution, 1.0 mmol) and **157** (228 mg, 1.1 mmol) using general Negishi coupling procedure 2 to afford **190** (174 mg, 57%) as colourless plates; R_f (15% diethyl ether in hexane) 0.25; mp 57-57.5 °C; (Found: C, 66.7; H, 5.7; N, 4.4; $C_{13}H_{15}F_2NO_2$ requires C, 66.9; H, 5.6; N, 4.6 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.92-7.82 (m, 4 H), 7.58 (dt, *J* 8.7, *J* 1.6, 1 H), 7.54-7.48 (m, 2 H), 3.53 (q, *J* 7.1, 2 H), 3.41 (q, *J* 7.1, 2 H), 1.34 (t, *J* 7.1, 3 H), 1.22 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.2 (app. t, $J_{C\text{-}F}$ 290.1), 153.0, 133.1, 132.9, 128.3, 128.3, 127.7 (br. d, $J_{C\text{-}F}$ 5.7), 127.6, 126.5, 126.5, 125.0 (t, $J_{C\text{-}F}$ 5.4), 123.0 (dd, $J_{C\text{-}F}$ 6.6, 2.8), 112.6 (dd, $J_{C\text{-}F}$ 38.1, 19.3), 42.6, 42.0, 14.2, 13.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -93.3 (d, *J* 48.1, 1 F), -103.7 (d, *J* 48.1, 1 F); HRMS (CI) m/z calcd for $C_{17}H_{21}F_2N_2O_2$ $[M + NH_4]^+$ 323.1571, found 323.1584.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(2'-methylphenyl) ethene 191

Prepared from iodide **139b** (101 mg, 0.33 mmol) and trifluoroborate **242** (78 mg, 0.4 mmol) using general Suzuki coupling procedure 1 to afford **191** (83 mg, 93%) as a pale yellow oil. R_f (40% diethyl ether in hexane) 0.50; ^{1}H NMR (400 MHz, $CDCl_3$)

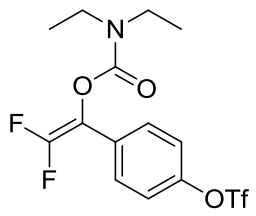
δ (ppm) 7.42 (br. d, *J* 7.5, 1 H), 7.31-7.19 (m, 3 H), 3.41-3.25 (m, 4 H), 2.43 (s, 3 H), 1.23-1.09 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.1 (dd, $J_{C\text{-}F}$ 290.0, 282.6), 153.0, 137.8, 130.4, 130.1, 129.3, 129.1 (d, $J_{C\text{-}F}$ 4.6), 125.7, 111.1 (dd, $J_{C\text{-}F}$ 46.1, 18.8), 42.4, 41.8, 19.5, 14.1, 13.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -97.4 (d, *J* 53.9, 1 F), -106.2 (d, *J* 53.9, 1 F). These data were consistent with those reported previously.[104]



1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-(4'-chlorophenyl)ethene 192

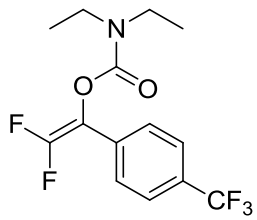
Prepared from **131b** (3.95 mL of a 0.25 M solution, 1.0 mmol) and **159** (192 mg, 1.1 mmol) using general Negishi coupling procedure 2 to afford **192** (147 mg, 51%) as a pale yellow oil; R_f (40% diethyl ether in light petroleum ether) 0.39; ν_{max}(film)/cm^{-1} 2982, 2939, 1727, 1499, 1424, 1260, 1140, 1094, 980, 818; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 (s, 4 H), 3.46 (q, *J* 7.0, 2 H), 3.38 (q, *J* 7.0, 2 H), 1.28 (t, *J* 7.1, 3 H), 1.20 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.4 (app. t, $J_{C\text{-}F}$ 291.1), 152.3, 133.5, 128.3 (d, $J_{C\text{-}F}$ 5.5), 128.3, 126.3 (dd, $J_{C\text{-}F}$ 6.7, 3.5), 111.3 (dd, $J_{C\text{-}F}$ 38.7, 20.1), 42.2, 41.5, 13.7, 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -93.1 (d, *J* 47.7, 1 F), -103.1 (d, *J* 47.7, 1 F); LRMS (CI) *m/z* 318 $[M + C_2H_5]^+$, 290 $[M + H]^+$; GC (98%) t_R 12.02 mins.; HRMS (EI) m/z calcd for $C_{13}ClH_{15}F_2NO_2$ $[M]^+$ 289.0681, found 289.0687.

Styrene **192** (84 mg, 88%) was also prepared from trifluoroborate **244** (87 mg, 0.4 mmol) and iodide **139b** (101 mg, 0.33 mmol) using general Suzuki coupling procedure 1. The data were consistent with those reported above.



1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-[4'' (trifluoromethanesulfonyloxy) phenyl] ethene 193

Prepared from **131b** (3.95 mL of a 0.25 M solution, 1.0 mmol) and **160** (387 mg, 1.1 mmol) using general Negishi coupling procedure 2 to afford **193** (240 mg, 60%) as a pale yellow oil; R_f (40% diethyl ether in hexane) 0.43; (Found: C, 41.72; H, 3.33; N, 3.82; $C_{14}H_{14}F_5NO_5S$ requires C, 41.69; H, 3.50; N, 3.47 %); ν_{max}(film)/cm^{-1} 2982, 1736, 1598, 1505, 1426, 1275, 1216, 1146, 888; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.55-7.50 (m, 2 H), 7.34-7.30 (m, 2 H), 3.47 (q, *J* 7.1, 2 H), 3.39 (q, *J* 7.1, 2 H), 1.29 (t, *J* 7.2, 3 H), 1.21 (t, *J* 7.2, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.6 (app. t, J_{C-F} 291.8), 152.1, 148.3, 130.3 (br. d, J_{C-F} 6.9), 126.9 (dd, J_{C-F} 6.9, 3.6), 121.1, 118.2 (q, J_{C-F} 320.9), 110.8 (dd, J_{C-F} 38.2, 20.3), 42.2, 41.6, 13.7, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -72.8 (s, 3 F), -91.7 (d, *J* 44.9, 1 F), -101.3 (d, *J* 44.9, 1 F); LRMS (CI) *m/z* 432 $[M + C_2H_5]^+$, 404 $[M + H]^+$; GC (98%) t_R 12.26 mins.; HRMS (ES-TOF) m/z calcd for $C_{14}H_{14}F_5NNaO_5$ $[M + Na]^+$ 426.0411, found 426.0413.

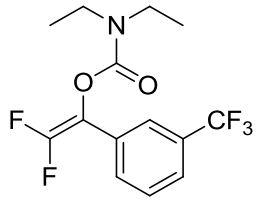


1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(4'-trifluoromethylphenyl) ethene 194

Prepared from **131b** (3.95 mL of a 0.25 M solution, 1.0 mmol) and **161** (248 mg, 1.1 mmol) using general Negishi coupling procedure 2 to afford **194** (172 mg, 53%) as a yellow oil; R_f (40% diethyl ether in light petroleum ether) 0.55; ν_{max}(film)/cm^{-1} 2982, 2939, 1731, 1427, 1412, 1327, 1273, 1148, 1116, 1050, 980, 844, 822; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.66 (d, *J* 8.4, 2 H), 7.55 (d, *J* 8.4, 2 H), 3.49 (q, *J* 7.2, 2 H), 3.38 (q, *J* 7.2, 2 H), 1.30 (t, *J* 7.1, 3 H), 1.21 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.8 (app. t, $J_{C\text{-}F}$ 292.6), 152.2, 133.5 (br. d, $J_{C\text{-}F}$ 6.9), 129.5 (q, $J_{C\text{-}F}$ 32.5), 125.0 – 125.2 (m, includes signals for 2 x (Ar)C-H), 123.4 (q, $J_{C\text{-}F}$ 272.6), 111.2 (dd, $J_{C\text{-}F}$ 37.8, 19.9), 42.2, 41.6, 13.7, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -62.9 (s, 3 F), -91.1 (d, *J* 43.1, 1 F), -101.3 (d, *J* 43.1, 1 F); LRMS (CI) *m/z* 352 $[M + C_2H_5]^+$, 324 $[M + H]^+$; GC (98%) t_R 10.71 mins.; HRMS (NSI) m/z calcd for $C_{14}H_{15}F_5NO_2$ $[M + H]^+$ 324.1023, found 324.1022.

Styrene **194** (94 mg, 88%) was also prepared from trifluoroborate **245** (100 mg, 0.4 mmol) and iodide **139b** (101 mg, 0.33 mmol) using general Suzuki coupling procedure 1. The data were consistent with those reported above.

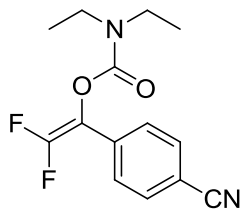
Styrene **194** (49 mg, 92%) was also prepared from boronic acid **285** (37 mg, 0.20 mmol) and iodide **139b** (50 mg, 0.16 mmol) using general Suzuki coupling procedure 6. The data were consistent with those reported above.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(3'-trifluoromethylphenyl) ethene 195

Prepared from **131b** (3.95 mL of a 0.25 M solution, 1.0 mmol) and **162** (248 mg, 1.1 mmol) using general Negishi coupling procedure 2 to afford **195** (120 mg, 37%) as a pale yellow oil; R_f (40% diethyl ether in hexane) 0.33; ν_{max}(film)/cm^{-1} 2982, 2939, 1728, 1424, 1345, 1252, 1144, 1127, 1073, 1000, 923, 808, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 (br. s, 1 H), 7.63 (br. d, *J* 7.7, 1 H), 7.58 (br. d, *J* 7.7, 1 H), 7.53 (t, *J* 7.7, 1 H), 3.49 (q, *J* 7.2, 2 H), 3.39 (q, *J* 7.2, 2 H), 1.30 (t, *J* 7.1, 3 H), 1.21 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.7 (app. t, $J_{C\text{-}F}$ 291.0), 152.1, 130.8 (br. d, $J_{C\text{-}F}$ 6.9), 130.6 (q, $J_{C\text{-}F}$ 32.6), 128.6, 128.1 (dd, $J_{C\text{-}F}$ 7.0, 3.0), 124.3 (d, $J_{C\text{-}F}$ 3.14), 123.2 (q, $J_{C\text{-}F}$ 271.2), 121.5-121.8 (m), 111.1 (dd, $J_{C\text{-}F}$ 37.3, 19.5), 42.2, 41.6, 13.6, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -63.9 (s, 3 F), -91.7 (d, *J* 45.3, 1 F), -102.1 (d, *J* 45.3, 1 F); LRMS (CI) *m/z* 352 $[M + C_2H_5]^+$, 324 $[M + H]^+$; GC (98%) t_R 10.55 mins.; HRMS (NSI) m/z calcd for $C_{14}H_{15}F_5NO_2$ $[M + H]^+$ 324.1023, found 324.1018.

Styrene **195** (32 mg, 60%) was also prepared from trifluoroborate **246** (50 mg, 0.2 mmol) and iodide **XXb** (50 mg, 0.17 mmol) using general Suzuki coupling procedure 2. These data were consistent with those reported earlier.

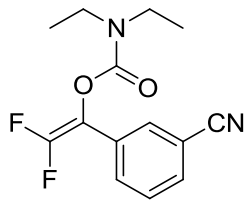


1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-(4'-cyanophenyl) ethene 196

Prepared from **131b** (3.95 mL of a 0.25 M solution, 1.0 mmol) and **163** (200 mg, 1.1 mmol) using general Negishi coupling procedure 2 to afford **196** (101 mg, 36%) as a pale yellow solid; R_f (40% diethyl ether in light petroleum ether) 0.23; mp 80-82 °C; (Found: C, 60.55; H, 4.99; N, 9.57; $C_{14}H_{14}F_2N_2O_2$ requires C, 60.00; H, 5.03; N, 9.57 %); ν_{max}(film)/cm^{-1} 2967, 2932, 2229, 1720, 1415, 1269, 1146, 982, 846, 822; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (br. d, *J* 8.3 2 H), 7.53 (br. d, *J* 8.3 2 H), 3.48 (q, *J* 7.2, 2 H), 3.38 (q, *J* 7.2, 2 H), 1.29 (t, *J* 7.2, 3 H), 1.20 (t, *J* 7.2, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.9 (app. t, $J_{C\text{-}F}$ 294.0), 152.0, 134.5 (br. d, $J_{C\text{-}F}$ 7.4), 131.8, 125.2 (dd, $J_{C\text{-}F}$ 7.4, 3.7), 117.9, 111.2 (dd, $J_{C\text{-}F}$ 37.4, 20.3), 111.1, 42.3, 41.6, 13.7, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -89.3 (d, *J* 39.1, 1 F), -99.3 (d, *J* 39.1, 1 F); LRMS (CI) *m/z* 309 $[M + C_2H_5]^+$, 281 $[M + H]^+$; GC (98%) t_R 12.62 mins.; HRMS (APCI) m/z calcd for $C_{14}H_{15}F_5N_2O_2$ $[M + H]^+$ 281.1102, found 281.1089.

Styrene **196** (135 mg, 48%) was also prepared from **131b** (4 mL of a 2.5 M solution, 1.0 mmol) and **163** (200 mg, 1.1 mmol) using general Negishi coupling procedure 3. The data were consistent with those reported above.

Styrene **196** (57 mg, 62%) was also prepared from trifluoroborate **247** (101 mg, 0.4 mmol) and iodide **139b** (50 mg, 0.33 mmol) using general Suzuki coupling procedure 1. The data were consistent with those reported above.



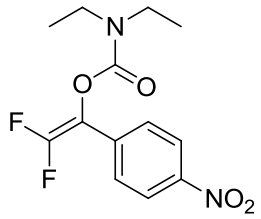
1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-(3'-cyanophenyl) ethene 197

Prepared from **131b** (3.95 mL of a 0.25 M solution, 1.0 mmol) and **164** (200 mg, 1.1 mmol) using general Negishi coupling procedure 2 to afford **197** (82 mg, 29%) as a pale yellow oil; R_f (40% diethyl ether in light petroleum ether) 0.30; ν_{max}(film)/cm^{-1} 2980, 2939, 2235, 1728, 1420, 1267, 1179, 1144, 1012, 928, 799, 754, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (br. d, *J* 1.1, 1 H), 7.67-7.66 (m, 1 H), 7.60 (app. br. d, *J* 7.7, 1 H), 7.52 (app. t, *J* 7.7, 1 H), 3.47 (q, *J* 7.1, 2 H), 3.40 (q, *J* 7.1, 2 H), 1.29 (t, *J* 7.1, 3 H), 1.21 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.7 (app. t, $J_{C\text{-}F}$ 291.7), 152.1, 131.4 (br. d, $J_{C\text{-}F}$ 7.0), 131.0, 129.1-129.0 (m, includes signals for 2 x (Ar)C-H), 128.4 (dd, $J_{C\text{-}F}$ 6.3, 4.0), 117.9, 112.6, 110.6 (dd, $J_{C\text{-}F}$ 37.8, 20.2), 42.3, 41.6, 13.7, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -90.7 (d, *J* 42.6, 1 F), -101.2 (d, *J* 42.6,

1 F); LRMS (CI) *m/z* 309 $[M + C_2H_5]^+$, 281 $[M + H]^+$; GC (98%) t_R 12.45 mins.; HRMS (APCI) m/z calcd for $C_{14}H_{15}F_5N_2O_2$ $[M + H]^+$ 281.1102, found 281.1093.

Styrene **197** (28 mg, 61%) was also prepared from trifluoroborate **247** (41 mg, 0.2 mmol) and iodide **139b** (50 mg, 0.17 mmol) using general Suzuki coupling procedure 2. The data were consistent with those reported above.

Styrene **197** (34 mg, 74%) was also prepared from boronic acid **286** (29 mg, 0.20 mmol) and iodide **139b** (50 mg, 0.16 mmol) using general Suzuki coupling procedure 6. The data were consistent with those reported above.

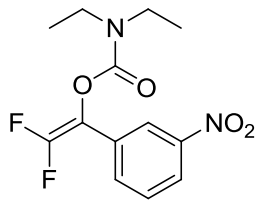


1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-(4'-nitrophenyl) ethene 198

Prepared from **131b** (3.95 mL of a 0.25 M solution, 1.0 mmol) and **141** (274 mg, 1.1 mmol) using general Negishi coupling procedure 2 to afford **198** (125 mg, 42%) as a pale yellow oil; R_f (40% diethyl ether in light petroleum ether) 0.42; ν_{max}(film)/cm^{-1} 1731, 1600, 1522, 1476, 1460, 1427, 1383, 1350, 1332, 1270, 1223, 1151, 988, 854, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, *J* 8.8, 2 H), 7.59 (d, *J* 8.8, 2 H), 3.49 (q, *J* 7.1, 2 H), 3.38 (q, *J* 7.1, 2 H), 1.30 (t, *J* 7.0, 3 H), 1.20 (t, *J* 7.0, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.0 (app. t, $J_{C\text{-}F}$ 294.3), 152.0, 146.5, 136.4 (br. d, $J_{C\text{-}F}$ 7.3), 125.4 (dd, $J_{C\text{-}F}$ 7.6, 3.8), 123.4, 111.1 (dd, $J_{C\text{-}F}$ 36.9, 20.4), 42.3, 41.6, 13.7, 12.7; ^{19}F

NMR (376 MHz, $CDCl_3$) δ (ppm) -88.7 (d, *J* 36.7, 1 F), -98.8 (d, *J* 36.7, 1 F); LRMS (CI) *m/z* 329 $[M + C_2H_5]^+$, 301 $[M + H]^+$; GC (95%) t_R 13.22 mins.; HRMS (ES-TOF) m/z calcd for $C_{13}H_{15}F_2N_2NaO_4$ $[M + Na]^+$ 323.0819, found 323.0830.

Styrene **198** (151 mg, 50%) was also prepared from **131b** (4 mL of a 2.5 M solution, 1.0 mmol) and iodide **141** (274 mg, 1.1 mmol) using general Negishi coupling procedure 3. The data were consistent with those reported above.



1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-(3'-nitrophenyl) ethene 199

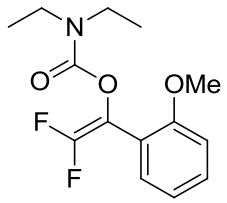
Prepared from **131b** (3.95 mL of a 0.25 M solution, 1.0 mmol) and **165** (222 mg, 1.1 mmol) using general Negishi coupling procedure 2 to afford **199** (53 mg, 18%) as a pale yellow oil; R_f (25% diethyl ether in light petroleum ether) 0.42; ν_{max}(film)/cm^{-1} 3012, 2943, 1729, 1620, 1424, 1343, 1254, 1168, 1148, 1096, 1075, 1002, 950, 801, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.29 (t, *J* 2.0, 1 H), 8.18 (dd, *J* 8.2, *J* 2.0, 1 H), 7.80-7.77 (m, 1 H), 7.60 (t, *J* 8.2, 1 H), 3.51 (q, *J* 7.1, 2 H), 3.39 (q, *J* 7.1, 2 H), 1.32 (t, *J* 7.2, 3 H), 1.22 (t, *J* 7.2, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.9 (app. t, $J_{C\text{-}F}$ 293.2), 152.0, 148.0, 131.9 (br. d, $J_{C\text{-}F}$ 7.3), 130.6 (dd, $J_{C\text{-}F}$ 8.1, 3.5), 129.2, 122.3, 119.8 (dd, $J_{C\text{-}F}$ 5.9, 4.4), 110.7 (dd, $J_{C\text{-}F}$ 37.5, 20.5), 42.3, 41.6, 13.7, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -90.3 (d, *J* 42.2, 1 F), -100.7 (d, *J* 42.2, 1 F); LRMS (CI) *m/z*

329 $[M + C_2H_5]^+$, 301 $[M + H]^+$; GC (95%) t_R 13.00 mins.; HRMS (NSI) m/z calcd for $C_{13}H_{15}F_2N_2O_4$ $[M + H]^+$ 301.0994, found 301.0991.

Styrene **199** (30 mg, 10%) was also prepared from **131b** (4 mL of a 2.5 M solution, 1.0 mmol) and **165** (222 mg, 1.1 mmol) using general Negishi coupling procedure 3. The data were consistent with those reported above.

Styrene **199** (37 mg, 75%) was also prepared from trifluoroborate **224** (45 mg, 0.2 mmol) and iodide **139b** (50 mg, 0.17 mmol) using general Suzuki coupling procedure 3. The data were consistent with those reported above.

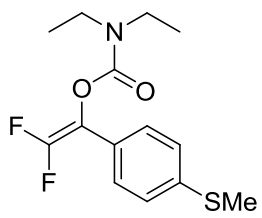
Styrene **199** (37 mg, 75%) was also prepared from boronic acid **288** (45 mg, 0.20 mmol) and iodide **139b** (50 mg, 0.16 mmol) using general Suzuki coupling procedure 6. The data were consistent with those reported above.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(2'-methoxyphenyl) ethene 264

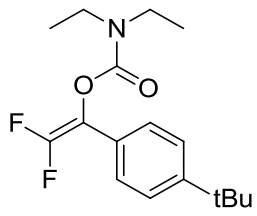
Prepared from **139b** (50 mg, 0.17 mmol) and trifluoroborate **240** (42 mg, 0.2 mmol) using general Suzuki coupling procedure 2 to afford **264** (33 mg, 59%) as a yellow oil; R_f (40% diethyl ether in hexane) 0.31; ν_{max}(film)/cm^{-1} 2977, 2939, 2842, 1724, 1497, 1437, 1422, 1264, 1142, 982, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42 (d, *J*

7.6, 1 H), 7.38-7.33 (m, 1 H), 6.99 (dt, *J* 7.6, *J* 0.9, 1 H), 6.94 (d, *J* 8.4, 1 H), 3.88 (s, 3 H), 3.41-3.29 (m, 4 H), 1.23-1.12 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.8 (d, $J_{C\text{-}F}$ 2.4), 154.0 (dd, $J_{C\text{-}F}$ 290.1, 284.4), 152.7, 130.3 (t, $J_{C\text{-}F}$ 3.0), 130.1, 119.9, 118.4 (br. d, $J_{C\text{-}F}$ 4.6), 110.7, 108.5 (dd, $J_{C\text{-}F}$ 45.1, 20.6), 55.1, 41.9, 41.4, 13.5, 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -96.2 (d, *J* 49.9, 1 F), -104.6 (d, *J* 49.9, 1 F); LRMS *m/z* (CI) 314 $[M + C_2H_5]^+$; GC (98%) t_R 11.70 mins.; HRMS (NSI) *m/z* calcd for $C_{14}H_{18}F_2NO_3$ $[M+H]^+$ 286.1249, found 286.1253.



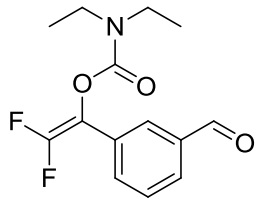
1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(4'-thioanisoyl) ethene 265

Prepared from **139b** (101 mg, 0.33 mmol) and trifluoroborate **241** (91 mg, 0.4 mmol) using general Suzuki coupling procedure 1 to afford **265** (92 mg, 93%) as a pale yellow oil; R_f (40% diethyl ether in hexane) 0.21; ν_{max}(film)/cm^{-1} 3014, 2947, 1724, 1442, 1166, 1116, 1096, 982, 812, 798, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (d, *J* 8.4, 2 H), 7.27 (d, *J* 8.4, 2 H), 3.46 (q, *J* 6.9, 2 H), 3.37 (q, *J* 6.9, 2 H), 2.50 (s, 3 H), 1.28 (t, *J* 6.9, 3 H), 1.20 (t, *J* 6.9, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.3 (app. t, $J_{C\text{-}F}$ 290.7), 152.4, 138.4, 126.4 (d, $J_{C\text{-}F}$ 6.6), 125.9, 125.4 (dd, $J_{C\text{-}F}$ 6.4, 3.6), 111.7 (dd, $J_{C\text{-}F}$ 38.4, 19.4), 42.1, 41.5, 15.1, 13.7, 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -94.1 (d, *J* 49.9, 1 F), -104.0 (d, *J* 49.9, 1 F); LRMS *m/z* (CI) 302 $[M + H]^+$; GC (98%) t_R 13.42 mins.; HRMS (NSI) *m/z* calcd for $C_{14}H_{18}F_2NO_2S$ $[M+H]^+$ 302.1021 found, 302.1025.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(4'-*t*-butylphenyl) ethene 266

Prepared from **139b** (101 mg, 0.33 mmol) and trifluoroborate **243** (95 mg, 0.4 mmol) using general Suzuki coupling procedure 1 to afford **266** (68 mg, 66%) as a colourless oil; R_f (40% diethyl ether in hexane) 0.25; ν_{max}(film)/cm^{-1} 2965, 2872, 1727, 1474, 1420, 1265, 1146, 982, 948, 927, 844, 825, 784, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43 (d, *J* 8.5, 2 H), 7.37 (d, *J* 8.5, 2 H), 3.47 (q, *J* 7.1, 2 H), 3.39 (q, *J* 7.1, 2 H), 1.34 (s, 9 H), 1.29 (t, *J* 6.9, 3 H), 1.21 (t, *J* 6.9, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.4 (app. t, $J_{C\text{-}F}$ 289.3), 152.5, 150.7, 126.8 (d, $J_{C\text{-}F}$ 6.7), 125.0, 124.7 (dd, $J_{C\text{-}F}$ 6.4, 3.4), 111.9 (dd, $J_{C\text{-}F}$ 38.6, 19.1), 42.1, 41.5, 34.1, 30.7, 13.6, 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -97.4 (d, *J* 53.9, 1 F), -106.2 (d, *J* 53.9, 1 F); LRMS *m/z* (CI) 312 $[M + H]^+$; GC (98%) t_R 12.70 mins.; HRMS (NSI) *m/z* calcd for $C_{17}H_{24}F_2NO_2$ $[M+H]^+$ 312.1770, found: 312.1771.

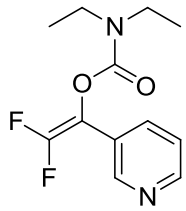


1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(3'-formylphenyl) ethene 267

Prepared from **139b** (50 mg, 0.17 mmol) and trifluoroborate **248** (42 mg, 0.2 mmol) using general Suzuki coupling procedure 2 to afford **267** (42 mg, 90%) as a pale yellow oil; R_f (40% diethyl ether in hexane) 0.17; ν_{max}(film)/cm^{-1} 2979, 2941, 1728,

1689, 1424, 1267, 1187, 1142, 1012, 796, 753, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.04 (s, 1 H), 7.93 (br. s, 1 H), 7.83 (app. br. d, *J* 7.7, 1 H), 7.72-7.69 (m, 1 H), 7.58 (app. t, *J* 7.7, 1 H), 3.49 (q, *J* 7.1, 2 H), 3.38 (q, *J* 7.1, 2 H), 1.30 (t, *J* 7.0, 3 H), 1.20 (t, *J* 7.0, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 191.2, 154.7 (app. t, $J_{C\text{-}F}$ 292.4), 152.2, 136.2, 131.1 (d, $J_{C\text{-}F}$ 6.7), 130.6 (dd, $J_{C\text{-}F}$ 7.0, 3.4), 128.9, 128.7, 126.1 (dd, $J_{C\text{-}F}$ 6.3, 3.9), 111.2 (dd, $J_{C\text{-}F}$ 38.1, 19.8), 42.2, 41.6, 13.7, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -91.8 (d, *J* 45.3, 1 F), -102.2 (d, *J* 45.3, 1 F); LRMS *m/z* (CI) 284 $[M + H]^+$; GC (98%) t_R 12.40 mins.; HRMS (NSI) *m/z* calcd for $C_{14}H_{19}F_2N_2O_3$ $[M+NH_4]^+$ 301.1358, found 301.1360.

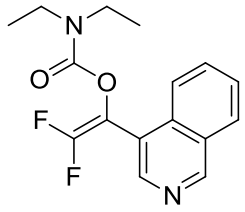
Styrene **267** (28 mg, 60%) was also prepared from boronic acid **287** (30 mg, 0.20 mmol) and iodide **139b** (50 mg, 0.16 mmol) using general Suzuki coupling procedure 6. The data were consistent with those reported above.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(3-pyridyl) ethene 201

Prepared from **139b** (50 mg, 0.17 mmol) and trifluoroborate **249** (37 mg, 0.2 mmol) using general Suzuki coupling procedure 2 to afford **201** (26 mg, 61%) as a colourless oil; R_f (60% diethyl ether in hexane) 0.12; ν_{max}(film)/cm^{-1} 2980, 2939, 1737, 1411, 1275, 1150, 82, 706; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.67 (d, *J* 2.2, 1 H), 8.53 (dd, *J* 4.8, 1.4, 1 H), 7.75 - 7.70 (m, 1 H), 7.31 (ddd, *J* 8.1, *J* 4.8, 0.7, 1 H), 3.44

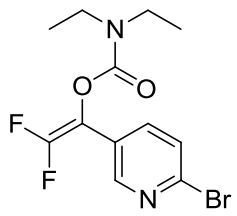
(q, *J* 6.9, 2 H), 3.35 (q, *J* 7.0, 2 H), 1.26 (t, *J* 7.1, 3 H), 1.18 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.6 (app. t, $J_{C\text{-}F}$ 292.3), 152.1, 148.6, 146.3 (dd, $J_{C\text{-}F}$ 6.7, 3.8), 132.4 (dd, $J_{C\text{-}F}$ 7.1, 3.5), 126.1 (br. d, $J_{C\text{-}F}$ 6.9), 122.8, 109.8 (dd, $J_{C\text{-}F}$ 39.7, 20.1), 42.2, 41.6, 13.7, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -91.5 (d, *J* 45.4, 1 F), -102.5 (d, *J* 45.4, 1 F); LRMS *m/z* (CI) 257 $[M + H]^+$; GC (98%) t_R 11.28 mins.; HRMS (NSI) *m/z* calcd for $C_{12}H_{15}F_2N_2O_2$ $[M+H]^+$ 257.1096, found 257.1099.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(4-isoquinolyl) ethene 268

Prepared from **139b** (50 mg, 0.17 mmol) and trifluoroborate **250** (46 mg, 0.2 mmol) using general Suzuki coupling procedure 2 to afford **268** (22 mg, 44%) as a colourless oil; R_f (100% diethyl ether) 0.65; ν_{max}(film)/cm^{-1} 2979, 2938, 1724, 1422, 1282, 1187, 1142, 1113, 958, 786, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.29 (s, 1 H), 8.70 (s, 1 H), 8.15 (br. d, *J* 8.5, 1 H), 8.04 (d, *J* 8.2, 1 H), 7.83 - 7.78 (m, 1 H), 7.70 – 7.64 (m, 1 H), 3.38 (q, *J* 6.9, 2 H), 3.29 (q, *J* 7.0, 2 H), 1.18 (t, *J* 7.0, 3 H), 1.12 (t, *J* 7.0, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.6 (dd, $J_{C\text{-}F}$ 293.7, 285.1), 153.6, 152.3, 144.3 (t, $J_{C\text{-}F}$ 3.0), 133.4, 130.7, 127.8, 127.6, 127.1, 123.6, 120.7 (d, $J_{C\text{-}F}$ 4.7), 107.8 (dd, $J_{C\text{-}F}$ 45.5, 20.2), 42.0, 41.5, 13.6, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -93.9 (d, *J* 49.1, 1 F), -104.2 (d, *J* 49.1, 1 F); LRMS *m/z* (CI) 307 $[M + H]^+$; GC (98%) t_R 13.65 mins.; HRMS (NSI) m/z calcd for $C_{16}H_{17}F_2N_2O_2$ $[M+H]^+$ 307.1253, found 307.1255.

