Generating Structural Diversity in $\alpha,\alpha$-Difluoromethyl Ketones

by

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2008 Addendum/Corrigenda

This document represents a re-publication of a 2002 doctoral thesis submitted to the Faculty of Science of the University of Birmingham.

Publications Update
As of April 2008, work from this thesis has been published as the following peer-reviewed articles:

Typographical and Grammatical Corrections
Several typographical and grammatical errors have been corrected, but in no way alter the meaning of the contents of the accepted thesis.

Nomenclature Errors/Omissions
The R/S configurations in the names for compounds 199, 200, 214 and 215 in the experimental section should be (4R,5S), not (2R,3S).

The correct names for compounds 202 and 203 in the experimental section using R/S terminology are, respectively:

Ethyl 2S-(N,N-diethylcarbamoyloxy)-3,3-difluoro-3-(tetrahydrofuran-2R'-yl)-propionate;

Ethyl 2R-(N,N-diethylcarbamoyloxy)-3,3-difluoro-3-(tetrahydrofuran-2R'-yl)-propionate
The systematic name using carbohydrate nomenclature for compound 201 in the experimental section is 2,3-O-isopropylidene-1-deoxy-1,1-difluoro-\(\beta\)-D-xylulo-furanose.

**Assignment of Anomeric Configuration in Sugars 155 and 173**

The assignments of the \(\alpha/\beta\) anomers for sugars 155 and 173 may well cause much confusion, especially in light of those used in the subsequent publications c) and d) referred to above. I was not involved in the preparation of these papers for publication.

I have subsequently found that there has been much confusion within the carbohydrate field itself as to the rules surrounding the assignment of anomeric configuration. This has been highlighted in the publication “On the Assignment of Anomeric Configuration”, Lee, Yuan; Lee, Reiko, *J. Chin. Chem. Soc.*, 1999, Vol. 46, No. 3, 283, which can be found on the internet as a downloadable pdf file.

The assignment of configuration in my original thesis was based upon the comparison of the configurations for the anomeric centre and the anomeric reference carbon atom, which is defined as the highest-numbered chiral carbon atom in the sugar. The resulting assignment to \(\alpha\) or \(\beta\) was based upon the definition of \(\alpha\) and \(\beta\) anomers as described in the textbook McMurry 4th edition Organic Chemistry. This procedure was correctly applied for sugar 155 but incorrectly for sugar 173.

However, according to the Chinese paper above, the assignment method described in McMurry is incorrect in any case. In addition, the use of R/S configurations has also been mentioned to be misleading, especially when some fluorinated sugars are used, as the presence of the fluorine atom can alter the R/S configuration when compared to its non-fluorinated analogue. This comment, however, deems that the use of the \(\alpha\) and \(\beta\) notation reflects a specific structural feature rather than simply a means of distinguishing the two anomers for the purpose of nomenclature, which is in contradiction both to logic and the recommended IUPAC protocol (see below).

It should also be said that, as highlighted in the Chinese paper, the assignment of the anomers should not be done by direct comparison to \(\alpha/\beta\)-glucose (i.e. \(\alpha\) means “down” at the anomeric centre) or by using the relative stereochemical relationships in Haworth representations (i.e. \(\alpha\) means trans), especially when this is further
complicated by issue of the chirality of the ring-closing hydroxyl-bearing carbon atom (i.e. ring-size).

The IUPAC recommendation of 1996, as described in “Nomenclature of Carbohydrates”, Pure & Appl. Chem., Vol. 68, No. 10, pp. 1919-2008, 1996, states that the assignment should be done on the basis of the relative configurations of the anomeric centre and the anomeric reference atom, when drawn in a Fischer projection: “in the α anomer, the exocyclic oxygen atom at the anomeric centre is formally cis, in the Fischer projection, to the oxygen attached to the anomeric reference atom; in the β anomer these oxygen atoms are formally trans”.

As a summary, the following table shows the results of applying different rules to the assignment of the anomers in sugars 155 and 173. The correct assignments, based upon the IUPAC recommendations, are highlighted in bold.

<table>
<thead>
<tr>
<th></th>
<th>155</th>
<th>173</th>
</tr>
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<tbody>
<tr>
<td>Thesis 2002</td>
<td>α</td>
<td>β</td>
</tr>
<tr>
<td>R/S McMurry</td>
<td>α</td>
<td>β</td>
</tr>
<tr>
<td>R/S</td>
<td>β</td>
<td>α</td>
</tr>
<tr>
<td>α-Glucose OH</td>
<td>α (down)</td>
<td>β (up)</td>
</tr>
<tr>
<td>α-Glucose (Haworth)</td>
<td>α (trans)</td>
<td>β (cis)</td>
</tr>
<tr>
<td>Fischer</td>
<td>β</td>
<td>α</td>
</tr>
</tbody>
</table>

As such, within this thesis, in reference to sugars 155 and 173, the α and β designations should be interchanged in all cases. This discrepancy does not alter in any way the conclusions regarding the absolute stereochemistry or anomeric ratios of the anomers as elucidated by NMR, but merely reflects a conflict in how to assign α or β to a particular absolute stereoisomer.
Stereo Representation for Sugars 155 and 173

There are several methods for depicting the stereochemistry of a carbohydrate. In this thesis, the Mills depiction was used as the work is not primarily associated with carbohydrate chemistry and hence carbohydrate nomenclature. However, in light of the issues above regarding assignment of anomeric configurations, the corresponding Haworth representations and Fischer projections for the two anomers of the two sugars are shown below for ease of comparison.

![Stereo representations of sugars 155 and 173]

Comments

Section 2.1.2

It should be said that, given the evidence for tin to copper transmetallation under the conditions used in these couplings, that the use of CuI may well be deleterious to the yields, due to homocoupling of any organocopper reagent and subsequent decomposition of the iodide or related palladium complexes.

Section 2.1.3

It is possible that the large amount of reduced product is as of a result of slow coupling and that the reaction was in fact incomplete. The use of the organozinc reagent in coupling was published in Arany et al., *Org. Biomol. Chem.*, 2004, 2, 455 – 465.
Section 2.2.3
In the section regarding attempts to trap the diol utilising boronate ester formation, it should have been said that the method was abandoned primarily because this procedure was only documented at that time for use with achiral ligands and not for use using Sharpless Asymmetric Dihydroxylation with the AD mixes.
In addition, it should have been stressed further that whilst the enantiomeric excess for asymmetric dihydroxylation was measured under standard conditions, the material used for the synthesis was produced under pH-controlled conditions. Thus there is an unproven assumption that the ee is not affected by pH control.

Finally, it should be mentioned that monodefluorination of alcohol 200 was attempted in an effort to synthesise sugar 169. The monofluoroalcohols were observed but the procedure was not investigated further due to a lack of time.

Section 2.2.4
It should be said that the O-C transfer of the MEM protecting group was not tested using trimethylsilyl triflate in the carbonate 214 due to the large amount of ketone 213 that was observed in the test reaction, associated with a high lability of the TMS enol ether.

Chapter 3
The discussion of future avenues for the work was insufficiently outlined in the conclusions and did not give justice to the success of the initial results within this thesis.
I have therefore taken this opportunity to expand upon these omissions in the original thesis for the benefit of interested readers.

Firstly, in the synthesis of α,α-difluoroketones, the initial success of using the corresponding difluorovinylzinc reagent provides promise for the omission of toxic tin compounds in the coupling protocol and simplification of purification of the products. Moreover, the initial successes in cleaving the MEM group under Mukaiyama-aldol
conditions suggest a method for generating larger structural diversity in these compounds.

Furthermore, monodefluorination of the coupling products provides the intriguing possibility of synthesising a novel fluorovinylstannane or fluorovinylzinc reagent which can further the scope of the diversity surrounding the CF$_2$ group after electrophilic cleavage with fluoride (Scheme A).

![Scheme A](image)

Some specific targets which utilise the methodology developed to date are shown in Figure A, representing either known compounds with use in drug discovery or novel compounds which are current targets.

The requisite difluoroaryl difluoroenol ether has already been synthesised and all that is required is the testing of alkylsulfenium chlorides as the electrophile. For the benzoxazole derivative, initial attempts at coupling with 2-iodobenzoxazole were met with failure. However, in hindsight, it would be more prudent to use 2-bromobenzoxazole as this should be more stable and coupling with brominated heterocycles was achieved in the original thesis.
In the synthesis of fluorinated sugars, there are many avenues which can be tested using the initial findings within this thesis.

As eluded to in the original thesis, the use of the difluorovinylzinc reagent should resolve the issues surrounding the synthesis of the key diene. The use of the para-methoxybenzyl group should also provide greater stability to the basic conditions used during dihydroxylation. A suitable protecting group strategy could deliver the key triol shown in **Scheme B**.

**Figure A**: Possible targets for coupling/cleavage methodology

**Scheme B**: Future delivery of pivotal triol using modified procedures
The development of a Mukaiyama-aldol procedure using this difluoroenol ether should open the way for the synthesis of a range of sugars. For instance, trapping with formaldehyde should provide a route to 2,2- and 5,5-difluorohexoses using appropriate protecting group strategies (Scheme C).

Scheme C: Route to difluorohexoses using key triol

Furthermore, coupling of the enol ether with acrolein provides a potential route to difluoroheptoses and difluorooctoses. Cleavage of the alkene using ozonolysis delivers an aldehyde which can be processed into 3,3- and 5,5-difluoroheptoses (Scheme D).
Scheme D: Possible route to difluoroheptoses

Dihydroxylation of the alkene unit provides a possible entry into difluoroheptoses after oxidation of the C-1 or C-8 primary alcohols using a suitable protecting group strategy (Scheme E).
A further development would involve the synthesis of 1,1-difluoro-1,3-butadiene bearing the methoxyethoxymethoxy protecting group. The synthesis of this diene would have to be attempted using the stannane as the corresponding iodide is unstable. The coupling would require the use of bromoethene and more reactive palladium catalysts would probably have to be employed. If this material can be synthesised then this could become a key building-block to pentoses, hexoses and heptoses.

Dihydroxylation of the alkene would be difficult but the observation of diol with the analogous DEC diene suggests that reaction is not impossible and the development of the improved pH-controlled protocol may be able to deliver the required diol. If so, then this diol could deliver a range of sugars.

Firstly, protection and cleavage of the enol ether with formaldehyde allows a facile synthesis of difluoropentoses (Scheme F).
Scheme F: Possible synthesis of difluoropentoses from a 1,1-difluoro-1,3-butadiene derivative

In addition, the application of the same strategies as proposed before, using acrolein as the aldol partner could provide a route to difluorohexoses and difluoroheptoses (Scheme G).

K
As can be seen, the results in this thesis provide encouraging results that a strategy has been found which could deliver powerful methods to the synthesis of a large range of difluoro- pentoses, hexoses, heptoses and octoses.

*In toto*, these strategies could deliver 2,2-, 3,3-, 4,4-, or 5,5-difluorohexoses in a concise manner from trifluoroethanol with variable control of the absolute stereochemistry of the sugars.

April 2008, Dr Jeremy J Fullbrook
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B15 2TT
UK

December 2002
Abstract

This thesis describes attempts to use palladium-catalysed cross-coupling methodology in the synthesis of \( \alpha,\alpha \)-difluoroketones contained within a diverse array of molecular motifs.  

1-(\(N,N\)-Diethylcarbamoyloxy)-2,2-difluoro-1-(tributylstannyl)ethene undergoes Stille cross coupling with a variety of aryl, heteroaryl, vinyl and allyl organic electrophiles. Conditions, which promote in situ transmetallation to a more reactive copper intermediate, were essential for obtaining significant quantities of product. 1-(\(N,N\)-Diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene also underwent coupling with a range of aryl, heteroaryl and vinyl stannanes. Due to the difficulties with cleavage of this protecting group, the synthesis and potential application of an \(N\)-ethyl-\(N\)-(2-methylallyl)carbamate has been studied. A 2-methoxyethoxymethyl (MEM) protecting group strategy proved very successful for the synthesis of a range of difluoromethyl aryl ketones. Two consecutive coupling reactions were possible from a difluoroeno\(l\) stannane, in which coupling of initial styrene products bearing a triflate group afforded a range of biarylethenes. Cleavage occurred under mild electrophilic conditions with protic, halogen, sulfur and carbon electrophiles. Diene products have been tested for reactivity in Sharpless Asymmetric Dihydroxylation. A 1,4-diene has been converted through to a fluorinated analogue of a dideoxyxylulose. A 1,3-diene has been successfully converted through to a difluorodeoxyxylulose of current interest. Key points involve regioselective and highly enantioselective dihydroxylation of the non-fluorinated olefin. Application of a special protecting group for the allylic alcohol was essential, as was control of the pH of the reaction medium.
Acknowledgments

I would like to thank Professor Jonathan Percy and Dr Liam Cox for supervision and guidance during the course of this PhD. I would also like to thank Dr Gareth Deboos of Avecia Ltd for contributions to this project as well as Avecia for support.

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I am grateful to the EPSRC and Avecia Ltd for funding this research and to the University of Birmingham for funding my third year as well as providing the necessary laboratory and sporting facilities.

I would also like to thank all the past members of the JMP research group for their academic and social support. Thanks also go to the current members at Leicester. A big thankyou must also go to the members of the LRC group for putting up with me for the last year.

Lastly, but certainly not least, I wish to thank all friends and family who have helped me over the entire course of my education. Your contributions, however inapparent, have been vital to my success. Special thanks go to Mom and Dad.
### Abbreviations

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<th>Abbreviation</th>
<th>Full Form</th>
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<td>Abs.</td>
<td>absolute</td>
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AD</td>
<td>asymmetric dihydroxylation</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>All</td>
<td>allyl</td>
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<tr>
<td>Ar</td>
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<td>aq.</td>
<td>aqueous</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
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<td>BOC</td>
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<td>BuLi</td>
<td>n-butyllithium</td>
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<tr>
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<td>ca.</td>
<td>circa, approximately</td>
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<tr>
<td>cat.</td>
<td>catalytic</td>
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<td>$N$-(tert-butylidiphenylsilyloxyethyl)-$N$-isopropylcarbamoyl</td>
</tr>
<tr>
<td>CDI</td>
<td>1,1-carbonyldiimidazole</td>
</tr>
<tr>
<td>CoA</td>
<td>coenzyme A</td>
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<td>Conc.</td>
<td>concentrated</td>
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<td>COSY</td>
<td>Correlation Spectroscopy</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
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d  
   days
DAC  
   \(N,N\)-diallylcarbamoyl
DAST  
   diethylaminosulfur trifluoride
dba  
   \(trans,trans\)-dibenzylideneacetone
DBU  
   1,8-diazabicyclo[4.3.0]undec-7-ene
DCM  
   dichloromethane, methylene chloride
DEC  
   \(N,N\)-diethylcarbamoyl
DHQ  
   dihydroquinine
DHQD  
   dihydroquinidine
Dibal-H  
   diisobutylaluminium hydride
DMAP  
   4-(\(N,N\)-dimethylamino)pyridine
DME  
   1,2-dimethoxyethane, ethylene glycol dimethyl ether
DMF  
   \(N,N\)-dimethylformamide
DMS  
   dimethyl sulfide
DMSO  
   dimethyl sulfoxide
dppb  
   1,4-\(bis\)(diphenylphosphino)butane
dppe  
   1,2-\(bis\)(diphenylphosphino)ethane
dppf  
   1,1\(^\prime\)-\(bis\)(diphenylphosphino)ferrocene
dppp  
   1,3-\(bis\)(diphenylphosphino)propane
E.coli  
   \textit{Escherichia coli}
eenantiomeric excess
Emac  
   \(N\)-ethyl-\(N\)-(2-methylallyl)carbamoyl
EPR  
   Electron Paramagnetic Resonance
Eq.  
   equivalents
er  enantiomeric ratio
ES  electrospray
Et  n-ethyl
FDA  Food and Drug Administration (US)
1-F-DX  1-deoxy-1-fluoro-D-xylulose
1,1-F_2-DX  1-deoxy-1,1-difluoro-D-xylulose
G  group
GC  gas chromatography
GOESY  Gradient Nuclear Overhauser Effect Spectroscopy
h  hours
Hetaryl  Heteroaryl
HIV  Human Immunodeficiency Virus
HMBC  Homonuclear Multiple Bond Correlation
HMG  hydroxymethylglutaryl
HMPA  hexamethylphosphoramide
HPLC  High Performance Liquid Chromatography
hrs  hours
HSQC  Heteronuclear Single Quantum Correlation
HWE  Horner-Wadsworth-Emmons
Hz  hertz
iPr  isopropyl
Im  imidazolyl
IUPAC  International Union of Pure and Applied Chemistry
K  thousand
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<td>KHMDS</td>
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<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
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<tr>
<td>M</td>
<td>molar</td>
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<td>MAC</td>
<td>N-methyl-N-allylcarbamoyl</td>
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<tr>
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<td>MS</td>
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<td>MTPA</td>
<td>2-methoxy-2-trifluoromethyl-2-phenylacetyl</td>
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<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
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<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
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<td>NMP</td>
<td>1-methyl-2-pyrrolidinone</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-Nucleoside Reverse Transcriptase Inhibitor</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
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<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>pH</td>
<td>-log [H⁺]</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<td>phenyl</td>
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<tr>
<td>PHAL</td>
<td>phthalazine</td>
</tr>
<tr>
<td>pMBz</td>
<td>para-methoxybenzoyl</td>
</tr>
<tr>
<td>pNBz</td>
<td>para-nitrobenzoyl</td>
</tr>
<tr>
<td>PNP</td>
<td>pyridoxine phosphate</td>
</tr>
<tr>
<td>pTSA</td>
<td>para-toluenesulfonic acid</td>
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<tr>
<td>ppm</td>
<td>parts per million</td>
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<tr>
<td>pyr.</td>
<td>pyridine</td>
</tr>
<tr>
<td>R</td>
<td>undefined group</td>
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<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>perfluoroalkyl group</td>
</tr>
<tr>
<td>Red-Al&lt;sup&gt;®&lt;/sup&gt;</td>
<td>sodium bis(2-methoxyethoxy)aluminium hydride</td>
</tr>
<tr>
<td>Ra-Ni</td>
<td>Raney nickel</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>SEM</td>
<td>2-(trimethylsilyl)ethoxymethyl</td>
</tr>
<tr>
<td>S&lt;sub&gt;N&lt;/sub&gt;2</td>
<td>bimolecular nucleophilic substitution</td>
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<td>S&lt;sub&gt;RN&lt;/sub&gt;1</td>
<td>unimolecular nucleophilic radical substitution</td>
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<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>half-life</td>
</tr>
<tr>
<td>TA</td>
<td>transacylation</td>
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<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
<tr>
<td>tBu (t'Bu, t'Bu)</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>TC</td>
<td>2-thiophenecarboxylate</td>
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TES  triethylsilyl
Tf   trifluoromethanesulfonyl
TFA  trifluoroacetic acid
TFP  trifurylphosphine
THF  tetrahydrofuran
THP  tetrahydropyranyl
TIPS triisopropylsilyl
TLC  thin layer chromatography
TMEDA $N,N,N',N'$-tetramethylethylenediamine
TMNO trimethylamine $N$-oxide
TMS  trimethylsilyl
TOF  time of flight
Ts   $para$-toluenesulfonyl
TS   transition state
UV   ultraviolet
vide ante see before
vide infra see below
vide supra see above
Z    benzyloxycarbonyl (Cbz)
μmol micromole(s)
# Contents

Abstract

Acknowledgments

Abbreviations

1.0 Introduction 1

1.1 Rationale for fluorine atom introduction 1

1.2 Current methods for the synthesis of fluorinated motifs 3

1.2.1 Aryl difluoromethyl ketones 4

1.2.2 Fluorinated carbohydrates 18

   Synthesis using fluorination methodology 20

   Nucleophilic fluorination 20

   Electrophilic fluorination 24

   Building-block methodology 27

1.3 Fluorovinyl organometallics 30

   Synthesis and application of fluorovinyl organometallics 31

1.4 Palladium-catalysed coupling reactions 37

   Introduction 37

   Co-catalytic copper in Stille coupling 40

   Application of transition-metal-mediated cross-coupling using fluorinated organometallics 41

1.5 Relevant recent advances in the use of trifluoroethanol as a building-block 48

1.6 Objectives 51
2.0 Results and Discussion

2.1 Palladium-catalysed Couplings

2.1.1 Coupling of 1-(N,N-diethylcarbamoyloxy)-2,2-difluoro-1-(tributylstannyl)ethene 53

Synthesis of stannane 53
Optimisation of couplings 54
Role of copper(I) iodide 60
Scope of coupling process 62