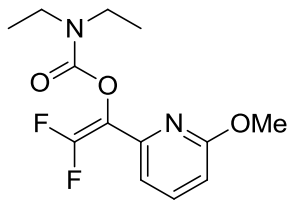
Styrene **268** (5 mg, 10%) was also prepared from boronic acid **289** (34 mg, 0.20 mmol) and iodide **139b** (50 mg, 0.16 mmol) using general Suzuki coupling procedure 6. The data were consistent with those reported above.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(6'-bromo-3-pyridyl) ethene 269

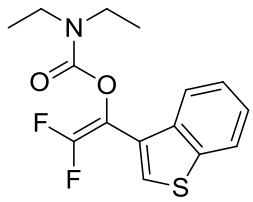
Prepared from **139b** (50 mg, 0.17 mmol) and trifluoroborate **251** (47 mg, 0.17 mmol) using general Suzuki coupling procedure 3 to afford **269** (29 mg, 52%) as a pale yellow oil; R_f (40% diethyl ether in hexane) 0.26; ν_{max}(film)/cm^{-1} 2979, 2941, 1731, 1461, 1424, 1280, 1148, 1090, 980; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.43 (d, *J* 2.5, 1 H), 7.60 (ddd, *J* 8.4, *J* 2.5, 0.7, 1 H), 7.52 (d, *J* 8.4, 1 H), 3.45 (q, *J* 7.2, 2 H), 3.37 (q, *J* 7.2, 2 H), 1.27 (t, *J* 7.1, 3 H), 1.20 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.6 (dd, $J_{C\text{-}F}$ 293.1, 291.8), 152.0 (t, $J_{C\text{-}F}$ 2.9), 146.5 (dd, $J_{C\text{-}F}$ 6.5, 4.0), 140.9, 134.8 (dd, $J_{C\text{-}F}$ 7.3, 3.3), 127.4, 125.6 (d, $J_{C\text{-}F}$ 6.8), 109.3 (dd, $J_{C\text{-}F}$ 39.4, 21.5), 42.3, 41.6, 13.7, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -90.4 (d, *J* 43.5, 1 F), -101.3 (d, *J* 43.5, 1 F); LRMS *m/z* (CI) 335 $[M + H]^+$; GC (98%) t_R 12.77 mins.; HRMS (NSI) *m/z* calcd for $C_{12}H_{14}BrF_2N_2O_2$ $[M+H]^+$ 335.0201, found 335.0206.

Styrene **269** (14 mg, 25%) was also prepared from boronic acid **290** (33 mg, 0.20 mmol) and iodide **139b** (50 mg, 0.16 mmol) using general Suzuki coupling procedure 6. The data were consistent with those reported above.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(6'-methoxy-2-pyridyl) ethene 270

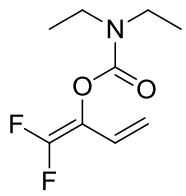
Prepared from **139b** (50 mg, 0.17 mmol) and trifluoroborate **263** (43 mg, 0.20 mmol) using general Suzuki coupling procedure 3 to afford **270** (33 mg, 70%) as a yellow oil; R_f (20% diethyl ether in cyclohexane) 0.1; ν_{max}(film)/cm^{-1} 2979, 2341, 1728, 1578, 1466, 1262, 1153, 1047, 800; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.56 (app. t, *J* 8.1, 1 H), 6.98 (d, *J* 7.6, 1 H), 6.63 (d, *J* 8.3, 1 H), 3.89 (s, 3 H), 3.48 (q, *J* 7.1 2 H), 3.43 (q, *J* 7.1 2 H), 1.29 (t, *J* 7.1, 3 H) 1.19 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.4, 156.5 (dd, $J_{C\text{-}F}$ 296, 292), 153.1 (t, $J_{C\text{-}F}$ 2.4), 146.8 (dd, $J_{C\text{-}F}$ 8.8, 3.3), 138.8, 113.4 (dd, $J_{C\text{-}F}$ 8.9, 4.4), 112.6 (dd, $J_{C\text{-}F}$ 34.3, 18.8), 109.9 (t, $J_{C\text{-}F}$ 2.2), 53.1, 42.6, 42.1, 14.2, 13.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -90.6 (d, *J* 34.4, 1 F), -97.9 (d, *J* 34.4, 1 F); LRMS *m/z* (ESI) 287 $[M + H]^+$; LC (98%) t_R 1.21 mins.; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}F_2N_2O_3$ $[M+H]^+$ 287.1202, found 287.1196.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(3-benzothiophenyl) ethene 271

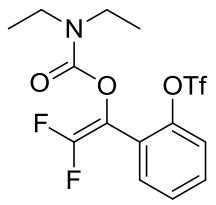
Prepared from **139b** (50 mg, 0.17 mmol) and trifluoroborate **252** (47 mg, 0.2 mmol) using general Suzuki coupling procedure 1 to afford **271** (35 mg, 57%) as a pale brown oil; R_f (40% diethyl ether in hexane) 0.52; ν_{max}(film)/cm^{-1}; 2977, 2938, 2878,

1726, 1422, 1295, 1215, 1154, 1107, 760, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.95-7.87 (m, 2 H), 7.67 (s, 1 H), 7.47-7.38 (m, 2 H), 3.41 (q, *J* 7.0, 2 H), 3.33 (q, *J* 7.0, 2 H), 1.22 (t, *J* 7.0, 3 H), 1.16 (t, *J* 7.0, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.6 (dd, $J_{C\text{-}F}$ 292.2, 284.5), 152.5, 139.3, 136.7 (d, $J_{C\text{-}F}$ 2.7), 127.5 (t, $J_{C\text{-}F}$ 3.7), 124.8 (d, $J_{C\text{-}F}$ 4.9), 124.2, 124.1, 122.3, 122.2, 107.1 (dd, $J_{C\text{-}F}$ 44.1, 21.2), 42.0, 41.4, 13.6, 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -94.9 (d, *J* 49.4, 1 F), -104.3 (d, *J* 49.4, 1 F); LRMS *m/z* (CI) 312 $[M + H]^+$; GC (98%) t_R 13.37 mins.; HRMS (NSI) m/z calcd for $C_{15}H_{16}F_2NO_2S$ $[M+H]^+$ 312.0864, found 312.0862.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(vinyl) ethene 272

Prepared from **139b** (569 mg, 1.87 mmol) and trifluoroborate **253** (300 mg, 2.24 mmol) using general Suzuki coupling procedure 3 to afford **272** (113 mg, 30%) as a colourless oil after Kugelrohr distillation (90 °C/100 mbar); R_f (40% diethyl ether in hexane) 0.46; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.36 (dddd, *J* 17.2, 11.2, $J_{H\text{-}F}$ 3.4, 1.6, 1 H), 5.23 (d, *J* 17.2, 1 H), 5.17 (dq, *J* 11.2, 1.2, 1 H), 3.44-3.32 (m, 4 H), 1.15-1.26 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.3 (dd, $J_{C\text{-}F}$ 295.0, 291.0), 152.4, 124.2 (d, $J_{C\text{-}F}$ 4.6), 113.2 (dd, $J_{C\text{-}F}$ 11.9, 4.3), 112.4 (dd, $J_{C\text{-}F}$ 40.6, 18.2), 42.6, 41.9, 14.1, 13.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -95.6 (d, *J* 40.6, 1 F), -105.6 (d, *J* 40.6, 1 F). These data were consistent with those reported previously.[103]



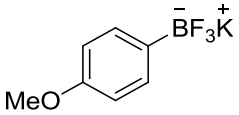
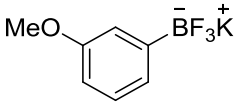
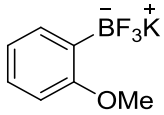
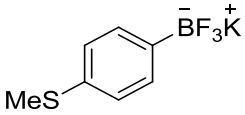
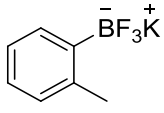
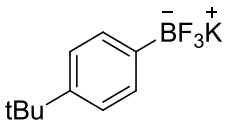
1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-[2'' (trifluoromethanesulfonyloxy) phenyl] ethene 146

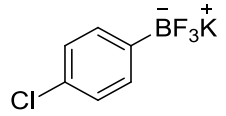
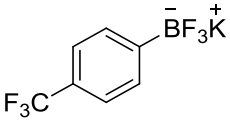
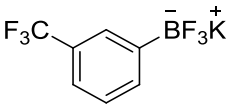
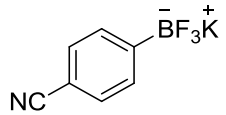
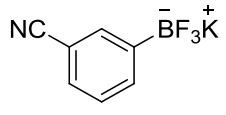
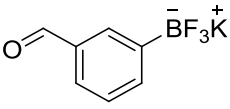
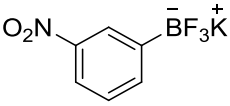
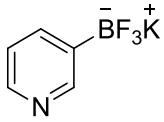
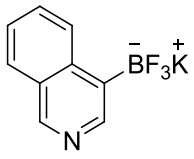
Prepared from **106b** (285 mg, 1.0 mmol) and **145** (352 mg, 1.0 mmol) using general Suzuki coupling procedure 5 to afford **146** (257 mg, 64%) as a pale yellow oil; R_f (40% diethyl ether in hexane) 0.40; ν_{max}(film)/cm^{-1} 2936, 1729, 1426, 1295, 1277, 1256, 1217, 1141, 1103, 999, 893, 790, 775, 640, 606; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69-7.65 (m, 1 H), 7.53-7.42 (m, 2 H), 7.37 (dd, *J* 8.1, 1.3, 1 H), 3.39 (q, *J* 7.1, 2 H), 3.33 (q, *J* 7.1, 2 H), 1.20 (t, *J* 7.1, 3 H), 1.16 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.4 (dd, $J_{C\text{-}F}$ 293.5, 288.2), 152.4, 146.8 (d, $J_{C\text{-}F}$ 3.1), 132.0 (app. t, $J_{C\text{-}F}$ 3.1), 130.7, 128.0, 123.5 (dd, $J_{C\text{-}F}$ 5.3, 2.3), 121.3, 118.1 (q, $J_{C\text{-}F}$ 320.6), 107.1 (dd, $J_{C\text{-}F}$ 44.2, 22.0), 42.0, 41.4, 13.3, 12.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -73.8 (s, 3 F), -93.5 (d, *J* 44.8, 1 F), -103.4 (d, *J* 44.8, 1 F); LRMS (CI) *m/z* 432 $[M + C_2H_5]^+$, 404 $[M + H]^+$; GC (98%) t_R 11.34 mins.; HRMS (NSI) m/z calcd for $C_{14}H_{15}F_5NO_5$ $[M + H]^+$ 404.0586, found 426.0586.

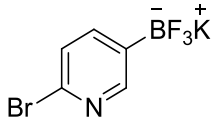
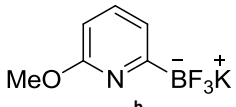
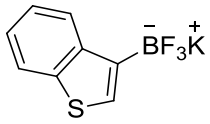
General procedure for the generation of potassium aryltrifluoroborates

A solution of potassium hydrogen difluoride (2.06 g, 26.3 mmol) in H_2O (15 mL) was added to a stirring solution of boronic acid (6.60 mmol) in methanol (15 mL) resulting in a white precipitate. The mixture was stirred for 2 h at room temperature (18 °C) and then concentrated under reduced pressure to afford a

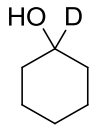
white solid. The product was extracted with methanol in acetone (3 x 20 mL of a 1:4 mixture). The extracts were combined and concentrated until a small amount of precipitation was observed. Diethyl ether (40 mL) was added to cause precipitation. The precipitate was filtered, washed with diethyl ether (2 x 5 mL) and dried on a Buchner funnel to afford the borate as a solid.

Trifluoroborate	Yield	Mp (°C)	δH (400 MHz, DMSO)	δF (376 MHz, DMSO)	δC[a] (100 MHz, DMSO)
 **238**	1.13 g (80%)	306-308 (decomp.)	7.24 (d, *J* 8.2, 2 H), 6.67 (d, *J* 8.1, 2 H),3.68 (s, OCH_3, 3 H),	(-138.8)–(-137.8) (m)	157.2, 132.2, 111.8, 54.5
 **239**	1.17 g (83%)	180-182	7.01 (t, *J* 7.6, 1 H), 6.91 (d, *J* 7.2, 1 H), 6.89 (d, *J* 2.44, 1 H), 6.59 (dd, *J* 7.9, 2.7, 1 H), 3.68 (s, 3 H)	(-139.6)–(-138.8) (m)	160.0, 127.1, 123.8, 116.3, 110.6, 54.4
 **240**	0.98 g (70%)	295-297	7.31 (dd, *J* 6.9, 1.6, 1 H), 7.04 (dt, *J* 7.7, 1.9, 1 H), 6.73-6.68 (m, 2 H), 3.63 (s, 3 H)	(-137.4)–(-136.7) (m)	162.5, 133.2 (q, J_{C-F} 3.1), 126.6, 119.1, 109.6, 54.7
 **241**	0.98 g (70%)	295-297	7.31 (dd, *J* 6.9, 1.6, 1 H), 7.04 (dt, *J* 7.7, 1.9, 1 H), 6.73-6.68 (m, 2 H), 3.63 (s, 3 H)	(-137.4)–(-136.7) (m)	162.5, 133.2 (q, J_{C-F} 3.1), 126.6, 119.1, 109.6, 54.7
 **242**	1.29 g (89%)	226-227	7.31 (d, *J* 6.7, 1 H), 6.83 - 6.93 (m, 3 H), 2.28 (s, 3 H)	(-137.9)–(-137.2) (m)	140.4, 131.5 (q, J_{C-F} 3.3), 128.1, 124.9, 123.2, 21.6
 **243**	0.99 g (73%)	301-303 (decomp)	7.24 (d, *J* 7.8, 2 H), 7.10 (d, *J* 7.8, 2 H), 1.25 (s, 9 H)	(-139.1)–(-138.3) (m)	146.6, 131.1, 122.8, 33.8, 31.4

 **244**	2.7 g (97%)	338-340 (decomp.)	7.24 (d, *J* 7.7, 2 H), 7.12 (d, *J* 7.7, 2 H),	(-139.8)–(-138.9) (m)	133.1, 129.8, 126.1
 **245**	1.17 g (88%)	338-340 (decomp.)	7.54 (d, *J* 7.7, 2 H), 7.43 (d, *J* 7.7, 2 H)	-60.4 (s, 3 F), (-140.5)–(-139.7) (m, 3 F)	131.7, 125.8 (q, J_{C-F} 30.8), 125.0 (q, J_{C-F} 271.5), 122.7 (q, J_{C-F} 3.6)
 **246**	0.60 g (99%)	80-82	7.59 (br. s, 2 H), 7.37 (br. d, *J* 7.9, 1 H), 7.32 (t, *J* 7.6, 1 H)	-56.0 (s, 3 F), (-135.7)–(-135.0) (m, 3 F)	139.9, 132.0, 131.6, 130.0 (q, J_{C-F} 272.0), 126.3 (q, J_{C-F} 3.9)
 **247**	0.96 g (68%)	351-353 (decomp.)	7.50 (dd, *J* 8.0, 10.4, 4 H)	(-140.9)–(-140.2) (m)	132.0, 129.9, 120.0, 107.6
 **247**	0.22 g (51%)	192-194	7.63 (br. d, *J* 7.62, 1 H), 7.59 (br. s, 1 H), 7.48 (dt, *J* 7.7, 1.6, 1 H), 7.31 (t, *J* 7.51, 1 H)	(-136.0)–(-135.3) (m)	140.8, 139.3, 133.6, 132.1, 124.9, 114.1
 **248**	1.3 g (92%)	208-210	9.94 (s, 1 H), 7.87 (br. s, 1 H), 7.66 (d, *J* 7.2, 1 H), 7.59 (d, *J* 7.6, 1 H), 7.32 (t, *J* 7.3, 1 H)	(-140.1)–(-139.4) (m)	194.2, 137.9, 134.7, 133.3, 127.0, 126.1
 **224**	1.29 g (94%)	235-236	8.12 (br. s, 1 H), 7.93 (d, *J* 8.1, 1 H), 7.76 (d, *J* 7.2, 1 H), 7.41 (t, *J* 7.7, 1 H)	(-140.8)–(-140.1) (m)	146.9, 138.1, 127.7, 125.2, 120.1
 **249**	1.14 g (76%)	235-236	8.47 (br. s, 1 H), 8.26 (br. d, *J* 4.2, 1 H), 7.62 (d, *J* 6.9, 1 H), 7.09 (app. t, *J* 6.0, 1 H)	(-139.6)–(-138.9) (m)	152.5, 146.4, 138.6, 122.3
 **250**	0.43 g (76%)	320-322 (decomp.)	9.00 (s, 1 H), 8.44 (s, 1 H), 8.32 (d, *J* 8.2, 1 H), 7.90 (d, *J* 8.1, 1 H), 7.57 (t, *J* 7.7, 1 H), 7.48 (t, *J* 7.7, 1 H)	(-131.0)–(-130.3) (m)	149.9, 145.4 (q, J_{C-F} 3.4), 138.9, 128.9, 127.9, 127.9, 127.0, 125.3

 **251**	1.15 g (88%)	198-200	8.21 (s, 1 H), 7.57 (dd, *J* 7.8, 1.9, 1 H), 7.34 (d, *J* 7.8, 1 H)	(-139.7)–(-139.0) (m)	153.1, 142.5, 138.9, 126.3
 **263**[b]	113 mg (17%)	182 - 184	7.35 (app. t, *J* 7.3, 1 H), 6.93 (d, *J* 6.8, 1 H), 6.41 (d, *J* 7.8, 1 H), 3.80 (s, 3 H)	-141.2 – (-142.0) (m)	162.2, 136.0, 118.9, 106.3, 52.1
 **252**	1.01 g (75%)	108-110	8.00 (br. d, *J* 7.7, 1 H), 7.84 (d, *J* 7.6, 1 H), 7.25-7.15 (m, 3 H)	(-136.3)–(-135.7) (m)	144.5, 140.6, 125.7, 125.2, 122.5, 121.6

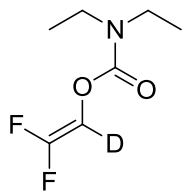
a) Quaternary carbon signal too weak to observe due to quadrupolar splitting from boron. b) 6-Methoxypyridine-2-boronic acid N-phenyldiethanolamine ester was used instead of a boronic acid in the general procedure.



1-Deuterio-1-cyclohexanol 236

A solution of cyclohexanone (9.82 g, 100.0 mmol) in ether (15 mL) was added dropwise to a suspension of lithium aluminum deuteride (2.31 g, 55.0 mmol) in ether (100 mL) at RT. An exotherm was apparent and the reaction mixture refluxed gently. The reaction mixture was stirred for 1 h then quenched by pouring carefully into an aqueous 10% H_2SO_4 solution (100 mL) and extracted with diethyl ether (2 x 100 mL). The organic layers were combined, washed with aqueous saturated $NaHCO_3$ solution (200 mL), separated and dried ($MgSO_4$). The ether was removed carefully under reduced pressure (40 °C/400 mbar) and the resulting colourless oil

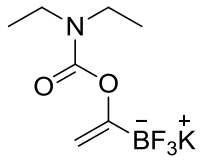
was distilled (Kugelrohr, 65 °C/ 3 mbar) to afford **236** as a colourless oil (6.32 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.96-1.84 (m, 2 H), 1.80-1.69 (m, 2 H), 1.60-1.52 (m, 1 H), 1.47-1.41 (m, 1 H), 1.37-1.26 (m, 4 H), O*H* not observed due to exchange; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 69.5 (t, $J_{C\text{-}D}$ 23.0), 34.0, 24.7, 23.9; LRMS *m/z* (CI) 101 [M], 84 [M-OH]; GC (99%) t_R 8.39 mins.. These data are consistent with those reported previously.[204]



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-deuterio-ethene 237

n-Butyllithium (720 µL of a 2 M solution in hexanes, 1.5 mmol) was added dropwise over 2 minutes to a solution of 1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(tributylstannyl) ethene (610 mg, 1.30 mmol) in THF (6 mL) stirring at -78 °C. The reaction solution turned pale yellow after butyllithium addition and was stirred for 45 minutes at -78 °C. Deuterated methanol (d_4, 53 µL, 1.30 mmol) was added in one portion and the reaction solution was stirred for a further 1 hour at -78 °C and 1 hour at room temperature (18 °C). Careful Kugelrohr distillation of the reaction mixture separated the volatile components. Hexane and THF were removed first (18 °C/50 mbar). Deuterated species **237** was then isolated (75 °C/25 mbar) as a colourless oil (97 mg, 41%). ν_{max}(film)/cm^{-1} 2982, 2941, 2883, 1726, 1424, 1293, 1275, 1178, 1100, 842, 740, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.38-3.29 (m, 4 H), 1.17 (t, *J* 7.1, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.6 (dd, $J_{C\text{-}F}$ 287.9,

274.7), 151.8, 101.2-99.9 (m, including $J_{C\text{-}F}$ and $J_{C\text{-}D}$) 42.0, 41.3, 13.4, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -97.5 (dt, *J* 72.8, $J_{F\text{-}D}$ 2.3, 1 F), -117.8 (d, *J* 72.8, 1 F); LRMS *m/z* (CI) 181 $[M + H]^+$; GC (98%) t_R 9.42 mins.; HRMS (APCI) m/z calcd for $C_7H_{11}DF_2NO_2$ $[M+NH_4]^+$ 198.1159, found 198.1159.

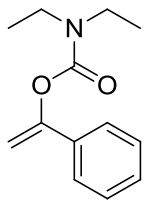


Potassium 1-(*N*,*N*-diethylcarbamoyloxy)-vinyl trifluoroborate 306

Preparation of 1-(N,N-diethylcarbamoyloxy)-ethene: *N,N*-diethyltrimethylsilyl amide (7.58 mL, 40 mmol) was added to a stirring solution of vinyl chloroformate (3.65 mL, 40 mmol) in dichloromethane (50 mL) at 0 ^{o}C and the mixture was stirred for 1.5 h. The solvent was removed under reduced pressure (~90%) and the resulting yellow oil was taken up in diethyl ether (50 mL) and washed with aqueous $NaHCO_3$ solution (3 x 50 mL). The organic phase was dried ($MgSO_4$) and the solvents were removed under reduced pressure to afford a yellow oil as crude vinyl carbamate **305** (5.62 g). δ_H (400 MHz, $CDCl_3$) 7.28 (dd, *J* 14.1, 6.3, 1 H), 4.81 (dd, *J* 13.9, 1.4, 1 H), 4.47 (dd, *J* 6.3, 1.4, 1 H), 3.37 (q, *J* 7.1, 4 H), 1.21 (t, *J* 7.1, 6 H). Enol carbamate **305** was used in the next synthetic step without further purification.

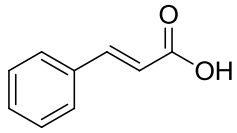
Preparation of potassium 1-(N,N-diethylcarbamoyloxy)-vinyl trifluoroborate: *n*-BuLi (31.89 mL of a 1.6 M solution, 51 mmol) was added dropwise to a solution of di*iso*propylamine (7.2 mL, 51 mmol) in anhydrous THF (30 mL) at -78 °C. The

solution was then allowed to warm to RT. The freshly formed LDA was then added dropwise to a solution of **305** (5.62 g, 39.3 mmol) in THF (30 mL) at -78 C *via* a cannula. The reaction solution turned a red/brown colour. Trimethyl borate (7.19 mL, 59 mmol) was added in one portion. The reaction solution was then allowed to warm to RT and stirred for a further 2 h. A solution of KHF_2 (18.4 g, 236 mmol) in H_2O (60 mL) was added in one portion and the mixture was stirred at RT for 18 h. The THF and H_2O were removed under reduced pressure to afford a white solid and brown residue. The brown residue was taken up in an acetone/methanol (4:1) mixture and filtered to remove the white precipitate. Removal of the solvent afforded a viscous brown oil. The oil was stirred in diethyl ether (20 mL) for 18 h at RT after which time a white precipitate was observed. The solid was collected, washed with diethyl ether (2 x 10 mL) and dried by filtration to afford trifluoroborate **306** (2.52 g, 26%) as a colourless crystalline solid; Mp 123-125 °C; δ_H (400 MHz, $CDCl_3$) 4.65 (br. s, 1 H), 4.63 (s, 1 H), 3.20 (q, *J* 7.1, 4 H), 1.05 (t, *J* 7.1, 6 H); δ_C(100 MHz, $CDCl_3$) 154.6, 103.5, 41.0, 13.8, The *C*-B carbon signal was too weak to observe due to quadrupolar splitting from boron; δ_F(376 MHz, $CDCl_3$) -142.9 – (-143.6) (m); LRMS *m/z* (ESI) 210 $[M - K]^-$; HRMS (NSI) m/z calcd for $C_7H_{12}BF_3NO_2$ $[M-K]^-$ 210.0919, found 210.0919.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(phenyl) ethene 307

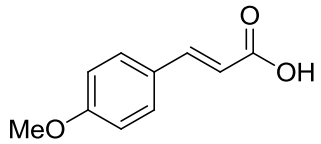
Prepared from **143** (157 mg, 1.0 mmol) and trifluoroborate **306** (249 mg, 1.0 mmol) using general Suzuki coupling procedure 5 to afford **307** (128 mg, 58%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.17; ν_{max}(film)/cm^{-1} 2974, 2358, 2341, 1702, 1417, 1250, 1153, 1095, 1074, 979, 769, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.52-7.47 (m, 2 H), 7.38-7.29 (m, 3 H), 5.43 (d, *J* 1.9, 1 H), 5.04 (d, *J* 1.9, 1 H), 3.53-3.32 (m, 4 H), 1.28 (t, *J* 6.5, 3 H), 1.19 (t, *J* 6.5, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.9, 153.5, 135.3, 128.6, 128.4, 124.9, 101.4, 42.1, 41.8, 14.3, 13.4; LRMS *m/z* (CI) 219 $[M + H]^+$, 146 $[M - NC_4H_{10}]$, 118 $[M - NC_5H_{10}O]$; GC (98%) t_R 13.04 mins.; HRMS (NSI) *m/z* calcd for $C_{13}H_{18}NO_2$ $[M+H]^+$ 220.1332, found: 220.1335.



Cinnamic acid 331a

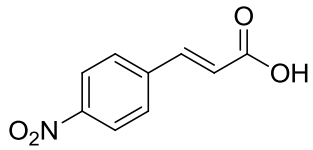
Benzaldehyde (5.3 g, 50 mmol) was added to a solution of malonic acid (10.4 g, 100 mmol) in pyridine (112 mL, 1.4 mol) containing piperidine (45 drops). The colourless solution was stirred at 100°C for 3 hours, then allowed to cool to room temperature. The solution was poured into a mixture of concentrated hydrochloric acid (75 mL) and ice (75 mL); a white precipitate formed. The solid was collected by filtration and was washed with sulfuric acid (10 mL of a 1% aqueous solution) then

water (30 mL). Recrystalisation from ethanol afforded cinnamic acid **331a** as a white powder (5.19 g, 70%); R_f (1:1 diethyl ether in Petroleum ether) 0.26, Mp 133-135 °C (lit. 135-136 °C); δ_H (400 MHz; $CDCl_3$) δ (ppm) 7.81 (d, *J* 16.1, 1 H), 7.60-7.54 (m, 2 H), 7.46-7.40 (m, 3 H), 6.48 (d, *J* 16.1, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.4, 147.1, 134.1, 130.8, 129.0, 128.4, 117.3; ESIMS *m*/*z* 147 $[M - H]^-$. The data were in agreement with those reported previously.[205]



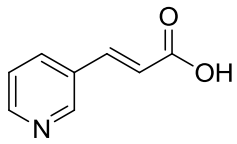
4-Methoxycinnamic acid 331b

Prepared from 4-methoxybenzaldehyde **78b** (6.81 g, 50 mmol) using the procedure described for **131a** to afford cinnamic acid **331b** as a white powder (6.08 g, 68%); R_f (1:1 ethyl acetate in hexane) 0.31; Mp 171-172 °C (lit. 173-175 °C); δ_H (400 MHz, MeOD) δ (ppm) 7.63 (d, *J* 16.0, 1 H), 7.54 (d, *J* 8.8, 2 H), 6.96 (d, *J* 8.8, 2 H), 6.33 (d, *J* 16.0, 1 H), 3.83 (s, 3 H); ^{13}C NMR (100 MHz, MeOD) δ (ppm) 167.8, 160.9, 143.7, 129.9, 126.8, 116.5, 114.3, 55.3; ESIMS *m*/*z* 177 $[M - H]^-$. The data were in agreement with those reported by Fraga.[206]



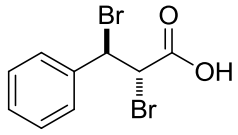
4-Nitrocinnamic acid 131c

Prepared from 4-nitrobenzaldehyde **78c** (7.56 g, 50 mmol) using the procedure described for **131a** to afford cinnamic acid **131c** as a yellow powder (9.42 g, 96%); R_f (1:1 ethyl acetate in hexane) 0.34; Mp 280-282 °C (lit. 288 °C); δ_H (400 MHz, d_6-DMSO) δ (ppm) 12.67 (br. s, 1 H), 8.23 (d, *J* 8.9, 2 H), 7.97 (d, *J* 8.9, 2 H), 7.69 (d, *J* 16.1, 1 H), 6.74 (d, *J* 16.1, 1 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 167.0, 147.9, 141.2, 140.7, 129.3, 123.9, 123.6; ESIMS *m*/*z* 192 $[M-H]^-$. The data were in agreement with those reported by Peng.[205]



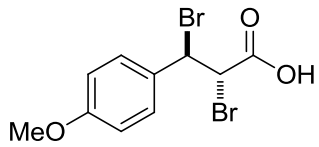
3-Pyridyl cinnamic acid 331d

Prepared from pyridinyl aldehyde **78d** (1.15 g, 11 mmol) using the procedure described for **131a** only the reaction solution was concentrated to dryness under reduced pressure. The resulting solid was washed with water (30 mL) and dried by filtration to afford cinnamic acid **331d** as a pale yellow powder (1.39 g, 87%); Mp 214-216 °C (lit. 211-213 °C); δ_H (400 MHz, DMSO) δ (ppm) 12.53 (s, 1 H), 8.84 (d, *J* 1.9, 1 H), 8.57 (dd, *J* 4.8, 1.6, 1 H), 8.14 (dt, *J* 8.1, 1.9, 1 H), 7.62 (d, *J* 16.1, 1 H), 7.43 (dd, *J* = 8.1, 4.8, 1 H), 6.67 (d, *J* 16.1, 1 H). The data were consistent with those reported previously.[207]



2,3-Dibromo-3-phenylpropanoic acid 332a

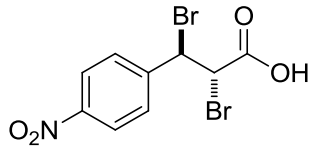
Bromine (16.9 mL of a 1 M solution in chloroform, 17 mmol) was added dropwise over a period of 20 minutes to a solution of cinnamic acid **331a** (2.5 g, 17 mmol) in chloroform (10 mL) at 0 °C. The orange mixture was stirred at 0 °C for 1 hour, a precipitate formed during this time. The solid was collected by filtration and washed with an aqueous 10% sulphuric acid solution (10 mL) then water (30 mL) to afford **332a** as a white powder (4.35 g, 84%); R_f (1:1 diethyl ether in petroleum ether) 0.05, Mp 196-198 °C (lit. 197-198 °C); δ_H (400 MHz, $CDCl_3$) δ (ppm) 7.46-7.36 (m, 5 H), 5.34 (d, *J* 11.8, 1 H), 4.90 (d, *J* 11.8, 1 H). Satisfactory mass spectrometric analysis could not be obtained for this compound. The data were consistent with those reported previously.[56]



2,3-Dibromo-3-(4'-methoxyphenyl)propanoic acid 332b

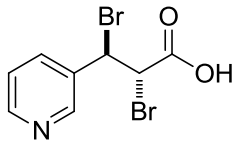
Prepared from cinnamic acid **331b** (6.0 g, 33.7 mmol) using the procedure described for **332a** to afford carboxylic acid **332b** as a white powder (9.19 g, 81%); R_f (1:1 ethyl acetate in hexane) 0.86, Mp 159-160 °C (lit. 155-156 °C); δ_H (400 MHz, CD_3OD) δ (ppm) 7.30 (d, *J* 8.7, 2 H), 6.94 (d, *J* 8.7, 2 H), 4.47 (d, *J* 9.9, 1 H), 4.22 (d, *J* 9.9, 1 H),

3.81 (s, 3 H). The following signals arise from the minor (*syn*) addition product: 7.33 (d, *J* 8.7, 2 H), 6.91 (d, *J* 8.7, 2 H), 4.91 (d, *J* 9.6, 1 H), 4.29 (d, *J* 9.6, 1 H), 3.80 (s, 3 H). Satisfactory mass spectrometric analysis could not be obtained for this compound. The data were consistent with those reported previously.[56]



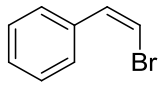
2,3-Dibromo-3-(4'-nitrophenyl)propanoic acid 332c

Bromine (10 mL of a 0.52M solution in acetic acid, 17 mmol) was added dropwise over a period of 20 minutes to a mixture of 4-nitrocinnamic acid **331c** (1 g, 5 mmol) in acetic acid (10 mL) at room temperature; this was refluxed at 100 °C for 3 hours. On cooling, a precipitate formed which was collected by filtration and washed with water (10 mL). The solid was taken up in ethanol (10 mL) leaving a yellow solid behind (starting material). The solvent was removed from the ethanolic extract under reduced pressure to afford **332c** as a pale yellow powder (1.1g, 60%); Mp 220-221 °C (lit. 216-217 °C); δ_H (400 MHz, d_6-DMSO) δ (ppm) 12.64 (s, 1 H), 8.23 (d, *J* 8.4, 2 H), 7.97 (d, *J* 8.4, 2 H), 7.69 (d, *J* 16.0, 1 H), 6.74 (d, *J* 16.0, 1 H); ^{13}C NMR (100 MHz, MeOD) δ (ppm) 168.7, 147.5, 145.5, 129.8, 123.8, 49.1, 46.3. Satisfactory mass spectrometric analysis could not be obtained for this compound. The data were consistent with those reported previously.[56]



2,3-Dibromo-3-pyridin-3-yl-propanoic acid 332d

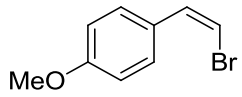
Prepared from cinnamic acid **331d** (1.0 g, 7.0 mmol) using the procedure described for **332a** only the reaction mixture was refluxed at 60 °C for three hours. Carboxylic acid **332d** was isolated as a pale yellow powder (1.54 g, 74%); Mp 164-166 °C (lit. 169-170 °C); δ_H (400 MHz, d_6-DMSO) 9.07 (d, *J* 1.9, 1 H), 8.77 (dd, *J* 5.3, 1.4, 1 H), 8.57 (dt, *J* 8.2, 1.6, 1 H), 7.84 (dd, *J* 8.2, 5.3, 1 H), 5.80 (d, *J* 11.7, 1 H), 5.50 (d, *J* 11.7, 1 H), ESIMS *m/z* 310 $[M+H]^+$, 308 $[M-H]^-$. The data were consistent with those reported previously.[56]



(*Z*)-β-Bromostyrene 79a

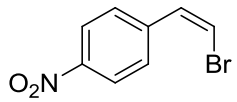
A solution of 2,3-dibromo-3-phenylpropanoic acid **332a** (2.65 g, 8.6 mmol) and triethylamine (1.26 mL, 9 mmol) in DMF (25 mL) was contained within a flask with condenser attached, and irradiated in a microwave cavity. The reaction solution was heated to 140 °C over a period of 3 minutes. The pale yellow reaction solution was cooled to room temperature then partitioned between diethyl ether (30 mL) and water (40 mL). The organic layer was separated and the aqueous layer was washed with diethyl ether (30 mL). The organic layers were combined, washed with brine (40 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure to afford crude bromide **79a** as a pale brown oil. This was filtered through a short plug

of silica (d = 4 cm, l = 2cm) with diethyl ether (50 mL) to afford **79a** as a colourless oil (1.35 g, 86%); δ_H (400 MHz, $CDCl_3$) δ (ppm) 7.72-7.67 (m, 2 H), 7.42-7.31 (m, 3 H), 7.09 (d, *J* 8.1, 1 H), 6.45 (d, *J* 8.1, 1 H), δ_C (100 MHz, $CDCl_3$) δ (ppm) 134.9, 132.4, 129.0, 128.3, 128.3, 106.4; LRMS (EI) *m/z* 182 $[M + H]^+$, GC (98%) t_R 8.71 mins.. The data were consistent with those reported previously.[56]



(*Z*)-β-Bromo-4-methoxystyrene 79b

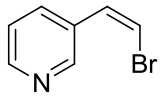
Prepared from carboxylic acid **332b** (1.0 g, 3.0 mmol) using the procedure described for **79a** to afford bromostyrene **79b** as a yellow oil (0.53 g, 83%); δ_H (400 MHz, $CDCl_3$) δ (ppm) 7.71 (d, *J* 8.8, 2 H), 7.02 (d, *J* 8.1, 1 H), 6.93 (d, *J* 8.8, 2 H), 6.33 (d, *J* 8.1, 1 H), 3.86 (s, 3 H), δ_C (100 MHz, $CDCl_3$) δ (ppm) 159.5, 131.6, 130.5, 127.6, 113.6, 104.2, 55.3. The following data correspond to the minor *E*-isomer: 7.23 (d, *J* 8.8, 2 H), 7.05 (d, *J* 14.0, 1 H), 6.88 (d, *J* 8.8, 2 H), 6.64 (d, *J* 14.0, 1 H), 3.84 (s, 3 H). The data were consistent with those reported previously.[56]



(*Z*)-β-Bromo-4-nitrostyrene 79c

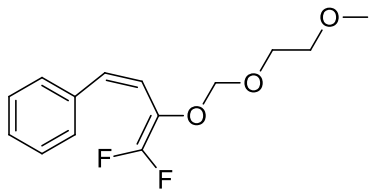
Prepared from carboxylic acid **332c** (946 mg, 2.7 mmol) using the procedure described for **79a** to afford bromostyrene **79b** as a beige solid (0.57 g, 93%); Mp 41-43 °C; δ_H (400 MHz, $CDCl_3$) δ (ppm) 8.23 (d, *J* 8.8, 2 H), 7.83 (d, *J* 8.8, 2 H), 7.16 (d, *J*

8.3, 1 H), 6.69 (d, *J* 8.3, 1 H); δ_C (100 MHz, $CDCl_3$) *δ* (ppm) 146.6, 141.3, 130.8, 129.7, 123.4, 111.4; ESIMS *m*/*z* 227 $[M - H]^-$. The data were consistent with those reported previously.[56]



(Z)-3-(β-Bromovinyl)pyridine 79d

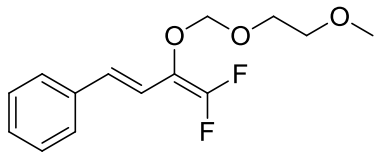
Prepared from carboxylic acid **332d** (1.5 g, 4.9 mmol) using the procedure described for **79a** to afford bromostyrene **79d** as a pale brown oil (0.37 g, 41%); δ_H (400 MHz, $CDCl_3$) *δ* (ppm) 8.78 (s, 1 H), 8.56 (d, *J* 4.7, 1 H), 8.16 (dd, *J* 8.1, 1.3, 1 H), 7.35-7.30 (m, 1 H), 7.08 (d, *J* 8.3, 1 H), 6.60 (d, *J* 8.3, 1 H); δ_C (100 MHz, $CDCl_3$) *δ* (ppm) 150.9, 149.5, 136.3, 131.4, 129.7, 123.4, 109.8. The data were consistent with those reported previously.[56]



1,1-Difluoro-2-(2'-methoxy-ethoxymethoxy)-4-(phenyl)-(*Z*)-butadiene 340

A solution of bromostyrene **79a** (189 mg, 1.04 mmol) and stannane **127a** (457 mg, 1.0 mmol) in DMF (2 mL) were added to a stirring solution of copper(I)iodide (42 mg, 0.22 mmol), triphenylphosphine (26 mg, 0.1 mmol) and palladium(II)acetate (6 mg, 0.027 mmol) in dry, degassed DMF (8 mL). The reaction solution was stirred at 50 °C for 16 hours then cooled to room temperature and partitioned between

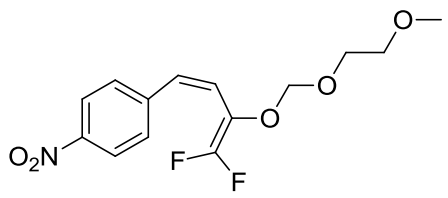
diethyl ether (30 mL) and water (40 mL). The organic layer was separated and washed with aqueous KF (2 x 30 mL of a saturated solution), resulting in a white precipitate between the layers. These layers were filtered through a pad of Kieselgur. The organic layer was separated, dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (10% diethyl ether in petroleum ether) afforded diene **340** as a pale yellow oil (205 mg, 76%); R_f (1:2 ethyl acetate in hexane) 0.55; δ_H (400 MHz, $CDCl_3$) *δ* (ppm) 7.38-7.35 (m, 2 H), 7.33-7.22 (m, 3 H), 6.59 (d, *J* 12.4, 1 H), 5.94 (dd, *J* 12.4, 4.3, 1 H) 4.4 (s, 2 H) 3.65-3.60 (m, 2 H) 3.50-3.46 (m, 2 H) 3.35 (s, 3 H); δ_C (100 MHz, $CDCl_3$) *δ* (ppm) 154.9 (dd, J_{C-F} 295.3, 291.5), 135.9, 132.1 (dd, J_{C-F} 9.4, 3.2), 129.2, 127.7, 127.6, 115.5 (d, J_{C-F} 4.6), 114.1 (dd, J_{C-F} 35.6, 19.3), 94.4, 71.5, 68.1, 59.0; δ_F (376 MHz, $CDCl_3$) *δ* (ppm) -98.2 (d, *J* 43.7, 1 F), -103.5 (dd, *J* 43.7, J_{F-H} 4.3, 1 F). This material decomposed before full characterisation could be achieved.



1,1-Difluoro-2-(2'-methoxy-ethoxymethoxy)-4-(phenyl)-(*E*)-butadiene 341

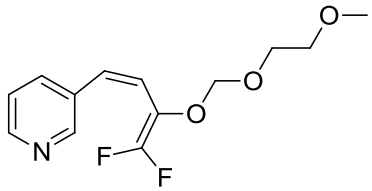
Prepared from *E*-β-bromostyrene (189 mg, 1.04 mmol) and stannane **127a** (457 mg, 1.0 mmol) using the procedure described for **340** to afford diene **341** as a pale orange oil (75 mg, 28%); R_f (1:2 ethyl acetate in hexane) 0.53; δ_H (400 MHz, $CDCl_3$) *δ* (ppm) 7.44-7.24 (m, 5 H), 6.74 (d, *J* 16.1, 1 H), 6.60 (dd, *J* 16.1, 3.7, 1 H), 5.02 (s, 2 H), 3.95-3.89 (m, 2H), 3.63-3.58 (m, 2 H), 3.41 (s, 3 H); δ_F (376 MHz, $CDCl_3$) *δ* (ppm) -

97.1 (d, *J* 44.3, 1 F), -106.1 (dd, *J* 44.3, $J_{F\text{-}H}$ 3.7, 1 F). No further characterisation was obtained.



1,1-Difluoro-2-(2'-methoxy-ethoxymethoxy)-4-(4'-nitrophenyl)-(*Z*)-butadiene 343

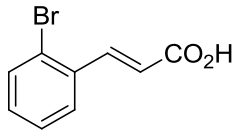
Prepared from bromostyrene **79c** (116 mg, 0.51 mmol) and stannane **127a** (229 mg, 0.5 mmol) using the procedure described for **340** to afford diene **343** as an orange oil (130 mg, 82%); R_f (1:2 ethyl acetate in hexane) 0.38; δ_H (400 MHz, $CDCl_3$) *δ* (ppm) 8.17 (d, *J* 8.8, 2 H), 7.52 (d, *J* 8.8, 2 H), 6.59 (d, *J* 12.5, 1 H), 6.14 (dd, *J* 12.5, 4.3, 1 H), 4.43 (s, 2 H), 3.66-3.63 (m, 2 H), 3.50-3.46 (m, 2 H), 3.35 (s, 3 H); δ_F (376 MHz, $CDCl_3$) *δ* (ppm) -95.3 (d, *J* 36.0, 1 F), -101.0 (dd, *J* 36.0, $J_{F\text{-}H}$ 4.3, 1 F). This material decomposed before full characterisation could be achieved.



1,1-Difluoro-2-(2'-methoxy-ethoxymethoxy)-4-(3'-piridyl)-(*Z*)-butadiene 344

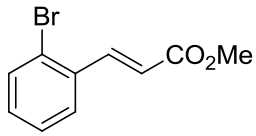
Prepared from bromostyrene **79d** (116 mg, 0.51 mmol) and stannane **127a** (229 mg, 0.5 mmol) using the procedure described for **340** to afford diene **344** as an orange oil (130 mg, 82%); R_f (1:1 ethyl acetate in Petroleum ether) 0.45, δ_H (400 MHz, $CDCl_3$) *δ* (ppm) 7.83 (br. s, 1 H), 7.71-7.64 (m, 1 H), 7.59-7.53 (m, 1 H), 7.50-7.44 (m,

1 H), 6.60 (d, *J* 12.5, 1 H), 6.11 (d, *J* 12.5, 1 H), 4.44 (s, 2 H), 3.64-3.61 (m, 2 H), 3.50-3.46 (m, 2 H), 3.35 (s, 3 H), δ_F (376 MHz, $CDCl_3$) δ (ppm) -96.3 (d, *J* 39.3, 1 F), -101.9 (d, *J* 39.3, 1 F). This material decomposed before full characterisation could be achieved.



2-Bromocinnamic acid 445

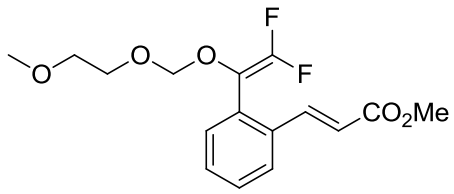
Prepared from 2-bromobenzaldehyde **80** (9.54 g, 52 mmol) using the procedure described for **331a** to afford cinnamic acid **445** as a white crystalline solid (8.33 g, 71%); Mp 230-232 °C; δ_H (400 MHz, d_6-DMSO) δ (ppm) 7.90 (dd, *J* 7.9, 1 H), 7.84 (d, *J* 16.0, 1 H), 7.70 (dd, *J* 7.9, 1.1, 1 H), 7.46-7.39 (m, 1 H), 7.37-7.31 (m, 1 H), 6.57 (d, *J* 16.0, 1 H); δ_C (100 MHz, d_6-DMSO) δ (ppm) 167.1, 141.3, 133.5, 133.1, 131.8, 128.3, 128.3, 124.5, 122.4. The data were consistent with those reported previously.[208]



2-Bromocinnamic methyl ester 81

Concentrated H_2SO_4 (40 drops) was added to a stirring solution of cinnamic acid **445** (2.0 g, 8.8 mmol) in MeOH (40 mL). The reaction solution was stirred at 75 °C for 3 h then cooled to RT and diluted with water (40 mL). The product was extracted with diethyl ether (2 x 40 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to afford methyl ester **81** as a colourless

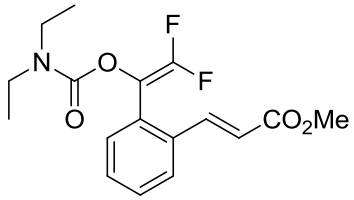
oil (1.96 g, 92%); ν_{max}(film)/cm^{-1} 2950, 2840, 1709, 1632, 1464, 1436, 1317, 1267, 1196, 1172, 1024, 974, 922, 756, 721; δ_H (400 MHz, $CDCl_3$) δ (ppm) 8.07 (d, *J* 16.0, 1 H), 7.65-7.60 (m, 2 H), 7.35 (t, *J* 7.5, 1 H), 7.25 (dt, *J* 7.7, 1 H), 6.41 (d, *J* 16.0, 1 H), 3.85 (s, 3 H); δ_C (100 MHz, $CDCl_3$) δ (ppm) 166.3, 142.7, 134.0, 132.9, 130.7, 127.3, 127.2, 124.8, 120.2, 51.4. The data were consistent with those reported previously.[209]



Methyl-1-[(2'-methoxy-ethoxymethyl)-2',2'-difluorovinyl] phenyl-β-acrylate 345

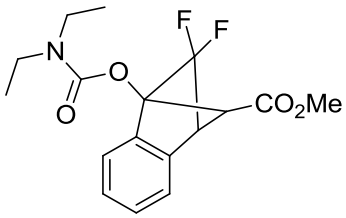
A mixture of trifluoroborate **106a** (60 mg, 0.22 mmol), ester **81** (48 mg, 0.20 mmol), caesium carbonate (196 mg, 0.60 mmol), 2-dicyclohexylphosphino-2',6'-di*iso*propoxybiphenyl (9.3 mg, 0.02 mmol) and palladium acetate (2.2 mg, 0.01 mmol) was taken up in a (2.7 : 1) solution of *tert*-butanol and H_2O (1 mL). The reaction mixture was stirred at 90 °C for 3.5 hours, then cooled to room temperature and partitioned between DCM (5 mL) and H_2O (5 mL). The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (10% diethyl ether in hexane) to afford **345** as a colourless oil (27 mg, 41%); R_f (40% diethyl ether in hexane) 0.13; ν_{max}(film)/cm^{-1} 2950, 2893, 1720, 1636, 1317, 1259, 1196, 1170, 1149, 1101, 1073, 976, 948, 845. 765, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94 (d, *J* 16.0, 1 H), 7.71-7.66 (m, 1 H), 7.47-7.39

(m, 3 H), 6.44 (d, *J* 16.0, 1 H), 4.74 (d, *J* 0.8, 2 H), 3.83 (s, 3 H), 3.82-3.79 (m, 2 H), 3.58-3.54 (m, 2 H), 3.39 (s, 3 H); δ_C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 166.6, 154.1 (dd, $J_{C\text{-}F}$ 291.9, 282.6), 141.6, 134.3, 130.8 (app. t, $J_{C\text{-}F}$ 2.6), 129.4 (br. s, 2 x Ar*C* signals), 128.9 (dd, $J_{C\text{-}F}$ 4.0, 2.1), 126.4, 119.4, 112.8 (dd, $J_{C\text{-}F}$ 40.9, 18.4), 93.2 (app. t, $J_{C\text{-}F}$ 2.2), 71.1, 67.6 (d, $J_{C\text{-}F}$ 1.3), 58.6, 51.3; ^{19}F NMR (376 MHz, $CDCl_3$) *δ* (ppm) -99.4 (d, *J* 58.6, 1 F), -107.9 (d, *J* 58.6, 1 F); LRMS (CI) *m/z* 329 $[M + H]^+$; GC (99%) t_R 13.31 mins.; HRMS (NSI) m/z calcd for $C_{16}H_{22}F_2NO_5$ $[M + NH_4]^+$ 346.1461, found 346.1465.



Methyl-2-[(1'-*N*,*N*-diethylcarbamoyloxy)-2',2'-difluorovinyl] phenyl-β-acrylate 346

Prepared from ester **81** (482 mg, 2.0 mmol) and trifluoroborate **106b** (627 mg, 2.2 mmol) using the same procedure as for **345** to afford divinyl benzene **346** as a pale yellow oil (618 mg, 91%); R_f (40% diethyl ether in hexane) 0.17; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 8.03 (dd, *J* 16.0, 1.2, 1 H), 7.69-7.64 (m, 1 H), 7.56-7.51 (m, 1 H), 7.46-7.40 (m, 2 H), 6.44 (d, *J* 16.0, 1 H), 3.83 (s, 3 H), 3.35 (q, *J* 7.1, 2 H), 3.28 (q, *J* 7.1, 2 H), 1.17 (t, *J* 7.1, 3 H), 1.12 (t, *J* 7.1, 3 H); δ_C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 166.9, 154.4 (dd, $J_{C\text{-}F}$ 292.4, 284.7), 152.6, 142.1, 133.7, 130.1 (app. t, $J_{C\text{-}F}$ 2.5), 129.9 (d, $J_{C\text{-}F}$ 4.6), 129.7, 129.5, 126.5, 119.5, 110.0 (dd, $J_{C\text{-}F}$ 44.3, 19.1), 51.6, 42.2, 41.7, 13.9, 13.0; ^{19}F NMR (376 MHz, $CDCl_3$) *δ* (ppm) -94.7 (d, *J* 49.2, 1 F), -105.1 (d, *J* 49.2, 1 F); LRMS (CI) *m/z* 340 $[M + H]^+$, 308 $[M - OCH_3]^-$; GC (99%) t_R 13.53 mins.; HRMS (NSI) m/z calcd for $C_{17}H_{20}F_2NO_4$ $[M + H]^+$ 340.1355, found 340.1357.

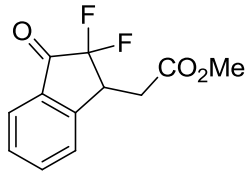


Methyl-1-((diethylcarbamoyl)oxy)-8,8-difluoro-2,3-dihydro-1H-1,3 methanoindene-2-carboxylate 352

Divinylbenzene **346** (2 mL of a 50 mM solution in acetonitrile, 0.1 mmol) was irradiated with a 9 W UV (254 nm) bulb in a 28 mL flow reactor run at 0.467 mL/ min. After the reaction time of 1 h, the acetonitrile was removed under reduced pressure to reveal a mixture of **352** and fluoroarene **351** as a pale yellow oil. Preparative HPLC afforded **352** as a colourless oil (12 mg, 35%); ν_{max}(film)/cm^{-1} 3726, 3608, 2978, 2341, 2317, 1722, 1428, 1325, 1278, 1246, 1223, 1163, 1148, 1101, 1077, 758, 713; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26-7.14 (m, 4 H), 3.95 (app. t, *J* 2.5, 1 H), 3.89 (dd, *J* 16.3, 1.5, 1 H), 3.77 (s, 3 H), 3.51-3.32 (m, 4 H), 1.28 (t, *J* 7.0, 3 H), 1.22 (t, *J* 7.0, 3 H); δ_C NMR (100 MHz, $CDCl_3$) δ (ppm); 167.6, 152.9, 142.5, 138.7 (d, $J_{C\text{-}F}$ 3.3), 130.7 (dd, $J_{C\text{-}F}$ 306.4, 294.3), 126.6 (d, $J_{C\text{-}F}$ 8.1), 120.6, 119.7, 85.7 (dd, $J_{C\text{-}F}$ 21.6, 16.5), 68.3 (dd, $J_{C\text{-}F}$ 11.6, 4.9), 52.1, 49.4 (dd, $J_{C\text{-}F}$ 19.6, 16.6), 42.2, 42.0, 31.2, 14.0, 13.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -110.8 (ddd, *J* 148.7, 16.2, 1.5, 1 F), -118.8 (app. dt, *J* 148.7, 2.4, 1 F); LRMS (ESI) *m/z* 339 [M]; LC (98%) t_R 1.25 mins.; HRMS (ES-TOF) m/z calcd for $C_{17}H_{20}F_2NO_4$ $[M + H]^+$ 340.1355, found 340.1361.

Bridged **352** was also prepared by irradiating a solution of divinylbenzene **346** (34 mg, 0.1 mmol) in acetonitrile (2 mL) contained within a sealed microwave vial with a full spectrum lamp for 48 h. The reaction solution was cooled to room temperature

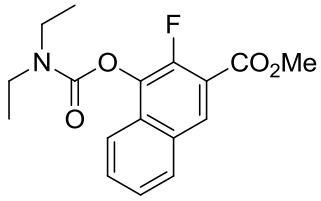
(vial had warmed to ~45 °C during irradiation) and the µW vial cap was pierced with a syringe containing a dry scrub (KF and $CaCO_3$). A stream of nitrogen was then passed through the vial before a saturated aqueous solution of KF (2 mL) was added via syringe. The quenched reaction mixture was stirred for 10 minutes then the µW vial was opened and the solution extracted with DCM (2 x 3 mL). The organic extracts were combined and passed through a hydrophobic frit and the solvent removed under reduced pressure to reveal a mixture of crude **352** and fluoroarene **351** as a yellow oil. The crude oil was purified by reverse phase flash column chromatography (5 – 70% acetonitrile in water) to afford a mixture of **352** and fluoroarene **351** (11% as judged by ^{1}H and ^{19}F NMR) as a yellow oil (18 mg, 53%). The data were consistent with those reported above.



2,2-Difluoro-3-methylacetate-1-indanone 348

A solution of a mixture of bridged species **352** and fluoroarene **351** (18 mg) in diphenylether (1 mL) was heated at 160 °C for 18 h in a sealed microwave vial. The reaction solution was cooled to room temperature and the vial cap was pierced with a syringe containing a dry scrub (KF and $CaCO_3$). A stream of nitrogen was then passed through the vial before a saturated aqueous solution of KF (1 mL) was added via syringe. The quenched reaction mixture was stirred for 10 minutes then the µW vial was opened and the solution extracted with DCM (2 x 3 mL). The organic

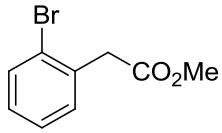
extracts were combined and passed through a hydrophobic frit and the solvent was removed under reduced pressure to afford a mixture of indanone **348** and fluoroarene **351** as a yellow oil. The crude oil was purified by preparative HPLC to afford indanone **348** as a colourless oil (5 mg, 40%); R_f (20% diethyl ether in cyclohexane) 0.13; ν_{max}(film)/cm^{-1} 3727, 3628, 2956, 2312, 1740, 1607, 1439, 1281, 1217, 1174, 1083, 950, 926, 761, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.89 (d, *J* 7.6, 1 H), 7.76 (dt, *J* 7.6, 1.3, 1 H), 7.55-7.49 (m, 2 H), 4.17-4.05 (m, 1 H), 3.78 (m, 3 H), 2.99-2.91 (m, 1 H), 2.83-2.75 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 190.3 (t, $J_{C\text{-}F}$ 25.7), 170.8, 150.5 (dd, $J_{C\text{-}F}$ 7.2, 4.0), 137.3, 131.7 (t, $J_{C\text{-}F}$ 3.2), 129.2, 125.6, 125.3, 116.6 (dd, $J_{C\text{-}F}$ 260.4, 259.7), 52.0, 42.4 (dd, $J_{C\text{-}F}$ 26.1, 20.6), 33.8 (d, $J_{C\text{-}F}$ 8.7); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -110.3 (dd, *J* 282.2, 18.4, 1 F), -122.0 (dd, *J* 282.2, 6.9, 1 F); LRMS (ESI) *m/z* 241 $[M + H]^+$; LC (98%) t_R 0.93 mins.; HRMS (ESI) m/z calcd for $C_{12}H_{11}F_2O_3$ $[M + H]^+$ 241.0671, found 241.0668.



1-(*N,N*-diethylcarbamoyloxy)-2-fluoro-3-methyl carboxy-naphthalene 351

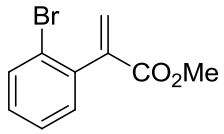
Fluoroarene **351** (1.5 mg) was isolated by preparative HPLC (see preparation of indanone **XX**) as a colourless oil; R_f (20% diethyl ether in cyclohexane) 0.18; ν_{max}(film)/cm^{-1} 3715, 2977, 2350, 2326, 1724, 1638, 1460, 1379, 1298, 1268, 1232, 1149, 1054, 962, 780, 760, 663; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.42 (d, *J* 6.6, 1 H), 7.95-7.89 (m, 2 H), 7.66-7.61 (m, 1 H), 7.55-7.50 (m, 1 H), 4.00 (s, 3 H), 3.63 (q, *J*

7.1, 2 H), 3.47 (q, *J* 7.1, 2 H), 1.41 (t, *J* 7.1, 3 H) 1.27 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.7 (d, $J_{C\text{-}F}$ 3.8), 152.9, 150.2 (d, $J_{C\text{-}F}$ 258.5), 134.2 (d, $J_{C\text{-}F}$ 13.1), 131.1, 130.4, 129.3, 129.2-129.3 (m, 2 x Ar*C* signals), 126.3 (d, $J_{C\text{-}F}$ 2.2), 121.2 (d, $J_{C\text{-}F}$ 6.3), 119.0 (d, $J_{C\text{-}F}$ 12.6), 52.5, 42.7, 42.4, 14.3, 13.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -131.7 (d, $J_{F\text{-}H}$ 6.9); LRMS (ESI) *m/z* 320 $[M + H]^+$; LC (98%) t_R 1.19 mins.; [HRMS (ESI, $[M+H]^+$) Found: 320.1290; Calc. for $C_{17}H_{19}FNO_4$: 320.1293].



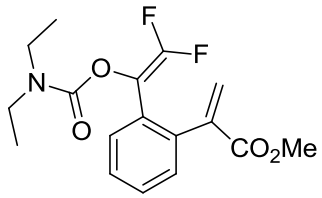
2-Bromobenzylmethyl ester 446

H_2SO_4 (2 mL) was added to a stirring solution of acid **362** (11.2 g, 52 mmol) in MeOH (100 mL). The reaction solution was stirred at reflux for 1.5 hours then allowed to cool to room temperature and quenched with H_2O (100 mL). The reaction mixture was extracted with diethyl ether (2 x 100 mL) and the extracts were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to reveal a pale yellow oil. The crude oil was purified by flash column chromatography on silica (10% diethyl ether in hexane) to afford ester **446** (11.9 g, 99%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.55 (d, *J* 8.1, 1 H), 7.29-7.23 (m, 2 H), 7.15-7.09 (m, 1 H), 3.78 (s, 2 H), 3.70 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.2, 134.5, 133.2, 131.8, 129.2, 127.9, 125.4, 52.5, 41.9; LC (98%) t_R 1.0 mins. These data were consistent with those reported previously.[210]



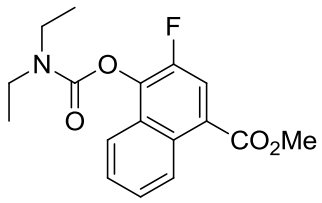
Methyl 2-(2'-bromophenyl) acrylate 363

Potassium carbonate (4.15 g, 30 mmol) and calcium oxide (1.68 g, 30 mmol) were added consecutively and in single portions to a stirring solution of bromide **446** (6.87 g, 30 mmol) and paraformaldehyde (1.8 g, 60 mmol) in DMF (25 mL). The reaction solution was stirred at 40 °C for 4 hours then cooled to room temperature, quenched with H_2O (50 mL) and extracted with DCM (2 x 50 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to reveal a cloudy, colourless oil. The crude oil was purified by flash column chromatography on silica (10% diethyl ether in hexane) to afford styrene **363** (3.95 g, 55%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.48; ν_{max}(film)/cm^{-1} 2997, 2950, 1722, 1433, 1318, 1204, 1182, 1101, 1026, 762, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58 (dd, *J* 7.9, 1.1, 1 H), 7.33 (dt, *J* 7.4, 1.3, 1 H), 7.27 (d, *J* 1.8, 1 H), 7.21 (dt, *J* 7.9, 1.8, 1H), 6.53 (d, *J* 1.3, 1 H), 5.77 (d, *J* 1.3, 1 H), 3.78 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.2, 141.9, 138.6, 132.5, 131.0, 129.6, 129.1, 127.3, 123.3, 52.6; LRMS (ESI) *m/z* 258 $[M + NH_4]^+$, 241 $[M + H]^+$; LC (98%) t_R 1.06 mins. These data were consistent with those reported previously.[176]



Methyl-2-[(1'-*N*,*N*-diethylcarbamoyloxy)-2',2'-difluorovinyl] phenyl-α-acrylate 364

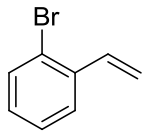
A mixture of potassium trifluoroborate **106b** (314 mg, 1.1 mmol), bromide **363** (241 mg, 1.0 mmol), caesium carbonate (3.26 g, 10 mmol), RuPhos (48 mg, 0.1 mmol) and palladium acetate (11 mg, 0.05 mmol) was taken up in a mixture of *tert*-butanol (4 mL) and H_2O (1.5 mL). The reaction mixture was stirred at 90 °C for 18 hours, then cooled to room temperature and partitioned between DCM (20 mL) and H_2O (20 mL). The organic phase was separated and dried by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (5% ethyl acetate in cyclohexane) to afford acrylate **364** (157 mg, 46%) as a pale yellow oil; R_f (20% diethyl ether in hexane) 0.28; ν_{max}(film)/cm^{-1} 2979, 2325, 1721, 1422, 1267, 1141, 984, 952, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.55-7.50 (m, 1 H), 7.40-7.33 (m, 2 H), 7.27-7.23 (m, 1 H), 6.46 (d, *J* 1.5, 1 H), 5.83 (d, *J* 1.5, 1 H), 3.74 (s, 3 H), 3.31-3.23 (m, 4 H), 1.18-1.06 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.7, 154.4 (dd, $J_{C\text{-}F}$ 291.6, 285.2), 152.8 (t, $J_{C\text{-}F}$ 2.8), 140.7, 136.6 (d, $J_{C\text{-}F}$ 2.4), 130.3, 129.8 (dd, $J_{C\text{-}F}$ 4.0, 2.4), 129.1, 129.0 (dd, $J_{C\text{-}F}$ 4.8, 1.6), 128.4, 128.3, 111.5 (dd, $J_{C\text{-}F}$ 42.5, 19.2), 52.0, 42.3, 41.7, 13.9, 13.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -96.6 (d, *J* 52.0, 1 F), -105.6 (d, *J* 52.0, 1 F); LRMS (ESI) *m/z* 340 $[M + H]^+$; LC (98%) t_R 1.17 mins.; HRMS (ESI) m/z calcd for $C_{17}H_{20}F_2NO_4$ $[M + H]^+$ 340.1355, found 340.1354.