2.1.2 Coupling of 1-(N,N-diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene 66

Synthesis of difluoriodoalkene 66
Scope of coupling process 67

2.1.3 Potential for Negishi couplings for styrene synthesis 73

2.1.4 Cleavage of the N,N-diethylcarbamoyl protecting group 74

Cleavage with nucleophiles 75
Cleavage with electrophiles 77

2.1.5 Generalising the coupling protocol to variable enol protection 78

An N-ethyl-N-(2-methylallyl)carbamoyl protecting group 80

2.1.6 Use of a 2-methoxymethoxymethyl (MEM) protecting group strategy 83

Synthesis of 2,2-difluoro-1-(2-methoxyethoxymethoxy)-1-(tributylstannyl)ethene 118 84
Stille coupling of stannane 118 84
Optimisation of the coupling process 84
Scope of couplings 85
Electrophilic cleavage of styrene derivatives 93
2.2 Building-block Approach to Fluorinated Carbohydrates

2.2.1 Asymmetric dihydroxylation of conjugated fluorinated dienes

2.2.2 Synthesis of 1,3-dideoxy-1,1-difluoro-D-glyceropent-2-ulofuranose

2.2.3 Synthesis of 1-deoxy-1,1-difluoro-D-xylulose

2.2.4 Evaluation of one carbon extension strategies

Radical additions
O to C protecting group transfer

3.0 Conclusions

4.0 Experimental

5.0 References

6.0 Appendices
“To make an end is to make a beginning, the end is where we start from”
Chapter One

Introduction
1.1 Rationale for Fluorine Atom Introduction

Naturally occurring fluorinated molecules are very rare. Organofluorine chemists are therefore interested in the possible effects on biological properties of molecules after introducing a limited number of highly electronegative fluorine atoms. Over the last thirty years, the interest and profile of selectively fluorinated biomolecules have risen dramatically. As such, much synthetic effort has been invested to synthesise biologically active organofluorine compounds. The drive to develop methodology allowing improved access to such compounds has arisen after the demonstration of the useful physical and chemical properties possessed by this class of compound. The rationale for the selective introduction of a limited number of fluorine atoms into key sites of bioactive molecules is based upon several relevant properties of the fluorine atom:

i) On steric grounds, exchanging a hydrogen atom for a fluorine atom involves the minimal possible change in molecular volume, thus minimising any change in complementarity between the substrate and the receptor site in the enzyme. Although it has often been claimed that the fluorine atom has a similar volume to the hydrogen atom, this is not the case. On comparing van der Waals radii, the fluorine atom is 23% larger than the hydrogen atom and so only the replacement of a small number of hydrogen atoms (one or two) with fluorine atoms will not greatly alter steric requirements. This difference is exemplified by comparing the conformational A value of the methyl (CH₃) and trifluoromethyl (CF₃) substituents (1.4 and 2.4 respectively). In fact, the CF₃ group is as sterically demanding as an isopropyl group. The largest F-steric effect recorded is illustrated in the rate differences between the *meta* ring-flip
The ring-flip occurs $10^{11}$ times faster when X is hydrogen, compared to when it is fluorine. This is presumably due to the increase in electronic repulsion between X and the circulating electrons in the $\pi$-cloud of the benzene ring when X is a fluorine atom. From these facts, it is more correct to describe the fluorine atom as isosteric with the oxygen atom or a hydroxyl group, and this interchange is very common in the literature.\textsuperscript{4}

ii) The high relative electronegativity of the fluorine atom (4.0 on the Pauling scale) compared to the hydrogen atom (2.1) may have a marked effect on the electronic surface of the molecule and may modify the behaviour of proximate functional groups. In addition, this property of fluorine is often used to stabilise a key linkage, by destabilising any positively charged intermediates or transition states (e.g. acetal or glycosidic linkages).\textsuperscript{5}

iii) The high bond dissociation energy of the C-F bond (489 kJ mol$^{-1}$) can effectively block metabolic oxidation at sites at which C-H bonds are cleaved by hydrogen atom abstraction.\textsuperscript{6} This property also severely reduces the possibility of losing a high-energy fluorine atom during radical processes. However, though the C-F bond is strong, the fluoride ion may function as a leaving group in certain circumstances,
albeit with low nucleofugacity. It may also be displaced at or near to the active sites of enzymes, resulting in the covalent attachment of the organic moiety to the enzyme.\(^7\)

iv) The introduction of fluorine atoms usually (but not always) increases lipid solubility (due to an increase in hydrophobicity), thereby enhancing the rate of absorption of drugs \textit{in vivo} and hence bioavailability. This is an important therapeutic property as it allows the administration of lower doses of drugs. The CF\(_3\) group is among the most lipophilic of all substituents, although, from limited data, it is apparent that mono- and trifluoromethylation reduces lipophilicity when the site of fluorination is separated from any heteroatom or \(\pi\)-bond by at least three carbon-carbon bonds. This is due to the relatively polar nature of these groups. Aromatic fluorination always increases lipophilicity and explains the ubiquitous presence of the fluorine atom (as fluoroarenes) in biocides.\(^8\)

Fluorine-containing medicinal compounds have contributed significantly to advances in such areas as cancer chemotherapy, anti-inflammatory agents, anti-parasitic agents, antibiotics and the chemistry of mental health.\(^9\) It is therefore clear that there is a great demand for new methodology allowing access to a range of fluorinated motifs, such that the full potential of fluorinated medicinals can be harnessed.

1.2 Current Methods for the Synthesis of Fluorinated Motifs

Many chemists, when targeting a fluorinated compound, utilise direct fluorination of a precursor at a late stage in the synthesis in order to reach their goal. This mode of fluorination takes place by a functional group transformation, notably of a ketone, an
alcohol or an epoxide. Chemists are currently able to utilise both electrophilic and nucleophilic sources of fluorine.

An alternative approach has become popular in which the fluorine atoms are present from the outset and the molecular dressing is added via adaptation of known synthetic methodology to the presence of the fluorine atom. The number of reactions studied is expanding and often highlights both the benefits and pitfalls of using this approach. The very nature of the initiative of fluorine atom introduction can cause severe synthetic limitations and it has become important to find improved strategies to subclasses of fluorinated molecules. This strategy is often denoted as the building-block approach. ¹⁰

1.2.1 Current Methods for the Synthesis of (Aryl) Difluoromethyl Ketones

α,α-Difluoromethyl ketones are ubiquitous targets in the literature. The continuing interest in this moiety has arisen from the activating effects of the fluorine atoms on the electrophilicity of the carbonyl, arising from a lowering of the LUMO energy level. ¹¹ This mode of action is frequently adopted in the field of drug discovery in which selected peptide linkages are replaced by a difluoroketone moiety to form a competitive inhibitor 1 of, for example, disfunctioning protease enzymes. Active site nucleophiles (such as a water molecule or a hydroxyl group of a serine residue) competitively react with the fluoroketone to form the stable hydrate 2 or hemiketal 3, respectively. The process occurs through mimicry of the intermediate 4 traversed during hydrolysis of a peptide linkage 5 by protease enzymes (Scheme 1).
Fluoroketones have been successfully used as inhibitors of renin, HMG CoA reductase, γ-secretase, HCMV protease and HIV-1 proteases.

The application of a difluoroketone moiety within other molecular frameworks is far less well explored, due to the lack of availability of appropriate methodologies for incorporating this group. However, Eto and co-workers have recently shown an interest in the use of aryl difluoromethyl ketone derivatives in the synthesis of antifungal agents (Scheme 2).

**Scheme 1**: Use of α-fluoro-α-peptidyl ketones as competitive inhibitors of proteases through TS mimicry

**Scheme 2**: Use of α-fluoro-α-peptidyl ketones as competitive inhibitors of proteases through TS mimicry
Reagents and Conditions: i) [Me₃SO]+I⁻, NaH, DMSO; ii) 1,2,4-triazole, K₂CO₃, DMF

Scheme 2: Antifungal synthesis using aryl difluoromethyl ketones

Treatment of difluoroketone 6 (prepared by addition of 2,4-difluorophenyllithium to the corresponding ester, formed by cross-coupling of ethyl bromodifluoroacetate with 2-iodothiophene with copper, 50% yield for two steps) with trimethylsulfoxonium iodide led to the formation of epoxide 7. Ring opening with 1,2,4-triazole afforded the potent antifungal agent 8. The (+)-isomer possessed significant in vitro activity against a range of yeasts and filamentous fungi. The same group has also described the synthesis and activity of similar compounds in which an alkylsulfanyl group has replaced the heteroaryl group (thienyl in 8).¹⁸

Other uses of difluoro- and trifluoromethyl ketones include the synthesis of the Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) efavirenz 9,¹⁹ novel fluorinated amino acids²⁰ 10, 3-aryl-4-fluoro-1,2,5-thiadiazoles²¹ 11 which possess herbicidal and nematicidal properties and C-10 fluorinated derivatives²² 12 of epi-dihydroartemisinin which may possess antimalarial properties (Figure 2).
α-Halo-α,α-difluoromethyl ketones can also serve as useful building blocks to other mid-chain difluoroketones through Reformatsky reactions\(^\text{23}\) or cross-coupling with aryl halides under nickel(0)\(^\text{24}\) or copper(0) catalysis.\(^\text{25}\)

A suitable methodology that is amenable to parallel synthesis should allow the generation of a diverse array of compounds, allowing structure-activity correlations to be made. In the future, other uses of aryl difluoromethyl ketones may be developed. In drug design, the aromatic rings may be applicable as a means of introducing conformational rigidity as well as directing units, a ploy used often in the pharmaceutical industry. It is clear that aryl difluoromethyl ketones are worthy targets for testing such molecular connections in future drug design.

Retrosynthetic analysis of a typical target, aldol product 13 is shown in **Scheme 3**.

**Scheme 3:** Initial disconnection of an aldol target 13
Disconnection of the CF₂-R bond can either lead to an α-chloro-α,α-difluoromethyl ketone 14 or a difluoroenol ether 15. Ishihara has reported Reformatsky-type reactions of α-chloro-α,α-difluoromethyl ketones with ketones using a variety of metal catalyst systems.²³α,b Alternatively, indium-mediated reaction of α-halo-α,α-difluoromethyl ketones (formed by halogenolysis of the corresponding silyl difluoroenol ethers) in aqueous media has been described by Welch.²³c Taguchi has described the aldol condensation of 1,1-difluoroenol methyl ether derivatives 15a,²⁶ whilst Portella has described an identical sequence using silyl difluoroenol ethers 15b.²⁷ The enol ethers 15a are available from chlorodifluoromethyl ketones 14 whilst several avenues to the corresponding silyl difluoroenol ethers 15b have been investigated. Scheme 4 shows the approaches studied.

\[ \text{Scheme 4: Approaches to silyl difluoroenol ethers 15b} \]
Ishihara has described the reaction of Zn(0) with chlorodifluoromethyl ketones in the presence of chlorotrimethylsilane to form the corresponding silyl difluoroenol ether.\textsuperscript{28} A milder version, in which Mg(0) is employed, has been recently described by Uneyama.\textsuperscript{29} This method is now the method of choice even though a large excess of Mg(0) and silane is required. However, the method has been put to good use by the sequential conversion of trifluoromethyl ketones to difluoromethyl ketones and then fluoromethyl ketones.\textsuperscript{30} Such a conversion using Mg(0) has also been achieved electrochemically.\textsuperscript{31} The last three approaches all rely upon the elimination of fluoride from a carbanion \textsuperscript{18}, resulting from Brook rearrangement of a 1-trifluoromethyl-1-aryl-1-trialkylsilylmethoxide anion \textsuperscript{19} (Scheme 5).

\begin{equation}
\begin{align*}
\text{F}_3\text{C} & \text{Ar} \text{O}^- \quad \text{Brook} \quad \text{Rearrangement} \quad \text{F}_3\text{C} \text{OSiR}_3 \quad \text{F}^- \\
\text{19} & \quad \text{18} \quad \text{15b}
\end{align*}
\end{equation}

\textbf{Scheme 5: A Brook rearrangement in the formation of silyl difluoroenol ethers 15b}

The three methods differ in the nature of the nucleophile used upon the carbonyl starting material. Fleming described the addition of \textit{tert}-butyldiphenylsilyllithium to trifluoromethyl ketones.\textsuperscript{32} The reaction, however, was difficult to control and the product \textbf{15b} \((\text{R}_3=\text{TBDP})\) was isolated in only moderate (51\%) yield. Xu reported the reaction of Grignard reagents with trifluoroacetyltriphenylsilane to form the corresponding silyl difluoroenol ethers \textbf{15b} in high (88-99\%) yield.\textsuperscript{33} On the other hand, Portella has examined the use of acylsilanes\textsuperscript{34} \textbf{16} in conjunction with Ruppert’s reagent \textbf{17}, which acts as a source of trifluoromethylide in the presence of a catalytic
fluoride source. Scheme 6 shows such an approach to a difluorinated analogue of egomaketone 18. One major drawback of this approach is the high cost (£1.44 /mmol) of the Ruppert reagent 17.

Many of the other approaches require the use of $\alpha$-halo-$\alpha$-$\alpha$-difluoromethyl aryl ketones. Such materials are typically accessed through the addition of a suitable organometal, typically aryllithium and Grignard reagents, to commercially available carbonyl derivatives, such as esters or amides. All of the monofluoro-, difluoro- and trifluoroacyl (except those containing iodine) starting materials are commercially available. Limitations of this method exist in the cost of some of the starting materials.
as well as the repetitive use of cold-temperature reactions for each aryl installation. More importantly, the nature of the reaction does not permit the presence of either acidic or electrophilic groups and therefore limits the degree of functionality present elsewhere in the product. As can be seen from Scheme 4, trifluoromethyl ketones are a major source of difluoroenol derivatives, which can be transformed into other fluoromethyl ketone derivatives.

Creary has studied the addition of aryllithium reagents to ethyl trifluoroacetate and has shown that the desired ketones could be isolated in good yield. Kerdesky utilised trifluoroacetic acid anhydride with heteroaryl copper reagents to afford products in good (65-85%) yield. DiMenna reported a similar protocol in which N,N-trifluoroacetamide was used as the trifluoroacetylationing agent with lithiated heterocycles. In a more direct approach, Keumi and co-workers used 2-(trifluoroacetoxy)pyridine (TFAP) as an effective trifluoroacetylationing agent for arenes in the presence of aluminium trichloride. Though good yields were isolated, structural variation of the aromatic ring was not studied (Scheme 7).

**Scheme 7:** Various methods of trifluoromethyl aryl ketone synthesis
Srogl and Yamamoto have described improved protocols to trifluoromethyl aryl ketones based upon cross-coupling of trifluorothioacetic and trifluoroacetic acid derivatives with boronic acids, respectively (Scheme 8).

Scheme 8: Coupling strategies from trifluoro(thio)acetic acid derivatives

Liebeskind and Srogl described the efficient cross-coupling of $o$-tolyl trifluorothioacetate with boronic acids under palladium catalysis in the presence of copper(I) thiophene-2-carboxylate (CuTC) to afford the corresponding ketone.\textsuperscript{40} However, only one example was provided and the starting thioester needs to be synthesised. The copper(I) salt is also used in excess. In addition, this methodology was superceded by the work of Yamamoto, in which inexpensive and commercially available phenyl trifluoroacetate could be used directly with boronic acids; heterocyclic boronic acids were unfortunately unable to undergo cross-coupling in addition to those substituted at the $ortho$ positions.\textsuperscript{41} Yamamoto has subsequently developed methodology that may allow the inexpensive trifluoroacetic anhydride and trifluoroacetic acid to be used as alternative starting materials.\textsuperscript{42}

A less direct approach has been described by Jiang and co-workers in which $\alpha$-(trifluoromethyl)vinyl boronic acid or the corresponding organozinc reagent have
been cross-coupled to iodo- and bromoarenes with excellent efficiency.\textsuperscript{43,44} Synthesis of the requisite boronic acid was facile and a range of \( \alpha \)-(trifluoromethyl)styrenes could be accessed. Osmium tetroxide/periodate could be used to install the ketone functionality in a synthesis of ketone 20, used in the preparation of efavirenz, a potent NNRTI approved by the FDA for the treatment of AIDS (Scheme 9).

\[ \text{F}_3\text{C} - \text{Br} \xrightarrow{\text{Mg, B(OEt)}_3} \xrightarrow{\text{THF, rt}} \text{F}_3\text{C} - \text{B(OH)}_2 \xrightarrow{2\% \text{Pd(PPh}_3)_4} \xrightarrow{\text{Na}_2\text{CO}_3 (aq.)} \text{F}_3\text{C} - \text{Ar} \]

\[ \text{F}_3\text{C} - \text{NO}_2 \xrightarrow{\text{NaIO}_4} \xrightarrow{\text{OsO}_4} \xrightarrow{\text{H}_2 / \text{Ra-Ni}} \text{F}_3\text{C} - \text{NH}_2 \xrightarrow{\text{Cl}} \text{Cl} - \text{F}_3\text{C} - \text{N}\text{H}_2 \xrightarrow{\text{O}} \text{F}_3\text{C} - \text{C} - \text{O} \]

\textbf{Scheme 9:} Jiang's approach to trifluoromethyl aryl ketones

Other building-block methods have used nucleophilic trifluoromethylation\textsuperscript{45} with either trifluoromethyltrimethylsilane\textsuperscript{46} 17 or trifluoromethylacetophenone-\(N, N\)-dimethyltrimethylsilane\textsuperscript{47} 21 (Figure 3). The latter reagent is considerably more stable and less expensive than Ruppert's reagent 17.

\[ \text{F}_3\text{C} - \text{SiMe}_3 \]

\[ \text{F}_3\text{C} - \text{PH} - \text{NMe}_2 \]

\textbf{Figure 3:} Nucleophilic trifluoromethylating reagents
Piettre has reported the difluoromethylation of aromatic aldehydes with a lithiated difluorophosphonate 22 to afford alcohols 23, which underwent oxidation to acyl phosphonates 24. Exposure to basic methoxide led to C-P bond cleavage and the subsequent formation of difluoromethyl ketones 25 (Scheme 10). This is one of the most useful methods for the formation of simple difluoromethyl aryl ketones, due to the large number of aldehydes available; however, the route does suffer for indirectness.

\[
\text{Ar H} \quad \xrightarrow{\text{i) LiCF}_2\text{PO(OEt)}_2} \quad \text{Ar CF}_2\text{PO(OEt)}_2 \quad \xrightarrow{\text{ii) H}_3\text{O}^+} \quad \text{Ar CF}_2\text{H}
\]

Scheme 10: Use of acyl phosphonates 24 to access difluoromethyl ketones 25

Several methods based upon fluorination have also been described. DesMarteau reported the fluorination of lithium enolates derived from benzophenones with N-fluoro-bis[(trifluoromethyl)sulfonyl]imide, which results in α-fluoromethyl aryl ketones as the major component, but in poor (26-38%) yield. Difluoromethyl aryl ketones could be formed as the sole product by the use of imines with two equivalents of the fluorinating agent. Zupan has described the fluorination of propiophenone with Accufluor™ to afford the monofluorinated aryl ketone in good (80%) yield (Scheme 14).
The reaction is slow however (30 h at 80°C) and does not appear to be general (acetophenone gave only 23% product).^{50}

![Scheme 11: Monofluorination using Accufluor™](image)

Zupan has also described a more attractive approach, in which substituted phenylacetylenes underwent reaction with Selectfluor™ in the presence of water to form difluoromethyl aryl ketones in moderate (36-51%) yield (Scheme 12). The scope of the reaction has not been fully explored, however.^{51}

![Scheme 12: Fluorination of acetylenes to difluoroketones](image)

It is also possible to access the target materials by reversing the sequence of events. Iseki^{52} has described the catalytic asymmetric aldol condensation of silyl difluoroketene acetals 26 with aldehydes to afford β-hydroxy-α,α-difluoropropionates 27 in high (81-97%) ee using Masamune’s catalyst 28 or Kiyooka’s catalyst 29 (Scheme 13).
Scheme 13: Synthesis of optically active β-hydroxy-α,α-difluoropropionates 27 from silyl difluoroketene acetals 26

These materials can be transformed into the corresponding Weinreb amides with an enhancement of the ee by recrystallisation (typically to 100% ee). Treatment with Grignard reagents then affords the enantiomerically pure α,α-difluoro-β-hydroxyketones in high (80-98%) yield. Protection of the hydroxyl group followed by exposure to a Grignard reagent should then deliver the desired materials. However, the same limitations already alluded to apply here (vide ante).

A similar reaction using silyl fluoroketene acetals and a range of aromatic aldehydes, in the presence of trimethylsilyl triflate, has been described by Chen. Fluorination methods to these materials have also been reported; β-ketoesters reacted with p-iodotoluene difluoride and Olah’s reagent (9HF-pyridine) at ambient temperature to afford the monofluorinated esters in good (72-80%) yield.

A particularly rare motif is the α-(heteroarylthio)-α,α-difluoromethyl aryl ketone, a species which has been used as a building-block to antifungal agents (vide ante) or as possible NNRTI candidates. Few methods are available for this connection. Brigaud and Fuchigami have reported electrochemical methods, whilst Kuroboshi used an oxidative fluorodesulfurisation approach using tetrabutylammonium dihydrogen trifluoride and
dimethylhydantoin with β-hydroxyorthothioesters at ambient temperature. However, the reaction gave variable yields of products and the reagents were required in excess.

Several authors have described fluorination methods employing α-(phenylsulfanyl)-acetates. Takeda and co-workers used a variety of N-fluoropyridinium salts to achieve the desired transformation, albeit under harsh (105°C) conditions. Variable yields of products were also observed. Motherwell used difluoriodotoluene as the fluoride source and both mono- and difluorination could be achieved by altering the stoichiometry. Good (64-80%) yields were typically achieved. A similar approach using an IF₅/Et₃N-3HF fluorination regime was successful in moderate (45-55%) yield (Scheme 14).

![Scheme 14: Fluorination of (α-phenylthio)acetophenone using IF₅](image)

The best method to date, however, involves the displacement of chloride from a chlorodifluoromethyl aryl ketone using a thiolate nucleophile. In this manner, Médebielle was able to synthesise a small number of the target compounds for biological testing. However, the method does require the use of α-chloro-α,α-difluoromethyl aryl ketones, which have limited diversity in the aryl unit, as already outlined.
1.2.2 Fluorinated Carbohydrates

Much attention has been paid to the synthesis of selectively fluorinated carbohydrate analogues over the last fifty years. During this period, many successful syntheses have been reported and the sugars have been used for probing glucose metabolism, hydrogen-bonding patterns in binding specificity studies and as drug candidates.

Biological activity

The largest single field of study is that of fluorination at the 2'– and 3'- positions of deoxypentoses. The parent sugars are key nucleosides in the replication of viral DNA in herpes, hepatitis-B and HIV viruses. Considerable effort has been put into the synthesis of selectively fluorinated deoxypentoses as potential anti-HIV, anti-hepatitis-B and anti-herpes viral agents. The design strategy is threefold:

i) Replication involves activation of the 5'-hydroxyl by phosphorylation followed by chain elongation at the 3'-hydroxyl group. Therefore, blockage of the 3'-group with a fluorine atom should lead to chain termination.

ii) Introduction of 2'-fluoro or 2',2'-difluoro substituents leads to significant stabilization of the glycosidic linkage by inductive destabilisation of the oxacarbenium ion intermediate. This leads to higher activity, better bioavailability and lower dosage requirements.

iii) The presence of fluorine atoms can alter the conformation of the sugar ring, leading to a change in activity, resulting from a change in complementarity with the receptor site.
The above points have been used to make a series of fluorinated sugar analogues, resulting in invaluable structure-activity correlation studies. Some fluorosugars of current interest are shown in Figure 4.

Current studies are also probing the use of unnatural L-nucleosides for incorporation into drug molecules. The use of fluorine in other carbohydrate systems is far less studied. Gem-difluorination at the 2'-position remains a key design point, improving stability to acidic conditions. Applications of 2-deoxy-2,2-difluorohexoses are rare in the literature. 2-Deoxy-2,2-[18-F]_{2}-difluoroglucose has attracted some attention as a possible alternative to 2-deoxy-2-[18-F]-fluoroglucose in the clinical study of glucose metabolism. However, the short half-life ($t_{1/2} = 110$ mins) precludes its synthesis by building-block approaches and the use of DAST remains the only viable option.
**Synthesis using fluorination methodology**

**Nucleophilic fluorination**

The introduction of fluorine atoms at a late stage in a synthesis can be achieved using either a nucleophilic or electrophilic fluorine source.

Nucleophilic sources consist of harsh regimes such as hydrofluoric acid, xenon(II) fluoride, sulfur(IV) fluoride and the family of alkylaminosulfur trifluorides (DAST, Morph-DAST, Deoxo-Fluor). Alkali metal fluorides have also been extensively used, especially in the developing years of the field.

The synthesis of 2-deoxy-3,5-di-O-benzyl-2,2-difluoro-D-ribose 30 by Castillón and co-workers exemplifies the use of DAST in the synthesis of fluorosugars (Scheme 15).\(^{75}\)

![Scheme 15: Use of DAST in 2-deoxy-2,2-difluoro-D-ribose synthesis](image)

Treatment of protected D-glucose 31 with an excess of DAST in dichloromethane at ambient temperature afforded the desired protected 3,3-difluoro-D-glucose 32 in
good (60%) yield. Deprotection of the benzylidene acetal with acid followed by double benzoylation afforded 33. Hydrogenolysis over palladium/charcoal gave glucose 34 in moderate (59%) yield as a mixture of anomers. Finally, oxidative cleavage of the diol, using periodate, afforded the target 2-deoxy-2,2-difluoro-D-ribose sugar 30 after hydrolysis of the intermediate 4-formyl derivative 35 with methanolic ammonia.

A similar ulose deoxyfluorination with DAST was used by Castillón and co-workers in an efficient synthesis of 2-deoxy-2,2-difluoro-D-arabinohexose 36 (Scheme 16).74

The general mechanism for deoxyfluorination using DAST is shown in Scheme 17.

However, whilst many successful applications have been documented, several problems with DAST 37 are apparent. The material is expensive (£1.47 / mmol for small amounts) and decomposes upon storage for extended periods. In addition, many equivalents are often required in order to achieve the desired transformation. A
major drawback to scale-up is the knowledge that under forcing conditions or on large scale the reagent is liable to explode or detonate. More stable analogues have consequently been developed such as Morph-DAST$^{38}$ and bis(2-methoxyethoxy)aminosulfur trifluoride$^{37}$ (Deoxo-Fluor$^{TM}$) 39 (Figure 5). Even though these analogues are less prone to thermal decomposition, they are also less chemically active than DAST.

![Figure 5: Family of alkylaminosulfur trifluorides](image)

It is also important to appreciate that reaction occurs via pathways with high carbenium ion character and several undesired pathways can be activated leading to elimination, rearrangement, 1,2-hydride shifts and neighbouring group participation (Scheme 18).$^{78}$
Apart from the desired fluorodeoxygenation pathway (a), two significant side reactions compete effectively; 1,2-hydride shift (b) and elimination of HF (c). Other more conventional amine protecting groups like BOC or Z lead to the formation of products arising from neighbouring group participation. Importantly, reactions involving DAST and similar reagents are highly sensitive to steric and conformational factors and reaction outcomes can be highly unpredictable.

Another popular approach is the use of metal fluorides as sources of nucleophilic fluoride. Reaction sequences typically involve trans-diaxial ring opening of epoxides or $S_N2$ displacement of a reactive hydroxyl leaving group, such as a mesylate or tosylate.

Ma et al. have described the use of potassium hydrogendifluoride as a nucleophilic source of fluoride in a synthesis of 1-(2-deoxy-2-fluoro-$\beta$-L-arabinofuranosyl)-pyrimidine nucleosides as potential anti-hepatitis B viral agents.\textsuperscript{69b} The key synthetic
step involved the protection of the hydroxyl group as an imidazolyl sulfonate, primed for $S_N2$ displacement by fluoride (Scheme 19).

\[
\begin{align*}
\text{ImO}_2\text{S} & \quad \text{OBz} \\
\text{BzO} & \quad \text{OBz} \\
\text{BzO} & \quad \text{OBz}
\end{align*}
\]

\[\text{KHF}_2 \quad 48\% \text{ HF} \quad \text{BzO} \quad \text{OBz} \quad \text{OBz}\]

**Scheme 19:** Installation of a fluorine substituent using $S_N2$ displacement of a sulfonate

**Electrophilic fluorination**

Although the term electrophilic fluorination suggests the generation of a positively charged fluorine atom, it merely indicates the reactivity of the reagents used. Such reactivity can be achieved by attachment to an electronegative element such as oxygen or nitrogen.

Trifluoromethyl hypofluorite ($\text{CF}_3\text{OF}$) has been used as an electrophilic source of fluorine whereby cis-addition occurs to a glycal. The intermediate carbenium ion is quenched either by the trifluoromethoxide ion or by fluoride to afford the saturated sugar. Adamson et al. used this approach in the conversion of 3,4,6-tri-O-acetyl-D-glucal 40 to 2-deoxy-2,2-difluoro-D-glucose 41 (Scheme 20).[^79]

\[\begin{align*}
\text{AcO} & \quad \text{OAc} & \quad \text{F} \\
\text{AcO} & \quad \text{OAc} & \quad \text{CF}_3\text{OF}
\end{align*}\]

\[\begin{align*}
\text{AcO} & \quad \text{OAc} & \quad \text{F} & \quad \text{R} = \text{OCF}_3 \text{ or } \text{F} \\
\text{AcO} & \quad \text{OAc} & \quad \text{F}
\end{align*}\]

\[\begin{align*}
\text{AcO} & \quad \text{OAc} & \quad \text{F} & \quad \text{OH} \\
\text{AcO} & \quad \text{OAc} & \quad \text{F}
\end{align*}\]

**Scheme 20:** Fluorination of a glycal using $\text{CF}_3\text{OF}$
The handling problems of CF₃OF have been overcome by the use of N-F reagents such as N-fluoro-O-benzenedisulfonamide\(^{80}\) 42 (NFOBS) and N-fluorobenzene-sulfonimide\(^{81}\) 43 (NFSi) (Figure 6).

![Figure 6: Electrophilic sources of fluorine](image)

Davis and co-workers have utilised these reagents in the facially selective fluorination of enolates. In their synthesis of 4-deoxy-4-fluoro-D-arabinopyranose \(^{44}\), chiral amide \(^{45}\) was treated with sodium hexamethyldisilazide to generate the sodium enolate, followed by quenching with NFSi to afford \(\alpha\)-fluoroamide \(^{46}\) in 94\% de. Removal of the auxiliary group with lithium borohydride followed by Dess-Martin oxidation afforded the pivotal aldehyde \(^{47}\) in 94\% ee. This was then converted in 7 steps to the desired peracetylated sugar \(^{44}\) (Scheme 21).\(^{82}\)
Reagents and Conditions: i) NaHMDS, -78°C, THF; ii) NFSi, 30 min, inverse addition, 78%; iii) 2.0 LiBH₄, THF, 0°C, 3 h, 93%; iv) Dess-Martin periodinane, DCM, 10 min, 95%.

Scheme 21: Asymmetric synthesis of a 4-deoxy-4-fluoroarabinose using NFSi

A similar approach was used to synthesise 2-deoxy-2-fluoro-γ-aldonolactones, which were converted to 2-deoxy-2-fluoropentoses. Treatment of unsaturated imide 48 with lithium hexamethyldisilazide led to an extended enolate, which was quenched with NFSi to afford the chiral imide 49 as a single diastereoisomer. Dihydroxylation with low selectivity (1:2.3) afforded the aldonolactone 50 as the minor product. 50 was converted in two steps to 2-deoxy-2-fluoro-D-xylopyranose 51 (Scheme 22).
Reagents and Conditions: i) LiHMDS, -78°C, THF, 1h; ii) NFSi, -78°C, 2 h, 76%; iii) OsO₄, TMNO, acetone-H₂O (20:1 v/v), 40%.

Scheme 22: Asymmetric synthesis of a 2-deoxy-2-fluoroxyllose using NFSi

Building-block methodology

There are relatively few building-block methods to fluorinated sugars. One well-researched approach is the use of the Reformatsky reaction of ethyl bromodifluoroacetate or a synthetic equivalent.

Kobayashi utilised bromodifluoromethylalkyne 52 in a Reformatsky-like reaction with D-iso-propylideneglyceraldehyde to form the alcohols 53 with poor diastereoselectivity. Acetal deprotection and stereoselective alkyne reduction using Lindlar’s catalyst afforded triol 54, which underwent ozonolysis to afford the parent 2-deoxy-2,2-difluoro-D-ribose. The free sugar was peracetylated to 55 in order to aid characterisation (Scheme 23).
Scheme 23: Use of a variant of the Reformatsky reaction in fluorosugar synthesis

Chou and co-workers at Lilly utilised ethyl bromodifluoroacetate in their synthesis of gemcitabine. Addition of the corresponding zinc reagent of ethyl bromodifluoroacetate to (R)-2,3-O-isopropylidenglyceraldehyde afforded alcohols as a mixture of diastereoisomers. The alcohols were protected as benzoate esters 56 and the acetal removed under acidic conditions to give diols which cyclised upon azeotropically removal of water to give lactones. Selective crystallisation gave pure lactone 57, which was reduced to the lactol 58. This was then converted into gemcitabine 59 in four steps (Scheme 24).
Scheme 24: Synthesis of gemcitabine using a Reformatsky reaction

Other possible routes to fluorosugars have been described by Taguchi\textsuperscript{85} and Uneyama,\textsuperscript{86} both of which hinge upon the hetero Diels-Alder cycloaddition between fluorinated versions (60 and 61) of Danishefsky’s diene 62 with aldehydes under Zn(II) catalysis to afford 2,3-dihydro-4\(H\)-pyran-4-one derivatives 63. Taguchi has demonstrated how pyrones 63 could be converted into 4-deoxy-4,4-difluoro-pyranosides 64 (Scheme 25).
1.3 Fluorovinyl Organometallics\textsuperscript{87}

The application of organometallic reagents has had a profound effect upon modern organic chemistry and the use of vinyllithium or Grignard reagents is very common. However, a similar approach with lithiated fluorovinyl organometallics has been limited due to their thermal instability.\textsuperscript{88} Typically, very low (-100°C) temperatures are required and isolated yields of products after quenching can be low due to significant decomposition. A clear example is shown in the attempted electrophilic trapping of lithiated fluorostyrenes. Exposure to lithium diisopropylamide at -100°C led to lithiation followed by spontaneous lithium fluoride expulsion to afford the acetylene. Further lithiation and trapping with aldehydes or ketones afforded the corresponding propargylic alcohols in good yields (Scheme 26).\textsuperscript{89}
The thermal stability of lithiated fluoroalkenes can be increased by the attachment of inductively stabilising electronegative atoms such as fluorine, chlorine or oxygen.

Several groups have reported the application of fluorovinylolithium reagents. Trifluorovinylolithium 65 was first generated by Seyferth and co-workers by exchange of phenyllithium with phenyltris(trifluorovinyl)tin in diethyl ether at between -40 and -30°C (Scheme 27). The generation of 65 at a relatively high temperature indicates that the presence of three fluorine atoms imparts some extra stability on the vinylolithium reagent.
Normant and Sauvêtre have described the reaction of 1,1-difluoroethene with alkyllithium reagents at low temperature. In a solvent-dependent process, lithiation with sec-butyllithium in THF at very low temperature afforded the lithiated alkene in quantitative yield (Scheme 28).\(^93\)

\[
\begin{align*}
\text{F} & \quad \text{H} \\
\text{H} & \quad \text{F} \\
\end{align*}
\]

Scheme 28: Lithiation of 1,1-difluoroethene

\(\alpha\)-Metallated vinyl ethers are useful umpolung reagents\(^94\) and the use of \(\alpha\)-oxygen-substituted difluorovinyl lithium reagents has received much attention as a means of both increasing the thermal stability of such species as well as for incorporating further functionality. Several groups have used trifluoroethanol as a starting material to lithiated difluoroenol derivatives.

In the first instance, Nakai and co-workers prepared 2,2-difluoro-1-tosyloxyvinyl lithium \(^66\) from the reaction of 2,2,2-trifluoroethyl tosylate with two equivalents of LDA in THF at \(-78^\circ\text{C}\). This intermediate reacted with carbonyl electrophiles to give allylic alcohols \(^67\), which afforded \(\alpha\)-ketoacids \(^68\) after hydrolysis (Scheme 29).\(^92d\)

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{OTs} \\
\end{align*}
\]

Scheme 29: Generation and use of a difluorovinyl lithium reagent \(^66\)
Ichikawa has utilised intermediate 66 in C-C bond formation via its interception with trialkylboranes to form intermediate boron-ate complexes 69. $^{95}$ 1,2-Migration of the alkyl group from boron to the vinylic carbon, with the loss of tosylate, afforded vinylboranes 70. Protonation afforded difluoroalkenes 71 in good yield (Scheme 30).

![Scheme 30: Synthetic use of difluorovinylboranes 70](image)

Furthermore, boranes 70 could undergo transmetallation with copper(I) to form a vinylcopper reagent 71.$^{95b}$ This reagent was capable of participating in coupling reactions with acid chlorides and iodoalkynes to form enones$^{96}$ 72 and enynes$^{97}$ 73, respectively (Scheme 31).

![Scheme 31: Synthetic use of a difluorovinylcopper reagent 71](image)
However, the requirement of trialkylboranes affords products of limited synthetic use due to the presence of a simple alkyl group attached to the olefin. Potentially more interesting chemistry has been developed within our group and that of Tius. In the case of Tius and co-workers, interception of vinyl lithium reagent 74 with enones afforded bis-allylic alcohols 75 which underwent Nazarov cyclisation to afford novel difluorocyclopentenones 76 (Scheme 32).

![Scheme 32: Difluorocyclopentenone synthesis by Nazarov cyclisation](image)

Patel, Howarth and Balnaves have achieved improved synthetic utility of the trifluoroethanol protecting-group strategy. Howarth used an $N,N$-diethylcarbamate (DEC) group in which the carbamate oxygen can co-ordinate to the lithium atom affording some degree of stabilisation. The vinyl lithium reagent 77 has been used to generate allylic alcohols 78, which can be used to generate the corresponding enolates in situ. These in turn undergo aldol condensation with non-enolisable aldehydes to afford a general route to molecules of class 79. Vinyllithium 77 could
also be trapped with chlorotrimethylsilane (to form silane \textit{80}), chlorotributyltin (to form stannane \textit{81}), and iodine, via a presumed vinylzinc intermediate (to form iodide \textit{82}) (Scheme 33).^{99}

\begin{align*}
\text{82} & \xrightarrow{75\%} \text{i) ZnBr}_2 \quad \text{ii) I}_2 \\
\text{77} & \xrightarrow{27-74\%} \text{i) BuLi} \quad \text{ii) R''CHO} \\
\text{79} & \xrightarrow{42-79\%} \\
\text{81} & \xrightarrow{70\%} \text{Bu}_3\text{SnCl} \\
\text{80} & \xrightarrow{69\%} \text{Me}_3\text{SiClF} \\
\end{align*}

\textbf{Scheme 33:} Use of a DEC protecting group in synthesis

Percy and Patel subsequently developed a 2-methoxyethoxymethoxy\textsuperscript{100} (MEM) derivative, in which double co-ordination to lithium can occur. Vinyllithium \textit{83} has been trapped with Group(IV) halides as well as carbonyl species to afford allylic alcohols \textit{84}.\textsuperscript{101} These have been transformed into mid-chain difluoroketones using rearrangement methodologies (Scheme 34).\textsuperscript{102}
The DEC group has been shown to be difficult to remove, so an identical methodology was attempted using the lithiated Hoppe carbamate 85. This protecting group proved successful in the synthesis of difluoropolyols (Figure 7).

Transmetallation of difluorovinyl lithium reagents with zinc(II) bromide, magnesium bromide etherate or copper(I) iodide affords the corresponding organometallic reagent. These species have been shown to possess higher thermal stability than the corresponding organolithium species and are stable at or just below ambient temperature. Balnaves used Grignard 86 for coupling to aldehydes bearing α-oxygen functionality at -30°C. Difluorovinylcopper reagent 87 has been used in allylation at ambient temperature and zinc reagent 88 is formed at 0°C as an intermediate in the synthesis of iodide 82 (Figure 8).
Thermal stability and ease of isolation and purification has been achieved through the development of difluorovinylltin reagents. These materials, although toxic, are stable at ambient temperature and can be stored without decomposition in a refrigerated (-5°C) environment for several months. They have played a central role in the use of fluorinated organometallics in palladium-catalysed cross-coupling methodology.

1.4 Palladium-catalysed Coupling Reactions

Introduction

Processes that construct C-C bonds hold a central role in organic synthesis. The use of metal-mediated C-C bond formation has had a revolutionary effect upon modern synthetic organic chemistry.\textsuperscript{105}

The catalytic cycles involved consist of several discrete steps fundamental to organometallic chemistry. Low valent metals such as palladium(0) and nickel(0) undergo a process known as oxidative addition with organic electrophiles, in which overall insertion into the C-X (X = halogen, OTf etc.) bond occurs. This process is thought to occur via a three-membered transition state and has characteristics of a polar addition process, such that electron-deficient centres undergo more facile insertion. The nature of the leaving group in the electrophile is expanding constantly.