1-(*N,N*-diethylcarbamoyloxy)-2-fluoro-4-methyl carboxy-naphthalene 365

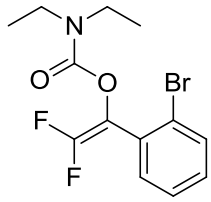
A solution of acrylate **364** (45 mg, 0.13 mmol) in diphenyl ether (1 mL) was stirred at 160 °C in a sealed μW vial for 18 hours. The reaction solution was cooled to room temperature and the μW vial cap was then pierced with a syringe containing a dry scrub (KF and $CaCO_3$). A stream of nitrogen was then passed through the vial before a saturated aqueous solution of KF (2 mL) was added via syringe. The quenched reaction mixture was stirred for 10 minutes then the μW vial was opened and the solution extracted with DCM (2 x 3 mL). The organic extracts were combined and passed through a hydrophobic frit and the solvent removed under reduced pressure to reveal a pale yellow solution of crude product in diphenyl ether. The crude solution was purified by flash column chromatography on silica (100% hexane then 20% diethyl ether in cyclohexane) to afford naphthalene **365** (33 mg, 78%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.14; ν_{max}(film)/cm^{-1} 3726, 3628, 2977, 2340, 2317, 1727, 1381, 1250, 1148, 980, 790, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.02-8.96 (m, 1 H), 8.11 (d, *J* 10.8, 1 H), 8.03-7.97 (m, 1 H), 7.63-7.57 (m, 2H), 4.01 (s, 3 H), 3.63 (q, *J* 6.8, 2 H), 3.47 (q, *J* 6.8, 2 H), 1.41 (t, *J* 6.8, 3 H), 1.28 (t, *J* 6.8, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4 (d, $J_{C\text{-}F}$ 2.4), 152.5, 150.2 (d, $J_{C\text{-}F}$ 248), 136.9 (d, $J_{C\text{-}F}$ 12.0), 129.6 (d, $J_{C\text{-}F}$ 2.4), 129.5 (d, $J_{C\text{-}F}$ 1.6), 127.3, 127.3 (d, $J_{C\text{-}F}$ 3.2), 126.2 (d, $J_{C\text{-}F}$ 1.6), 125.5 (d, $J_{C\text{-}F}$ 6.4), 121.4 (d, $J_{C\text{-}F}$ 6.4), 120.9 (d, $J_{C\text{-}F}$ 24.0), 52.4, 42.8, 42.4, 14.3, 13.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -130.8 (d, $J_{F\text{-}H}$ 10.8); LRMS

(ESI) *m/z* 337 $[M + NH_4]^+$, 320 $[M + H]^+$; LC (98%) t_R 1.25 mins.; HRMS (ESI) m/z calcd for $C_{17}H_{19}FNO_4$ $[M + H]^+$ 320.1293, found 320.1289.



2-Vinyl bromobenzene 368

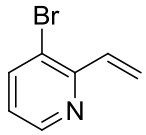
Prepared from iodide **366** (283 mg, 1.0 mmol) and borate **367** (134 mg, 1.0 mmol) using general Suzuki procedure 5 (90 °C, 3 h) to afford styrene **368** (172 mg, 94%) as a colourless oil after passing through a pad of silica (hexane); R_f (100% petroleum ether) 0.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.56 (dd, *J* 7.9, 1.3, 2 H), 7.29 (t, *J* 7.5, 1 H), 7.15-7.10 (m, 1 H), 7.07 (dd, *J* 17.4, 11.0, 1 H), 5.71 (dd, *J* 17.4, 1.0, 1 H), 5.38 (dd, *J* 11.0, 1.0, 1 H). LRMS *m/z* (CI) 183 $[M + H]^+$; GC (96%) t_R 11.63 mins.. These data were consistent with those reported previously.[211]



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(2'-bromophenyl) ethene 370

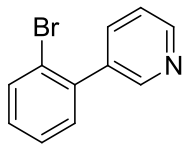
Prepared from aryl halide **366** (170 mg, 0.6 mmol) and trifluoroborate **106b** (188 mg, 0.66 mmol) using the same procedure as for **XX** to afford styrene **370** as a pale orange oil (93 mg, 46 %); R_f (40% diethyl ether in hexane) 0.44; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.64 (dd, *J* 8.0, 7.2, 1 H), 7.57 (dd, *J* 7.7, 1.5, 1 H), 7.36 (dt, *J* 7.5, 1.3, 1 H), 7.26 (dt, *J* 7.7, 1.7, 1 H), 3.40 (q, *J* 7.0, 2 H), 3.31 (q, *J* 7.0, 2 H), 1.21 (t, *J* 7.0, 3

H), 1.15 (t, *J* 7.0, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.5 (dd, $J_{C\text{-}F}$ 291.0, 284.5), 152.9, 133.1, 132.9 (t, $J_{C\text{-}F}$ 2.9), 130.9, 130.7 (dd, $J_{C\text{-}F}$ 5.2, 2.4), 127.3, 124.0, 111.1 (dd, $J_{C\text{-}F}$ 44.5, 21.1), 42.4, 41.9, 14.0, 13.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -96.2 (d, *J* 49.5, 1 F), -104.3 (d, *J* 49.5, 1 F); LRMS (CI) *m/z* 334 $[M + H]^+$; GC (99%) t_R 11.75 mins.; HRMS (NSI) m/z calcd for $C_{13}H_{14}BrF_2NO_2$ [M] 333.0176, found 333.0170.



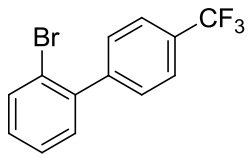
3-Bromo-2-vinyl pyridine 384

Prepared from pyridyl dibromide (237 mg, 1.0 mmol) and borate **367** (134 mg, 1.0 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (20% EtOAc in hexane) afforded styrene **384** (44 mg, 26%) as an orange oil; R_f (20% ethyl acetate in hexane) 0.46; ν_{max}(film)/cm^{-1} 2994, 1730, 1568, 1440, 1427, 1386, 1265, 1150, 1130, 1033, 1007, 984, 937, 787; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.54 (dd, *J* 4.6, 1.4, 1 H), 7.86 (dd, *J* 8.0, 1.4, 1 H), 7.27 (dd, *J* 16.9, 10.6, 1 H), 7.07 (dd, *J* 8.0, 4.6, 1 H), 6.47 (dd, *J* 16.9, 1.9, 1 H), 5.59 (dd, *J* 16.9, 1.9, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.6, 147.5, 140.2, 133.1, 123.2, 121.0, 120.2; LRMS (CI) *m/z* 184 $[M]^+$; GC (99%) t_R 8.04 mins.. These data were consistent with those reported previously.[212]



2-(3'-pyridyl)-1-bromobenzene 385

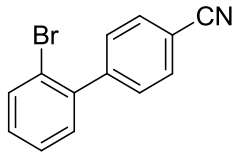
Prepared from iodide **366** (283 mg, 1.0 mmol) and borate **249** (185 mg, 1.0 mmol) using general Suzuki procedure 5 (90 °C, 3 h). Flash column chromatography (30% EtOAc in hexane) afforded biaryl **385** (44 mg, 26%) as an orange oil; R_f (20% ethyl acetate in hexane) 0.13; ν_{max}(film)/cm^{-1} 2361, 2342, 1460, 1406, 1024, 1003, 752, 714, 660; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.69 (dd, *J* 2.4, 0.7, 1 H), 8.66 (dd, *J* 4.9, 1.7, 1 H), 7.79 (app. dt, *J* 7.9, 2.0, 1 H), 7.73 (dd, *J* 8.0, 1.1, 1 H), 7.43 (dt, *J* 7.6, 1.2, 1 H), 7.39 (ddd, *J* 7.9, 4.9, 0.8, 1 H), 7.35 (dd, *J* 7.6, 1.9, 1 H), 7.29 (dt, *J* 7.7, 1.8, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.5, 148.3, 138.5, 136.3, 136.2, 132.9, 130.7, 129.1, 127.2, 122.3, 122.3; LRMS (CI) *m/z* 234 $[M + H]^+$; GC (99%) t_R 11.75 mins.; HRMS (EI) m/z calcd for $C_{11}H_8BrN$ [M] 232.9840, found 232.9837.



1-Bromo-2-(4'-trifluoromethylphenyl) benzene 386

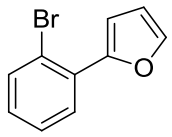
Prepared from iodide **366** (283 mg, 1.0 mmol) and borate **245** (252 mg, 1.0 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (100% hexane) afforded biaryl **386** (70 mg, 23%) as a colourless oil; R_f (hexane) 0.79; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.74-7.70 (m, 3 H), 7.56 (d, *J* 8.0, 2 H), 7.42 (dt, *J* 7.4, 1.2, 1 H), 7.34 (dd, *J* 7.6, 1.8, 1 H), 7.28 (dt, *J* 7.6, 1.8, 1 H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ (ppm) 144.1, 140.7, 132.8, 130.6, 129.3, 128.9, 127.2, 127.1, 124.5 (q, $J_{C\text{-}F}$ 3.7), 123.6 (q, $J_{C\text{-}F}$ 272), 121.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -62.5 (s); LRMS (CI) *m/z* 302 $[M + H]^+$; GC (95%) t_R 11.08 mins.. The data were consistent with those reported previously.[213]



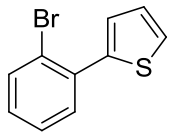
1-Bromo-2-(4'-cyanophenyl) benzene 387

Prepared from iodide **366** (566 mg, 2.0 mmol) and boronic acid **378** (294 mg, 2.0 mmol) using general Suzuki procedure 6 (90 °C, 18 h) to afford a yellow solid. This crude solid was recrystallised from hexane to afford biaryl **387** (252 mg, 51%) as white crystals; Mp. 82-84 °C (lit. 88-89 °C); ν_{max}(film)/cm^{-1} 2301, 2279, 2227, 1609, 1466, 1396, 1024, 1001, 839, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.77-7.70 (m, 3 H), 7.55 (d, *J* 8.2, 2 H), 7.42 (dt, *J* 7.5, 1.1, 1 H), 7.32 (dd, *J* 7.5, 1.7, 1 H), 7.28 (dd, *J* 7.5, 1.7, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 145.1, 140.2, 132.9, 131.4, 130.4, 129.8, 129.2, 127.2, 121.6, 118.2, 111.1; LRMS (CI) *m/z* 259 $[M + H]^+$; GC (99%) t_R 13.13 mins.. The data were consistent with those reported previously.[214]



1-Bromo-2-(2'-furyl) benzene 388

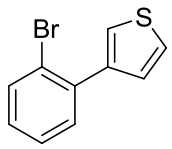
Prepared from iodide **366** (849 mg, 3.0 mmol) and borate **379** (522 mg, 3.0 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (100% hexane) afforded biaryl **388** (110 mg, 16%) as a colourless oil; R_f (hexane) 0.45; ν_{max}(film)/cm^{-1} 3057, 2332, 1499, 1466, 1159, 1026, 1005, 903, 739, 716; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.82 (dd, *J* 7.9, 1.7, 1 H), 7.68 (dd, *J* 8.0, 1.2, 1 H), 7.55 (dd, *J* 1.8, 0.6, 1 H), 7.39 (dd, *J* 7.6, 1.2, 1 H), 7.19 (dd, *J* 3.5, 0.6, 1 H), 7.15 (dt, *J* 7.6, 1.7, 1 H), 6.55 (dd, *J* 3.5, 1.8, 1 H); LRMS (CI) *m/z* 223 [M]; GC (98%) t_R 10.51 mins.. These data were consistent with those reported earlier.[215]



1-Bromo-2-(2-thiophenyl) benzene 389

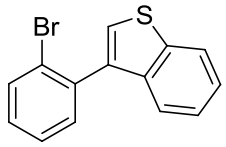
Prepared from iodide **366** (849 mg, 3.0 mmol) and boronic acid **380** (384 mg, 3.0 mmol) using general Suzuki procedure 6 (90 °C, 18 h). Flash column chromatography (100% hexane) afforded biaryl **389** (204 mg, 28%) as a colourless oil; R_f (hexane) 0.44; ν_{max}(film)/cm^{-1} 3040, 2320, 1466, 1433, 1261, 1240, 1024, 851, 831, 754, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70 (dd, *J* 8.0, 1.2, 1 H), 7.51 (dd, *J* 7.7, 1.1, 1 H), 7.41 (dd, *J* 5.2, 1.1, 1 H), 7.36 (dt, *J* 7.5, 1.2, 1 H), 7.32 (dd, *J* 3.7, 1.2, 1 H), 7.21 (dt, *J* 7.7, 1.7, 1 H), 7.14 (dd, *J* 5.2, 3.7, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ (ppm) 141.3, 134.8, 133.2, 131.5, 128.5, 127.3, 126.9, 126.4, 125.6, 122.4; LRMS (CI) *m/z* 240 $[M + H]^+$; GC (97%) t_R 12.93 mins.. These data were consistent with those reported earlier.[215]



1-Bromo-2-(3-thiophenyl) benzene 390

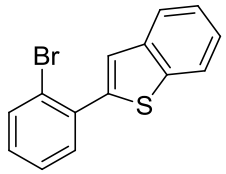
Prepared from iodide **366** (849 mg, 3.0 mmol) and borate **381** (570 mg, 3.0 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (100% hexane) afforded biaryl **390** (381 mg, 53%) as a colourless oil; R_f (hexane) 0.45; ν_{max}(film)/cm^{-1} 3111, 3069, 1466, 1435, 1020, 856, 787, 748, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 (dd, *J* 8.0, 1.0, 1 H), 7.43-7.41 (m, 2 H), 7.38 (dd, *J* 5.0, 3.0, 1 H), 7.35 (dt, *J* 7.5, 1.3, 1 H), 7.31 (dd, *J* 5.0, 1.3, 1 H), 7.19 (dt, *J* 7.7, 1.7, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 141.1, 137.5, 133.4, 131.3, 128.9, 128.7, 127.4, 124.8, 124.0, 122.6; LRMS (CI) *m/z* 240 $[M + H]^+$; GC (99%) t_R 12.94 mins.; HRMS (APCI) m/z calcd for $C_{10}H_8BrS$ $[M + H]^+$ 238.9525, found 238.9525.



1-Bromo-2-(3-benzothiophenyl) benzene 391

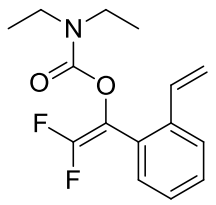
Prepared from iodide **366** (283 mg, 1.0 mmol) and boronic acid **382** (240 mg, 1.0 mmol) using general Suzuki procedure 5 (90 °C, 6 h). Flash column chromatography

(100% hexane) afforded biaryl **391** (229 mg, 79%) as a colourless oil; R_f (30% ethyl acetate in hexane) 0.78; ν_{max}(film)/cm^{-1} 3041, 2359, 1460, 1425, 1022, 939, 829, 758, 726, 671; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.96-7.93 (m, 1 H), 7.76 (d, *J* 8.0, 1 H), 7.55-7.51 (m, 1 H), 7.45 (s, 1 H), 7.43 (d, *J* 4.4, 2 H), 7.42-7.37 (m, 2 H), 7.34-7.29 (m, 1 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 139.7, 138.3, 136.7, 136.5, 133.2, 132.0, 129.4, 127.3, 125.3, 124.4, 124.2, 124.0, 123.3, 122.7; LRMS (CI) *m/z* 290 [M + H]$^+$; GC (99%) t_R 14.01 mins.. These data were consistent with those reported previously.[216]



1-Bromo-2-(2-benzothiophenyl) benzene 392

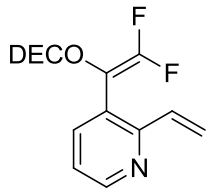
Prepared from iodide **366** (283 mg, 1.0 mmol) and boronic acid **383** (178 mg, 1.0 mmol) using general Suzuki procedure 6 (90 °C, 18 h). Flash column chromatography (100% hexane) afforded biaryl **392** (77 mg, 27%) as a colourless oil; R_f (30% ethyl acetate in hexane) 0.75; ν_{max}(film)/cm^{-1} 3038, 2327, 1466, 1431, 1246, 1155, 1026, 941, 858, 831, 746, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.91-7.87 (m, 2 H), 7.74 (dd, *J* 8.0, 1.2, 1 H), 7.58 (dd, *J* 7.7, 1.7, 1 H), 7.53 (s, 1 H), 7.44-7.36 (m, 3 H), 7.26 (dt, 7.7, 1.7, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 141.9, 140.3, 139.8, 135.4, 133.7, 132.2, 129.6, 127.4, 124.5 (3 overlapping signals), 123.9, 123.0, 122.1; LRMS (CI) *m/z* 289 [M + H]$^+$; GC (98%) t_R 14.53 mins.; HRMS (APCI) m/z calcd for $C_{14}H_{10}BrS$ [M + H]$^+$ 288.9681, found 288.9684.



1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-(2'-vinylphenyl) ethene 369

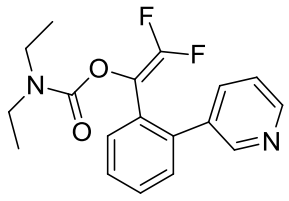
Prepared from styrene **370** (27 mg, 0.08 mmol) and trifluoroborate **367** (13 mg, 0.1 mmol) using the same procedure as for **XX** to afford divinyl benzene **369** as a pale yellow oil (19 mg, 84%); R_f (40% diethyl ether in hexane) 0.53; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (dd, *J* 7.8, 0.9, 1 H), 7.47 (dd, *J* 7.6, 1.4, 1 H), 7.38 (dt, *J* 7.8, 1.4, 1 H), 7.31 (dt, *J* 7.6, 1.3, 1 H), 7.08 (ddd, *J* 17.8, 11.0, 1.3, 1 H), 5.77 (dd, *J* 17.8, 1.3, 1 H), 5.35 (dd, *J* 17.8, 1.3, 1 H), 3.41-3.26 (m, 4 H), 1.25-1.09 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.3 (dd, $J_{C\text{-}F}$ 292.5, 284.3), 152.5, 136.9, 134.0, 129.9 (t, $J_{C\text{-}F}$ 2.8), 129.1, 127.7 (d, $J_{C\text{-}F}$ 4.5), 127.1, 125.1, 115.1, 109.9 (dd, $J_{C\text{-}F}$ 45.1, 18.9), 41.9, 41.4, 13.5, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -96.3 (d, *J* 50.2, 1 F), -105.5 (d, *J* 50.2, 1 F); LRMS (CI) *m/z* 282 $[M + H]^+$; GC (96%) t_R 11.39 mins.; HRMS (APCI) m/z calcd for $C_{15}H_{18}F_2NO_2$ $[M + H]^+$ 282.1300, found 282.1304.

Divinyl benzene **369** (228 mg, 59%) was also prepared from styrene **368** (250 mg, 1.37 mmol) and borate **106b** (467 mg, 1.64 mmol) using the same procedure as above. The data were consistent with those reported above.



3-[(1'-*N*,*N*-diethylcarbamoyloxy)-2'-difluoroethenyl]-2-vinyl pyridine 393

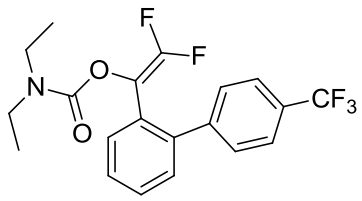
Prepared from styrene **384** (43 mg, 0.23 mmol) and borate **106b** (79 mg, 0.28 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (30% ethyl acetate in hexane) afforded divinyl benzene **393** (14 mg, 22%) as a colourless oil; ν_{max}(film)/cm^{-1} 2978, 2361, 1743, 1423, 1287, 1265, 1142, 979, 797; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.63 (dd, *J* 4.7, 1.7, 1 H), 7.79 (dd, *J* 7.8, 1.7, 1 H), 7.23 (dd, *J* 7.8, 4.7, 1 H), 7.10 (ddd, *J* 17.2, 10.8, 1.2, 1 H), 6.50 (dd, *J* 17.2, 1.9, 1 H), 5.57 (dd, *J* 10.7, 1.9, 1 H), 3.40-3.25 (m, 4 H), 1.23-1.10 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.5 (dd, $J_{C\text{-}F}$ 294.0, 284.6), 153.7, 152.8, 150.3, 138.8, 133.1, 123.8, 122.2, 120.3, 109.3 (dd, $J_{C\text{-}F}$ 44.8, 19.8), 42.5, 41.9, 14.0, 13.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -94.8 (d, *J* 49.2, 1 F), -104.8 (d, *J* 49.2, 1 F); LRMS (CI) *m/z* 283 $[M + H]^+$; GC (96%) t_R 11.49 mins.; HRMS (EI) m/z calcd for $C_{14}H_{17}F_2N_2O_2$ $[M + H]^+$ 283.1253, found 283.1255.



1-(1'-*N*,*N*-Diethylcarbamoyloxy-2'-difluoroethenyl)-2-(3''-pyridyl) benzene 394

Prepared from biaryl **385** (75 mg, 0.32 mmol) and borate **106b** (110 mg, 0.39 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (30%

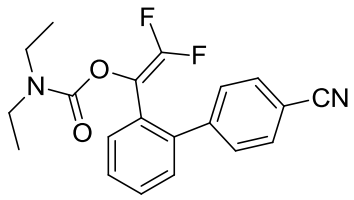
ethyl acetate in hexane) afforded biaryl **394** (64 mg, 60%) as a yellow gum; R_f (30% ethyl acetate in hexane) 0.17; ν_{max}(film)/cm^{-1} 3082, 2359, 2342, 1741, 1421, 1265, 1144, 982, 756, 716; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.72 (s, 1 H), 8.61 (d, *J* 4.6, 1 H), 7.93 (dt, *J* 7.8, 1.9, 1 H), 7.64-7.61 (m, 1 H), 7.51-7.42 (m, 2 H), 7.38-7.34 (m, 2 H), 3.22 (q, *J* 7.1, 2 H), 2.93 (q, *J* 7.1, 2 H), 1.08 (t, *J* 7.1, 3 H), 0.98 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.1 (dd, $J_{C\text{-}F}$ 292.2, 284.8), 152.6, 149.3, 148.4, 137.6, 136.7, 135.9, 130.5, 130.4, 129.7, 128.7 (d, $J_{C\text{-}F}$ 5.2), 128.2, 123.0, 111.2 (dd, $J_{C\text{-}F}$ 43.5, 19.5), 42.3, 41.6, 13.9, 13.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -95.5 (d, *J* 49.6, 1 F), -105.6 (d, *J* 49.6, 1 F); LRMS (CI) *m/z* 333 $[M + H]^+$; GC (98%) t_R 13.77 mins.; HRMS (EI) m/z calcd for $C_{18}H_{19}F_2N_2O_2$ $[M + H]^+$ 333.1409, found 333.1413.



1-(1'-*N*,*N*-Diethylcarbamoyloxy-2'-difluoroethenyl)-2-(4''-trifluoromethylphenyl) benzene 395

Prepared from biaryl **386** (74 mg, 0.25 mmol) and borate **106b** (84 mg, 0.29 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (20% diethyl ether in hexane) afforded biaryl **395** (47 mg, 48%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.31; ν_{max}(film)/cm^{-1} 3051, 2362, 1724, 1422, 1320, 1269, 1144, 1126, 1070, 984, 845, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 (d, *J* 8.2, 2 H), 7.65-7.59 (m, 3 H), 7.49-7.41 (m, 2 H), 7.37-7.33 (m, 1 H), 3.21 (q, *J* 7.1, 2 H), 2.83 (q, *J* 7.1, 2 H), 1.07 (t, *J* 7.1, 3 H), 0.93 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$)

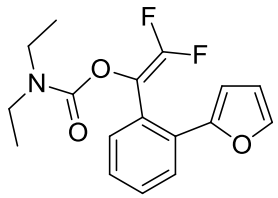
δ (ppm) 154.3 (dd, $J_{C\text{-}F}$ 292.0, 285.7), 152.6, 144.8, 139.6 (d, $J_{C\text{-}F}$ 2.6), 130.4, 129.6, 129.2, 128.9, 128.5, 128.3 (d, $J_{C\text{-}F}$ 4.4), 128.1, 125.1 (q, $J_{C\text{-}F}$ 3.7), 124.2 (q, $J_{C\text{-}F}$ 272.4), 111.4 (dd, $J_{C\text{-}F}$ 43.5, 19.2), 42.2, 41.4, 13.7, 13.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -62.5 (s, 3 F), -95.6 (d, *J* 49.6, 1 F), -105.8 (d, *J* 49.6, 1 F); LRMS (CI) *m/z* 400 $[M + H]^+$; GC (99%) t_R 13.04 mins.; HRMS (EI) m/z calcd for $C_{20}H_{19}F_5NO_2$ $[M + H]^+$ 400.1131, found 400.1330.



1-(1'-*N*,*N*-Diethylcarbamoyloxy-2'-difluoroethenyl)-2-(4''-cyanophenyl) benzene 396

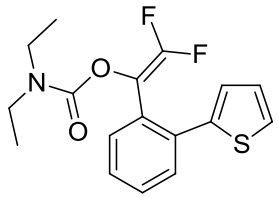
Prepared from biaryl **387** (97 mg, 0.38 mmol) and borate **106b** (116 mg, 0.41 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (30% ethyl acetate in hexane) afforded a black oil. Crystallisation from hexane afforded biaryl **396** (80 mg, 60%) as a yellow solid; R_f (30% ethyl acetate in hexane) 0.54; Mp. 161-163 °C; ν_{max}(film)/cm^{-1} 3048, 2361, 2228, 1722, 1421, 1269, 1148, 984, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.75-7.68 (m, 4 H), 7.63-7.59 (m, 1 H), 7.51-7.44 (m, 2 H), 7.36-7.33 (m, 1 H), 3.25 (q, *J* 7.1, 2 H), 3.00 (q, *J* 7.1, 2 H), 1.10 (t, *J* 7.1, 3 H), 1.02 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.3 (dd, $J_{C\text{-}F}$ 291.8, 286.3), 152.7, 145.9, 139.1, 132.0, 130.3, 130.1 (t, $J_{C\text{-}F}$ 3.0), 129.6, 129.4, 128.4, 128.3 (d, $J_{C\text{-}F}$ 4.6), 118.9, 111.1 (dd, $J_{C\text{-}F}$ 43.3, 19.5), 111.0, 42.3, 41.6, 13.9, 13.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -95.2 (d, *J* 48.7, 1 F), -105.1 (d, *J* 48.7, 1 F); LRMS (CI) *m/z* 357

$[M + H]^+$; GC (99%) t_R 16.24 mins.; HRMS (EI) m/z calcd for $C_{20}H_{19}F_2N_2O_2$ $[M + H]^+$ 357.1409, found 357.1406.



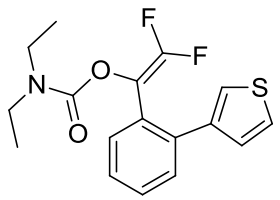
1-(1'-*N*,*N*-Diethylcarbamoyloxy-2'-difluoroethenyl)-2-(2''-furyl) benzene 397

Prepared from biaryl **388** (110 mg, 0.49 mmol) and borate **106b** (155 mg, 0.54 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (20% diethyl ether in hexane) afforded biaryl **397** (70 mg, 44%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.22; ν_{max}(film)/cm^{-1} 2978, 2359, 1741, 1422, 1279, 1260, 1129, 982, 760, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.77 (dd, *J* 7.9, 1.2, 1 H), 7.61 (d, *J* 7.7, 1 H), 7.53 (dd, *J* 1.8, 0.7, 1 H), 7.45 (dt, *J* 7.6, 1.4, 1 H), 7.34 (dt, *J* 7.6, 1.3, 1 H), 6.82 (dd, *J* 3.4, 0.6, 1 H), 6.51 (dd, *J* 3.4, 1.8, 1 H), 3.26 (q, *J* 7.1, 2 H), 3.15 (q, *J* 7.1, 2 H), 1.11 (t, *J* 7.1, 3 H), 1.03 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.0 (dd, $J_{C\text{-}F}$ 291.6, 283.4), 152.4, 151.5, 141.7, 131.6 (t, $J_{C\text{-}F}$ 2.8), 130.0 (d, $J_{C\text{-}F}$ 3.0), 129.3, 127.0, 126.7, 125.2 (d, $J_{C\text{-}F}$ 4.4), 111.2, 110.8 (dd, $J_{C\text{-}F}$ 44.8, 25.0), 107.9, 41.9, 41.3, 13.3, 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -96.7 (d, *J* 52.7, 1 F), -106.0 (d, *J* 52.7, 1 F); LRMS (CI) *m/z* 322 $[M + H]^+$; GC (98%) t_R 12.78 mins.; HRMS (EI) m/z calcd for $C_{17}H_{18}F_2NO_3$ $[M + H]^+$ 322.1249, found 322.1252.



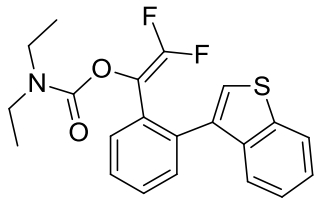
1-(1'-*N*,*N*-Diethylcarbamoyloxy-2'-difluoroethenyl)-2-(2''-thiophenyl) benzene 398

Prepared from biaryl **389** (190 mg, 0.79 mmol) and borate **106b** (270 mg, 0.95 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (20% ethyl acetate in hexane) afforded biaryl **398** (68 mg, 26%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.21; ν_{max}(film)/cm^{-1} 2978, 2358, 2336, 1721, 1421, 1271, 1258, 1126, 982, 758, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (d, *J* 7.5, 1 H), 7.51 (dd, *J* 7.5, 1.5, 1 H), 7.44-7.33 (m, 3 H), 7.29 (dd, *J* 3.6, 1.1, 1 H), 7.08 (dd, *J* 5.2, 3.6, 1 H), 3.24 (q, *J* 7.1, 2 H), 3.02 (q, *J* 7.1, 2 H), 1.09 (t, *J* 7.1, 3 H), 0.98 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.5 (dd, $J_{C\text{-}F}$ 291.7, 285.3), 152.9, 141.9, 134.4 (d, $J_{C\text{-}F}$ 3.0), 131.6 (t, $J_{C\text{-}F}$ 3.0), 130.5, 129.7, 128.1 (d, $J_{C\text{-}F}$ 4.8), 127.7, 127.3, 126.2, 125.7, 111.2 (dd, $J_{C\text{-}F}$ 44.0, 19.6), 42.2, 41.6, 13.8, 13.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -95.9 (d, *J* 50.2, 1 F), -106.1 (d, *J* 50.2, 1 F); LRMS (CI) *m/z* 338 $[M + H]^+$; GC (98%) t_R 13.49 mins.; HRMS (EI) m/z calcd for $C_{17}H_{18}F_2NO_2S$ $[M + H]^+$ 338.1021, found 338.1025.