\textbf{Figure 8:} Metallated difluoroenol derivatives with improved thermal stability

![Chemical structures](image-url)
and now includes such groups as anhydrides,\textsuperscript{42a} thiolates,\textsuperscript{106} mesylates,\textsuperscript{107} nonaflates,\textsuperscript{108} fluorosulfonates\textsuperscript{109} and carboxylic acids\textsuperscript{42b} (via anhydride formation \textit{in situ}) as well as the typical iodides, bromides, chlorides\textsuperscript{110} and triflates.\textsuperscript{111}

In order to make progress in expanding the scope of useful electrophiles, a greater understanding of catalyst structure has had to be developed. New methodologies include using better $\sigma$-donor ligands such as trifurylphosphine\textsuperscript{112} as replacements for triphenylphosphine. In addition, softer ligands such as triphenylarsine\textsuperscript{112} or triphenylantimony\textsuperscript{113} have also been employed. The type of ligand has also changed dramatically; bidentate phosphorus ligands\textsuperscript{114} (such as dppb, dppp, dppe and dppf) and also tetradeutate phosphorus ligands\textsuperscript{115} have been used to produce highly active catalysts. Other ligands include bis-carbenes,\textsuperscript{116} phosphites,\textsuperscript{117} 2-aryl-2-oxazolines\textsuperscript{118} and fluorous dialkylsulfides.\textsuperscript{119} Importantly, it has been shown that stoichiometry is a key issue, with reactivity being balanced with stability. It is not uncommon to see “naked” palladium as a catalyst.\textsuperscript{120} In addition, the metal component of the catalyst is also being varied. Although palladium is by far the most commonly used,\textsuperscript{121} procedures employing nickel,\textsuperscript{122} copper,\textsuperscript{123} manganese,\textsuperscript{123c,124} platinum\textsuperscript{125} and iron\textsuperscript{126} have also been described.

The resulting organometal halide is susceptible to attack by another organometal in an overall transmetallation step. This occurs through a four-centre transition state and again portrays polar characteristics. The organopalladium halide is weakly electrophilic and nucleophilic species such as organozinc,\textsuperscript{127} copper\textsuperscript{128} or magnesium\textsuperscript{129} reagents are required for coupling. Organotin\textsuperscript{130} compounds will undergo coupling but often require high temperatures or additives in order to increase the electrophilicity of the palladium complex. Organosilicon\textsuperscript{131} and
organoboron\textsuperscript{132} reagents are usually insufficiently reactive to undergo unassisted coupling and nucleophilic additives have to be added in order to form silicate or boron-ate complexes \textit{in situ}. In the case of silicon this is achieved by adding a fluoride source; in the case of boronic acids a base (source of hydroxide or alkoxide) is added. Once again, the use of other organometals is being studied in order to investigate trends in reactivity, functional-group tolerance, toxicity and selectivity. Such metals studied include aluminium,\textsuperscript{133} gallium,\textsuperscript{134} zirconium\textsuperscript{135} and tellurium.\textsuperscript{136} The final step in the cycle is reductive elimination in which the two organic fragments combine with the concomitant release of the palladium catalyst. The overall cycle is shown in Scheme 35.\textsuperscript{229}

\begin{center}
\begin{tikzpicture}[scale=0.8]
    % Diagram code here...
\end{tikzpicture}
\end{center}

\textbf{Scheme 35:} Overall catalytic cycle for Pd(0)-catalysed cross-coupling

Once again, important insights into catalyst reactivity have resulted in the development of ligands with varying bite angles, a property directly affecting the rate of reductive elimination and the ability to turn over the cycle.\textsuperscript{137}
Co-catalytic copper in Stille coupling

The use of co-catalytic copper(I) salts in the literature is becoming increasingly common.\textsuperscript{138} Liebeskind and Farina were the first to study this effect and our understanding of the relevant roles has increased further over the last few years, although some uncertainty in the exact mechanisms in operation still remains. The seminal paper\textsuperscript{139} was published in 1990 and describes the effect of added copper(I) iodide on the rate of two Stille couplings in apolar dioxane and polar aprotic NMP. The results in dioxane indicated that the addition of Cu(I) led to a rate enhancement in parallel with the Cu(I)/triphenylphosphine ratio until such time that the conversion to product was sacrificed at the expense of the initial rate, which in fact decreased slightly. When the softer triphenylarsine ligand was used, the initial rates were several orders of magnitude greater and the effect of added Cul was far less pronounced. This led the authors to suggest that the role of Cul in apolar solvents is to scavenge free triphenylphosphine and promote the transmetallation step. The optimum ratio was found to be 1:4:2 (Pd:PPh\textsubscript{3}:CuI). A lower phosphine/Cul ratio leads to catalyst instability and resulted in precipitation of palladium black.

The results in the polar NMP solvent were markedly different. The rate of reaction increased as the amount of Cul was added and no plateau was reached. NMR experiments indicated that phenyltributyltin underwent transmetallation with Cul to form the presumed phenylcopper species.\textsuperscript{140} No such reaction occurred when triphenylphosphine was used, consistent with a dual transmetallation/ligand scavenger role.
Application of transition-metal-mediated cross-coupling using fluorinated organometallics

The use of fluorinated coupling agents is relatively scant in the literature, although the field is slowly expanding. Beletskaya and co-workers provided the initial contribution to the field, who demonstrated that trifluorovinyltributyltin \(89\) could be coupled to a limited range of aryl iodides under relatively mild conditions. Coupling to iodobenzene occurred in either HMPA or DMF at 50-70°C in a relatively short (3 hours) reaction time. Less polar solvents (DMSO, THF, benzene) were ineffective. Attempted coupling with 1,4-diiodobenzene and 1-iodo-4-nitrobenzene under these conditions proved too harsh and oligomeric products were formed. However, greatly improved results could be obtained by the addition of tetrabutylammonium halides, promoting reaction at ambient temperature, although no details were provided (Scheme 36).

```
\[ \begin{align*}
\text{F} & \quad \text{F} \\
\text{SnBu}_3 & \quad \text{I} \\
\text{F} & \quad \text{F} \\
\end{align*} \]
\[ \text{89} \]
\[ \rightarrow \]
\[ \begin{align*}
\text{F} & \quad \text{F} \\
\text{I} & \quad \text{I} \\
\text{F} & \quad \text{F} \\
\end{align*} \]
\[ \text{87\%} \]
```

Scheme 36: First successful coupling of a fluorinated vinylmetal component

The next major contribution was made by Normant and Sauvêtre, who described the synthesis and palladium-catalysed cross-coupling of several difluoro- and trifluorovinylzinc reagents. Coupling has been achieved under mild conditions using vinyl, aryl and heterocyclic iodides. Acid chlorides have also been successfully employed as the electrophilic component. Typical examples are shown in Scheme 37.
Burton has recently expanded the scope of couplings of fluorinated vinylzinc reagents with reports that (Z)-1,2-difluorovinylzinc iodide undergoes CuBr-catalysed cross-coupling with aryl iodides using tetrais(triphenylphosphine)palladium(0) in N,N-dimethylacetamide (DMA) as solvent at RT-40°C.\textsuperscript{143}

Although the above results are interesting, one drawback is the moisture-sensitive nature of the organozinc reagent, calling for an \textit{in situ} preparation without the possibility of rigorous purification. Several other groups have therefore studied the coupling of thermally and moisture stable fluorovinyltin reagents. However, it should be appreciated that such a protocol necessitates the use and disposal of toxic tin residues.

\textbf{Scheme 37:} Scope of couplings with fluorovinylzinc reagents
McCarthy has described the couplings of stannane\textsuperscript{144} 90 and stannane\textsuperscript{145} 91, both of which underwent coupling with a range of organic electrophiles under orthodox conditions. However, (1-fluorovinyl)tributyltin 91 was synthesised in five steps from commercially available ethyl phenyl sulfide using DAST to install the fluorine atom \textit{via} a fluoro-Pummerer reaction of the corresponding sulfoxide. Re-oxidation, $\alpha$-stannylation followed by sulfoxide elimination afforded the product stannane 91. Although stannane 90 could be made in three steps using a Horner-Wadsworth-Emmons olefination using a fluorinated ylid, the removal of the TMS group required either forcing conditions or long reaction times at ambient temperature. However, successful coupling in the absence of Cul is of note (Scheme 38).

\begin{center}
\textbf{Scheme 38:} Couplings of 1-fluoro-1-tributylstannylenes
\end{center}
Further functionality in the fluorovinylstannanes was described by Shi and co-workers, who reacted β-fluoro-β-stanny-α-methoxyacrylate 92 with a range of aryl iodides. Reaction occurred rapidly and in good to excellent yield using 75 mol% CuI in the presence of 10 mol% tetrakis(triphenylphosphine)palladium(0) in DMF at ambient temperature. Poor couplings were observed in the absence of CuI and homocoupling predominated at higher reaction temperatures (no CuI). Bromobenzene failed to react effectively, even at 80°C. An example is shown, where the product was transformed into β-fluorophenylalanine 93 (Scheme 39).

Burton and McCarthy have reported further successful couplings of fluorinated stannanes. Burton described palladium(0)/copper(I) halide-catalysed couplings of 1,2-difluorovinylstannanes with aryl and vinyl iodides. No coupling was observed under orthodox conditions and decomposition occurred at higher temperatures. However, excellent yields could be obtained by using 50 mol% CuI in DMF at ambient temperature in the presence of 3-4 mol% tetrakis(triphenylphosphine)-palladium(0). At the same time, McCarthy described the coupling of 1-fluorovinylstannanes with aryl iodides and acyl chlorides. Attempted coupling under orthodox conditions in THF resulted in very poor conversions. When DMF was used at reflux the conversion was improved but significant amounts of homocoupling.

Scheme 39: Synthesis of β-fluorophenylalanine 93 via a Stille coupling
and protodestannylation were observed. When one equivalent of CuI was used in the presence of 5 mol% Pd(PPh₃)₄ in THF at reflux, smooth coupling occurred to afford the desired products in a short reaction time. Typical examples are depicted below (Scheme 40).

\[
\begin{align*}
\text{SnBu}_3\text{F} + \text{I} & \xrightarrow{3 \text{ mol}\% \text{ Pd(PPh}_3)_4 / 50 \text{ mol}\% \text{ CuI}} \text{DMF, rt} \quad \text{F} & \xrightarrow{92\%} \text{NO}_2 \\
\text{SnBu}_3\text{F} + \text{I} & \xrightarrow{3 \text{ mol}\% \text{ Pd(PPh}_3)_4 / 100 \text{ mol}\% \text{ CuI}} \text{THF, reflux} \quad \text{F} & \xrightarrow{89\%} \text{NO}_2
\end{align*}
\]

**Scheme 40**: Coupling of 1,2-difluorovinyl- and 1-fluorovinylstannanes

Our group has described the attempted coupling of a functionalised 1-fluorovinylstannane with iodobenzene and benzoyl chloride. However, poor yields were obtained under standard Stille conditions although an improved conversion (ca. 40%) could be achieved by employing Farina conditions, in which triphenylarsine was used to increase the rate of transmetallation. It should be noted, however, that no attempt with CuI was tried and the catalyst system employed (2 mol% Pd₂dba₃ / 4 mol% AsPh₃) is very prone to decomposition before full conversion could be achieved (Scheme 41).
Bu₃SnF₃OMEMEtOAll + I₂ mol% Pd₂dba₃ 4 mol% AsPh₃NMP, rt, 18 h → \[
\begin{array}{c}
\text{OMEMEtOAll} \\
\text{F}
\end{array}
\]
40% by $^{19}\text{F}$ NMR

**Scheme 41:** Inefficient coupling of a 1-fluorovinylstannane in the absence of Cul

A further notable success of Cul in fluoroalkene synthesis was provided by Jeong and co-workers\textsuperscript{150} who coupled $\beta,\beta$-diphenyl-$\alpha$-(trifluoromethyl)tributyltin with aryl iodides using 10 mol% Cul in DMF at ambient temperature with 10 mol% tetrakis(triphenylphosphine)palladium(0).

As an extension, Ichikawa has also reported the successful coupling of difluorovinylcopper reagents\textsuperscript{151} and difluorovinylzirconium halides\textsuperscript{152} (via zinc transmetallation). Hanamoto has also described the application of fluorovinylsilanes as coupling components.\textsuperscript{153} In such a way, several difluoroolefin motifs can now be accessed.

It has also been acknowledged that the use of a fluorinated electrophilic component should lead to rapid, facile couplings due to the $–I$ inductive effect of the fluorine atoms. This should lead to facile palladium(0) insertion, resulting in an electron-deficient palladium complex primed for transmetallation.\textsuperscript{154}

Indeed, Burton and McCarthy have been the main instigators of such investigations and have demonstrated the coupling of halofluoroalkenes with organoboronic acids,\textsuperscript{154,155} organostannanes,\textsuperscript{154,156} organozinc reagents\textsuperscript{157} and alkynylcopper reagents\textsuperscript{158} in Suzuki, Stille, Negishi and Sonogashira cross-coupling methodologies, respectively. Of note is the ability of chlorofluoroalkenes to undergo efficient cross-
coupling with aryl boronic acids under standard Suzuki conditions. Wilkes has also described the inefficient coupling of a functionalised 1-fluoro-1-iodoalkene with vinyl tributyltin under Farina conditions. However, Sonogashira couplings were successful and a range fluorinated enynes were synthesised. Some examples of couplings of halofluoroalkenes are given below (Scheme 42).

![Scheme 42: Selected couplings of fluorinated alkenyl halides](image)

Successful couplings of β-fluoroenol triflates have also been described, as well as the couplings of iodofluoro- and iododifluoroalkenes with diethyl phosphite and carbon monoxide, respectively.

In summary, the use of fluorovinyl organometallics in palladium-catalysed cross-coupling is increasing rapidly and the necessity of co-catalytic copper(I) iodide in order to achieve good yields is becoming more apparent. However, the range of fluorinated motifs is limited and a ubiquitous feature is the presence of a sterically
undemanding fluorine atom at the $\alpha$-carbon. In addition, no couplings of 1-oxygenated-2,2-difluorovinylstannanes have been reported.

1.5 Relevant Recent Advances in the use of Trifluoroethanol as a Building-Block

Although difluoroacyl anion equivalents 77 and 83 have been extensively used in the construction of lightly-fluorinated molecules, severe limitations exist in the scope of structure around the fluorinated core. To date, within our group, carbonyl and imine electrophiles have been used and these intermediates have been shown to be a rich source of mid-chain difluoroketones (Scheme 43).

\[
\begin{array}{c}
\text{Li} \quad \text{OR} \\
\text{F} \quad \text{F} \\
\text{F} \quad \text{OR} \\
\text{R'} \quad \text{XH} \\
\text{R} = \text{CONEt}_2 \\
\text{MEM} \\
\text{X} = \text{O or NR''} \\
\text{Y} = \text{OCONEt}_2 \\
\text{Y'} = \text{H}
\end{array}
\]

**Scheme 43: Current use of difluoroacyl anion equivalents 77 and 83**

An attempt at trapping with the soft electrophile iodomethane failed, associated with the deactivating effect of the fluorine atoms, although the use of the more reactive methyl triflate did lead to the observation of product.\textsuperscript{92b} In a recent advance, it was found that transmetallation of the organolithium derivative using a CuI.2LiCl mixed salt afforded a much more nucleophilic organocopper species. Carbon-carbon bond forming reactions were then possible using soft electrophiles such as methyl, benzyl and allyl halides, as well as acid chlorides, to afford unstable enones (Scheme 44).\textsuperscript{104}
In the course of this group’s efforts to utilise Diels-Alder chemistry for constructing difluorinated cyclitol derivatives, $\beta,\beta$-difluorinated alkenoate 94 became a key synthetic target (Figure 9).

Initially, Stansfield attempted the synthesis of 94 using ethyl chloroformate as the reactive electrophile with the copper reagent; unfortunately, reduction occurred in preference to C-C bond formation. Eventually, it was found that palladium(0) mediated an efficient coupling between organocopper reagent 87 and ethyl chloroformate in THF at ambient temperature. However, attempts by Moralee to repeat this work led to capricious results, with reduction being the major pathway. In
a second major advance, Moralee successfully employed a Stille coupling protocol to the synthesis of a range of alkenoate derivatives\textsuperscript{163} in which difluorinated vinyl stannane 81 was used as the organometal. Stannane 81 can be routinely synthesised on up to a mole scale; it is both thermally and air-stable and can be easily handled and stored. Importantly, it was found that Farina-Liebeskind conditions, where CuI is present to activate the palladium(II) complex by phosphine complexation, was required in order to obtain good results. The requirement of this additive goes some way to explain previous failures at utilising this difluorovinyl metal species in coupling protocols. **Scheme 45** shows a comparison between the two routes to this important target.

**Scheme 45**: Synthesis of alkenoate 94 using palladium-catalysed coupling

During the course of this PhD, Thomas showed how 1-(\(N,N\)-diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene 82 can participate in Suzuki-Miyaura couplings with aryl boronic acids to afford a range of \(\beta,\beta\)-difluorostyrenes 95.\textsuperscript{164} The methodology was
limited, however; heteroaryl, vinyl and alkyl boronic acids or their derivatives failed to afford the desired products, producing the reduced product instead (Scheme 46).

\[
\begin{align*}
\text{Scheme 46: Styrene synthesis by Suzuki-Miyaura coupling of iodoalkene 82}
\end{align*}
\]

1.6 Objectives

(Aryl) difluoromethyl ketones

A study of the current approaches to this class of molecule shows that none are capable of generating diversity in the aromatic core or in generating a large array of materials quickly and efficiently. A novel and more succinct approach would involve pre-formation of a single difluoroenol scaffold from which aryl attachment followed by general cleavage would afford the desired materials. One such approach will be described in this thesis. Scheme 47 outlines the idea.

\[
\begin{align*}
\text{Scheme 47: Outline of our approach to } \alpha,\alpha\text{-difluoromethyl aryl ketones}
\end{align*}
\]
**Fluorinated carbohydrates**

A successful outcome to the initial study outlined above would be a method that allowed the generation of fluorinated 1,3-dienes. These materials are particularly rare in the literature and their use as building-blocks to highly oxygenated materials has not been studied. We wish to manipulate the initial diene products through asymmetric dihydroxylation reactions to afford enantiomerically enriched diols. Cleavage of the difluoroenoil motif would then form a difluoroketodiol, which could serve as a building block to fluorinated carbohydrate analogues in a catalytic asymmetric fashion. **Scheme 48** outlines the approach discussed in this Thesis.

![Scheme 48: Proposed catalytic asymmetric approach to oxygenated organofluorine compounds](image_url)

**Scheme 48**: Proposed catalytic asymmetric approach to oxygenated organofluorine compounds
Chapter Two

Results and Discussion
In order to expand upon the synthetic utility of difluoroacyl anion equivalent chemistry, a study was initiated in which potentially useful \( \alpha,\alpha \)-difluoromethyl aryl ketones were targeted using palladium-catalysed cross-coupling methodology. Retrosynthetic analysis of the target materials identified a difluorovinyl organometallic reagent as the key starting material and the known 1-(N,N-diethylcarbamoyloxy)-2,2-difluoro-1-(tributylstannyl)ethene \( 81 \) was chosen to develop the approach (Scheme 49).

![Scheme 49: Retrosynthetic analysis of \( \alpha,\alpha \)-difluoromethyl aryl ketone synthesis using a protected metallated difluoroenol](image)

2.1 Palladium-catalysed Coupling

2.1.1 Coupling of 1-(N,N-Diethylcarbamoyloxy)-2,2-difluoro-1-(tributylstannyl)ethene \( 81 \)

Synthesis of stannane \( 81 \)

The requisite stannane \( 81 \) was prepared successfully according to the procedure of Haworth.\(^99\) Deprotonation of trifluoroethanol with sodium hydride and subsequent trapping of the resultant sodium alkoxide with \( N,N \)-diethylcarbamoyl chloride afforded \( N,N \)-diethylcarbamate \( 96 \). On treatment with two equivalents of LDA in THF at \(-78^\circ\text{C}\), this undergoes deprotonation with concomitant anti-elimination of LiF to afford an enol carbamate (an overall dehydrofluorination step). A second, more rapid metallation step\(^{165}\) follows to afford thermally unstable difluorovinylolithium \( 77 \).
Quenching of this intermediate with tributyltin chloride leads to the formation of 2,2-difluorovinylstannane 81. Purification by column chromatography on silica gel led to 81 in excellent (94%) yield (Scheme 50).

Reagents and Conditions: i) 1.0 NaH, THF, 0°C; ii) Et₂NCOCl, 0°C to rt, 16 h, 88%; iii) 2.0 LDA, THF, -78°C; iv) Bu₃SnCl, -78°C to rt, 94%

Scheme 50: Synthesis of vinyl stannane 81

Optimisation of couplings

In order to develop an efficient coupling protocol for stannane 81, an extensive series of experiments was conducted in which the role of solvent, temperature, catalyst, additive and ligand was studied. 4-Iodoanisole has been previously used with success in couplings to fluorinated stannanes with good efficiency and was chosen as the test substrate.¹⁴²ᵃ, ¹⁴⁷ᵃ⁻ᵇ

In order to ascertain the general reactivity of stannane 81, conditions previously developed by Moralee to couple to chloroformates were investigated.¹⁶³ᵃ⁻ᵇ When a solution of stannane 81, 4-iodoanisole, copper(I) iodide (10 mol%),
tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (Pd$_2$dba$_3$.CHCl$_3$, 5 mol% Pd) and triphenylphosphine (20 mol%, Pd:PPh$_3$ = 1:4) was heated at 50°C for 165 hours in THF, analysis by $^{19}$F NMR indicated a 1:1 mixture of 81 and a new material exhibiting a set of doublets at -95 and -105 ppm. Isolation of this material and analysis by $^1$H NMR and mass spectrometry identified it as the desired anisole derivative 95a (Scheme 51).

Scheme 51: Initial coupling using Farina conditions

The observation of product was pleasing although the low rate of reaction was surprising, given that ethyl chloroformate, albeit a more reactive partner (via formation of an electron-deficient acyl palladium complex), undergoes complete reaction in 3 hours with as little as 2.5 mol% palladium(0).

Increasing the reaction temperature to reflux (65°C) allowed the complete consumption of the stannane 81 in 18 hours, but also led to the formation of three side-products with distinct sets of fluorine signals. Two such sets (at -90 and -98 ppm and -97 and -117 ppm respectively) had been previously independently identified as dimer 97 and enol carbamate 98. These materials result from oxidative homocoupling or protodestannylation of the organostannane, respectively.$^{148b}$ A third set, at -95 and -103 ppm had not previously been observed. The similarity of the chemical shifts with the anisole 95a suggested an aryl derivative. Indeed, upon
isolation of a small amount of this material and analysis by $^1$H NMR, all signals were similar to 95a except for the absence of the methyl singlet corresponding to the methoxy group. A mass spectrum confirmed its identity as unsubstituted styrene 95d. This was also later corroborated by its independent synthesis (Figure 10).

![Chemical Structures](image)

**Figure 10:** Three side-products formed by coupling in THF at reflux

The formation of 95d is due to aryl transfer from palladium-phosphine complexes. Novak and co-workers have described the insertion of palladium(0) into a variety of aryl iodides in the presence of different phosphine ligands. Aryl group interchange was found to be strongly dependent upon the identity of the phosphine ligand and the substituent on the aryl iodide. Interestingly, of those tested, the complex resulting from insertion of palladium(0) into 4-iodoanisole in the presence of triphenylphosphine gave the fastest rate of phenyl group transfer, thus explaining the presence of styrene 95d in our case (Scheme 52).
In order to increase the rate of transmetallation, triphenylarsine was used as a soft ligand, in which the palladium(II) complex should become more electrophilic. However, no significant change was observed in product ratio although the change of ligand did suppress the formation of styrene $95d$. This proved to be a common observation in all runs with triphenylarsine, and aryl exchange only occurred with this substrate.

The persistent observation of large amounts of enol carbamate $98$ and the presence of dimer $97$ are both associated with a slow transmetallation step and the consequent long reaction times, resulting in decomposition of the enol stannane.$^{148b}$

In order to attempt to increase the rate of transmetallation, a solvent change to DMF was investigated, for which precedence suggests that in situ transmetallation to a more reactive organocopper species should occur.$^{139}$

**Scheme 52: Proposed formation of styrene $95d$**
When DMF (first run at 120°C, triphenylphosphine as ligand, entry 5 in Table 1) was used as a reaction solvent this led to a dramatic 500-fold increase in the rate with reaction complete within 20 minutes. Analysis by $^{19}$F NMR indicated the presence of only the desired product 95a and traces of styrene 95d (vide ante). In order to rule out a temperature effect, a survey was undertaken in order to establish whether this result was due to the solvent medium, or the fact that the reaction was undertaken at this higher reaction temperature. Entries 5-7 in Table 1 (runs at 120°C, 70°C and 50°C) clearly indicate that the effect is purely due to the presence of a more polar reaction medium, although the rate does indeed drop on lowering the temperature. The lower isolated yield on increasing temperature possibly indicates the progressively lower stability of the organocopper intermediate at increasing temperature. This degree of rate enhancement was unexpected and suggested that transmetallation was the rate-determining step. Comparision of entries 1 and 7 clearly indicate a positive change in the mode of action of the copper(I) salt.

The presence of the styrene impurity was duly solved by the use of triphenylarsine as the ligand. In a run at 100°C in DMF in the presence of triphenylarsine, anisole 95a was the sole product by $^{19}$F NMR, with an estimated yield of 80% using 4-fluorotoluene as an internal standard (entry 8, Table 1).

As a final demonstration of the effect of DMF, a run was made in which THF was used as the initial solvent at ambient temperature. After 150 hours, $^{19}$F NMR indicated the slow (50%) reduction of the stannane to the enol carbamate (transmetallation is further compromised by a reduction in temperature; thermal dimerisation is presumably too slow at this temperature) with no detection of product. Addition of an equal volume of DMF with stirring for 18 hours resulted in clean
coupling of the residual stannane to afford the product (overall 1:1 \textbf{95a:98}) as judged by \textsuperscript{19}F NMR. The ability of DMF to mediate couplings at ambient temperature \textit{in the presence of triphenylphospine} was remarkable, since it demonstrates that transmetallation occurs even at this temperature. This observation is in contradiction with the literature,\textsuperscript{139} which states that, based upon NMR evidence of the reaction between phenyltributyltin and CuI in DMF (at a probe temperature of 30°C) to form phenylcopper, that triphenylphosphine completely suppressed the reaction. In a separate run, 4-idoanisole underwent efficient coupling under arsine conditions (loading of copper(I) iodide was increased to 50 mol\%) in DMF to afford \textbf{95a} as the sole product (entry 11).

In order to verify the necessity of copper(I) iodide co-catalysis, two runs were made in which both copper(I) iodide and palladium(0) were individually omitted. When a reaction was run in the absence of copper(I) iodide, a low (10\%) yield was obtained with starting material being recovered, emphasising the importance of the co-catalyst (entry 9). In order to test whether copper(I) iodide could mediate the coupling alone, a run was made in the absence of palladium catalyst. In this instance, all material was converted through to enol carbamate \textbf{98} (entry 10). This is not too surprising, since aryl iodides are unreactive to S\textsubscript{N}2 reaction, and oxidative addition into a carbon-iodine bond by copper(I) is a difficult process and usually requires activated copper(I) complexes\textsuperscript{123a} or additives.\textsuperscript{123c} \textbf{Table 1} summarises these results.
Table 1. Effect of temperature and solvent on the cross-coupling of stannane 81 with 4-iodoanisole using a 5% Pd(0) /20% PPh₃ /10% Cul catalytic system

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp/°C</th>
<th>Reaction Time /h</th>
<th>Yield% (NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>50</td>
<td>165</td>
<td>-ᵃ</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>65</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>3ᵇ</td>
<td>THF</td>
<td>65</td>
<td>24</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>THF/DMFc</td>
<td>23</td>
<td>168</td>
<td>- (50)</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>120</td>
<td>0.3</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>70</td>
<td>0.5</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>50</td>
<td>2</td>
<td>83</td>
</tr>
<tr>
<td>8ᵇ</td>
<td>DMF</td>
<td>100</td>
<td>1.5</td>
<td>63</td>
</tr>
<tr>
<td>9ᵈ</td>
<td>DMF</td>
<td>100</td>
<td>48</td>
<td>10</td>
</tr>
<tr>
<td>10⁹</td>
<td>DMF</td>
<td>100</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>11ᶠ</td>
<td>DMF</td>
<td>23</td>
<td>6</td>
<td>69⁹</td>
</tr>
</tbody>
</table>

ᵃ Reaction was incomplete by NMR. ᵇ Triphenylarsine was used as ligand. ᵈ Reaction was run with THF for 150 hours, with NMR indicating 81 plus 98; equal volume of DMF then added and stirred overnight, affording a 1:1 mixture of 98 and 95a by NMR. ᵉ No CuI added. ᵉ No palladium(0) source or phosphine ligand added. ᵇ 50 mol% Cul used. ᵉ Estimate by ¹⁹F NMR using 4-fluorotoluene as standard.

Role of copper(I) iodide

In order to probe the role of the copper(I) iodide further, test reactions were performed with allyl bromide, so that it would be possible to study the palladium-free cross-coupling reaction. The previously successful coupling of our organocopper reagent,¹⁰⁴ along with literature precedents suggest that organocopper reagents can undergo unassisted reaction with soft electrophiles¹⁰⁴ and only require transition-metal assistance with chloroformates¹⁶² and aryl halides.¹⁵¹ᵃ
When stannane 81 was reacted with allyl bromide under standard palladium(0) catalysis (i.e. in the absence of copper(I) iodide) at 50°C in DMF, a sluggish reaction proceeded to afford a very poor yield of diene 99d. When the reaction was repeated with the copper(I) salt as the sole coupling catalyst at 50°C in DMF, reaction occurred to afford a significant percentage (30%) of the desired diene by $^{19}$F NMR. The large amount of reduced product and especially that of homocoupled material is characteristic of an organocopper intermediate 87 (Scheme 53). Though the reaction flask was pump-purged to remove oxygen and the solvent degasssed, the reaction vessel may well have several leaks, leading to the presence of sufficient oxygen to facilitate dimerisation.

**Scheme 53:** Cul-catalysed formation of allyl product 99d in the absence of palladium(0)
Coupling under Pd(0)/Cu(I) co-catalytic conditions successfully formed diene 99d in high (75-87%) yield with only traces of dimer 97 and enol carbamate 98 present (see pg 64).

If transmetallation does indeed occur then it should be beneficial to use high loadings of copper(I) iodide in these couplings in order to increase the reaction rate. Indeed, literature methods often use 50-75 mol% for this type of coupling with fluorinated stannanes.\textsuperscript{146,147a}

\textit{Scope of coupling process}

Having developed favourable conditions (entries 7 and 8, \textbf{Table 1}), a series of couplings was then attempted to assess the reactivity of a range of aryl, heteroaryl, allyl and vinyl halides. The aryl substrates used would test the coupling system to changes in both the steric and electronic nature of the electrophilic component. \textbf{Tables 2} and 3 show the results.
Table 2: Coupling of stannane 81 with aryl iodides

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield/% (NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-Ph-OEt</td>
<td>A</td>
<td>95a</td>
<td>83</td>
</tr>
<tr>
<td>I-Ph-OEt</td>
<td>C</td>
<td>95b</td>
<td>49</td>
</tr>
<tr>
<td>I-Ph-MeO</td>
<td>D</td>
<td>95c</td>
<td>0 (0)</td>
</tr>
<tr>
<td>I-Ph</td>
<td>A</td>
<td>95d</td>
<td>80</td>
</tr>
<tr>
<td>I-Ph-OTf</td>
<td>A</td>
<td>95e</td>
<td>82-91(^a)</td>
</tr>
<tr>
<td>CO(_2)Me</td>
<td>B</td>
<td>95f</td>
<td>55</td>
</tr>
<tr>
<td>I-Ph-N(_2)O</td>
<td>D</td>
<td>95g</td>
<td>18</td>
</tr>
<tr>
<td>I-Ph-OH</td>
<td>B</td>
<td>95h</td>
<td>- (84)</td>
</tr>
<tr>
<td>I-Ph-NH(_2)</td>
<td>A</td>
<td>95j</td>
<td>- (41)</td>
</tr>
</tbody>
</table>

A: 2.5% Pd\(_{2}\)dba\(_3\), CHCl\(_3\), 20% PPh\(_3\), 10% Cul, DMF, 50°C;
B: 2.5% Pd\(_{2}\)dba\(_3\), CHCl\(_3\), 20% AsPh\(_3\), 10% Cul, DMF, 100°C;
C: 5% Pd(OAc)$_2$, 20% AsPh$_3$, 10% Cul, DMF, 100°C;
D: 5% Pd(OAc)$_2$, 20% PPh$_3$, 10% Cul, DMF, 50°C;

\(^a\) Determined over 2 runs
Table 3: Coupling of stannane 81 with other organic electrophiles

\[
\text{81} \xrightarrow{\text{DECO SnBu}_3} \xrightarrow{\text{Pd(0)} \text{ R-I}} \text{DECO} \quad \text{99}
\]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IO</td>
<td>A</td>
<td>99a</td>
<td>44</td>
</tr>
<tr>
<td>IO-THP</td>
<td>B</td>
<td>99b</td>
<td>46</td>
</tr>
<tr>
<td>OBn</td>
<td>A</td>
<td>99c</td>
<td>25</td>
</tr>
<tr>
<td>Br-</td>
<td>A</td>
<td>99d</td>
<td>64-87(^b)</td>
</tr>
</tbody>
</table>

A: 2.5% Pd\(_{2}\)dba\(_3\).CHCl\(_3\), 20% PPh\(_3\), 10% Cul, DMF, 50\(^\circ\)C;
B: 2.5% Pd\(_{2}\)dba\(_3\).CHCl\(_3\), 20% AsPh\(_3\), 10% Cul, DMF, 100\(^\circ\)C;
\(^b\) Determined over 4 runs
This study provides the most diverse set of examples currently known for couplings of fluorinated stannanes. It was observed that electron-deficient aryl iodides readily underwent reactions to afford crude products with clean $^{19}\text{F}$ NMR spectra. Therefore, under these optimised conditions which facilitate transmetallation, palladium(0) insertion into the carbon-iodine bond presumably becomes the rate-determining step. It is presumed that tin-copper transmetallation occurs readily at or just above ambient temperature (30-40°C) affording a low concentration (equal to the amount of copper(I) iodide added) of the organocopper reagent, primed to undergo reaction. If the corresponding concentration of the organopalladium(II) complex resulting from oxidative addition is low, decomposition of the organocopper reagent occurs, via reduction and homocoupling.

Given the fact that tetakis(triphenylphosphine)palladium(0) will insert spontaneously into iodobenzene at ambient temperature, aromatic rings bearing electron-withdrawing groups such as nitro (NO$_2$), alkoxy carbonyl (CO$_2$R), fluoro (F) and trifluoromethanesulfonyl (OSO$_2$CF$_3$) should perform particularly well. The presence of electron-donating substituents has variable effects. Though a methoxy group at the para position exerts a resonance (mesomeric) $\pi$-donor effect at the carbon atom bearing the iodine atom, the observed $^{19}\text{F}$ NMR spectrum was still clean, except for traces of 98. This indicates that the rate of palladium(0) insertion is not greatly affected by the presence of such electron-donating groups. A meta-methoxy group only possesses a weak $-I$ effect and therefore performs well. A limitation was found with aryl units bearing a para-amino or para-hydroxyl group. In this case, the degree of resonance donation to the $\pi$-framework is inferred to greatly affect the ease with which palladium(0) can insert into the carbon-iodine bond.
Reduction and dimerisation therefore account for the major reaction products. In addition, ortho sp$^3$ substituents were not tolerated (entry 3), although ortho sp$^2$ centres proved to react smoothly (entry 6).

2.1.2 Coupling of 1-(N,N-diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene 82

The successful coupling with the 2,2-difluorovinylstannane 81 prompted us to turn our attention to the corresponding iodoalkene 82. One would anticipate that 82 would undergo oxidative addition rapidly to afford a reactive vinylpalladium complex; the electron-deficient fluoroalkenol group should then increase the electrophilicity of the metal centre facilitating the transmetallation reaction. The requirement of copper(I) co-catalysis should therefore be less important. In addition, this coupling is synthetically complementary to the coupling with stannane 81, since steric effects should not affect the oxidative addition. Therefore, use of ortho-substituted organometals should lead to the desired products, with fewer problems, as demonstrated by the work of Thomas.164

Synthesis of difluoroiodoalkene 82

The requisite difluorovinyl iodide 82 was successfully prepared according to the procedure of Howarth.99 The lithiated intermediate 77 was generated in an identical manner to that previously described (vide ante) from carbamate 96. In this instance, anhydrous zinc(II) bromide (as a solution in THF) was added presumably to afford thermally stable vinylzinc reagent 88. Quenching with elemental iodine (as a solution in THF) at 0°C, followed by Kügelrohr distillation of the crude material afforded vinyl iodide 82 in moderate (57%) isolated yield (Scheme 54).
Scheme 54: Synthesis of iodoalkene 82

**Scope of coupling process**

In order to test the generality of this coupling process, a range of stannanes differing in structure were reacted with vinyl iodide 82 under two sets of conditions taken from the coupling of vinyl stannane 81. Vinyl, aryl, heteroaryl and allyl stannanes were tested. The results are shown in Table 4.
Table 4: Stille Couplings of iodoalkene 82

<table>
<thead>
<tr>
<th>Stannane</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield/% (NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu$_3$Sn</td>
<td>A: 5% Pd(OAc)$_2$, 20% AsPh$_3$, 10% Cul, DMF 100°C, 16 h; B: 2.5% Pd$_2$dba$_3$.CHCl$_3$, 20% PPh$_3$, 10% Cul, DMF 50°C, 16 h; C: 2.5% Pd$_2$dba$_3$.CHCl$_3$, 20% AsPh$_3$, 10% Cul, DMF 100°C, 16 h</td>
<td>DECO</td>
<td>99e 36</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>77</td>
</tr>
<tr>
<td>Bu$_3$Sn</td>
<td>A</td>
<td>DECO</td>
<td>99f 72-80$^a$</td>
</tr>
<tr>
<td>C$<em>5$H$</em>{11}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bu$_3$Sn</td>
<td>A</td>
<td>DECO</td>
<td>99c 40</td>
</tr>
<tr>
<td>OTHP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bu$_3$Sn</td>
<td>B</td>
<td>DECO</td>
<td>95a 35</td>
</tr>
<tr>
<td>OMe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bu$_3$Sn</td>
<td>B</td>
<td>DECO</td>
<td>99g 81</td>
</tr>
<tr>
<td>α,β-unsaturated bond</td>
<td>A</td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>Bu$_3$Sn</td>
<td>B</td>
<td>DECO</td>
<td>99a 36$^b$</td>
</tr>
<tr>
<td>S</td>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Bu$_3$Sn</td>
<td>A</td>
<td>DECO</td>
<td>99h 0</td>
</tr>
<tr>
<td>N-CHO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bu$_3$Sn</td>
<td>B</td>
<td>DECO</td>
<td>99j 0</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bu$_3$Sn</td>
<td>A</td>
<td>DECO</td>
<td>99k 0 (65)</td>
</tr>
<tr>
<td>O, O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bu$_3$Sn</td>
<td>B</td>
<td>DECO</td>
<td>99d - 0$^c$</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td></td>
<td>18$^d$</td>
</tr>
</tbody>
</table>

A: 5% Pd(OAc)$_2$, 20% AsPh$_3$, 10% Cul, DMF 100°C, 16 h; B: 2.5% Pd$_2$dba$_3$.CHCl$_3$, 20% PPh$_3$, 10% Cul, DMF 50°C, 16 h; C: 2.5% Pd$_2$dba$_3$.CHCl$_3$, 20% AsPh$_3$, 10% Cul, DMF 100°C, 16 h

$^a$ Yields determined over 5 runs, 1 mmole scale. $^b$ Stannane was added over 1 hour. $^c$ Products 97 and 98 only. $^d$ Along with 82 (16%), 98 (34%) and 97 (32%) by NMR.
The coupling of vinyltributytin with 82 was initially attempted using the conditions described for coupling to the corresponding stannane (conditions 8, Table 1). A rapid (ca. 10 min) and efficient reaction ensued to afford diene 99e, but a poor isolated yield and a continuing problem of co-elution of the product with the dibenzylideneacetone (dba) ligand led to the investigation of using a palladium(II) source and generating the palladium(0) in situ. Repetition with palladium(II) acetate led to a cleaner reaction with 1,3-diene 99e being isolated in up to 77% yield on a 5 mmol scale.

The use of a 5:1 isomeric mixture of E/Z-heptenyltributylstannanes 100a also led to a reproducible (5 runs, 1 mmol scale), high-yielding (72-80%), clean and stereospecific reaction to afford dienes 99f (5:1 E/Z).

In order to test the possibility of coupling protected allylic alcohol fragments (as required for sugar targets, see pg 110), stannane 100b was synthesised according to the procedure of Corey in 71% yield.\textsuperscript{168} However, attempted coupling led to a complex mixture of products, although the desired product 99c could be isolated in moderate (40%) yield.