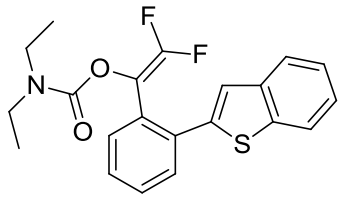
1-(1'-*N*,*N*-Diethylcarbamoyloxy-2'-difluoroethenyl)-2-(3''-thiophenyl) benzene 399

Prepared from biaryl **390** (200 mg, 0.84 mmol) and borate **106b** (287 mg, 1.0 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (20% diethyl ether in hexane) afforded biaryl **399** (78 mg, 28%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.22; ν_{max}(film)/cm^{-1} 2976, 2358, 2343, 1716, 1421, 1257, 1258, 1126, 981, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58 (d, *J* 7.5, 1 H), 7.48 (t, *J* 2.2, 1 H), 7.50-7.30 (m, 5 H), 3.25 (q, *J* 7.1, 2 H), 3.03 (q, *J* 7.1, 2 H), 110 (t, *J* 7.1, 3 H), 1.02 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.2 (dd, $J_{C\text{-}F}$ 291.1, 285.1), 152.9, 141.2, 136.2 (d, $J_{C\text{-}F}$ 2.4), 130.6 (t, $J_{C\text{-}F}$ 3.0), 130.1, 129.5, 128.2, 128.0 (d, $J_{C\text{-}F}$ 5.2), 127.2, 125.1, 122.6, 111.6 (dd, $J_{C\text{-}F}$ 43.9, 19.4), 42.3, 41.2, 13.9, 13.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -96.4 (d, *J* 50.4, 1 F), -106.1 (d, *J* 50.4, 1 F); LRMS (CI) *m/z* 338 $[M + H]^+$; GC (98%) t_R 13.55 mins.; HRMS (EI) m/z calcd for $C_{17}H_{18}F_2NO_2S$ $[M + H]^+$ 338.1021, found 338.1024.



1-(1'-*N*,*N*-Diethylcarbamoyloxy-2'-difluoroethenyl)-2-(3''-benzothiophenyl) benzene 400

Prepared from biaryl **391** (250 mg, 0.87 mmol) and borate **106b** (298 mg, 1.05 mmol) using general Suzuki procedure 5 (70 °C, 18 h). Flash column chromatography (20% diethyl ether in hexane) afforded biaryl **400** (140 mg, 42%) as a colourless gum; R_f (30% ethyl acetate in hexane) 0.50; ν_{max}(film)/cm^{-1} 2925, 1724, 1423, 1271, 1144, 984, 766, 735; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.93-7.90 (m, 1 H), 7.70-7.65 (m, 1 H), 7.59-7.55 (m, 1 H), 7.51 (s, 1 H), 7.50-7.44 (m, 3 H), 7.41-7.32 (m, 2 H), 3.13 (q, *J* 7.1, 2 H), 2.60 (q, *J* 7.1, 2 H), 1.00 (t, *J* 7.1, 3 H), 0.80 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.4 (dd, $J_{C\text{-}F}$ 291.2, 283.3), 152.7, 140.0, 138.8, 136.0, 135.0 (d, $J_{C\text{-}F}$ 3.3), 130.9, 130.6 (t, $J_{C\text{-}F}$ 2.7), 129.8 (d, $J_{C\text{-}F}$ 4.7), 129.2, 127.9, 124.3, 124.2, 124.0, 122.7, 122.5, 111.7 (dd, $J_{C\text{-}F}$ 43.3, 19.0), 42.0, 41.1, 13.5, 13.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -96.3 (d, *J* 50.9, 1 F), -106.4 (d, *J* 50.9, 1 F); LRMS (CI) *m/z* 388 $[M + H]^+$; GC (98%) t_R 15.34 mins.; HRMS (APCI) m/z calcd for $C_{21}H_{20}F_2NO_2S$ $[M + H]^+$ 388.1177, found 388.1181.



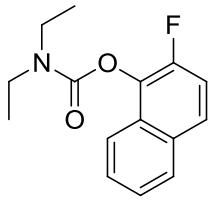
1-(1'-*N*,*N*-Diethylcarbamoyloxy-2'-difluoroethenyl)-2-(2''-benzothiophenyl) benzene 401

Prepared from biaryl **392** (58 mg, 0.20 mmol) and borate **106b** (68 mg, 0.24 mmol) using general Suzuki procedure 5 (70 °C, 18 h). Flash column chromatography (20% diethyl ether in hexane) afforded biaryl **401** (51 mg, 66%) as a colourless gum; R_f (30% ethyl acetate in hexane) 0.54; ν_{max}(film)/cm^{-1} 2931, 1726, 1422, 1269, 1144, 982, 760, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.87-7.83 (m, 1 H), 7.82-7.79 (m, 1 H), 7.66-7.62 (m, 1 H), 7.61-7.58 (m, 1 H), 7.48 (s, 1 H), 7.48-7.31 (m, 4 H), 3.21 (q, *J* 7.1, 2 H), 2.90 (q, *J* 7.1, 2 H), 1.06 (t, *J* 7.1, 3 H), 0.83 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.5 (dd, $J_{C\text{-}F}$ 292.7, 284.6), 152.8, 142.2, 140.3, 140.2, 134.2 (d, $J_{C\text{-}F}$ 3.3), 131.4 (t, $J_{C\text{-}F}$ 3.0), 130.9, 129.6, 128.6 (d, $J_{C\text{-}F}$ 4.5), 128.3, 124.3, 124.2, 123.7, 122.9, 122.0, 111.6 (dd, $J_{C\text{-}F}$ 44.0, 19.3), 42.2, 41.6, 13.6, 13.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -95.3 (d, *J* 50.1, 1 F), -105.5 (d, *J* 50.1, 1 F); LRMS (CI) *m/z* 388 $[M + H]^+$; GC (98%) t_R 15.66 mins.; HRMS (APCI) m/z calcd for $C_{21}H_{20}F_2NO_2S$ $[M + H]^+$ 388.1177, found 388.1180.

General electrocyclisation method

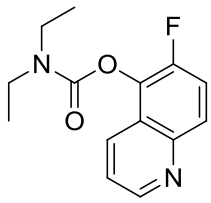
A solution of electrocyclisation precursor (0.13 mmol) in diphenyl ether (1 mL) was stirred at 180 °C in a sealed μW vial for 24 hours. The reaction solution was cooled to room temperature and the vial cap was then pierced with a syringe containing a

dry scrub (KF and $CaCO_3$). A stream of nitrogen was then passed through the vial before a saturated aqueous solution of KF (2 mL) was added via syringe. The quenched reaction mixture was stirred for 10 minutes then the μW vial was opened and the solution extracted with DCM (2 x 3 mL). The organic extracts were combined and passed through a hydrophobic frit and the solvent removed under reduced pressure to reveal a solution of crude product in diphenyl ether. The crude solution was purified by flash column chromatography on silica (100% hexane then 20% diethyl ether in cyclohexane) to afford fluoroarene product.



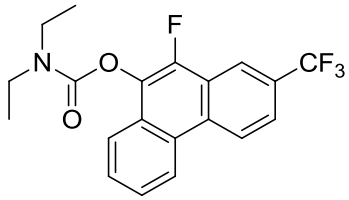
1-(*N,N*-diethylcarbamoyloxy)-2-Fluoronaphthalene 402

Prepared from divinyl **369** (40 mg, 0.14 mmol) using the general electrocyclisation procedure (180 °C, 24 h) to afford fluoroarene **402** (31 mg, 84%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.93 (d, *J* 8.4, 1 H), 7.84 (d, *J* 8.4, 1 H), 7.71 (dd, *J* 9.2, 4.9, 1 H), 7.55 (t, *J* 7.6, 1 H), 7.49-7.44 (m, 1 H), 7.35 (t, *J* 9.2, 1 H), 3.69-3.42 (m, 4 H), 1.46-1.22 (m, 6 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.8, 151.4 (d, $J_{C\text{-}F}$ 247.5), 132.5 (d, $J_{C\text{-}F}$ 12.0), 130.6, 128.7 (d, $J_{C\text{-}F}$ 2.4), 127.6 (d, $J_{C\text{-}F}$ 1.6), 126.7, 126.2 (d, $J_{C\text{-}F}$ 8.0), 125.0 (d, $J_{C\text{-}F}$ 2.4), 120.7 (d, $J_{C\text{-}F}$ 6.4), 116.0 (d, $J_{C\text{-}F}$ 22.4), 42.3, 42.0, 14.0, 13.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -130.9 (dd, $J_{F\text{-}H}$ 9.2, 4.6); LRMS (CI) *m/z* 262 $[M + H]^+$; GC (99%) t_R 13.36 mins.; HRMS (EI) m/z calcd for $C_{15}H_{17}FNO_2$ $[M + H]^+$ 262.1238, found 262.1244.



5-*N*,*N*-Diethylcarbamoyloxy-6-fluoroquinoline 403

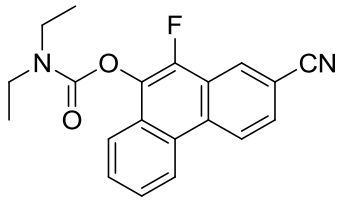
Prepared from divinyl pyridine **393** (6 mg, 0.02 mmol) using the general electrocyclisation procedure (180 °C, 24 h) to afford fluoroquinoline **403** (3 mg, 54%) as a white solid; R_f (30% ethyl acetate in hexane) 0.08; Mp. 110-112 °C; ν_{max}(film)/cm^{-1} 2974, 2357, 1717, 1423, 1379, 1271, 1246, 1150, 1074, 968, 827, 802; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.91 (dd, *J* 4.2, 1.6, 1 H), 8.28-8.25 (m, 1 H), 8.02 (dd, *J* 9.5, 4.9, 1 H), 7.59 (t, *J* 9.5, 1 H), 7.46 (ddd, *J* 8.5, 4.2, 0.6, 1 H), 3.62 (q, *J* 7.0, 2 H), 3.46 (q, *J* 7.0, 2 H), 1.40 (t, *J* 7.0, 3 H), 1.27 (t, *J* 7.0, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 152.8, 151.8 (d, $J_{C\text{-}F}$ 250.1), 149.7 (d, $J_{C\text{-}F}$ 2.3), 145.0, 132.3 (d, $J_{C\text{-}F}$ 13.5), 130.1 (d, $J_{C\text{-}F}$ 6.7), 128.2 (d, $J_{C\text{-}F}$ 7.9), 124.4 (d, $J_{C\text{-}F}$ 3.2), 121.6, 119.7 (d, $J_{C\text{-}F}$ 22.8), 42.8, 42.4, 14.3, 13.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -128.6 (s); LRMS (CI) *m/z* 263 $[M + H]^+$; GC (99%) t_R 13.35 mins.; HRMS (APCI) m/z calcd for $C_{14}H_{16}FN_2O_2$ $[M + H]^+$ 263.1190, found 263.1187.



2-Trifluoromethyl-9-(*N*,*N*-Diethylcarbamoyloxy)-10-fluorophenanthrene 404

Prepared from biaryl **395** (47 mg, 0.12 mmol) using the general electrocyclisation procedure (240 °C, 72 h) to afford fluorophenanthrene **404** (3 mg, 4%) as a white

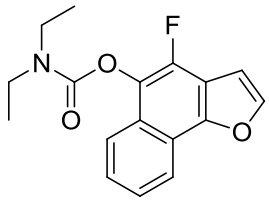
solid; R_f (30% ethyl acetate in hexane) 0.48; Mp. 84-86 °C; ν_{max}(film)/cm^{-1} 2978, 1721, 1422, 1383, 1360, 1346, 1263, 1250, 1111, 1098, 1043, 1006, 922, 777, 748, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.80 (br. d, *J* 8.8, 1 H), 8.72-8.68 (m, 1 H), 8.48 (br. s, 1 H), 8.07-8.04 (m, 1 H), 7.91 (dd, *J* 8.8, 1.7, 1 H), 7.78-7.70 (m, 2 H), 3.70 (q, *J* 7.1, 2 H), 3.52 (q, *J* 7.1, 2 H), 1.47 (t, *J* 7.1, 3 H), 1.31 (t, *J* 7.1, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 152.9, 147.5 (d, $J_{C\text{-}F}$ 252.8), 131.2, 131.1, 129.2, 129.0, 128.5, 127.4, 126.9, 124.2 (q, *J* 270.2), 123.9 (d, $J_{C\text{-}F}$ 16.9), 123.7 (d, $J_{C\text{-}F}$ 3.0), 123.3, 123.0 (d, $J_{C\text{-}F}$ 3.1), 122.1 (d, $J_{C\text{-}F}$ 7.0), 118.9 (dd, $J_{C\text{-}F}$ 6.2 4.0), 42.8, 42.4, 14.4, 13.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -62.3 (s, 3 F), -140.1 (d, $J_{F\text{-}H}$ 1.5, 1 F); LRMS (CI) *m/z* 380 [M + H]$^+$; GC (98%) t_R 15.63 mins.; HRMS (NSI) m/z calcd for $C_{20}H_{18}F_4NO_2$ [M + H]$^+$ 380.1268, found 380.1271.



2-cyano-9-(*N*,*N*-Diethylcarbamoyloxy)-10-fluorophenanthrene 405

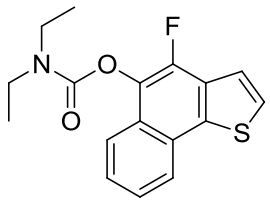
Prepared from biaryl **396** (100 mg, 0.28 mmol) using the general electrocyclisation procedure (240 °C, 144 h) to reveal a brown solid. Recrystallisation from ethyl acetate and hexane afforded fluorophenanthrene **405** (5 mg, 5%) as pale orange crystals; R_f (20% diethyl ether in hexane) 0.24; Mp. 193-195 °C; ν_{max}(film)/cm^{-1} 2980, 2361, 2332, 1726, 1260, 1088, 1016, 791, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.76 (dd, *J* 8.7, 1.7, 1 H), 8.66 (dd, *J* 8.2, 1.5, 1 H), 8.52 (d, *J* 1.6, 1 H), 8.06 (dd, *J* 7.5, 1.6, 1 H), 7.88 (dd, *J* 8.7, 1.7, 1 H), 7.80-7.71 (m, 2 H), 3.69 (q, *J* 7.1, 2 H), 3.51 (q, *J*

7.1, 2 H), 1.47 (t, *J* 7.1, 3 H), 1.32 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.7, 145.7 (d, $J_{C\text{-}F}$ 253.5), 130.5 (d, $J_{C\text{-}F}$ 3.9), 128.3 (d, $J_{C\text{-}F}$ 2.3), 128.0, 127.5, 126.1, 126.1, 125.4 (d, $J_{C\text{-}F}$ 6.4), 123.2, 123.0, 122.9 (d, $J_{C\text{-}F}$ 2.4), 122.4, 121.2 (d, $J_{C\text{-}F}$ 6.7), 117.7, 109.7, 41.8, 41.4, 13.4, 12.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -140.0 (s); LRMS (CI) *m/z* 337 $[M + H]^+$; GC (99%) t_R 18.82 mins.; HRMS (EI) m/z calcd for $C_{20}H_{18}F_2N_2O_2$ $[M + H]^+$ 337.1347, found 337.1342.



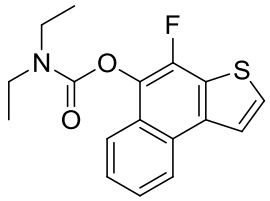
1-*N*,*N*-Diethylcarbamoyloxy-2-fluoro[3,2-b]furanyl naphthalene 406

Prepared from biaryl **397** (48 mg, 0.15 mmol) using the general electrocyclisation procedure (240 °C, 48 h) to afford fluoroarene **406** (14 mg, 31%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.19; ν_{max}(film)/cm^{-1} 2974, 2358, 2342, 1743, 1472, 1418, 1375, 1323, 1259, 1148, 1051, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31-8.26 (m, 1 H), 7.98-7.93 (m, 1 H), 7.77 (d, *J* 2.1, 1 H), 7.60-7.53 (m, 2 H), 7.03 (d, *J* 2.1, 1 H), 3.66 (q, *J* 7.1, 2 H), 3.48 (q, *J* 7.1, 2 H), 1.43 (t, *J* 7.1, 3 H), 1.28 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.5, 149.3 (d, $J_{C\text{-}F}$ 10.2), 146.0 (d, $J_{C\text{-}F}$ 251.1), 144.6, 128.5 (d, $J_{C\text{-}F}$ 11.7), 126.4, 126.3, 125.7 (d, $J_{C\text{-}F}$ 2.1), 121.9 (d, $J_{C\text{-}F}$ 6.6), 120.4, 118.6, 114.7 (d, $J_{C\text{-}F}$ 23.0), 104.6, 42.7, 42.2, 14.4, 13.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -136.3 (s); LRMS (CI) *m/z* 302 $[M + H]^+$; GC (99%) t_R 14.90 mins.; HRMS (APCI) m/z calcd for $C_{17}H_{17}FNO_3$ $[M + H]^+$ 302.1187, found 302.1186.



1-*N*,*N*-Diethylcarbamoyloxy-2-fluoro[3,2-b]thiophenyl naphthalene 407

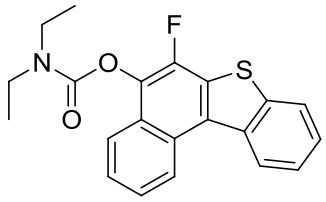
Prepared from biaryl **398** (65 mg, 0.19 mmol) using the general electrocyclisation procedure (240 °C, 48 h) to afford fluoroarene **407** (17 mg, 28%) as a brown oil; R_f (20% diethyl ether in hexane) 0.24; ν_{max}(film)/cm^{-1} 2976, 2359, 2332, 1722, 1443, 1423, 1259, 1151, 1076, 951, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.13-8.08 (m, 1 H), 8.00-7.95 (m, 1 H), 7.61-7.53 (m, 4 H), 3.67 (q, *J* 7.0, 2 H), 3.49 (q, *J* 7.0, 2 H), 1.44 (t, *J* 7.0, 3 H), 1.29 (t, *J* 7.0, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.4, 147.6 (d, $J_{C\text{-}F}$ 253.0), 136.6 (d, $J_{C\text{-}F}$ 6.9), 129.8 (d, $J_{C\text{-}F}$ 12.0), 128.6 (d, $J_{C\text{-}F}$ 20.3), 126.9, 126.5, 126.1, 126.0, 126.0, 123.8, 122.4 (d, $J_{C\text{-}F}$ 6.6), 120.5, 42.7, 42.3, 14.5, 13.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -135.9 (s); LRMS (CI) *m/z* 318 $[M + H]^+$; GC (99%) t_R 15.92 mins.; HRMS (APCI) m/z calcd for $C_{17}H_{17}FNO_2S$ $[M + H]^+$ 318.0959, found 318.0958.



1-*N*,*N*-Diethylcarbamoyloxy-2-fluoro[2,3-b]thiophenyl naphthalene 408

Prepared from biaryl **399** (71 mg, 0.19 mmol) using the general electrocyclisation procedure (240 °C, 48 h) to afford fluoroarene **408** (39 mg, 59%) as a pale brown oil; R_f (20% diethyl ether in hexane) 0.21; ν_{max}(film)/cm^{-1} 2974, 2359, 2342, 1718, 1425, 1352, 1271, 1254, 1120, 1045, 1005, 752, 721; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)

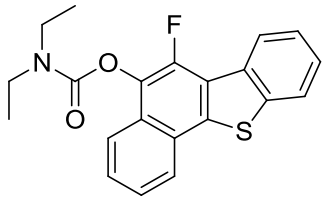
8.33-8.28 (m, 1 H), 8.02-7.94 (m, 2 H), 7.63-7.57 (m, 3 H), 3.67 (q, *J* 7.1, 2 H), 3.50 (q, *J* 7.1, 2 H), 1.44 (t, *J* 7.1, 3 H), 1.29 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.3, 147.6 (d, $J_{C\text{-}F}$ 248.8), 136.4 (d, $J_{C\text{-}F}$ 4.7), 129.5 (d, $J_{C\text{-}F}$ 11.3), 127.7, 127.1, 126.9, 126.6, 126.3, 125.9 (d, $J_{C\text{-}F}$ 2.1), 123.9, 122.2, 122.0 (d, $J_{C\text{-}F}$ 6.5), 42.7, 42.3, 14.4, 13.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -135.9 (s); LRMS (CI) *m/z* 318 $[M + H]^+$; GC (99%) t_R 16.07 mins.; HRMS (APCI) m/z calcd for $C_{17}H_{17}FNO_2S$ $[M + H]^+$ 318.0959, found 318.0956.



1-*N*,*N*-Diethylcarbamoyloxy-2-fluoro[2,3-b]benzothiophenyl naphthalene 409

Prepared from biaryl **400** (73 mg, 0.19 mmol) using the general electrocyclisation procedure (240 °C, 72 h) to afford fluoroarene **409** (29 mg, 42%) as white crystals (the crystals formed in the chromatography fractions and were collected and dried by filtration); R_f (30% ethyl acetate in hexane) 0.48; Mp. 175-177 °C; ν_{max}(film)/cm^{-1} 2976, 1722, 1423, 1385, 1362, 1346, 1265, 1250, 1148, 748, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.00 (d, *J* 8.5, 1 H), 8.83 (d, *J* 8.4, 1 H), 8.12 (dd, *J* 8.4, 1.3 1 H), 8.03 (d, *J* 8.0, 1 H), 7.76-7.70 (m, 1 H), 7.68-7.60 (m, 2 H), 7.56-7.52 (m, 1 H), 3.70 (q, *J* 7.1, 2 H), 3.52 (q, *J* 7.1, 2 H), 1.47 (t, *J* 7.1, 3 H), 1.32 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.0, 147.0 (d, $J_{C\text{-}F}$ 247.4), 139.8, 136.2, 131.0 (d, $J_{C\text{-}F}$ 10.8), 129.3 (d, $J_{C\text{-}F}$ 3.8), 128.5 (d, $J_{C\text{-}F}$ 18.6), 127.8, 127.6, 126.4 (d, $J_{C\text{-}F}$ 2.1), 125.7, 125.6, 125.1, 124.6, 123.3, 123.2, 122.4 (d, $J_{C\text{-}F}$ 6.6), 42.7, 42.3, 14.3, 13.3; ^{19}F NMR (376

MHz, $CDCl_3$) δ (ppm) -131.1 (s); LRMS (CI) *m/z* 368 $[M + H]^+$; GC (99%) t_R 18.98 mins.; HRMS (NSI) m/z calcd for $C_{21}H_{19}FNO_2S$ $[M + H]^+$ 368.1115, found 368.1119.

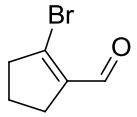


1-*N*,*N*-Diethylcarbamoyloxy-2-fluoro[3,2-b]benzothiophenyl naphthalene 410

Prepared from biaryl **401** (45 mg, 0.12 mmol) using the general electrocyclisation procedure (240 °C, 48 h) to afford fluoroarene **410** (27 mg, 63%) as a pale yellow solid; R_f (20% diethyl ether in hexane) 0.16; Mp. 158-160 °C; ν_{max}(film)/cm^{-1} 2976, 2360, 2342, 1726, 1427, 1263, 1152, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.52-8.45 (m, 1 H), 8.16-8.10 (m, 1 H), 8.06-8.00 (m, 1 H), 7.98-7.93 (m, 1 H), 7.67-7.57 (m, 2 H), 7.55-7.48 (m, 2 H), 3.70 (q, *J* 7.1, 2 H), 3.52 (q, *J* 7.1, 2 H), 1.47 (t, *J* 7.1, 3 H), 1.31 (t, *J* 7.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.4, 149.4 (d, $J_{C\text{-}F}$ 253.4), 138.7, 136.0 (d, $J_{C\text{-}F}$ 7.3), 134.4 (d, $J_{C\text{-}F}$ 3.7), 130.5 (d, $J_{C\text{-}F}$ 12.0), 127.6, 127.2, 126.4, 126.1 (d, $J_{C\text{-}F}$ 2.1), 125.7, 125.1, 125.0, 124.5, 123.3 (d, $J_{C\text{-}F}$ 17.8), 122.6, 122.3 (d, $J_{C\text{-}F}$ 6.5), 42.7, 42.3, 14.4, 13.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -136.3 (s); LRMS (CI) *m/z* 368 $[M + H]^+$; GC (99%) t_R 18.74 mins.; HRMS (APCI) m/z calcd for $C_{21}H_{19}FNO_2S$ $[M + H]^+$ 368.1115, found 368.1113.

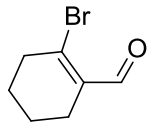
General Vilsmeier formylation procedure

Neat PBr_3 (0.11 mol) was added dropwise over 30 min to a stirring solution of DMF (0.13 mol) in DCM (50 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 1.5 h then a solution of ketone (0.04 mol) in DCM (50 mL) was added dropwise over 30 min. The reaction mixture was then allowed to warm to RT (after ~3 h a red solution had formed) and stirred for 18 h. The solution was quenched carefully with ice water (150 mL) and then neutralised with solid $NaHCO_3$ (to pH 7). The product was then extracted with diethyl ether (2 x 200 mL). The organic layers were separated, combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to reveal crude product. Flash column chromatography (0-2% ethyl acetate in cyclohexane) afforded pure aldehyde.



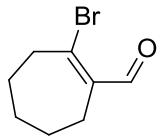
1-Bromo-2-formyl cyclopent-1-ene 420

Prepared from cyclopentanone **418** (4.0 g, 48.0 mmol), DMF (11.04 mL, 143.0 mmol) and PBr_3 (11.17 mL, 119.0 mmol) using the general Vilsmeier formylation procedure to afford aldehyde **420** (4.56 g, 55%) as a brown oil; ν_{max}(film)/cm^{-1} 2955, 2835, 1668, 1602, 1429, 1379, 1329, 1242, 1074, 918, 907, 719; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.85 (s, 1 H), 2.89-2.83 (m, 2 H), 2.51-2.45 (m, 2 H), 2.02-1.93 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 189.1, 141.3, 140.0, 42.5, 29.2, 21.4. These data were consistent with those reported previously.[217]



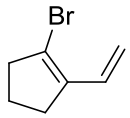
1-Bromo-2-formyl cyclohex-1-ene 421

Prepared from cyclohexanone **84** (4.35 g, 44.0 mmol), DMF (10.3 mL, 133.0 mmol) and PBr_3 (10.42 mL, 111.0 mmol) using the general Vilsmeier formylation procedure to afford aldehyde **421** (6.26 g, 75%) as a pale orange oil; R_f (20% diethyl ether in hexane) 0.49; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.99 (s, 1 H), 2.75-2.69 (m, 2 H), 2.27-2.22 (m, 2 H), 1.77-1.70 (m, 2 H), 1.70-1.62 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.5, 143.4, 135.3, 38.8, 25.0, 24.3, 21.1; LRMS (CI) *m/z* 189 $[M + H]^+$; GC (96%) t_R 8.95 mins.. These data were consistent with those reported previously.[218]



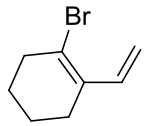
1-Bromo-2-formyl cyclohept-1-ene 422

Prepared from cycloheptanone **419** (2.24 g, 20.0 mmol), DMF (4.65 mL, 60.0 mmol) and PBr_3 (4.70 mL, 50.0 mmol) using the general Vilsmeier formylation procedure to afford aldehyde **422** (1.16 g, 29%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.93 (s, 1 H), 3.05-3.00 (m, 2 H), 2.53-2.48 (m, 2 H), 1.84-1.78 (m, 2 H), 1.71-1.64 (m, 2 H), 1.50-1.42 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.2, 148.2, 140.5, 44.2, 31.3, 25.7, 25.2, 24.8. These data were consistent with those reported previously.[219]



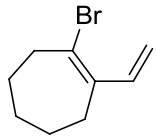
1-Bromo-2-vinyl cyclopent-1-ene 423

n-Butyllithium (4.15 mL of a 1.8 M solution in hexane, 7.5 mmol) was added dropwise over twenty minutes to a suspension of methyltriphenylphosphonium iodide (3.02 g, 7.5 mmol) in dry THF (100 mL) at -78 ^{o}C. The reaction solution turned yellow in colour and was stirred for 1 hour at -78 ^{o}C. Aldehyde **420** (1.0 g, 5.8 mmol) was added dropwise over ten minutes then the reaction solution was allowed to warm to room temperature and left to stir overnight. The reaction was quenched by the careful addition of H_2O (50 mL) and extracted with diethyl ether (3 x 100 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to afford a yellow oil. The crude oil was triturated with cold pentane (3 x 50 mL), concentrated under reduced pressure then purified by eluting through a short pad of silica (cyclohexane) to afford diene **423** (575 mg, 58%) as a pale yellow oil; R_f (20% diethyl ether in hexane) 0.61; ν_{max}(film)/cm^{-1} 2959, 2849, 1634, 1325, 1082, 988, 902; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.68 (dd, *J* 17.3, 10.8, 1 H), 5.29-5.19 (m, 2 H), 2.77 (t, *J* 7.4, 2 H), 2.52-2.46 (m, 2 H), 2.05-1.97 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.7, 130.6, 120.4, 116.3, 40.2, 30.2, 20.9. These data were consistent with those reported previously.[57]



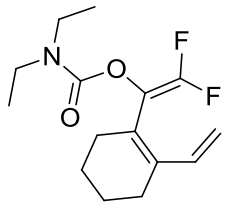
1-Bromo-2-vinyl cyclohex-1-ene 85

Prepared from aldehyde **421** (1.0 g, 5.3 mmol), *n*-Butyllithium (3.44 mL of a 2 M solution in hexane, 6.9 mmol) and methyltriphenylphosphonium iodide (2.78 g, 6.9 mmol) using the same procedure as for **423** to afford diene **85** (697 mg, 70%) as a pale yellow oil; R_f (20% diethyl ether in hexane) 0.58; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.92 (dd, *J* 17.5, 11.0, 1 H), 5.27 (dd, *J* 17.5, 1.0, 1 H), 5.14 (dd, *J* 11.0, 1.0, 1 H), 2.64 (br. s, 2 H), 2.32-2.25 (m, 2 H), 1.75-1.71 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.1, 132.3, 125.1, 114.3, 37.6, 26.9, 24.7, 22.1. These data were consistent with those reported previously.[57]



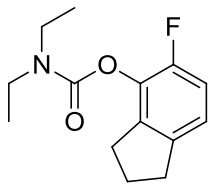
1-Bromo-2-vinyl cyclohept-1-ene 424

Prepared from aldehyde **422** (1.6 g, 7.9 mmol), *n*-Butyllithium (6.4 mL of a 1.6 M solution in hexane, 10.2 mmol) and methyltriphenylphosphonium iodide (4.14 g, 10.2 mmol) using the same procedure as for **423** to afford diene **424** (1.02 g, 69%) as a pale yellow oil; R_f (20% diethyl ether in hexane) 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.82 (dd, *J* 17.3, 10.9, 1 H), 5.27 (d, *J* 17.3, 1 H), 5.15 (d, *J* 10.9, 1 H), 2.90-2.85 (m, 2 H), 2.44-2.40 (m, 2 H), 1.80-1.75 (m, 2 H), 1.62-1.56 (m, 2 H), 1.53-1.48 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 138.7, 137.8, 127.6, 114.4, 41.7, 31.4, 27.9, 25.4, 25.2. These data were consistent with those reported previously.[57]



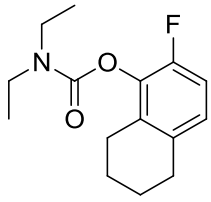
1-[1'-*N*,*N*-Diethylcarbamoyloxy-2'-difluoroethenyl]-2-vinylcyclohex-1-ene 425

Prepared from diene **85** (50 mg, 0.27 mmol) and borate **106b** (84 mg, 0.29 mmol) using general Suzuki procedure 5 (50 °C, 18 h). Flash column chromatography (15% diethyl ether in cyclohexane) afforded triene **425** (24 mg, 32%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.50; ν_{max}(film)/cm^{-1} 2977, 2935, 1727, 1422, 1275, 1245, 1125; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.88 (ddd, *J* 17.4, 11.0, 3.0, 1 H), 5.26 (d, *J* 17.4, 1 H), 5.10 (d, *J* 11.0, 1 H), 3.32 (q, *J* 7.1, 4 H), 2.30-2.21 (m, 4 H), 1.73-1.61 (m, 4 H), 1.17 (t, *J* 7.1, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.3 (dd, $J_{C\text{-}F}$ 292.2, 283.0), 153.2 (t, $J_{C\text{-}F}$ 2.8), 136.6 (d, $J_{C\text{-}F}$ 2.6), 135.7 (d, $J_{C\text{-}F}$ 1.9), 125.7 (d, $J_{C\text{-}F}$ 4.6), 113.2, 111.2 (dd, $J_{C\text{-}F}$ 44.4, 17.6), 42.4, 41.9, 27.5 (t, $J_{C\text{-}F}$ 2.6), 24.8, 22.3, 22.0, 14.1, 13.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -97.9 (d, *J* 50.5, 1 F), -105.4 (d, *J* 50.5, 1 F); LRMS (ESI) *m/z* 286 $[M + H]^+$; LC (98%) t_R 1.4 mins.; HRMS (ESI) m/z calcd for $C_{15}H_{22}F_2NO_2$ $[M + H]^+$ 286.1613, found 286.1610.