In order to establish a direct comparison between the two approaches, (4-methoxyphenyl)tributyltin was synthesised. Treatment of 4-iodoanisole with two equivalents of n-BuLi (in order to destroy iodobutane) at -78°C led to a yellow solution, presumably containing aryllithium 101, which was trapped with tributyltin chloride to afford stannane 100c in high (95%) yield. Traces of residual tributyltin chloride could not be removed, however (Scheme 55).
Coupling under conditions A (see Table 4) led to the isolation of styrene \textit{95a} in relatively poor (35\%) yield (cf. 83\% for couplings with stannane 81). This result suggests that either couplings with iodoalkene 82 are sensitive to stannane structure or that the conditions used were not optimal and that further optimisation is required. Couplings with the commercially available heterocyclic stannanes were then pursued. 2-(Tributylstannyl)furan proved to be reactive both under conditions A and B (see Table 4) and furan \textit{99g} could be isolated in good (81\% and 72\%) yield, respectively. The reaction also proceeded efficiently without copper(I) iodide co-catalyst, although the product was isolated in a poor yield. (2-Tributylstannyl)thiophene was observed to be a poorer reactant than its furyl congener, contrary to observations by McCarthy in the coupling of 1-fluoro-1-bromo-olefins.\textsuperscript{154} Crude $^{19}$F NMR were uniformly contaminated with side-products \textit{97} and \textit{98}, as well as the presence of signals consistent with the desired product \textit{99a} (Figure 11).
Figure 11: Main products of coupling with 2-(tributylstannyl)thiophene

In addition, other resonances were observed which Thomas had previously assigned by NMR and mass spectrometric evidence to the dimers 102a and 102b, resulting from acid or thermally-promoted [2+2] cycloadditions (Scheme 56).

Scheme 56: Decomposition of thiophene 99a by dimerisation

Similar observations have been made by both Normant and Uneyama, who have described the thermal dimerisation of difluorovinyl species to afford the corresponding tetrafluorocyclobutane derivatives.
Given the susceptibility to dimerisation described by Normant of a thienyl derivative, and that coupling of the iodide should be facile, reaction was attempted under Farina conditions (copper(I) iodide plus triphenylarsine) at ambient temperature in THF. Although the reaction was slow, an 88% conversion in 48 hours could be achieved, without the formation of any side-products.

No reaction was observed with 2-(tributylstanny1)furan at ambient temperature using a palladium(II) source, suggesting that pre-reduction of the catalyst by the stannane requires temperatures higher than ca. 20°C, though reduction does occur at 50°C. Further failures were obtained with pyrrolyl stannane 100d and thiazolyl stannane 100e, which both preferentially underwent protodestannylation. An initial attempt using functionalised furyl stannane 100f led to formation of furan 99k in good yield by NMR though no product could be obtained by column chromatography. Subsequent attempts led to the recovery of starting material, possibly due to the poor quality of the stannane.

The most notable result was obtained with allyltributyltin. Under conditions A, the product mixture was extremely complex affording very low, if any, amounts of coupled product 99d. Attempts at applying Farina conditions led to the return of starting material. The reasons for these observations are unknown, although it has been shown that the allyl group transfers from tin very slowly. It is possible that this transfer is so slow that the organopalladium complex can fragment to afford decomposition products. However, Liebeskind and Farina reported near identical results in the coupling of both vinyltributyltin and allyltributyltin with iodobenzene under Cul co-catalysed conditions.
These results indicate that the difluoroiodoalkene 82 can be used in palladium-catalysed couplings but that further optimisation is required. The results of Thomas suggest that palladium(0) insertion may not be as facile as expected, since high (100°C) temperatures are required, even with nucleophilic boron-ate species. However, conditions have appeared in the literature for coupling similar halides and should be more successful (see pages 46-47). It should be noted that Cul was not required, as predicted.

2.1.3 Potential for Negishi couplings for styrene synthesis

Although Stille couplings have afforded a rich array of products, with potential for further elaboration, the inherent problems associated with the use of tin must be addressed. Tin compounds are toxic and tributyltin chloride is highly toxic and difficult to remove from reaction mixtures, so alternatives need to be sought. Zinc is a good candidate as an alternative to tin in order to avoid these problems since it is readily available, less toxic and produces water-soluble by-products.

It was decided to briefly investigate the possibility of using organozinc reagent 88 in cross-coupling with iodobenzene.

Following the usual procedure, the organolithium intermediate 77 was generated and trapped with anhydrous zinc(II) bromide. The red solution quickly changed to a pale orange solution, which persisted when the presumed zinc intermediate 88 was warmed to ambient temperature, with no indication of decomposition. A solution of iodobenzene in THF was added, followed by triphenylphosphine and [Pd_{2}dba_{3}.CHCl_{3}] adduct. After stirring for 48 hours at ambient temperature, work-up
and $^{19}$F NMR analysis indicated a 66:34 ratio of styrene 95d and reduced product 98. Purification was facile affording pure 95d in 55%, isolated yield (Scheme 57).

Scheme 57: Successful Negishi coupling of vinylzinc reagent 88 with iodobenzene

Reagents and Conditions: i) 2.0 LDA, THF, -78°C; ii) ZnBr2, -78°C to rt; iii) 2.5% Pd$_2$dba$_3$.CHCl$_3$, 20% PPh$_3$, iodobenzene, THF, rt, 48 h, 55%

The large amount of reduced product was seen as possibly being associated with the high hygroscopicity of the zinc bromide, so the reaction was repeated using a commercial solution of zinc chloride in THF. Unfortunately, the system appears prone to opportunistic hydrolysis, since large amounts of reduced product were again observed, along with a small amount of coupled product 95d. ZnCl$_2$(TMEDA) represents a non-hygroscopic source of zinc(II) chloride$^{171}$ and could be used in future studies. Nevertheless, these initial results represent a promising move forward away from a tin protocol.

2.1.4 Cleavage of the N,N-diethylcarbamoyl protecting group

Balnaves has demonstrated that treatment of tertiary and some secondary N,N-diethylcarbamoyloxy aldol products with methanolic KOH resulted in the required deprotection of the carbamate moiety.$^{172}$ Reaction occurred in a considerably cleaner fashion with tertiary aldols. Secondary alcohols were much less reactive and often
led to complex mixtures, although the desired products could be isolated by column chromatography. In addition, only those with 1,3-syn relationships underwent reaction (Scheme 58).

![Scheme 58: Cleavage of a N,N-diethylcarbamoyloxy group from tertiary and secondary centres](image)

In styrene derivatives, the latent ketone must be revealed by cleaving the N,N-diethylcarbamoyl group with an external nucleophile or electrophile.

**Cleavage with nucleophiles**

Férézou and co-workers have described the use of methyllithium as a nucleophilic species capable of deprotecting vinyl N,N-diisopropylcarbamates. The reaction is facilitated by the addition of TMEDA to activate the methyllithium by forming a monomeric species and three equivalents are used in order to produce simple by-products (Scheme 59).

![Scheme 59: Deprotection of N,N-diisopropylcarbamates](image)
Given the known reactivity of silyl difluoroenol ethers to cleavage, it was decided to attempt a reaction with methyllithium, using chlorotrimethylsilane to trap the potential lithium enolate.

Following the literature procedure, anisole derivative 95a was treated with three equivalents of MeLi at 0°C for 1 hour, followed by the addition of ten equivalents of TMEDA. The reaction was then allowed to stir for 15 minutes. Quenching with chlorotrimethylsilane followed by analysis by $^{19}$F NMR after work-up indicated the consumption of starting material, though no fluorinated components survived the reaction. Inspection of the $^1$H NMR indicated the absence of any carbamate signals, suggesting that successful cleavage of the DEC group had indeed occurred. Repetition of the reaction with quenching at -78°C led to the observation of a clean conversion to a single monofluorinated compound rather than silyl difluoroenol ether 103. Column chromatography allowed the isolation and characterisation of (E)-fluorovinylstyrene 104, formed by single stereoselective fluoride replacement by a methyl group (Scheme 60).

\[
\begin{align*}
\text{Reagents and Conditions:} & \quad \text{i)} 3.0 \text{ MeLi, THF, -78°C, 1h;} \\
& \quad \text{ii)} \text{TMEDA, 15 min;} \\
& \quad \text{iii)} \text{Me}_3\text{SiCl, -78°C to rt, 64%}
\end{align*}
\]

**Scheme 60: Monodefluorination by MeLi at -78°C**
This result shows that the difluoromethylene centre is more electrophilic than the carbamate carbonyl group. This reactivity precludes the use of nucleophilic reagents to cleave the enol \( N,N \)-diethylcarbamate.

**Cleavage with electrophiles**

It was hoped that the carbonyl group could be activated to attack by a nucleophile by reacting the olefin with an electrophile to form a carbocation that should fragment to release the ketone.

Indeed, treatment of anisole 95a with one equivalent of bromine in dichloromethane for 16 hours led to the disappearance of starting material and the formation of a new material by TLC. Analysis by \( ^{19}\text{F} \) NMR revealed a singlet at -60 ppm, consistent with the formation of bromodifluoromethyl ketone 105 (Scheme 61).

![Scheme 61: Cleavage of the DEC group with bromine](image)

A similar outcome was observed when sulfuryl chloride was used as a source of electrophilic chlorine. After 3 h, starting material was absent by TLC, although the initial violet colour of the reaction had not cleared. Water was added to quench the reaction and the violet colour disappeared. After an extractive work-up, analysis by \( ^{19}\text{F} \)-NMR revealed chlorodifluoromethyl ketone 106 as the major component (\( \delta_F \) -60.2) in addition to a minor by-product (Scheme 62).
The cleavage of the DEC group with halogen electrophiles shows that this approach to \(\alpha,\alpha\)-difluoromethyl aryl ketones is feasible. However, although the DEC group can be cleaved, it was hoped that a more diverse cleavage strategy could be achieved.

2.1.5 Generalising the coupling protocol to variable enol protection

With successful coupling results, it was decided to briefly study the \(\alpha\)-steric effect of the enol protecting group, since it was thought that the DEC group might well be superseded by others at a later date.

The cleavage of the enol-protecting group is the key step in the approach to aryl ketones and the mode of cleavage should be compatible with other functional groups present in the substrate. Balnaves has studied the installation and cleavage modes of several carbamate derivatives,\(^{172}\) including those shown in Figure 12.

![Figure 12: Carbamate protecting groups investigated to date for use in difluoroketone synthesis](image)
In order to study the $\alpha$-steric effect in coupling efficacy, two difluoroenol C-stannane derivatives were synthesised using our standard procedures and the coupling reaction examined with allyl bromide. $^{19}$F NMR of crude reaction mixtures was used to determine the efficiency of the reaction. Table 5 shows the results.

Table 5: Effect of enol protecting group upon efficiency of coupling

<table>
<thead>
<tr>
<th>Carbamate</th>
<th>Stannane</th>
<th>Yield/%</th>
<th>Product</th>
<th>Yield/% by $^{19}$F NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>F$_3$C=O</td>
<td>F=O DAC</td>
<td>94%</td>
<td>F=O DAC</td>
<td>107         63%</td>
</tr>
<tr>
<td>O=O</td>
<td>F=O SnBu$_3$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F$_3$C=O</td>
<td>O=O TBDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O=O</td>
<td>F=O SnBu$_3$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F$_3$C=O</td>
<td>O=O ODEC</td>
<td>94%</td>
<td>F=O ODEC</td>
<td>99d         87%</td>
</tr>
<tr>
<td>O=O</td>
<td>F=O SnBu$_3$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Generation of the lithio derivatives occurred without any problems and electrophilic trapping with tributyltin chloride led to the stannane derivatives in good yield after simple purification.

Coupling of each derivative occurred with reasonable efficiency under the previously optimised conditions and the 1,4-dienes were the major products by $^{19}$F NMR with the corresponding enol carbamates present as the by-products.

HPLC of the Hoppe-derived product allowed the separation of the two materials, resulting in 60% yield for the allyl product 108, in addition to 13% for the proto-destannylation product. The high proportion of coupled material is important, as it
indicates that the steric demands around the carbamate has minimal effect on the efficiency of the coupling. The large protecting group could potentially sweep a large volume around the reaction centre.

**An N-ethyl-N-(2-methylallyl)carbamato protecting group**

Although the Hoppe carbamate has been successfully used in difluoropolyol synthesis,\textsuperscript{103,172} the high cost detracts from its use in the possible large-scale synthesis of aryl difluoromethyl ketones. It was hoped that it would be possible to mimic the mode of cleavage of this protecting group through the formation of an $N$-alkylated allylcarbamate derivative $109$, such as those shown in Figure 13.

![Figure 13: Possible $N$-allyl carbamates in synthesis](image)

Early attempts at synthesising carbamate $109a$ (designated MAC) resulted in limited success. The corresponding secondary carbamate could be synthesised in good (86%) yield by treating trifluoroethanol with allyl isocyanate in the presence of copper(II) chloride according to the method of Duggan.\textsuperscript{174} However, many attempts to $N$-methylate with iodomethane and various bases resulted in isocyanate expulsion followed by multiple addition to form the carbamate, allophanate and isocyanurate.\textsuperscript{175} Carbamate $109b$ (designated Emac) was a more attractive target since it could be
potentially formed in one step and from the cheap and commercially available secondary amine.

Treatment of trifluoroethanol with 1,1’-carbonyldiimidazole presumably afforded an intermediate imidazolide\textsuperscript{172,176} \textbf{110} which underwent reaction with \textit{N}-ethyl-\textit{N}-(2-methylallyl)amine in the presence of imidazole to form carbamate \textbf{109b} in excellent 96% yield on a 100 mmol scale (\textbf{Scheme 63}).

\begin{center}
\includegraphics[width=\textwidth]{Scheme63}
\end{center}

\textbf{Scheme 63: Formation of carbamate 109b}

Exposure to LDA at -78°C resulted presumably in the formation of vinyllithium \textbf{111} which could be intercepted with both tributyltin chloride and propionaldehyde to form the stannane \textbf{112} and allylic alcohol \textbf{113} respectively (\textbf{Scheme 64}). The isolated yields indicated that the vinyllithium \textbf{111} was a “well-behaved” nucleophile.

\begin{center}
\includegraphics[width=\textwidth]{Scheme64}
\end{center}

\textbf{Scheme 64: Electrophilic trapping of vinyllithium 111}
Stille coupling of stannane 112 with iodobenzene under the optimised conditions afforded styrene 114 in good (76%) yield after distillation. Coupling with 4-iodophenyl triflate was also successful and aryl triflate 115 could be isolated in good (59%) yield (Scheme 65).

\[
\begin{align*}
\text{SnBu}_3 & \quad \text{F} \\
\text{F} & \quad \text{Pd(0), CuI, PPh}_3 \\
& \quad \text{ArI, DMF, 50°C}
\end{align*}
\]

112

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{ArF} \\
& \quad \text{F}
\end{align*}
\]

\[
\begin{align*}
& \quad \text{O} \\
& \quad \text{N}
\end{align*}
\]

Scheme 65: Coupling of stannane 112 with aryl iodides

Initial attempts at cleavage have provided some encouraging results. Exposure of a dichloromethane solution of styrene 114 to ozone led to molozonide formation as judged by the appearance of the characteristic blue colour of ozone along with the disappearance of starting material by TLC. Work-up with triphenylphosphine, followed by purification by column chromatography afforded ketone 116 as a colourless oil in excellent (94%) yield (Scheme 66).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{F}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{F}
\end{align*}
\]

94%

Scheme 66: Ozonolysis of styrene 114 to afford ketone 116
Treatment with sodium borohydride presumably formed the corresponding sodium alkoxymethylborohydride, which underwent partial cleavage, in a similar manner to levulinate esters,\textsuperscript{177} to form traces of the acetophenone derivative. It may be possible to isolate the alcohol and generate a more nucleophilic sodium alkoxide by treating the alcohol with an appropriate sodium base, such as NaH.

In an alternative approach, treatment with catalytic osmium tetroxide in the presence of NMO presumably afforded the diol, which underwent cleavage with sodium periodate in the presence of diethylamine to form traces of the deallylated carbamate 117 (Scheme 67)\textsuperscript{178}. Treatment with alkylthium reagents should then release the desired enolate after elimination of ethyl isocyanate.

\[
\begin{align*}
&\text{O} \\
&\text{O} \\
&\text{i) OsO}_4, \text{NMO} \\
&\text{ii) NaIO}_4, \text{Et}_2\text{NH} \\
\end{align*}
\]

\begin{align*}
&\text{δF} -93.0 \ d \ 2J_{FF} 47.9 \ Hz \\
&-103.1 \ d \ 2J_{FF} 47.9 \ Hz
\end{align*}

\textbf{Scheme 67:} Formation of carbamate 117 from carbamate 114

Further development of this protecting group to aryl difluoroketone synthesis was cut short due to a lack of time. The development of a suitable carbamate to difluoroketone synthesis is therefore ongoing.

\textit{2.1.6 Use of a 2-methoxyethoxymethyl (MEM) protecting group strategy}

The inherent problem with DEC deprotection and the successful cleavage of enol MEM acetics\textsuperscript{102c} suggested that a much more straightforward route to functionally diverse difluoromethyl aryl ketones was feasible.
Synthesis of 2,2-difluoro-1-(2-methoxy-ethoxymethoxy)-1-(tributylstannyl)-ethene

The requisite stannane 118 was prepared according to the procedure of Patel. Exposure of the MEM acetal of trifluoroethanol 119 to 2.0 equivalents of LDA at -78°C in THF led presumably to vinyllithium 83 which was trapped with tributyltin chloride to afford enol stannane 118 (Scheme 68).

\[
\begin{align*}
\text{119} & \xrightarrow{\text{i)}} \text{83} & \xrightarrow{\text{ii)}} \text{118}
\end{align*}
\]

*Reagents and Conditions: i) 2.0 LDA, THF, -78°C; ii) Bu₃SnCl, -78°C to rt, 89%*

Scheme 68: Synthesis of MEM stannane 118

Dilution with diethyl ether and treatment with potassium fluoride could remove trace amounts of residual tributyltin chloride. It was also found that n-butyllithium could be used directly, although the reaction had to be run under more dilute (0.3 M) conditions in order to avoid decomposition.

*Stille coupling of stannane 118*

*Optimisation of coupling process*

Initial coupling conditions were based upon those found for the DEC derivatives (2.5% Pd₂dba₃-CHCl₃, 10% CuI, 20% PPh₃) using 4-iodophenyl triflate 120a as the electrophile. In an attempt to reduce the cost, a reaction with 2.5 mol% palladium(0) was undertaken by using 1.25 mol% of the Pd₂dba₃-CHCl₃ catalyst. It was found that
no significant change was observed in the crude reaction. However, the persistent problem with co-elution of the dba ligand with products led to the successful application of palladium(II) acetate as the palladium(0) source instead. In two final optimisation steps, the amount of CuI was increased to 20% in order to increase the rate of reaction and reactions were run at 0.3-0.5 M rather than 0.1-0.2 M. This led to the eradication of the reduced material.

Scope of couplings

The use of MEM stannane 118 under our optimised conditions (vide supra) with 4-iodophenyl triflate proceeded efficiently and aryl triflate 121a could be isolated in excellent (96%) yield. The meta (121b) and ortho (121c) isomers were subsequently synthesised in an identical manner using 3-iodophenyl triflate and 2-iodophenyl triflate, respectively. The requisite aryl triflates were synthesised by treating the appropriate iodophenol with trifluoromethanesulfonic anhydride in pyridine. The three isomeric aryl triflates 120a, 120b and 120c could be isolated in 93%, 95% and 94% yield, respectively (Scheme 69).

![Scheme 69: Synthesis of regioisomeric aryl triflates 120a-c](image)

Although the meta- triflate 121b could be isolated in high (86%) yield, the more sterically demanding ortho- triflate 121c was formed in only low (21%) yield (33% by NMR), with large amounts of reduced and dimerised material present. 
Coupling also proceeded with varying efficiency with a range of other electrophiles (Table 6).
Table 6: Couplings of MEM stannane 118

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-phen-OTf 120a</td>
<td><img src="image1.png" alt="Product Image" /></td>
<td>121a 96</td>
</tr>
<tr>
<td>I-phen-OTf 120b</td>
<td><img src="image2.png" alt="Product Image" /></td>
<td>121b 86</td>
</tr>
<tr>
<td>TfO-phen 120c</td>
<td><img src="image3.png" alt="Product Image" /></td>
<td>121c 21</td>
</tr>
<tr>
<td>CO2Bn-phen 122</td>
<td><img src="image4.png" alt="Product Image" /></td>
<td>121d 70</td>
</tr>
<tr>
<td>I-phen-OMe 121e</td>
<td><img src="image5.png" alt="Product Image" /></td>
<td>121e 81</td>
</tr>
<tr>
<td>I-phen-F 121f</td>
<td><img src="image6.png" alt="Product Image" /></td>
<td>121f 71</td>
</tr>
<tr>
<td>I-phen-F 121g</td>
<td><img src="image7.png" alt="Product Image" /></td>
<td>121g 55</td>
</tr>
<tr>
<td>CHO-bn 123</td>
<td><img src="image8.png" alt="Product Image" /></td>
<td>121h 25</td>
</tr>
<tr>
<td>S 121j</td>
<td><img src="image9.png" alt="Product Image" /></td>
<td>121j 45</td>
</tr>
<tr>
<td>Br-phen 121e</td>
<td><img src="image10.png" alt="Product Image" /></td>
<td>121e 0</td>
</tr>
<tr>
<td>O-phen 124</td>
<td><img src="image11.png" alt="Product Image" /></td>
<td>121k 0</td>
</tr>
<tr>
<td>Br-bn 121m</td>
<td><img src="image12.png" alt="Product Image" /></td>
<td>121m 30</td>
</tr>
</tbody>
</table>
Coupling with functionalised triflate 122 also worked satisfactorily and functionalised triflate 121d could be isolated in good (70%) yield.

Coupling with iodobenzene afforded styrene derivative 121e in good (81%) yield after kügelrohr distillation. Use of an electron-rich aryl iodide such as 4-iodoanisole also led to a clean conversion and anisole 121f could be isolated in good (71%) yield.

Interestingly, the use of 2,4-difluoro-1-iodobenzene as the electrophile led to a slower reaction and large amounts of the enol carbamate and dimer were observed. The desired product 121g could be isolated in moderate (55%) yield. This observation indicates that even a relatively small fluorine atom at the ortho position is sufficient to significantly affect the rate of insertion of Pd(0) into the carbon-iodine bond, although electronic factors may also be relevant.

In order to test the steric requirements and given the slow insertion with 2-iodophenyl triflate, bis-iodide 123 was used, in which selective coupling to the less hindered carbon-iodine bond should predominate. Indeed, analysis of the crude reaction mixture suggested selective coupling to afford 121h, although some bis-coupled material and traces of the presumed regioisomeric styrene were visible. Functionalised iodide 121h could be isolated in low (25%) yield.

Coupling with a heteroaryl iodide, namely 2-idothiophene, also proceeded smoothly and unstable thiophene 121j could be isolated in moderate (45%) yield. In addition, it was hoped that 2-iodobenzoxazole 124 could be used in order to access benzoxazole 121k, since certain difluoroketones potentially accessible from this material could possess interesting properties.\textsuperscript{56,63a}
2-Iodobenzoxazole 124 was synthesised by trapping the corresponding organozinc reagent\textsuperscript{181} 126 (derived from organolithium 125)\textsuperscript{182} with elemental iodine (Scheme 70).

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{1.0 BuLi} \\
\text{THF, } & \quad -78^\circ\text{C} \\
\text{1.0 ZnCl} & \quad -78^\circ\text{C} \text{ to rt} \\
\text{I}_2 & \quad \text{rt} \\
\text{79\%} & \quad \text{I}_2, \text{ rt} \\
\end{align*}
\]

Scheme 70: Synthesis of 2-iodobenzoxazole 124

Unfortunately, attempted coupling with this substrate failed to afford any of the desired benzoxazole 121k. Instead, isolation of the major product and analysis by \textsuperscript{19}F and \textsuperscript{1}H NMR identified the reaction product as the iodide 127 (Figure 14).

This is a strange result that may result from decomposition of 2-iodobenzoxazole under the reaction conditions with the liberation of iodine. Reaction with the stannane
could then potentially form iodide. Further avenues to benzoazole were not attempted due to a lack of time.

Although successful coupling reactions have been achieved with aryl iodides, the most interesting compounds with pharmaceutical appeal are those containing heterocycles. Unfortunately, the vast majority of commercially available heterocyclic compounds with coupling potential consist of aryl bromides or aryl chlorides, which do not participate well in the current coupling reaction and is thus a severe limitation to generalisation.

When coupling was attempted with bromobenzene, analysis of the reaction mixture indicated complete conversion to either the reduced product or to the dimer. This has been observed several times in the literature. This result reiterates that the rate of insertion into the carbon-halogen bond must be of a rate comparable to that of tin-copper transmetallation, otherwise decomposition of the organocopper intermediate can occur. Indeed, the absence of starting material means that the difluorovinyl stannane itself undergoes both oxidative dimerisation and reduction.

It is known, however, that heterocycles are activated towards nucleophilic attack due to the $-I$ inductive effect of the ring heteroatoms. The insertion of palladium(0) also follows a similar pattern and Pd(PPh$_3$)$_4$ can insert into 2-bromopyridine at ambient temperature, whilst 2-chloropyrimidine and even 3-chloropyridine react at reflux in THF and DME respectively, though a more reactive catalyst is required in the latter case (Scheme 71).
The coupling ability of 2,5-dibromopyridine 128 and 5-bromo-2-iodopyridine 129 were compared to test the ability of heteroatoms to increase the lability of α- and γ- carbon-bromine bonds, and to a lesser degree β- carbon-bromine bonds. The latter compound was prepared from 128 according to the procedure of Song (Scheme 72).

Several sets of reaction conditions were tried, in which the CuI:Pd(0) ratio was changed from 8:1 through to 1:2. The results are depicted in Table 7.
Table 7: Coupling of 2-iodo- or 2-bromo-5-bromopyridine

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Conditions</th>
<th>NMR Yield/%</th>
<th>CuI:Pd(0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>A</td>
<td>20</td>
<td>8:1</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>A</td>
<td>39</td>
<td>8:1</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>B</td>
<td>51</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>B</td>
<td>30</td>
<td>2:1</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>C</td>
<td>55</td>
<td>1:1</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>D</td>
<td>57</td>
<td>1:2</td>
</tr>
</tbody>
</table>

| A: 2.5% Pd(OAc)$_2$, 10% PPh$_3$, 20% Cul, DMF, 50°C; B: 2.5% Pd(OAc)$_2$, 10% PPh$_3$, 5% Cul, DMF, 50°C; C: 5% Pd(OAc)$_2$, 20% PPh$_3$, 5% Cul, DMF, 50°C; D: 5% Pd(OAc)$_2$, 20% PPh$_3$, 2.5% Cul, DMF, 50°C |

Entry 1 shows that the rate of insertion is too slow at 50°C to prevent the organocopper intermediate from undergoing decomposition. In entry 2, clearly the rate of insertion into the carbon-iodine bond is higher than that of the corresponding carbon-bromine bond, as expected (entry 2 vs 1). Upon reducing the concentration of the copper intermediate, the rates of the decomposition pathways were lowered, allowing a greater proportion of cross-coupling (entry 3 vs 1). The corresponding reaction with the iodopyridine (entry 4) gave an anomalous amount of the reduced product, probably due to poor quality DMF. Upon reducing the Pd(0):Cu(I) ratio two fold (entry 5), a slight increase in coupling efficiency was observed. Under the best set of conditions, in which the ratio was reversed, coupling occurred in 57% efficiency. These conditions give rise to the swamping of the organocopper intermediate with the organopalladium complex, promoting the cross-coupling reaction. Isolation of the product from the reaction mixture gave unstable bromopyridine 121m in moderate (30%) yield.
Electrophilic cleavage of styrene derivatives

In order to confirm that the MEM enol ether could be cleaved under mild conditions, styrene 121a was treated with a range of electrophiles and analysed by $^{19}$F NMR for product formation.

Protolysis

Prime showed how vinyl MEM ethers could be cleaved by the treatment with thionyl chloride in dry methanol (forming dry HCl in situ). Treatment of chlorotrimethylsilane with methanol also generates the desired acid. In a single example, Thomas showed how allylic amine 130 underwent deprotection using the above method to form difluoromethyl ketone 131 as a mixture of isotopomers (Scheme 72).

![Scheme 72: Protolysis of a difluoroenol MEM ether with DCI](image)

In order to test the ability of these latter conditions to generally cleave difluorovinyl MEM ethers, triflate 121a was added to a solution of chlorotrimethylsilane at 0°C in methanol. After stirring overnight, analysis by NMR indicated complete consumption of the starting material with the production of the desired difluoroketone 132, after azeotropic distillation with toluene in order to remove traces of the hemiacetal and hydrate (Scheme 73).
The difluoromethyl ketone 132 could be isolated, albeit in low (22%) yield, possibly due to methanolysis of the O-S bond. This material possessed a doublet at -122 ppm for the difluoromethylene group.

*Halogenolysis*

Silyl difluoroenol ethers have been previously shown to be labile to a range of halogen electrophiles. Howarth and Laily showed how fluorine, bromine, iodine and chlorine electrophiles could be used to cleave triethylsilyl ethers to the corresponding halodifluoromethyl ketones (*Scheme 74*).\(^{189}\)

In a series of NMR experiments, different electrophiles were tested against triflate 121a. Addition of bromine, chlorine and iodine electrophiles successfully converted the difluoroenol MEM ethers to the corresponding halodifluoromethyl ketones.
Scheme 75 shows the conditions used. The shifts of the difluoromethylene centre in the $^{19}$F NMR are also shown.

Several coupling products were then treated with various halogen electrophiles to provide the range of materials shown in Table 8.
Table 8: Cleavage of difluoroenol MEM ethers with halogen electrophiles

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="OMEM F F BrF2C O OMEM F F ClF2C O OMEM F F IF2C O" /></td>
<td><img src="image" alt="121e" /> A</td>
<td><img src="image" alt="BrF2C O" /></td>
<td>133a 71</td>
</tr>
<tr>
<td><img src="image" alt="OMEM F F S ClF2C O" /></td>
<td><img src="image" alt="121e" /> B</td>
<td><img src="image" alt="ClF2C O" /></td>
<td>133b 60</td>
</tr>
<tr>
<td><img src="image" alt="OMEM F F S BrF2C O OMe" /></td>
<td><img src="image" alt="121f" /> C</td>
<td><img src="image" alt="IF2C O Me" /></td>
<td>133c 65</td>
</tr>
<tr>
<td><img src="image" alt="OMEM F F S" /></td>
<td><img src="image" alt="121j" /> B</td>
<td><img src="image" alt="ClF2C O S" /></td>
<td>133d 36</td>
</tr>
<tr>
<td><img src="image" alt="OMEM F F S" /></td>
<td><img src="image" alt="121j" /> A</td>
<td><img src="image" alt="BrF2C O S" /></td>
<td>133e 29</td>
</tr>
<tr>
<td><img src="image" alt="MEMO F F BrF2C O" /></td>
<td><img src="image" alt="121g" /> A</td>
<td><img src="image" alt="BrF2C O F" /></td>
<td>133f 36</td>
</tr>
<tr>
<td><img src="image" alt="OMEM F F BrF2C O" /></td>
<td><img src="image" alt="134" /> B</td>
<td><img src="image" alt="ClHFC O" /></td>
<td>133g 76</td>
</tr>
</tbody>
</table>

A: 1.0 Br₂, DCM, rt, 16 h  
B: 1.0 SO₂Cl₂, DCM, rt, 16 h  
C: 1.0 I₂, DCM, rt, 16 h

All cleavages occurred smoothly at ambient temperature to afford a diverse array of halodifluoromethyl ketones. It was found that particularly fast and clean chlorinations could be achieved by the use of sulfuryl chloride, SO₂Cl₂ (see pg 99). This therefore represents a good method for accessing such species.
Styrene 134 (1:1 E/Z) was synthesised by reducing difluorostyrene 121e with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al®)\(^{102a}\) (Scheme 76).

**Scheme 76: Formation of monofluorostyrenes 134**

Chlorination with sulfuryl chloride was observed to occur very rapidly. In a competition reaction between styrene 121e and monofluorostyrenes 134, highly selective cleavage of the monofluorostyrenes was observed. This can be related to the increased stability of the initial carbocation due to the reduction in the number of inductively destabilising fluorine atoms.

\(\alpha-(\text{Heteroarylthio})-\alpha,\alpha\text{-difluoroacetophenones}\)

Recently, Dolbier and co-workers described the synthesis of a range of \(\alpha-(\text{heteroarylthio})-\alpha,\alpha\text{-difluoromethyl benzoxazole derivatives 136 via } S_{RN1}\) methodology using (bromodifluoromethyl)-benzoxazole 135 and a range of aryl thiols (Scheme 77).\(^{63a,190}\)

**Scheme 77: Synthesis of a range of benzoxazole derivatives 136 using } S_{RN1} \text{ methodology**}
Following these initial results, the group successfully extended the methodology to difluoroacetophenone derivatives, using chlorodifluoromethyl ketones as starting materials (Figure 15).

![Figure 15: Difluoroketones synthesised by Médebielle](image)

Therefore, electrophilic cleavage of the MEM enol ether with a sulfur electrophile would represent a valuable extension of the methodology. The key step is the addition of a sulffenyl halide to the enol ether.

Treatment of styrene 121e with phenylsulfonyl chloride led to the clean formation of ketone 137a, which could be isolated in good (64%) yield (Scheme 78).

![Scheme 78: Synthesis of (phenylthio)difluoromethyl ketone 137a](image)

However, in order to avoid repetitious isolation of several heteroaryl sulffenyl chlorides, a separate method of in situ generation was investigated. The literature contains several methods for the synthesis of aryl sulffenyl halides, so a survey as to their simplicity and reliability was undertaken. All attempts to generate phenylsulfonyl halides using NCS/PhSH, Br₂/PhSH or Br₂/PhSSPh failed in
my hands. Two of the aforementioned procedures still require the use of an aryl thiol each time a cleavage reaction is attempted. In a much more attractive method, Suzuki et al. described the use of disulfides\textsuperscript{195} and sulfuryl chloride (SO\textsubscript{2}Cl\textsubscript{2}) as a facile and rapid method for sulfenyl chloride production at room temperature.\textsuperscript{196} Tsanaktsidis has also used this method for the synthesis of more complex heteroaryl sulfenyl chlorides.\textsuperscript{197} Tsanaktsidis also described the addition of catalytic amounts of pyridine in order to increase the rate of formation of the sulfenyl halide.\textsuperscript{197}

On addition of sulfuryl chloride to diphenyl disulfide at ambient temperature, an immediate red solution was produced. Addition of styrene \textit{121e} after 30 min afforded a 75:25 ratio of (phenylthio)difluoro- and chlorodifluoromethyl ketones by NMR after stirring overnight. The presence of the chlorinated material indicated that sulfenyl chloride formation was incomplete under these conditions (\textbf{Scheme 79}).

\begin{center}
\includegraphics[width=0.9\textwidth]{scheme79.png}
\end{center}

\textbf{Scheme 79:} Sulfenylation using sulfuryl chloride and diphenyl disulfide

Extending the initial stirring time to 1.5 hours led to the near complete conversion to phenylsulfenyl chloride, as indicated by a crude NMR of the reaction mixture after addition of styrene \textit{121e}. Purification afforded $\alpha$-(phenylthio)-$\alpha$-$\alpha$-difluoro-acetophenone \textit{137a} in good (76\%) yield. The procedure was repeated using dipyridyl disulfide and dibenzothiazolyl disulfide to produce the ketones shown in \textbf{Table 9}.
**Table 9:** Synthesis of some (α-heteroaryltio)difluoromethyl ketones

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>HetS-Cl</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-SCl</td>
<td><img src="image1" alt="Chemical structure" /></td>
<td>137a</td>
</tr>
<tr>
<td>N-SCl</td>
<td><img src="image2" alt="Chemical structure" /></td>
<td>137b</td>
</tr>
<tr>
<td>N,N-SCl</td>
<td><img src="image3" alt="Chemical structure" /></td>
<td>137c</td>
</tr>
</tbody>
</table>

**Possibility of Mukaiyama-type aldol condensations**

A valuable extension to the above methodology would be the possibility of direct aldol condensation reactions of the MEM enol ether linkage with aldehydes. This is a particularly important option for fluorinated carbohydrate synthesis (see Section 2.2.4). In order to investigate briefly the possibility of such a transformation, styrene 121e was treated with benzaldehyde in the presence of Lewis acids at varying temperature. **Table 10** shows the results.
Table 10: Attempted aldol condensation of styrene 121e with benzaldehyde

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>Solvent</th>
<th>Temp./°C</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZnCl₂</td>
<td>THF</td>
<td>-20</td>
<td>121e</td>
</tr>
<tr>
<td>TiCl₄</td>
<td>DCM</td>
<td>-78</td>
<td>121e</td>
</tr>
<tr>
<td>TiCl₄</td>
<td>DCM</td>
<td>-40</td>
<td>138, 139ᵃ</td>
</tr>
<tr>
<td>TiCl₄</td>
<td>DCM</td>
<td>-20</td>
<td>138, 139ᵃ</td>
</tr>
</tbody>
</table>

ᵃ An unknown aldol product was also present but could not be identified by NMR or MS

These initial results indicate that the MEM enol linkage can be used for aldol reactions with benzaldehyde. Zinc(II) chloride was found to be insufficiently Lewis acidic to promote the reaction. On the other hand, titanium(IV) chloride successfully promoted the reaction, as long as the reaction temperature was controlled. The recovery of starting material at -78°C suggests that the difluoroenol or difluoroenolate has reduced nucleophilicity, as previously observed.⁹⁹,¹⁹⁸
With the aryl triflates 121a-d in hand, attempts were made to utilise the C-O bond of the triflate as a second coupling site.

Initial coupling of aryl triflate 95e with 2-(tributylstannyl)furan was attempted using a catalytic amount of lithium chloride (30 mol%) to assist in the transmetallation step, but work-up and analysis of the mixture after 24 hours indicated a modest 65% conversion to the product. Separation of the furan 139 from the starting triflate proved to be difficult, so an attempt was made to drive the reaction to completion. Repetition of the reaction with a three-fold excess of lithium chloride and extending the reaction time to 72 hours, failed to improve the relative progress of reaction, with only an 89% conversion being achieved. These initial results indicated that the use of lithium chloride was detrimental to the reaction rate. In accordance with this observation, reaction with 1.5 equivalents of 2-(tributylstannyl)furan in the presence of tetrakis(triphenylphosphine)palladium(0) in THF resulted in the fast, clean reaction to give furan 139. Purification afforded furan 139 in good (60%) yield (Table 11). Table 11 shows the results with coupling of other triflate derivatives.
Aryl triflate 121a was coupled with 2-(tributylstannyl)furan under standard Stille conditions. Reaction at 90°C in DMF, followed by flash column chromatography allowed the isolation of furyl adduct 139a in good (86%) isolated yield, with complete consumption being achieved to a single fluorinated material by $^{19}$F NMR. Coupling of
triflate 121b with 2-(tributylstannyl)thiophene was also successful affording thiophene 139b in good (71%) yield. However, attempted coupling with triflate 121c using 2-(tributylstannyl)furan resulted in the recovery of starting material; no furan 139c was observed.

Of particular note was the reaction of triflate 121d with 2-(tributylstannyl)furan to afford highly UV active furan 139d. Use of a palladium(0) catalyst with triphenylphosphine (1:4 ratio) led to the clean coupling in 18 hours. Upon changing to dichloro(bis(triphenylphosphine)palladium(II), an even more rapid (3 minutes) reaction was observed. A similar observation was made in the presence of lithium chloride. In addition, palladium(II) acetate with triphenylphosphine (ratio 1:2) could also be used as the catalyst system.

It was also noted that no appreciable reaction was observed when DMF was replaced with dioxane or toluene; instead, palladium black was precipitated due to catalyst decomposition. Jutand and co-workers have indicated that such a solvent medium effect is possibly due to the formation of intermediate complexes with differing reactivity and stability profiles. Similar reactivity was shown with 2-(tributylstannyl)thiophene and thiophene 139e could be isolated in 85% yield after a short (10 minutes) reaction time.

Although Stille couplings are prominent in the literature, the availability, and moreover, the toxicity of both the reagents and by-products has led to the use of boronic acids as alternative nucleophiles.