4-*N*,*N*-Diethylcarbamoyloxy-5-fluoroindane 428

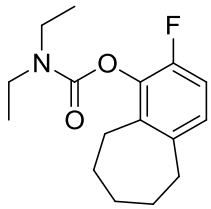
Prepared from diene **423** (100 mg, 0.58 mmol) and borate **106b** (181 mg, 0.64 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (20% diethyl ether in cyclohexane) afforded fluoroarene **428** (57 mg, 39%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.27; ν_{max}(film)/cm^{-1} 2970, 2361, 1719, 1416, 1265, 1198, 1150, 1098, 959, 806; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.97 (dd, *J* 8.2, 4.5, 1 H), 6.94-6.88 (m, 1 H), 3.51-3.37 (m, 4 H), 2.94-2.84 (m, 4 H), 2.16-2.07 (m, 2 H), 1.32-1.18 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.5 (d, $J_{C\text{-}F}$ 244.8), 153.0, 140.9 (d, $J_{C\text{-}F}$ 2.9), 139.0, 135.3 (d, $J_{C\text{-}F}$ 13.7), 121.3 (d, $J_{C\text{-}F}$ 7.7), 114.2 (d, $J_{C\text{-}F}$ 20.0), 42.5, 42.1, 32.6, 30.0, 25.6, 14.1, 13.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -135.5 (dd, $J_{F\text{-}H}$ 10.4, 3.3); LRMS (CI) *m/z* 252 $[M + H]^+$; GC (99%) t_R 12.40 mins.; HRMS (ESI) m/z calcd for $C_{14}H_{19}FNO_2$ $[M + H]^+$ 252.1394, found 252.1393.



5-*N*,*N*-Diethylcarbamoyloxy-6-fluorotetralin 426

Prepared from diene **85** (100 mg, 0.54 mmol) and borate **106b** (168 mg, 0.59 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (20% diethyl ether in cyclohexane) afforded fluoroarene **426** (64 mg, 45%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.10; ν_{max}(film)/cm^{-1} 2933, 2325, 1719, 1493, 1415, 1264, 1205, 1151, 1067, 937, 799, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.90-6.86 (m, 2 H), 3.51-3.35 (m, 4 H), 2.73 (t, *J* 5.0, 2 H), 2.66 (t, *J* 5.0, 2 H), 1.82-

1.73 (m, 4 H), 1.34-1.18 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.7 (d, $J_{C\text{-}F}$ 244.9), 153.0, 136.8 (d, $J_{C\text{-}F}$ 12.4), 135.4 (d, $J_{C\text{-}F}$ 3.7), 132.2, 126.2 (d, $J_{C\text{-}F}$ 7.1), 112.9 (d, $J_{C\text{-}F}$ 18.6), 42.4, 42.0, 28.8, 23.3 (d, $J_{C\text{-}F}$ 2.0), 22.5, 22.1, 14.1, 13.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -134.5 (app. t, $J_{F\text{-}H}$ 7.5); LRMS (CI) *m/z* 266 $[M + H]^+$; GC (97%) t_R 14.62 mins.; HRMS (ESI) m/z calcd for $C_{15}H_{21}FNO_2$ $[M + H]^+$ 266.1551, found 266.1559.



1-*N*,*N*-Diethylcarbamoyloxy-2-fluoro-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene 430

Prepared from diene **424** (108 mg, 0.54 mmol) and borate **106b** (168 mg, 0.59 mmol) using general Suzuki procedure 5 (90 °C, 18 h). Flash column chromatography (20% diethyl ether in cyclohexane) afforded fluoroarene **430** (72 mg, 48%) as a colourless oil; R_f (20% diethyl ether in hexane) 0.24; ν_{max}(film)/cm^{-1} 2973, 2926, 2853, 1722, 1492, 1416, 1269, 1153, 970, 808; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.91 (dd, *J* 8.4, 5.4, 1 H), 6.84 (dd, *J* 9.6, 8.4, 1 H), 3.55-3.37 (m, 4 H), 2.82-2.72 (m, 4 H), 1.87-1.79 (m, 2 H), 1.69-1.61 (m, 4 H), 1.35-1.19 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.8 (d, $J_{C\text{-}F}$ 244.4), 153.0, 139.7 (d, $J_{C\text{-}F}$ 3.5), 137.7, 135.9 (d, $J_{C\text{-}F}$ 12.7), 125.4 (d, $J_{C\text{-}F}$ 7.4), 112.0 (d, $J_{C\text{-}F}$ 18.3), 42.0, 41.6, 35.7, 32.0, 27.6, 26.7 (d, $J_{C\text{-}F}$ 2.0), 26.6, 13.7, 12.9; LRMS (CI) *m/z* 280 $[M + H]^+$; GC (98%) t_R 14.88 mins.; HRMS (ESI) m/z calcd for $C_{16}H_{23}FNO_2$ $[M + H]^+$ 280.1707, found 280.1707.

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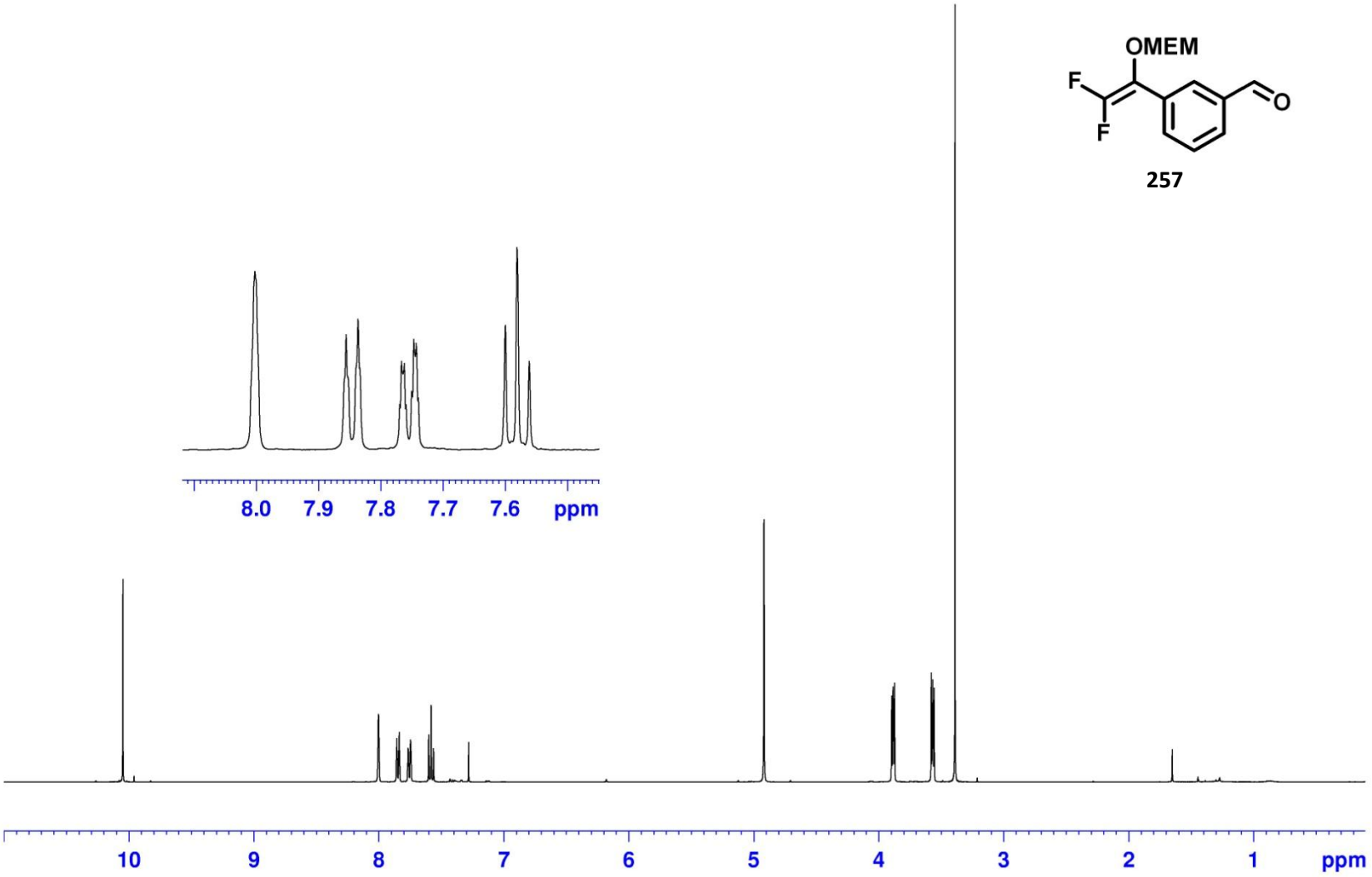
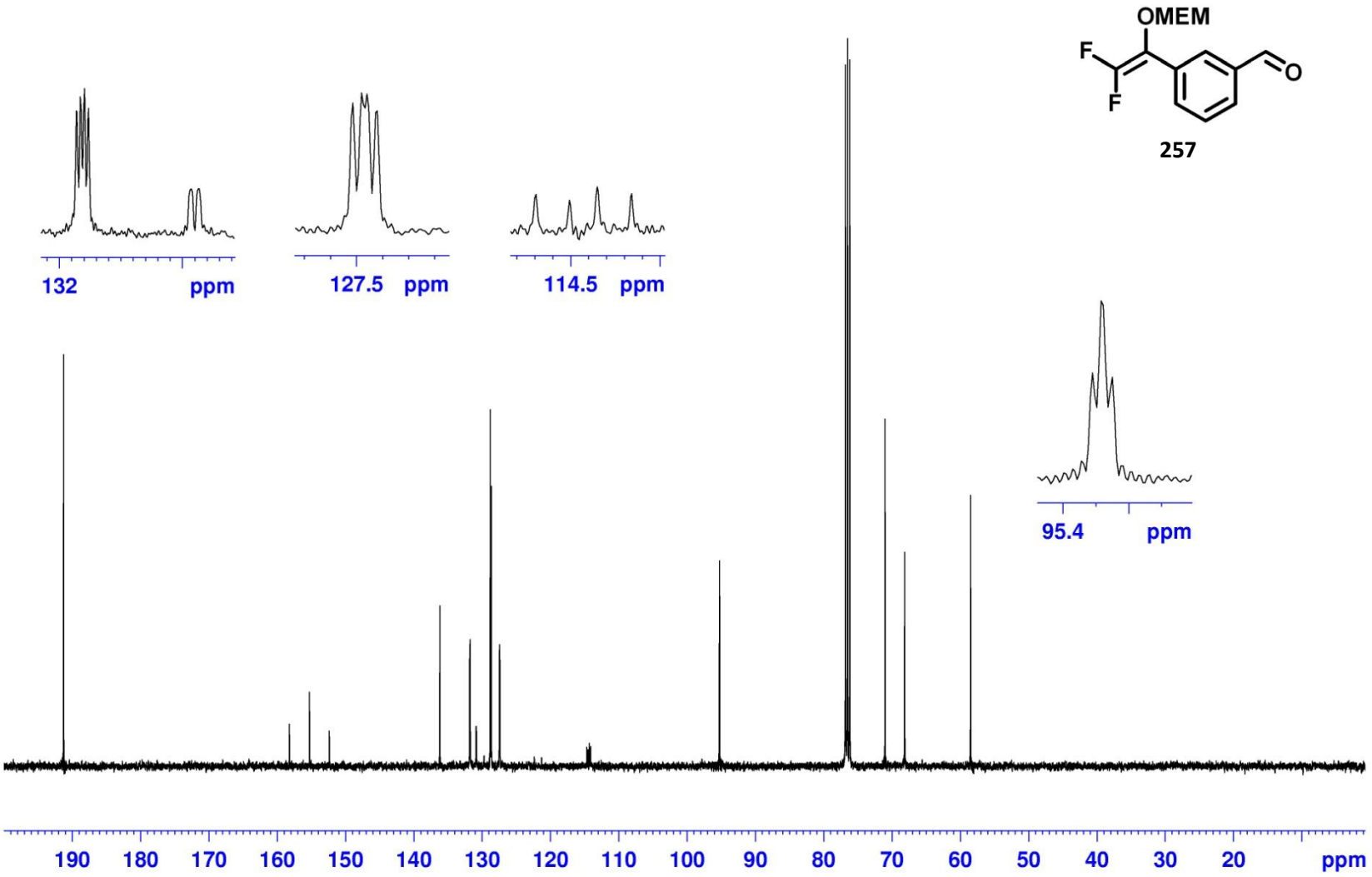
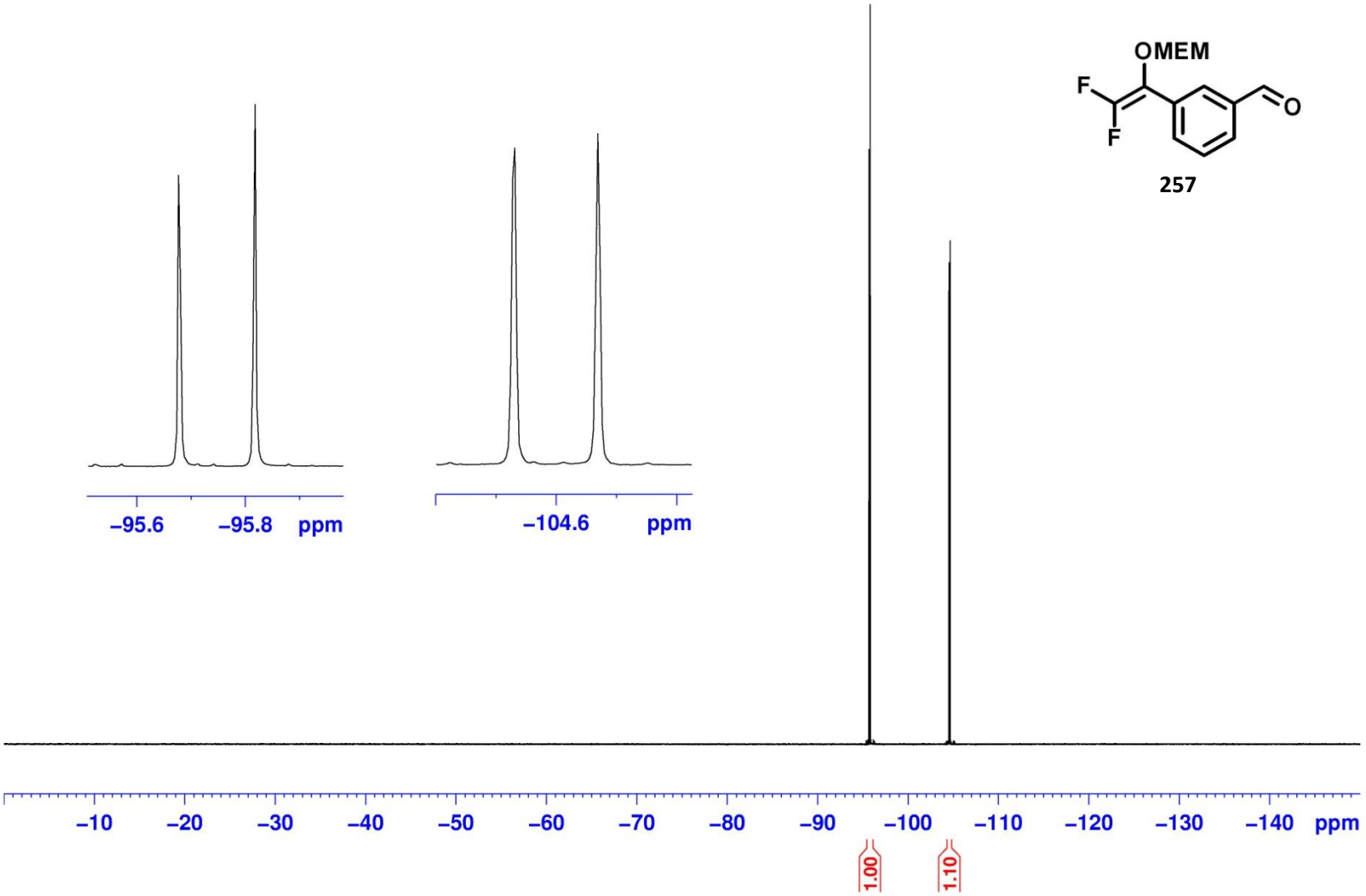
6 Appendices



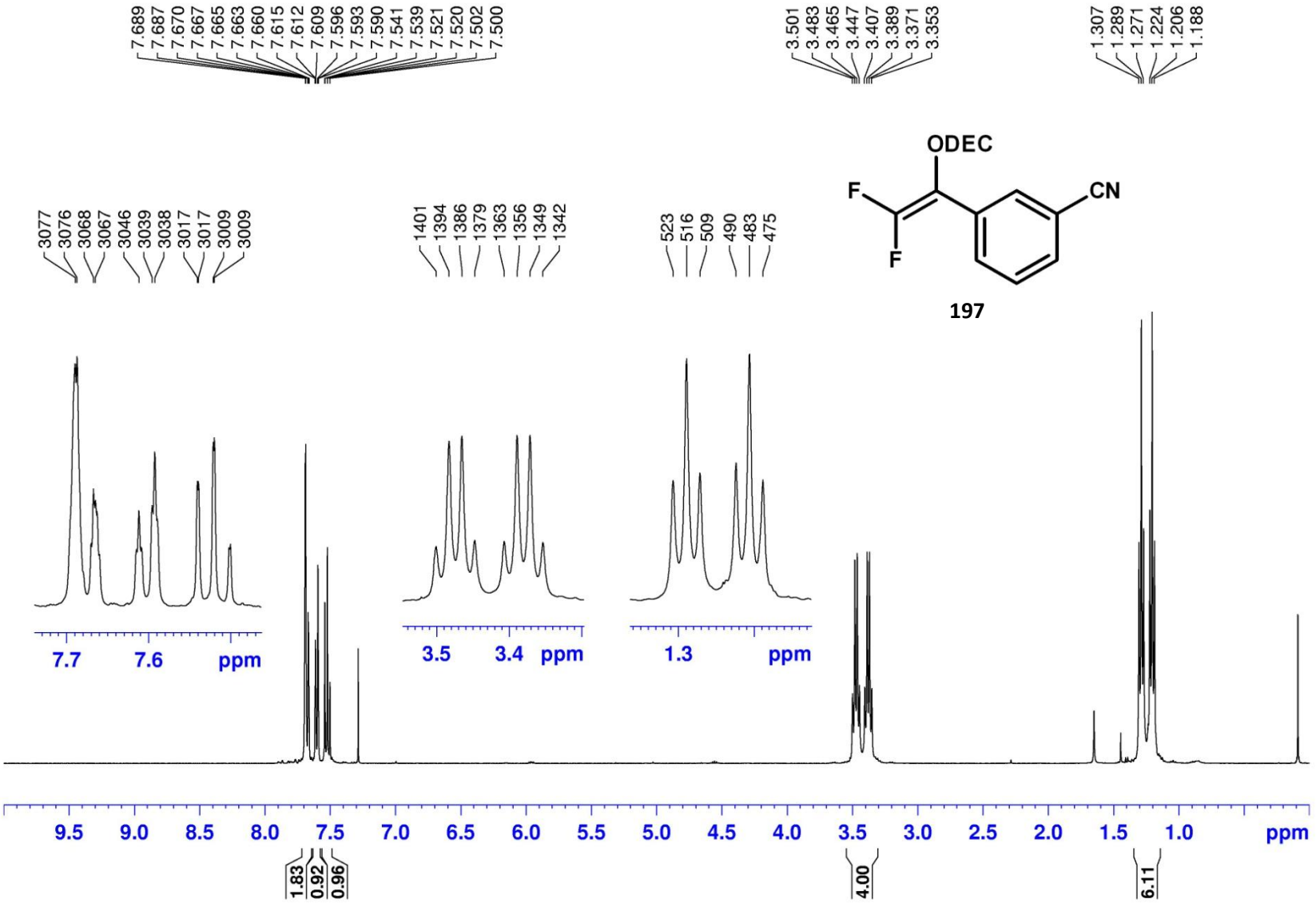
Appendix i: ^{1}H NMR of **257**



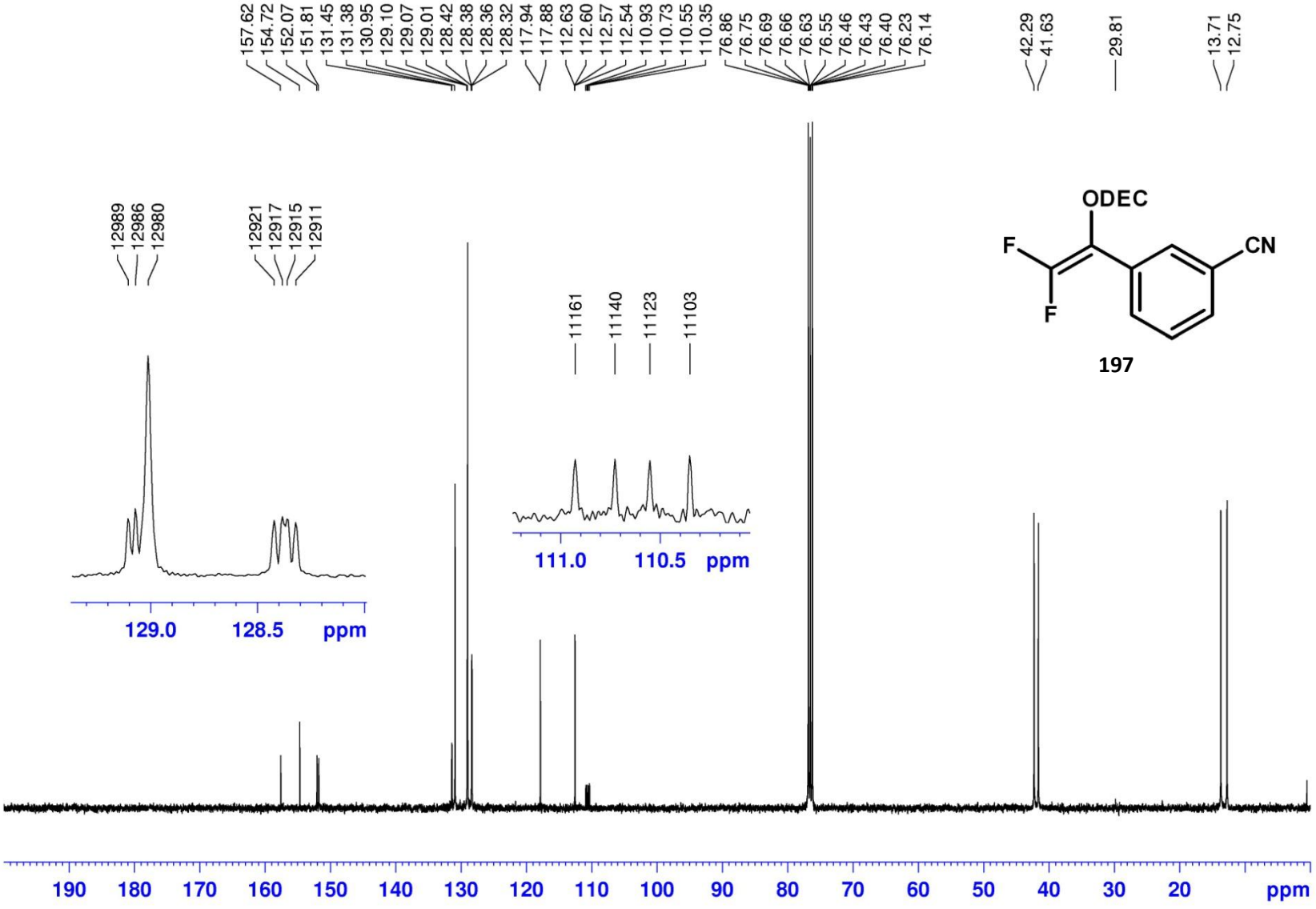
Appendix ii: ^{13}C NMR of **257**



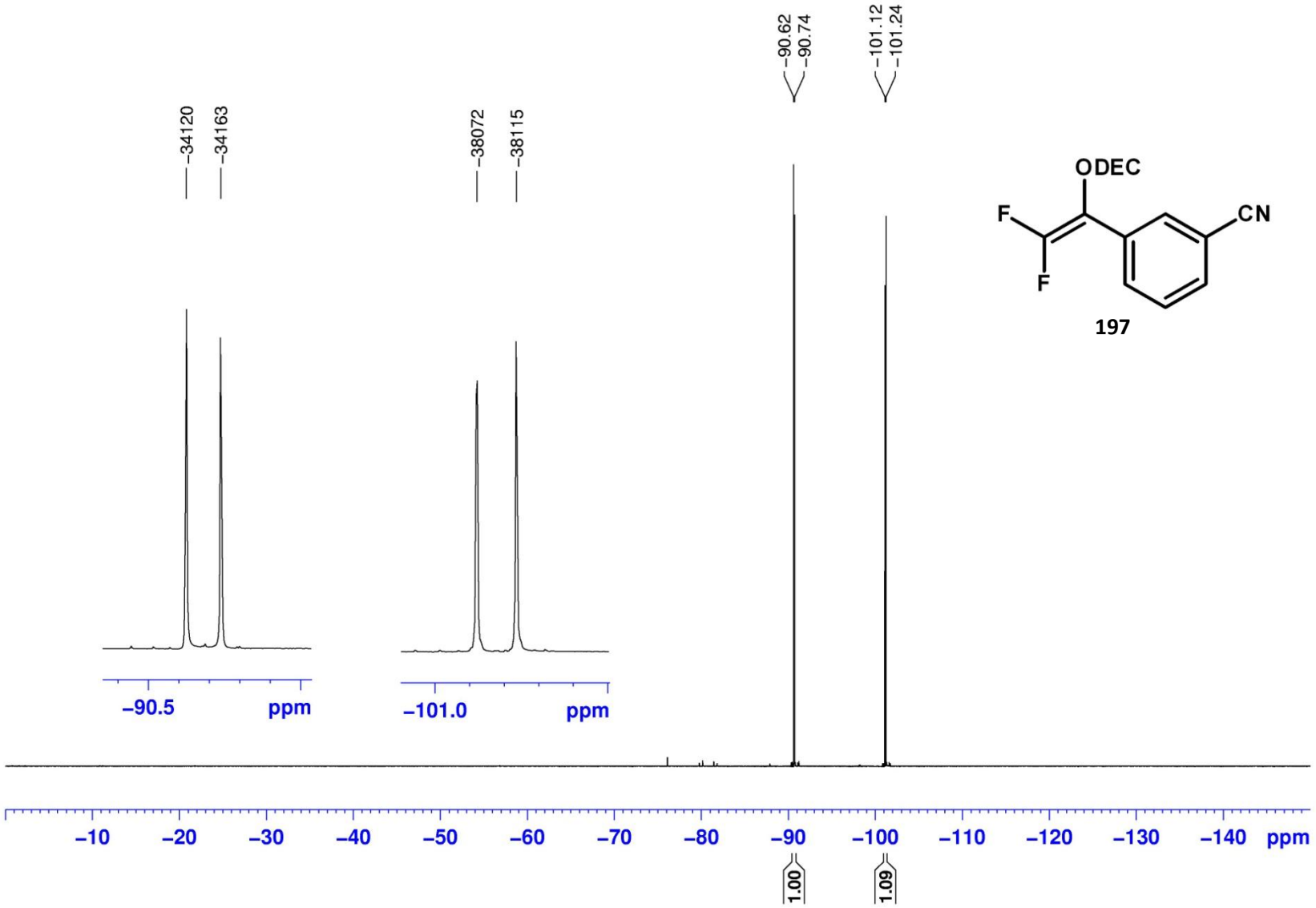
Appendix iii: ^{19}F NMR of **257**



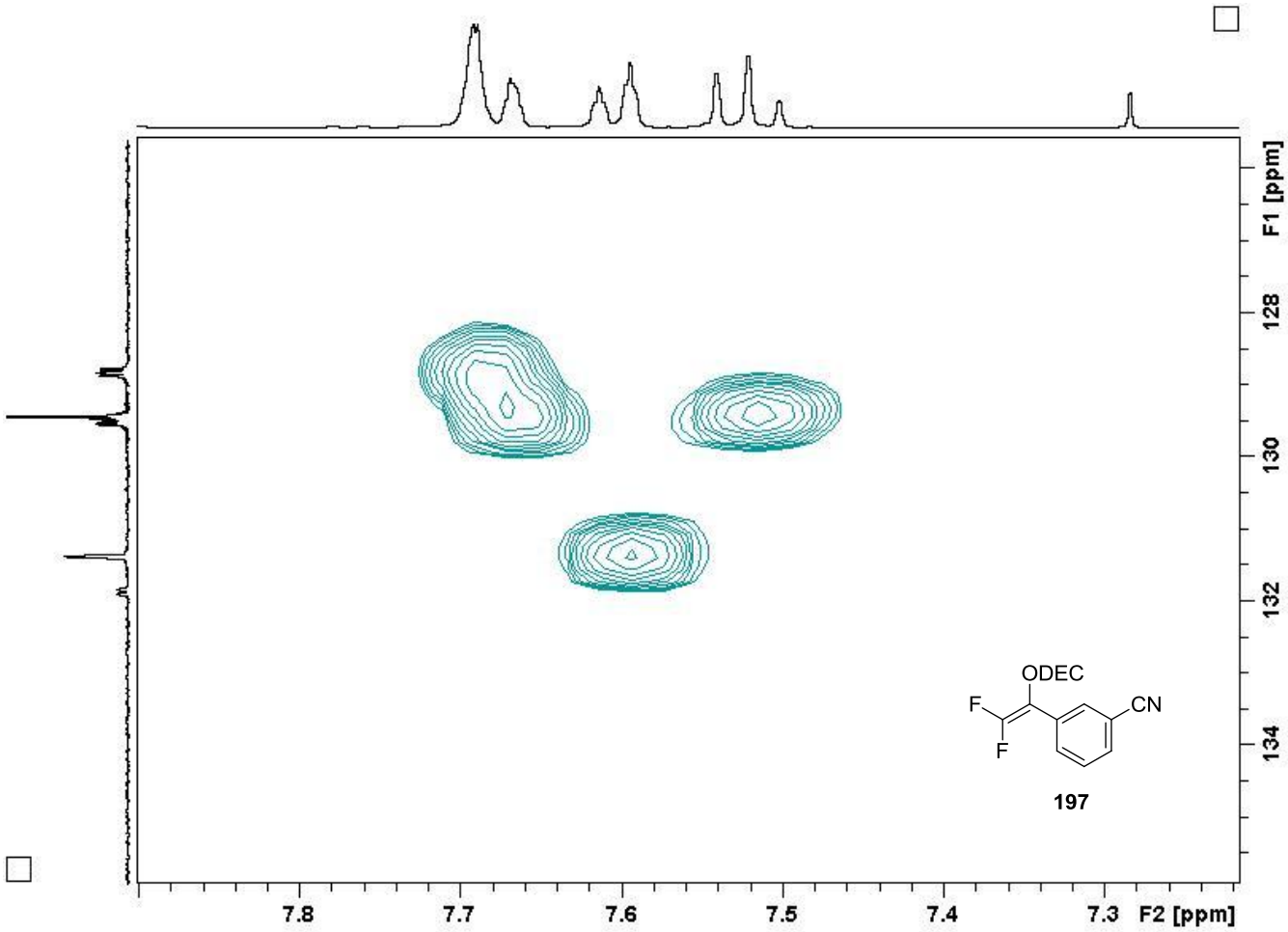
Appendix iv: ^{1}H NMR of **197**



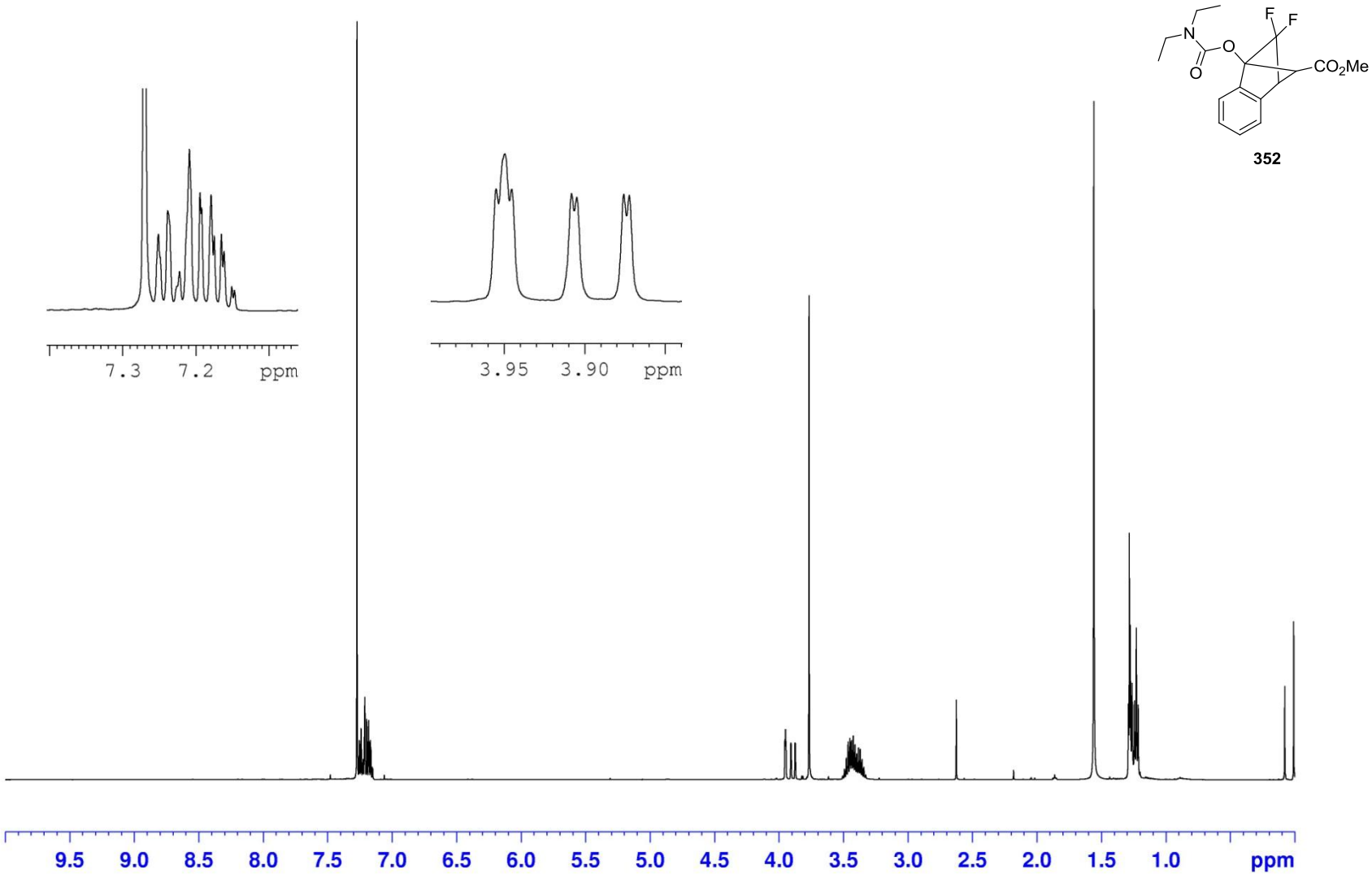
Appendix v: ^{13}C NMR of **197**



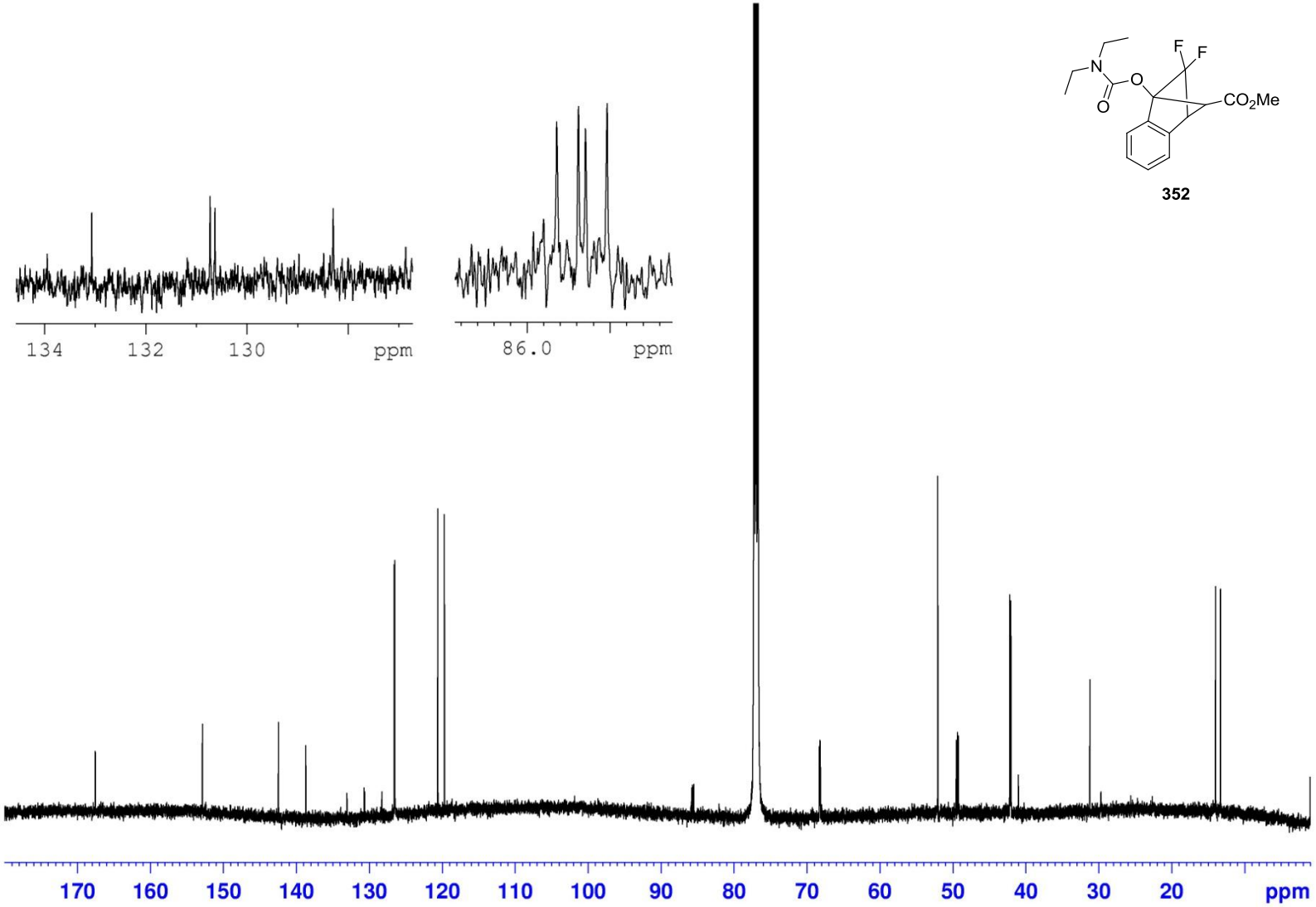
Appendix vi: ^{19}F NMR of **197**



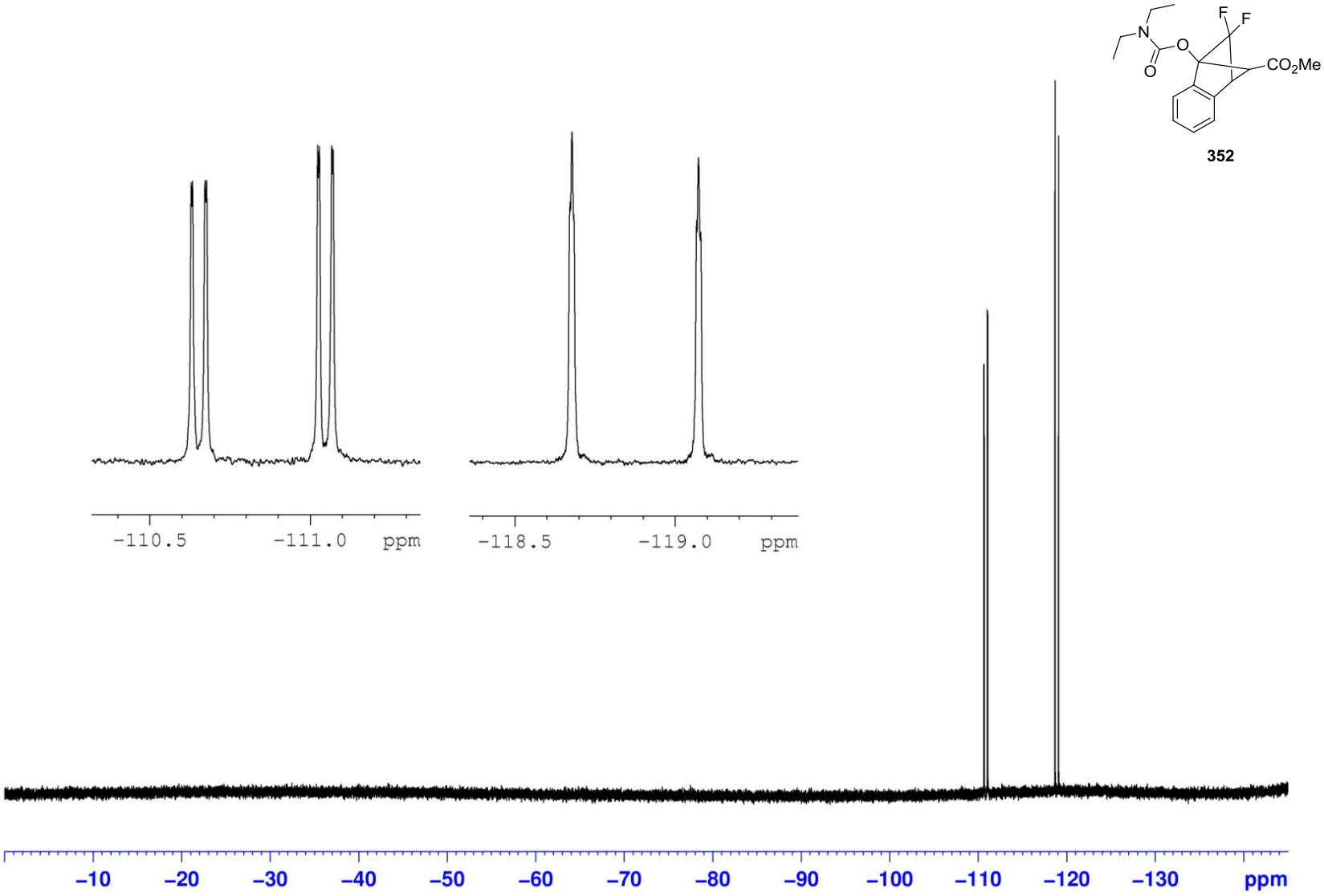
Appendix vii: Expanded HSQC of **197**



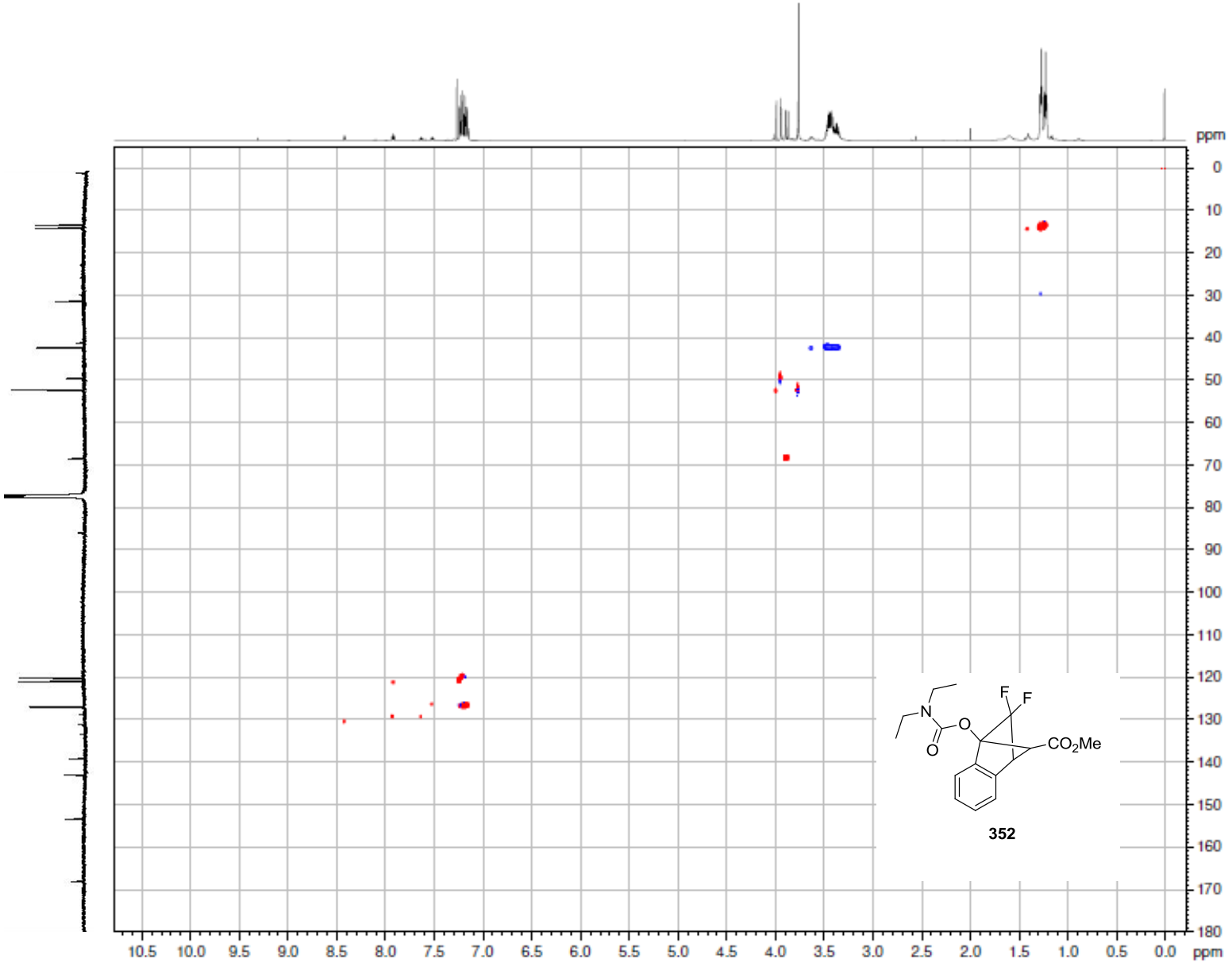
Appendix viii : ^{1}H NMR of **352**



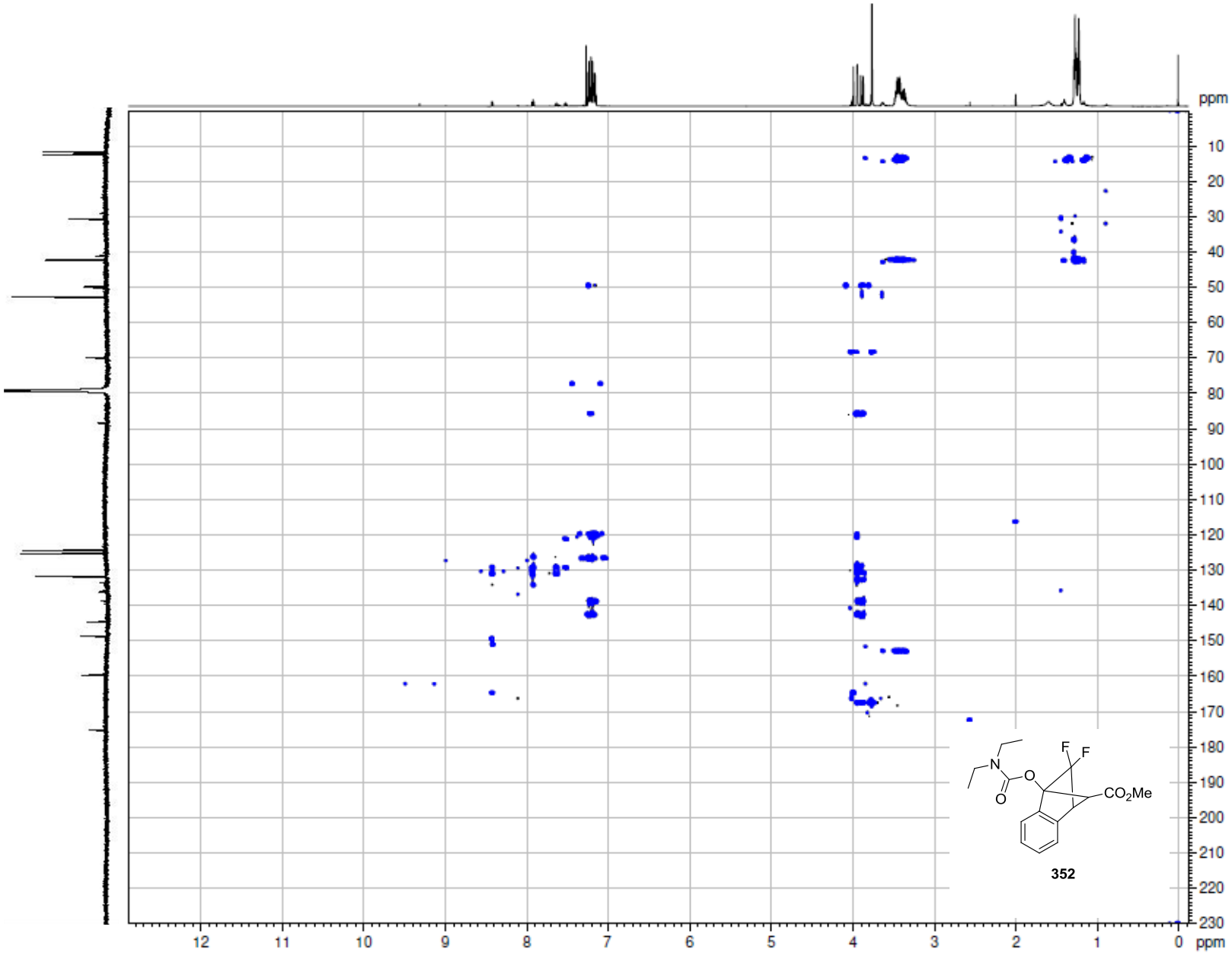
Appendix iX: ^{13}C NMR of **352**



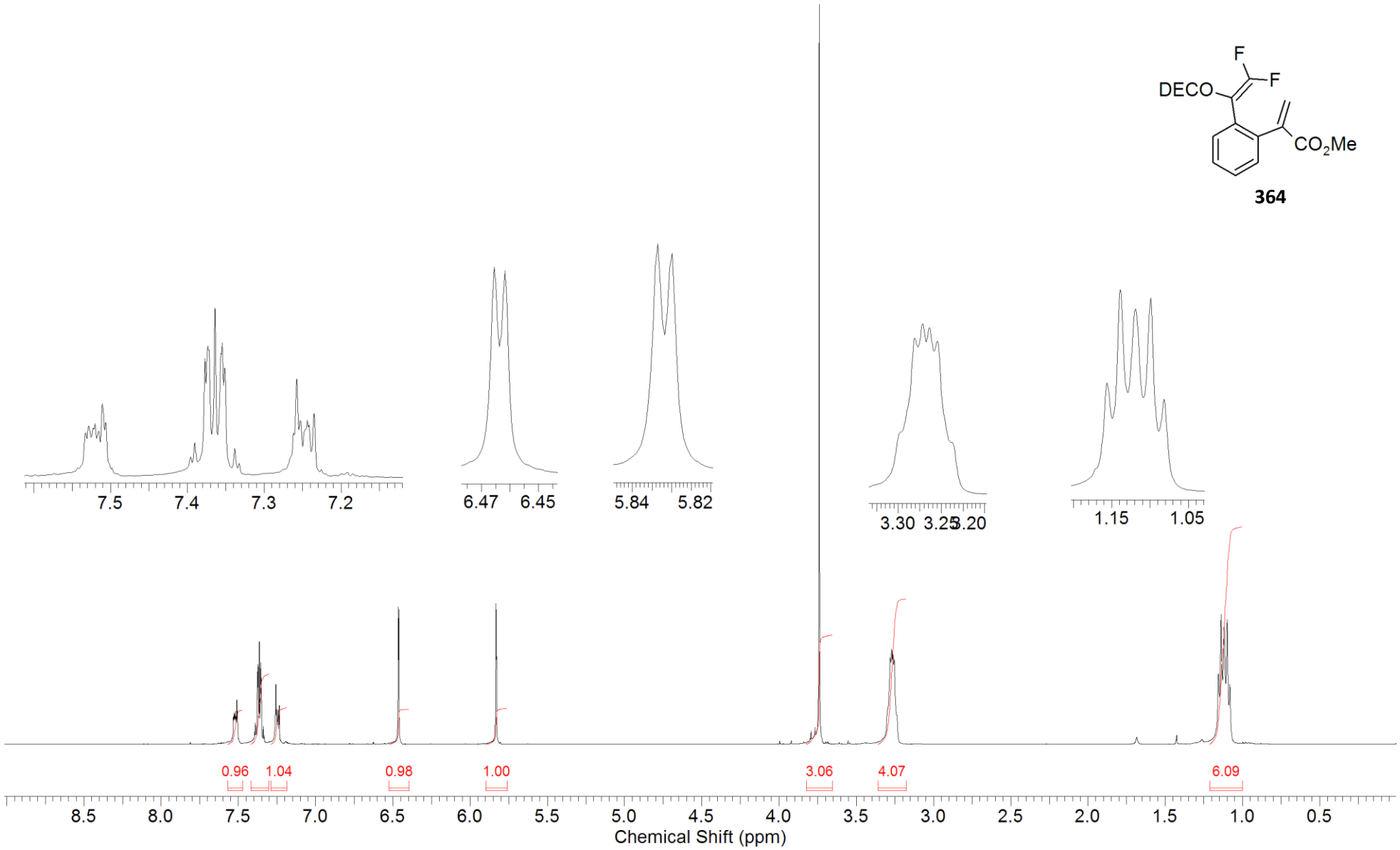
Appendix X: ^{19}F NMR of **352**



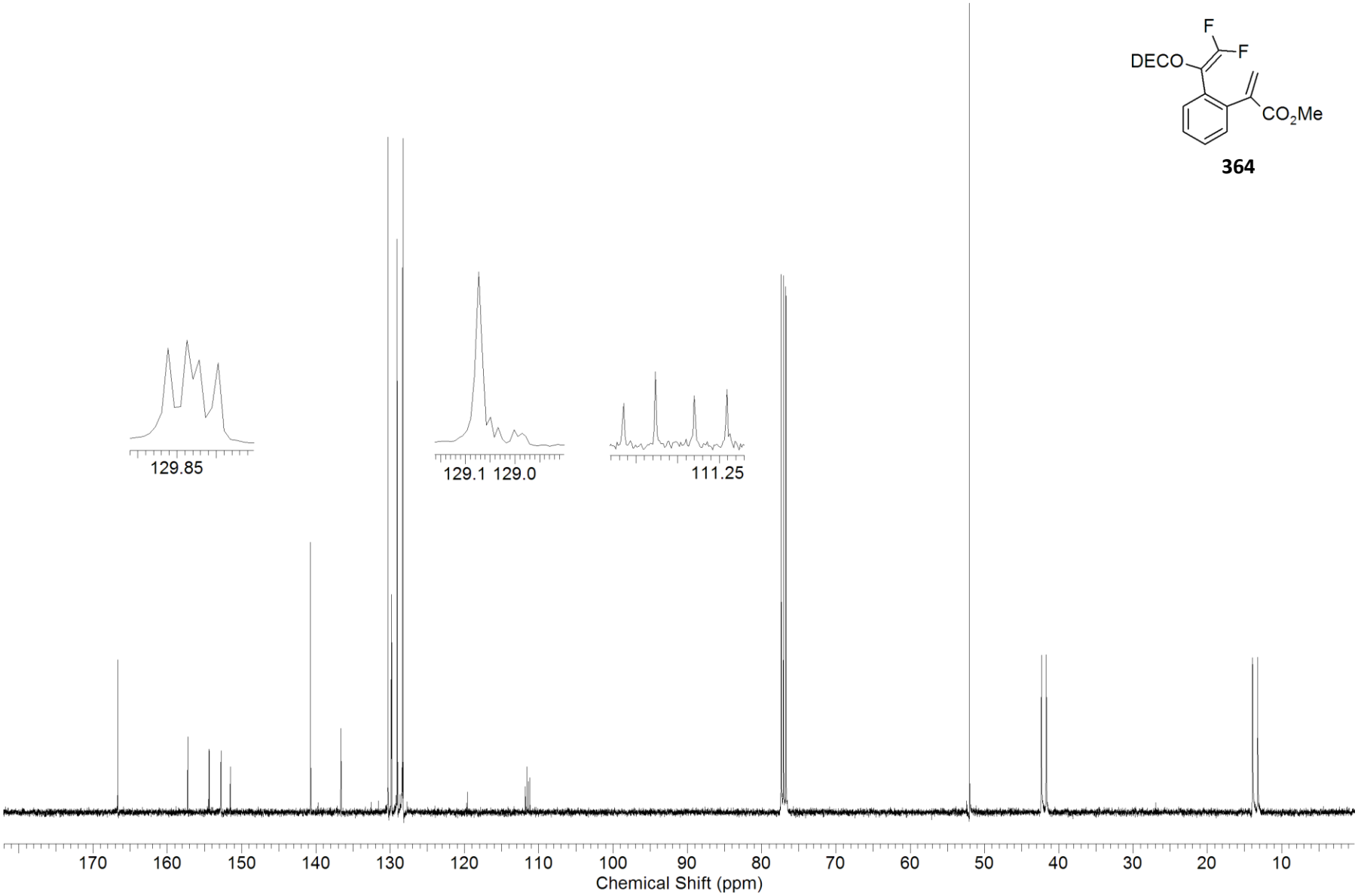
Appendix Xi: HSQC of **352**



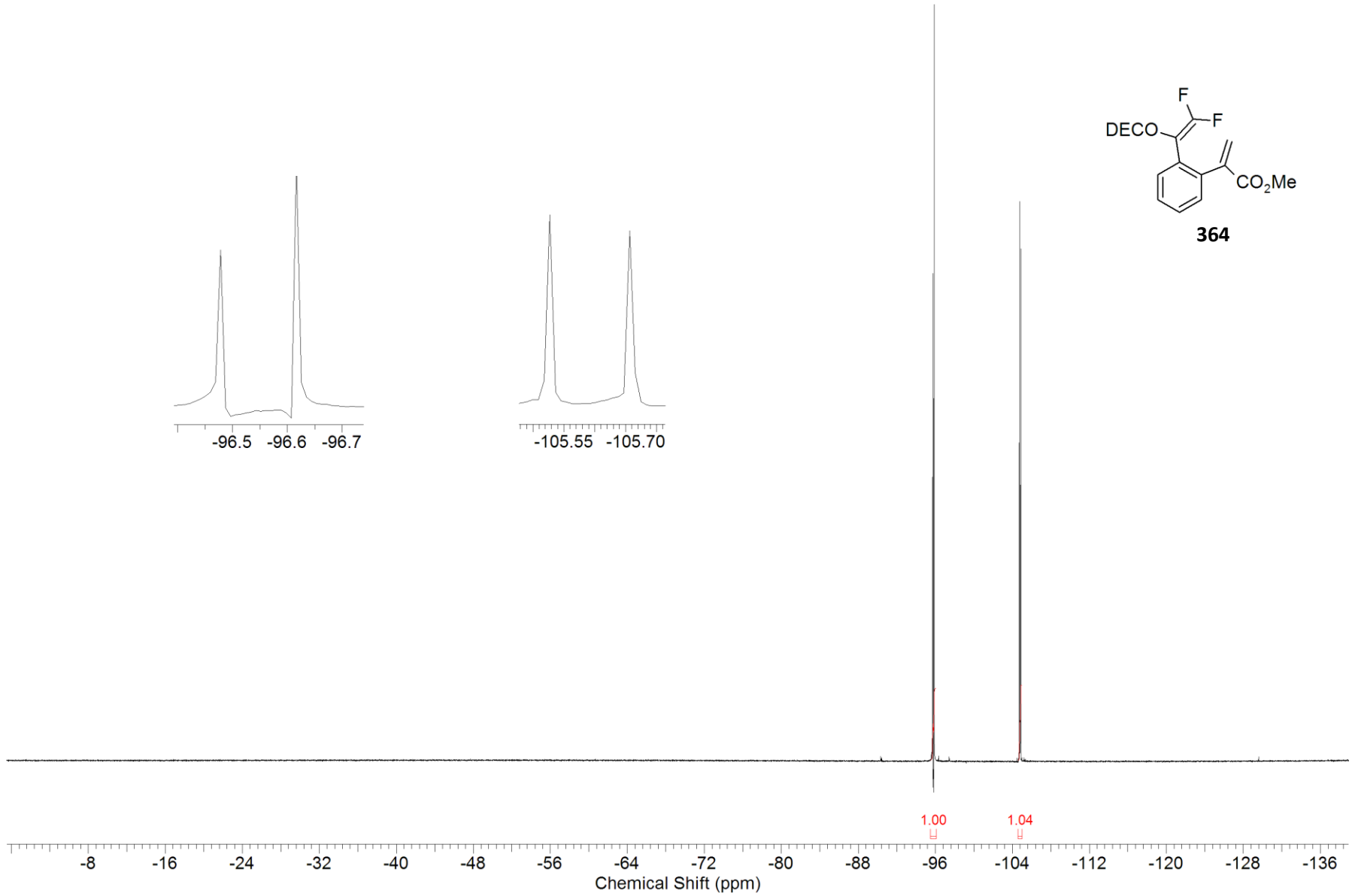
Appendix Xii: HMBC of **352**



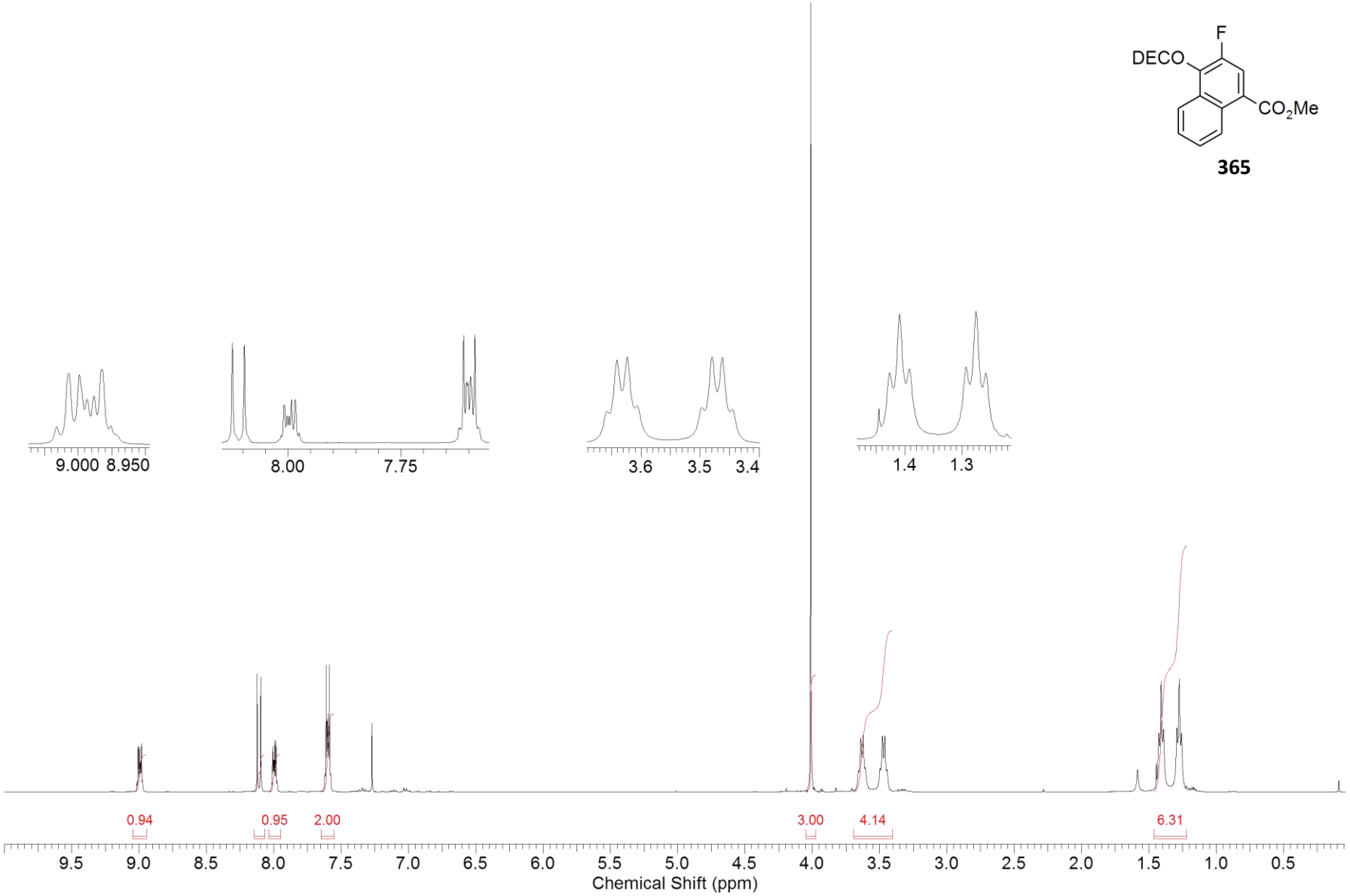
Appendix Xiii: ^{1}H NMR of **364**



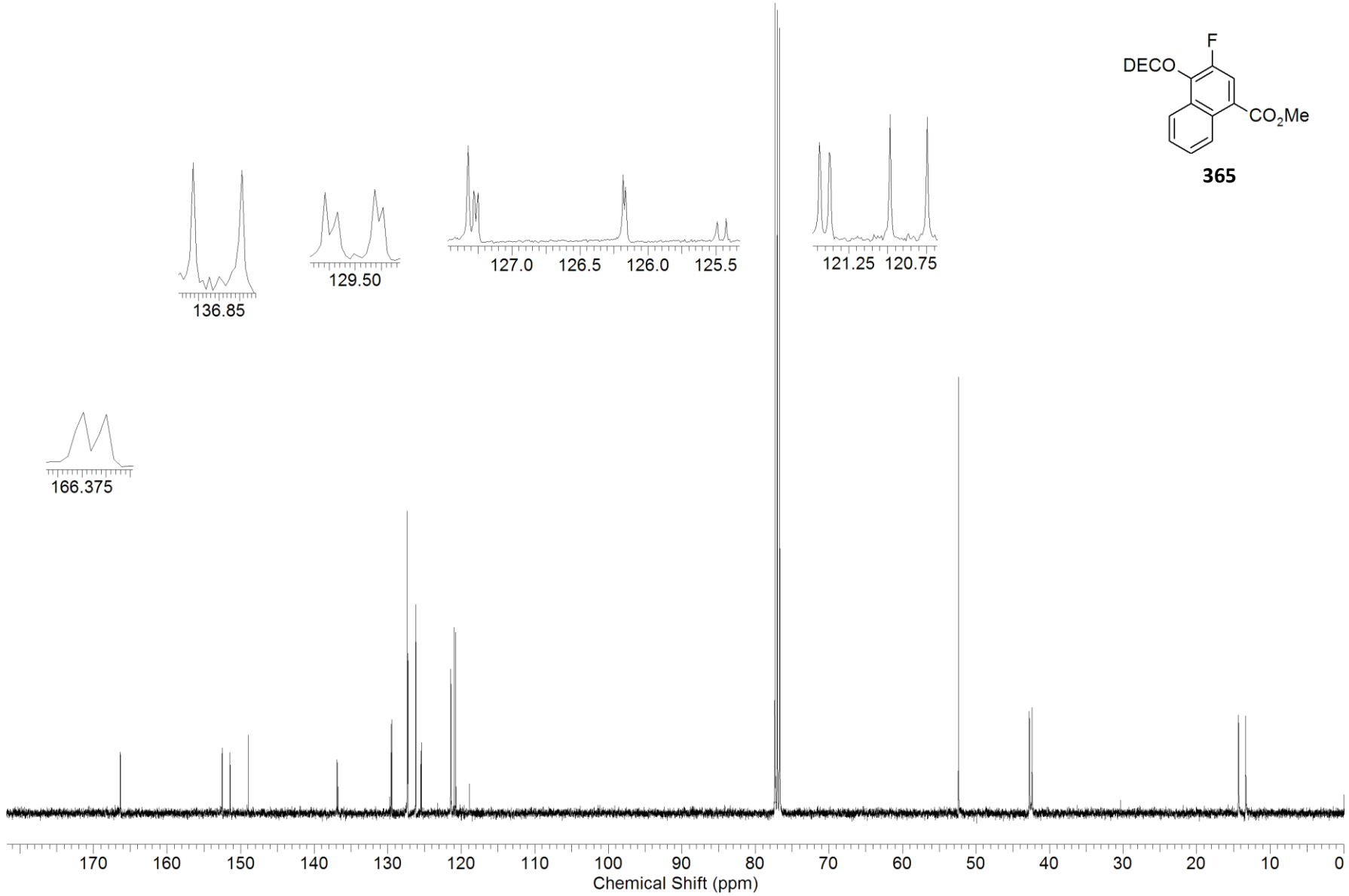
Appendix XiV: ^{13}C NMR of **364**



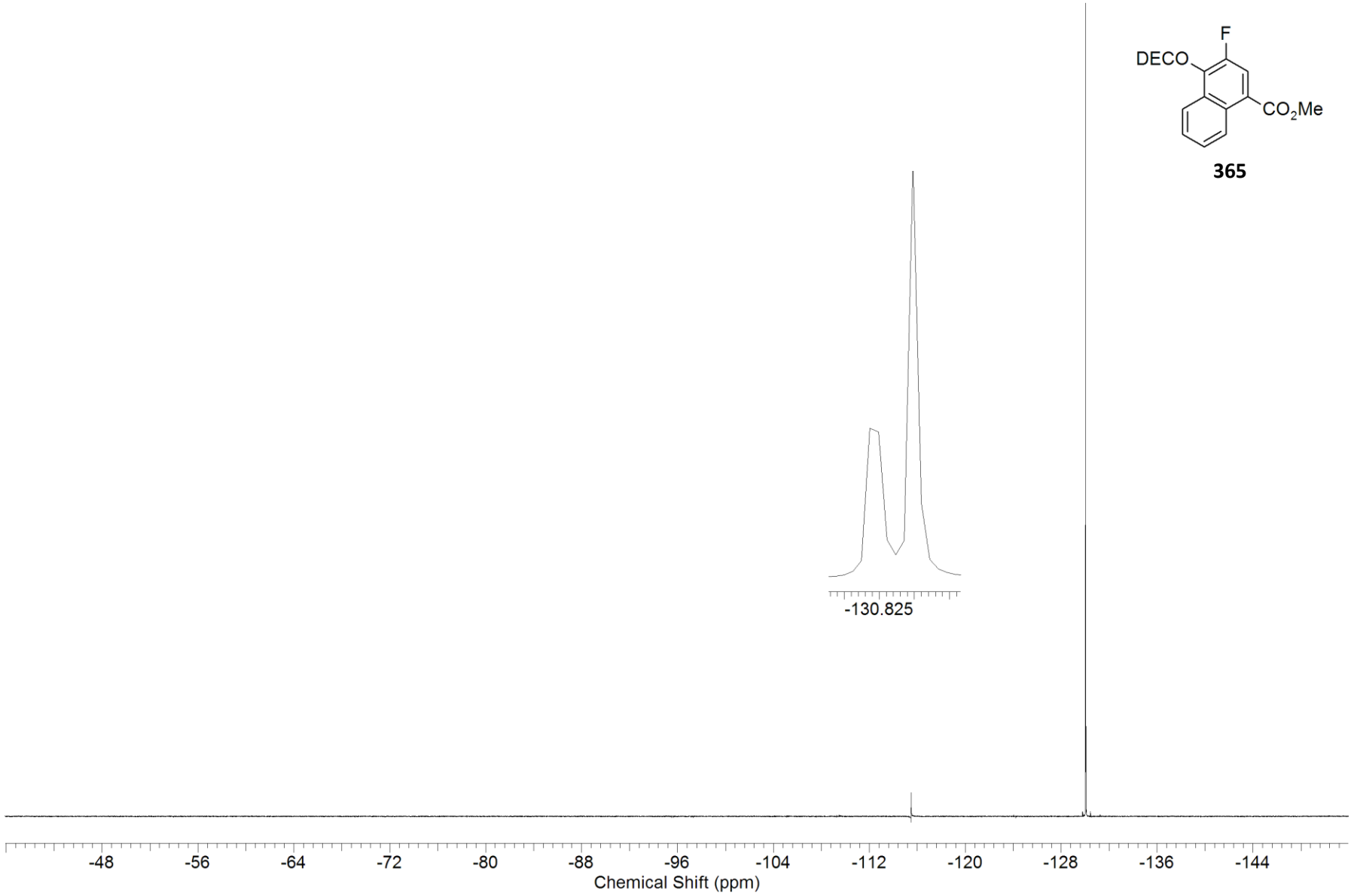
Appendix XV: ^{19}F NMR of **364**



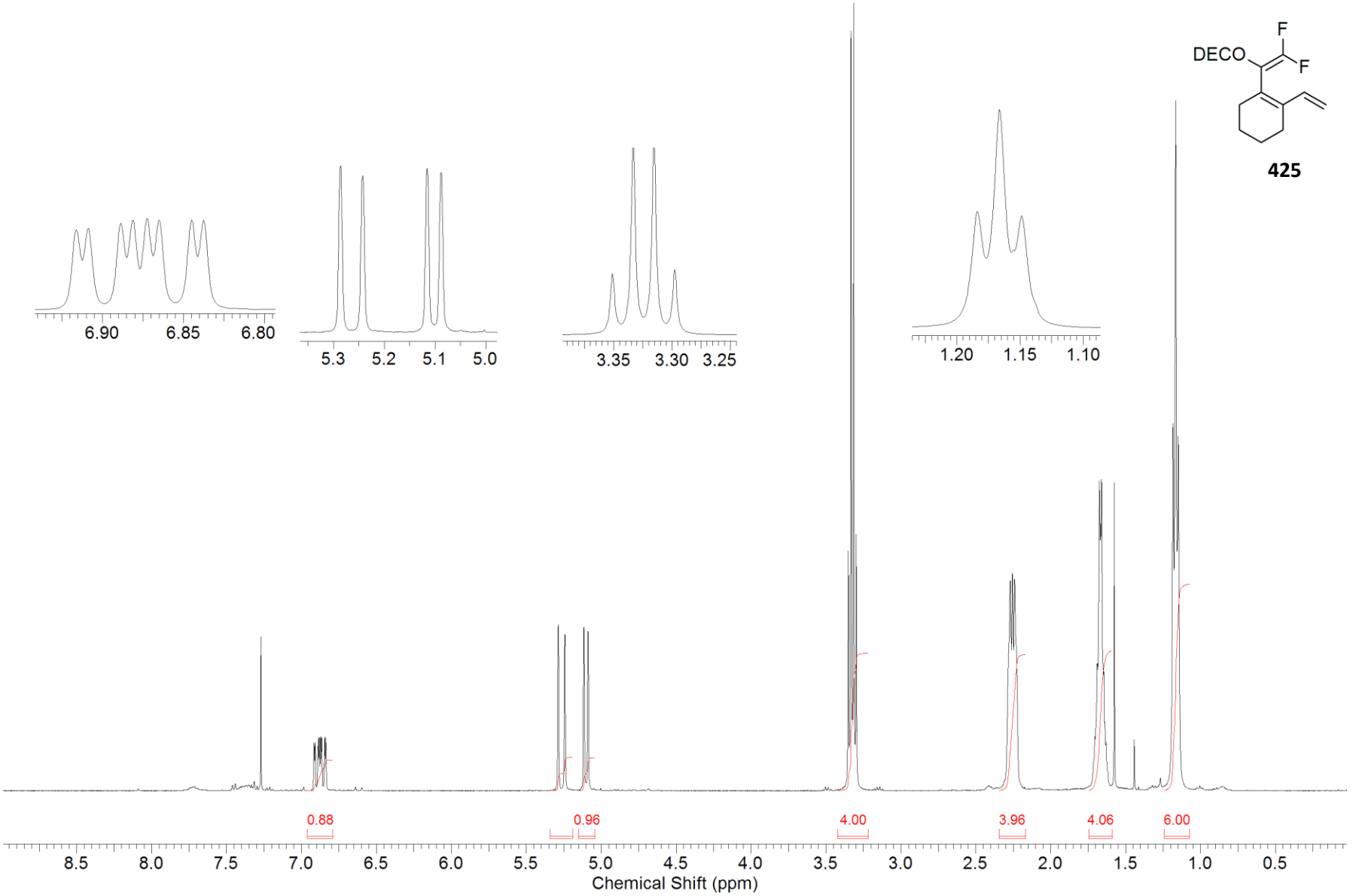
Appendix XVi: ^{1}H NMR of **365**



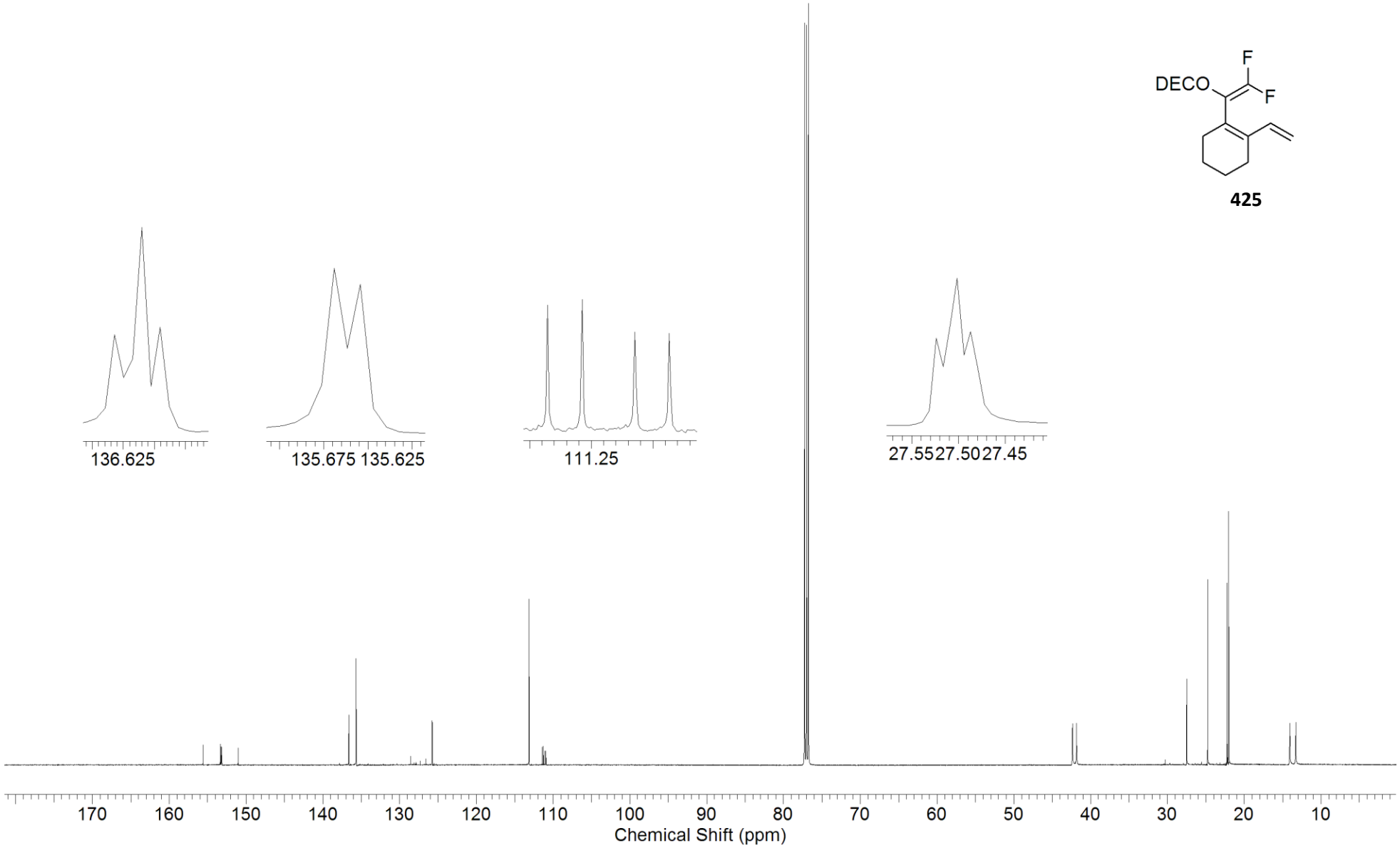
Appendix XVii: ^{13}C NMR of **365**



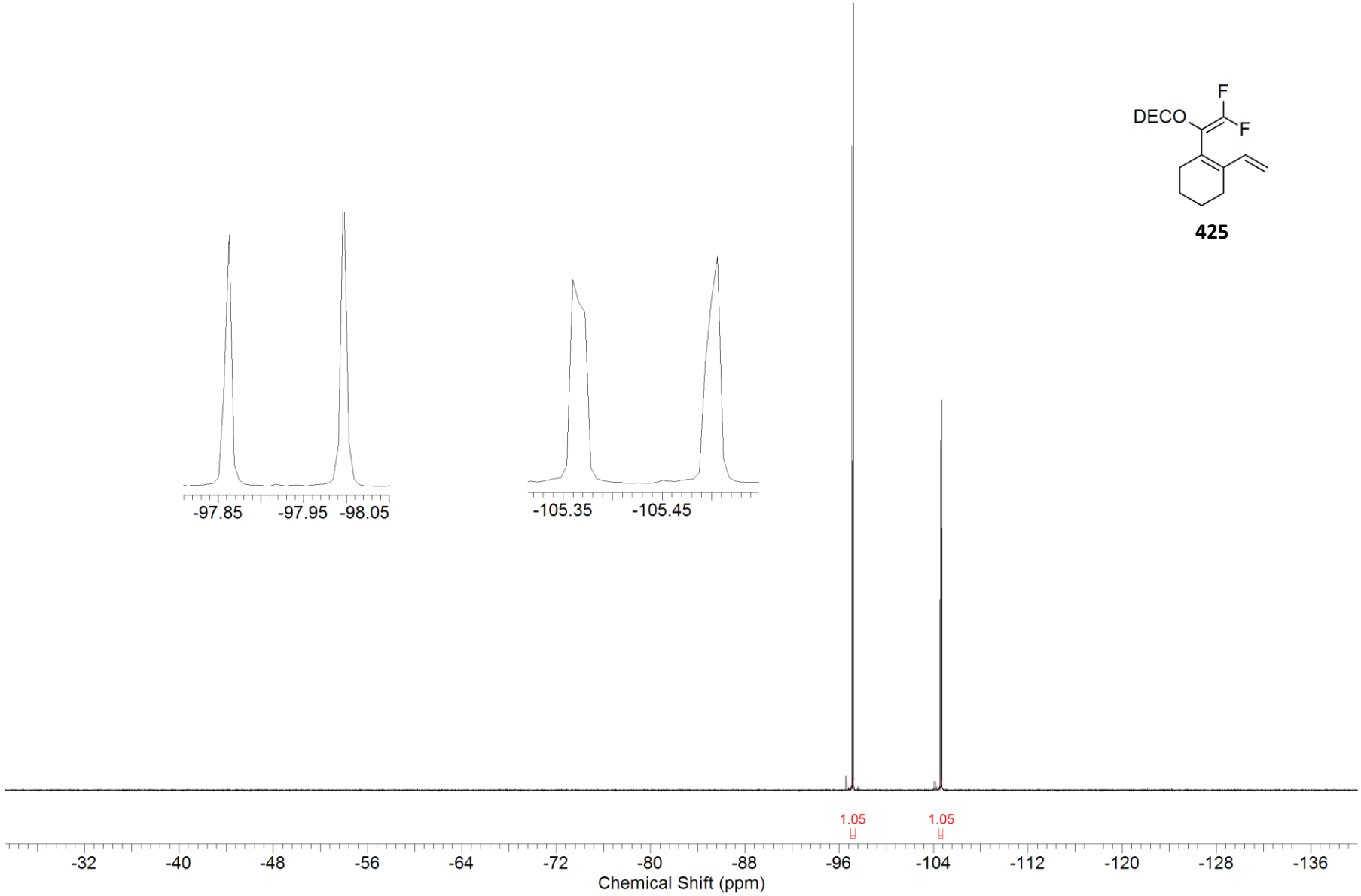
Appendix XViii: ^{19}F NMR of **365**



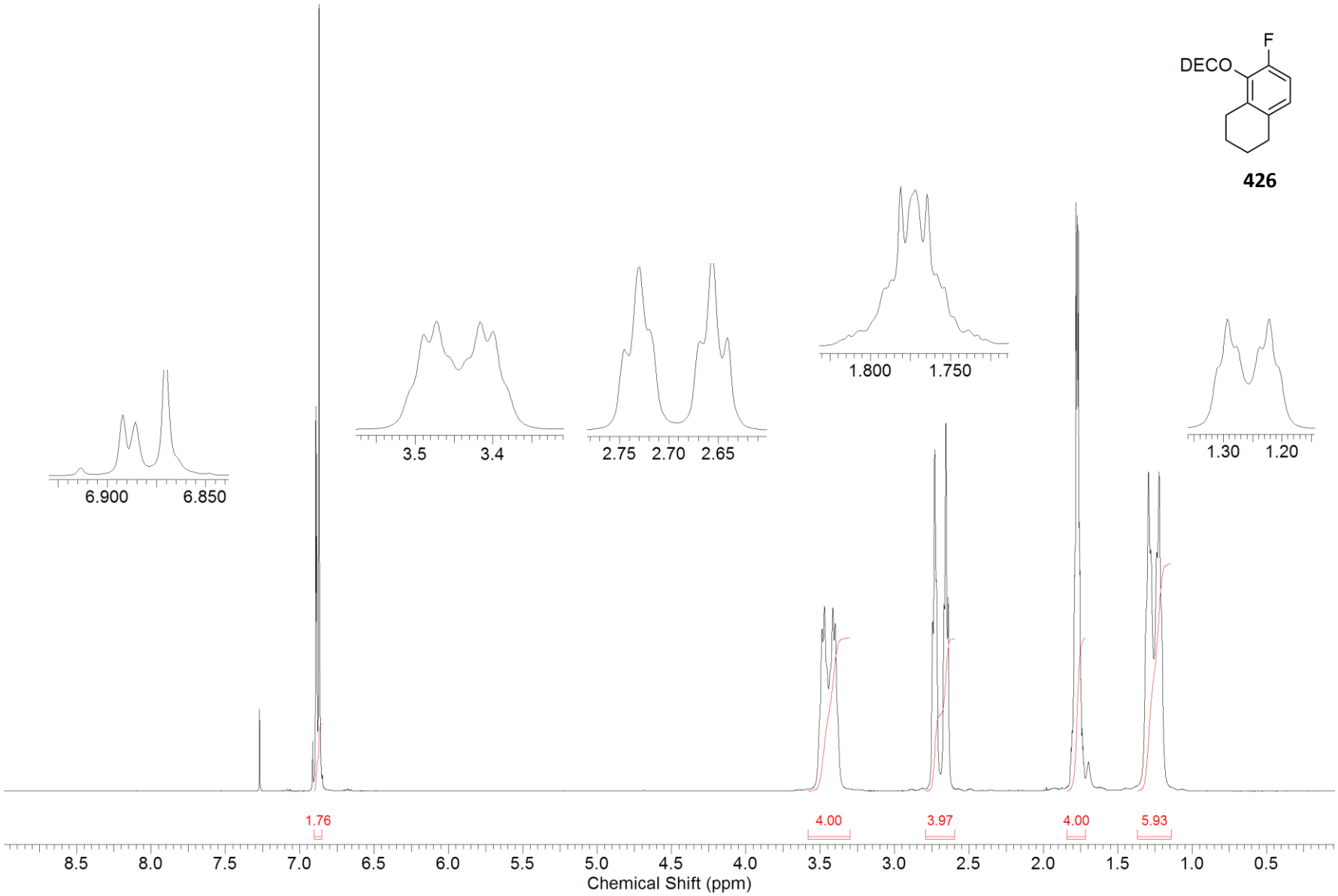
Appendix XiX: ^{1}H NMR of **425**



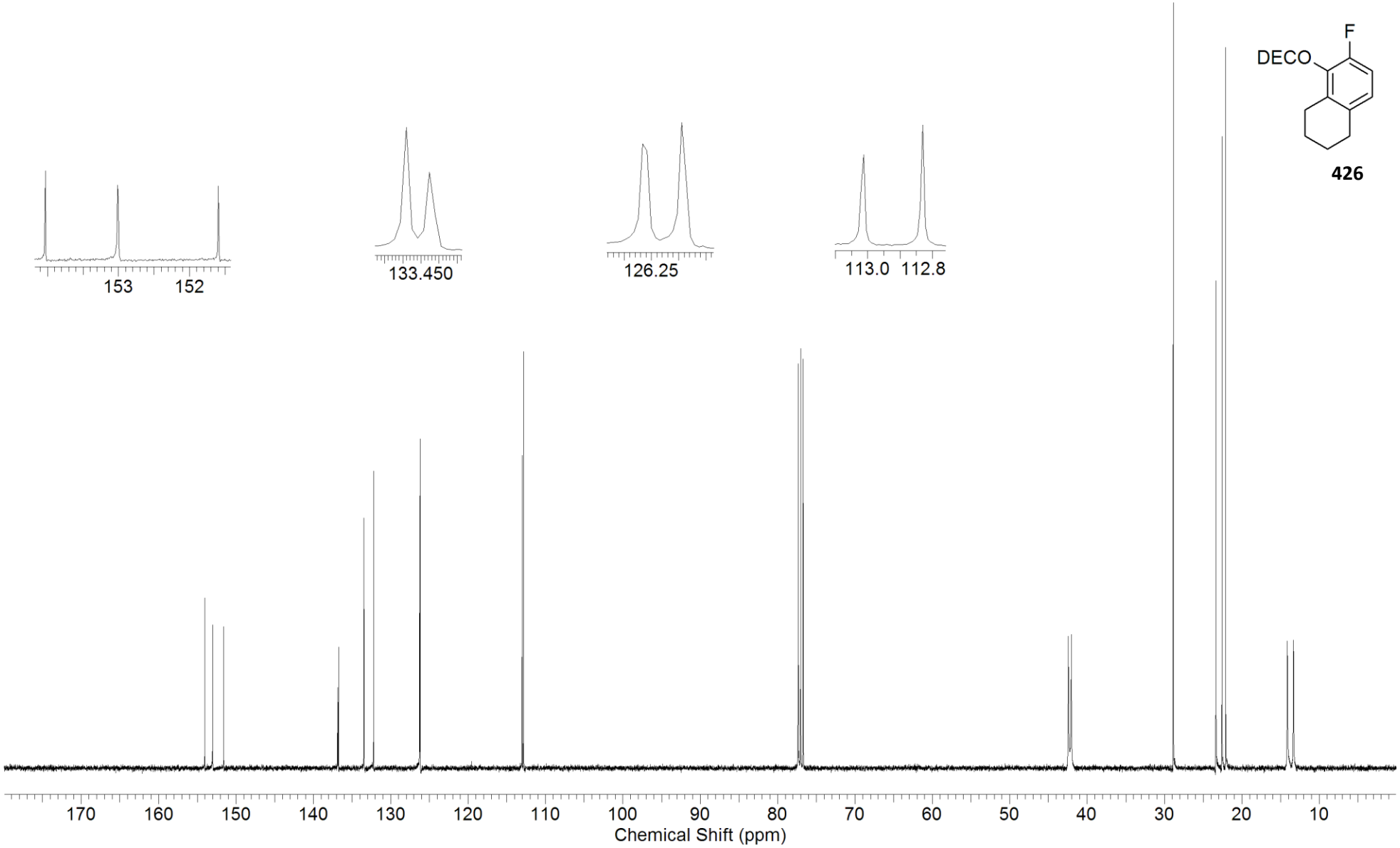
Appendix XX: ^{13}C NMR of **425**



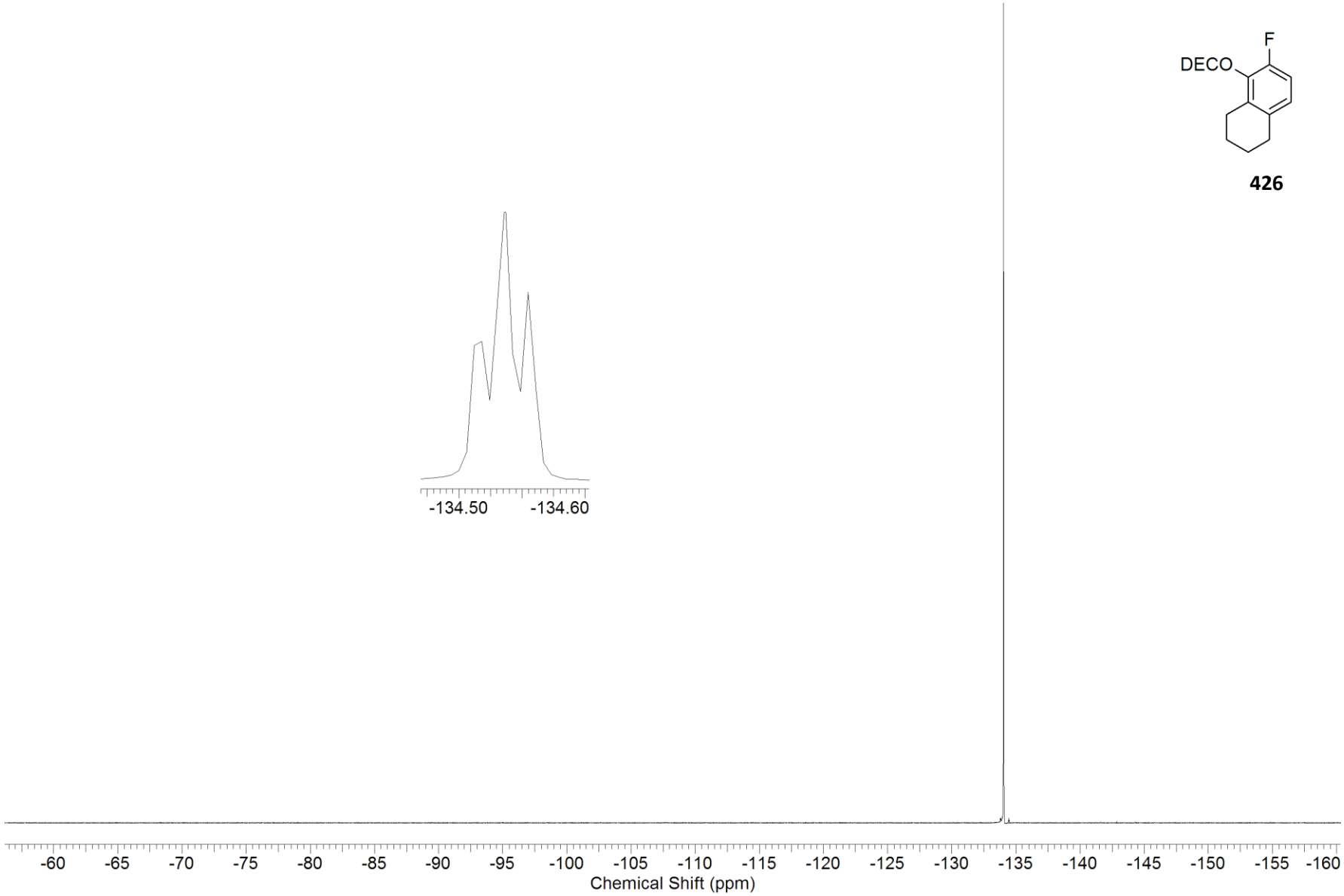
Appendix XXi: ^{19}F NMR of **425**



Appendix XXii: ^{1}H NMR of **426**



Appendix XXiii: ^{13}C NMR of **426**



Appendix XXiV: ^{19}F NMR of **426**