Several literature sets of conditions were used in order to optimise the reaction. Table 12 shows the results with a range of boronic acids.
### Table 12: Coupling of aryl triflates with aryl boronic acids

<table>
<thead>
<tr>
<th>Aryl Triflate</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield/% (conv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>121a</td>
<td>A</td>
<td>FOMEM</td>
<td>49</td>
</tr>
<tr>
<td>121a</td>
<td>B</td>
<td>139f</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>121a</td>
<td>C</td>
<td>139g</td>
<td>67</td>
</tr>
<tr>
<td>121a</td>
<td>A</td>
<td></td>
<td>- (15)</td>
</tr>
<tr>
<td>121a</td>
<td>B</td>
<td>139h</td>
<td>73</td>
</tr>
<tr>
<td>121a</td>
<td>C</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>121a</td>
<td>A</td>
<td>139j</td>
<td>84</td>
</tr>
<tr>
<td>121a</td>
<td>B</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>121a</td>
<td>A</td>
<td>139k</td>
<td>- (50)</td>
</tr>
<tr>
<td>121a</td>
<td>C</td>
<td>139m</td>
<td>- (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>139n</td>
<td>48 (87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>67</td>
</tr>
</tbody>
</table>

A: 5% PdCl₂(PPh₃)₂, 4.0 Et₃N, 2.0 ArB(OH)₂, DMF, 90°C
B: 8% Pd(PPh₃)₄, 1.5 K₃PO₄, 1.5 ArB(OH)₂, DMF, 85°C
C: 2.5% Pd₂dba₂·CHCl₃, 20% PPh₃, 1.5 K₃PO₄, 1.1 ArB(OH)₂, 1,4-dioxane, 85°C
Attempts to employ the conditions described by Chen (conditions A) were found to be only moderately successful over the range of boronic acids tested. Reaction with electron-rich aryl units led to full conversions to a single product by $^{19}$F NMR (see 139a, 139f, 139j). Electron-deficient aryl units gave uniformly poor conversions (see 139h, 139k, 139m). 3-Nitrophenylboronic acid represented the lowest level of reactivity and starting material was recovered in all trials.

The second set of conditions (B) was far more successful; much more rapid couplings were observed to afford the products in good (65-80%) isolated yields. The conditions described by Oh-e et al. (conditions C) also proved successful in converting triflate 121a into biphenyl 139h bearing a meta-methoxy substituent. Once again, 3-nitrophenylboronic acid failed to react.

In an extension to the substrates able to undergo coupling to aryl triflate 121a, a Sonogashira procedure was attempted with 1-decyne. Although no reaction occurred under standard conditions, decyne 139p could be isolated in moderate (51%) yield under the conditions described by Chen (Scheme 80).
**Electrophilic cleavage of biphenyl derivatives**

Having accomplished a second coupling to afford several biphenyl derivatives, the MEM enol ether linkage was cleaved with both protic, halogen and sulfur electrophiles to afford a range of biphenyl-ethanones.

**Protolysis**

Cleavage of a range of enol ethers occurred cleanly in methanol in the presence of chlorotrimethylsilane and pure $\alpha,\alpha$-difluoroketones 140a-d could be isolated after filtration through a short plug of silica (Table 13).

<table>
<thead>
<tr>
<th>G</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mathrm{C}<em>8\mathrm{H}</em>{17}=$</td>
<td>$\mathrm{C}<em>8\mathrm{H}</em>{17}$</td>
<td>78</td>
</tr>
<tr>
<td>$\mathrm{O}$</td>
<td>$\mathrm{O}$</td>
<td>60</td>
</tr>
<tr>
<td>$\mathrm{S}$</td>
<td>$\mathrm{S}$</td>
<td>62</td>
</tr>
<tr>
<td>$\mathrm{X}$</td>
<td>$\mathrm{X}$</td>
<td>53</td>
</tr>
</tbody>
</table>
Other cleavage reactions

Cleavage of some biphenyl derivatives was also attempted with chlorine, bromine and sulfur electrophiles.

Addition of one equivalent of bromine to a solution of furan 139d in DCM led to a major product presumed to be bromoketone 141. However, several side products were present and these could not be removed by column chromatography.

A similar observation was made when one equivalent of sulfuryl chloride was added to a solution of thiophene 139e in DCM. A major product was observed by $^{19}$F NMR, presumed to be chloroketone 142, but trace impurities could not be removed (Scheme 81).

![Scheme 81: Formation of functionalised halodifluoromethyl ketones](image)

The complexity of the reaction mixtures is probably due to the high reactivity of furan and thiophene to halogen electrophiles at ambient temperatures.\(^{203}\)

It should also be noted that these halodifluoromethyl ketones are difficult to purify due to their tendency to streak badly on stationary phases.
Treatment of furan 139d with phenylsulfenyl chloride led to ketone 143 as the major product. Purification by chromatography afforded 143 in good (80%) yield, although several minor side-products could not be removed (Scheme 82).

Scheme 82: Synthesis of functionalised ketone 143

2.1.7 Summary of this approach

This research has demonstrated that a stable difluoroenol stannane can be taken through two consecutive coupling reactions followed by cleavage with a range of electrophiles to afford a range of aryl difluoromethyl ketones.
2.2 Building-block Approach to Fluorinated Carbohydrates

Regioselective and enantioselective dihydroxylation of a suitably functionalised fluorinated diene unit would represent a valuable methodology to highly oxygenated fluorinated molecules. Fluorinated carbohydrates represent possible targets. Retrosynthetic analysis of 2-deoxy-2,2-difluorohexose analogues indicates two possible strategies (Scheme 83).

Scheme 83: Aldohexose synthesis from trifluoroethanol
Balnaves has studied the left-hand approach in which disconnection of the β- and γ-hydroxyl groups affords known allylic alcohol 144.98b Benzylation and dihydroxylation of the non-fluorinated double bond affords diol 145 which can be orthogonally protected and taken through a transacylation/aldol reaction sequence affording a protected sugar analogue precursor 146 (Scheme 84).172

\[
\begin{align*}
&\text{(±)-144} \\
&\text{Reagents and Conditions: i) NaH, BnBr, DMF; ii) 0.05 mol\% OsO}_4, 2.5 \text{ eq. NMO, } t\text{-BuOH, RT, 16 h, 78\%; iii) 1.1 eq. TIPS-Cl, 2.5 eq. imidazole, DCM, 3 d, 76\%; iv) 1.0 eq. NaH, -10^\circ C, THF, 4 h then benzaldehyde, 16 h.}
\end{align*}
\]

Scheme 84: Balnaves’s synthesis of aldol 146

Unfortunately the route suffers from lack of control of absolute stereochemistry given the racemic nature of the allylic alcohol 144. An alternative route is to perform a regio-231 and enantioselective Sharpless Asymmetric Dihydroxylation204 on a 5,5-difluoropenta-2,4-dienol fragment 147 (see the right-hand approach in Scheme 83). With suitable hydroxyl group protection, a transacylation reaction (in the case of a carbamate-protected enol) would release a metal enolate capable of condensation with suitable aldehyde electrophiles (Scheme 85).
Furthermore, dienol 147 can also potentially undergo asymmetric epoxidation and aminohydroxylation, which would deliver products with potential for transformation into sugars or aminosugars.

2.2.1 Asymmetric dihydroxylation of conjugated fluorinated dienes

Diene 99e was chosen as the initial substrate for testing the reactivity towards osmylation. The potential diol 148 had been targeted for hexose synthesis (Scheme 86).

When diene 99e was subjected to racemic dihydroxylation conditions (0.4 mol% Os, 3 mol% quinuclidine, 3 eq. K$_2$CO$_3$, 3 eq. K$_3$Fe(CN)$_6$, 1:1 v/v tBuOH-H$_2$O), $^{19}$F NMR
indicated a slow conversion (27% after 3 hours) to a material consistent with diol 148 ($\delta_F$ -93.62, d, $^2J$ 50.1 Hz; -105.44, dd, $^2J$ 50.1, $^4J_{HF}$ 4.0 Hz). However, repetition led to an inconsistent, low (6%) conversion after 21 hours. Attempts to increase the rate of turnover, by addition of methanesulfonamide to possibly aid osmate ester hydrolysis$^{204}$ were unsuccessful. Attempts at Sharpless Asymmetric Dihydroxylation using AD-mix-$\beta$ resulted in recovery of the starting material, even after extended (75 hours) reaction times.

Upon changing to alkyl-substituted diene 99f (using AD-mix-$\beta$), an immediate change was observed, with the characteristic change from orange to yellow, as the ferricyanide is reduced to ferrocyanide. TLC after 19 hours indicated the near complete consumption of starting material. However, column chromatography afforded a poor (19%) yield of the diol 149 (Scheme 87). Traces of cis 99f were also observed in the crude $^{19}$F NMR spectrum, confirming the lower reactivity of cis dienes with the (DHQD)$_2$PHAL ligand.$^{204}$ Facial selectivity is represented consistent with the model proposed by Sharpless.$^{204}$

![Scheme 87: Dihydroxylation of isomeric 1,1-difluoronona-1,3-dienes 99f](image)

113
Repetition of the reaction with crude $^{19}$F NMR analysis indicated that \textit{in situ} transacylation to several ketones (presumably \textit{via} 150) had occurred under the basic (pH 12.2) reaction conditions.

Sharpless has described the formation of epoxides upon attempted dihydroxylation of allylic halides. The use of a sodium bicarbonate buffer, to reduce the pH to ca. 10.3 allowed the shutdown of this undesired pathway (Scheme 88).

\[ \text{Scheme 88: Buffering of an AD reaction with NaHCO}_3 \]

In accordance with these observations, the addition of three molar equivalents of sodium bicarbonate (1:1 with potassium carbonate) led to the complete shutdown of ketone formation, although the desired diol was only obtained in a low (23%) isolated yield, presumably due to problems of extraction from the aqueous phase. Attempts to increase the amount of bicarbonate to greater than six equivalents led to an extremely slow reaction, indicative of a low hydroxide concentration and consequent problems in osmium recycling.
The positive effect of the hyperconjugative \( \pi \)-donor effect of the alkyl group is of particular note, and indicated that electron donation to the alkene \( \pi \)-system, however small, results in a positive change in the reactivity profile.

When an attempt was made to asymmetrically dihydroxylate the THP-protected allylic alcohol 99c, none of the desired diol 151 was formed even after extended reaction times and after increasing the osmium loading to 3 mol% (Scheme 89).

![Scheme 89: Unreactivity of allylic alcohol 99c to AD reagents](image)

Overall, the extreme lack of reactivity of certain substrates, especially of the parent diene 99e, suggests that subtle effects are in operation. Presumably, the reactivity of the system is in balance between the \(-I\) inductive effects of the two fluorine atoms and the carbamoyloxy substituent as well as polarisation effects caused by the presence of the vinylic fluorine atoms.\(^{205}\) The ability of a \( \pi \)-donor to restore the reactivity is not in itself enough evidence to suggest simple fluorine atom inductive deactivation. Sharpless\(^{206}\) has described the efficient AD of 1,1,1-trifluoropropene in 63\% ee, a substrate in which three fluorine atoms reside alpha to the reactive olefin (rather than two residing beta) (Scheme 90).
Scheme 90: Reactivity of 1,1,1-trifluoropropene

Furthermore, Zhu and Li\textsuperscript{207} have described a successful AD reaction (albeit at a slow rate) of an octafluoroalkyl acrolein diethyl acetal (Scheme 91).

Scheme 91: Successful AD of a highly electron-deficient olefin

The general lack of reactivity of difluorinated 1,3-dienes was disappointing, since we require an enantiomerically enriched triol unit in order to pursue sugar synthesis.
2.2.2 Synthesis of 1,3-dideoxy-1,1-difluoro-D-glyceropent-2-ulofuranose

Retrosynthetic analysis of 2,4-dideoxy-2,2-difluorohexose analogues 152 is shown in Scheme 92 and relies upon an intermediate enediol 153 which should be available from 1,1-difluoro-1,4-pentadiene 154. Pentulose 155 was seen as an initial target to test the synthetic methodology (Scheme 92).

![Chemical structure](image)

Scheme 92: Retrosynthetic analysis of target dideoxy sugars

In the first approach, the N,N-diethylcarbamoyl protecting group (G = DEC) was chosen with a transacylation step via a six-membered ring being the key step. Coupling of stannane 81 with allyl bromide afforded 1,1-difluoro-1,4-pentadiene 99d, which underwent smooth dihydroxylation with AD-mix-β to afford diol 156 in good (88%) yield on a 10 mmol scale. Regioselective protection of the primary alcohol as a silyl ether afforded alcohol 157 in quantitative yield (Scheme 93). The assignment of absolute stereochemistry is based upon the Sharpless model.
Reagents and Conditions: i) 2.5% Pd$_2$dba$_3$.CHCl$_3$, 20% PPh$_3$, 10% Cul, DMF, 50°C, 75%; ii) AD-mix-β, 3.0 NaHCO$_3$, tBuOH-H$_2$O (1:1 v/v), rt, 88%; iii) 1.0 TIPS-Cl, 1.1 imidazole, DMAP (cat.), DCM, rt, 100%.

**Scheme 93:** Synthesis of alcohol 157 from stannane 81

In order to determine the extent of asymmetric induction, the diene 99d was taken through a racemic dihydroxylation process using quinuclidine as an achiral donor nitrogen ligand. Racemic diol 158 was formed in moderate (49%) yield. Protection of the primary alcohol as a TIPS ether afforded racemic alcohol 159 ([Scheme 94](#)).

Reagents and Conditions: i) 0.8% K$_2$OsO$_2$(OH)$_4$, 3.0 eq. K$_3$Fe(CN)$_6$, 3.2 eq. K$_2$CO$_3$, 1.0 eq. NaHCO$_3$, tBuOH-H$_2$O (1:1 v/v), rt, 49%; ii) 1.0 eq. TIPS-Cl, 1.1 eq. imidazole, DMAP (cat.), DCM, rt, 95%.

**Scheme 94:** Preparation of racemic alcohol 159

Alcohols 157 and 159 were analysed by chiral HPLC using a Chiralcell OD column. The racemic mixture was found to be a 50:50 mixture of two enantiomeric alcohols, as expected (Appendix I). Chiral alcohol 157 was analysed and found to consist of a 95:5 mixture of two alcohols (Appendix II). The two HPLC traces had a perfect overlay with each other (Appendix III). These data therefore represented a very pleasing 95:5 er (90% ee) for the AD reaction with AD-mix-β.
**Attempted transacylation of enantiomerically enriched alcohols**

With enantiomerically enriched alcohol 157 in hand, attempts were made to employ the key transacylation (TA) reaction to afford ketone 160 (Scheme 95). Control of this step could also allow the extension of the carbon backbone via aldol chemistry.

![Scheme 95](image)

Scheme 95: Proposed transacylation from a chiral centre to afford difluoroketone 160

Addition of n-butyllithium to a solution of alcohol 157 in THF at -78°C presumably led to the intermediate alkoxide, but warming to -10°C and stirring for 1 hour, followed by a protic quench, returned starting material. In order to increase the nucleophilicity of the alkoxide oxygen atom, the counterion was changed to sodium (using NaH or NaHMDS as base) or potassium (using KH, KHMDS or KOtBu as base). However, in all cases, the only products observed were those resulting from protonation of the intermediate alkoxide or those resulting from decomposition (Scheme 96). The use of crown ethers to increase the reactivity of the resultant alkoxide was not studied.

![Scheme 96](image)

Scheme 96: Failure to initiate enolate formation using lithium, sodium or potassium bases
This lack of reactivity is presumably due to the requirement of transacylation through a six-membered ring, which occurs very slowly at these reaction temperatures. It should be noted that the difluoroenolates are believed to be unstable above -10°C, so higher temperatures were not investigated. Balnaves has reported a transacylation reaction of this nature, in which a benzyloxy group was present at the allylic centre (see pg 111). The presence of a group at this position appears to be critical in determining the ease of the transacylation step. Due to this disappointing result, this line of research using the carbamate (DEC) group was abandoned. A more direct approach employing a MEM protecting group strategy was therefore pursued.

*Application of a MEM group protection strategy*

Use of a cleavable enol derivative, such as the MEM acetal, could allow a facile synthesis of the simple dideoxydifluoropentulose 155.

Stille coupling of the stannane 118 derived from MEM acetal 119 with allyl bromide proceeded uneventfully to afford diene 161, along with a minor amount of the inseparable reduced product 162. Sharpless Asymmetric Dihydroxylation proceeded surprisingly slowly (*vide ante*), although diol 163 could be isolated in 10% yield. De-protection with chlorotrimethylsilane in methanol presumably afforded ketodiol 164, which spontaneously cyclised to afford the target dideoxy sugar 155 as a slowly equilibrating 1.3:1 mixture of α:β anomers in 65% isolated yield (*Scheme 97*).
Scheme 97: Synthesis of pentulose 155 from penta-1,4-diene 161

Analysis by 2D NMR techniques allowed the identification of the two anomers and the anomer stereochemistry was successfully elucidated using 1-D GOESY techniques (Appendices IV-XII).

This line of work successfully concluded in the synthesis of a difluorinated dideoxy-D-xylulose analogue and demonstrates the possible application of geminally difluorinated 1,4-pentadienes in target synthesis. On the success of this work, a similar approach using difluorinated 1,3-pentadienes was investigated.
2.2.3 Synthesis of 1-deoxy-1,1-difluoro-D-xylulose

Introduction

In recent years, the profile of 1-deoxy-D-threo-pent-2-ulose (1-deoxy-D-xylulose, 1-DX) and its phosphate (1-DXP) has risen dramatically.\(^{209}\) Recent reports have shown that 1-DX/1-DXP are pivotal metabolites in the biosynthesis (catabolism) of the bacterial co-factors (vitamins) pyridoxal phosphate (PLP), thiamine pyrophosphate (TPP, vitamin B\(_1\)) and the phytol chain of ubiquinone (co-enzyme Q) in \(E.\) \textit{coli}.\(^{210,211}\) O’Hagan and co-workers became interested in the synthesis of fluorinated analogues of 1-deoxy-D-xylulose, in the hope that they may act as anti-metabolites and hence show antibiotic behaviour against \(E.\) \textit{coli}.\(^{211}\) Both 1-deoxy-1-fluoro- and 1-deoxy-1,1-difluoro-D-xylulose were prepared (\textbf{Schemes 98 and 99}).

\begin{center}
\begin{tikzpicture}

\begin{scope}[scale=0.8]

\node at (-2,0) {FH$_2$C\(\text{O}\)PPh$_3$ \quad + \quad \text{O\quad OTBDMS}};
\node at (2,0) {FH$_2$C\(\text{O}\)OTBDMS};
\node at (0,0) {DCM \(\text{reflux}\), 3 d \(60\%\)};
\node at (2,-0.5) {OsO$_4$, t-BuOOH \[Et$_4$N\]$^+$ AcO$^-$, rt, 12 h \(56\%\)};
\node at (2,-1) {TBAF, THF \(\text{RT}\), 1 h, 88\%};
\node at (2,-2) {\(\pm\)-168};
\node at (-2,-2) {169};
\end{scope}
\end{tikzpicture}
\end{center}

\textbf{Scheme 98:} Synthesis of racemic 1-deoxy-1-fluoro-D-xylulose (1-F-DX)

The route to 1-F-DX starts with a Wittig condensation reaction between fluorinated ylid 165 and silyl-protected hydroxyacetaldehyde 166 to afford \(\alpha,\beta\)-unsaturated ketone 167. Dihydroxylation under racemic conditions afforded racemic ketodiol 168.
which underwent fluoride-promoted desilylation to afford pentuloses 169 as a mixture of anomers.

\[
\begin{align*}
&\text{CO}_2\text{Me} &\text{NaBH}_4 &\text{MeOH, 0°C} &\text{CO}_2\text{Me} &\text{TBDMS} \\
&\text{MeOH, 0°C} &\text{Imidazole, DMF} &\text{rt} &\text{MeOH, 0°C} &\text{THF, -78°C} \\
&\text{CO}_2\text{Me} &\text{(EtO)}_2\text{POCF}_2\text{Li} &\text{22} &\text{OH} &\text{OH} \\
&\text{TBDMSCl} &\text{Imidazole, DMF} &\text{rt} &\text{NaOMe, MeOH} &\text{rt, 5 h} \\
&\text{OTBDMS} &\text{CF}_2\text{H} &\text{CF}_2\text{H} &\text{CF}_2\text{H} &\text{CF}_2\text{H} \\
&\text{OH} &\text{OH} &\text{OH} &\text{OH} &\text{OH} \\
&\text{172b} &\text{172a} &\text{171} &\text{173} \\
&\text{i) HCl (1M), rt, 12 h} &\text{NaOMe, MeOH} &\text{rt, 5 h} &\text{HCl (1M), rt, 12 h} \\
&\text{ii) TBAF, THF, rt, 1 h} &\text{THF, -78°C} &\text{NaOMe, MeOH} &\text{THF, -78°C} \\
\end{align*}
\]

**Scheme 99: Synthesis of 1-deoxy-1,1-difluoro-D-xylulose (1,1-F$_2$-DX) 173**

The route to 1,1-F$_2$-DX relies upon the condensation of a lithiated difluorophosphonate 22 with tartrate derivative 170 to afford phosphonate 171. Cleavage of the C-P bond occurs under basic conditions to afford ketone 172a (hydrate 172b was also present). Deprotection then affords the desired xylulose 173. The fluoroketones should have a higher reactivity in the initial imine formation step and hence an ability to decrease the amount of natural vitamin B$_6$ in the bacterium (thereby acting as anti-metabolites). However, the observation that the sugar existed exclusively in the cyclic furanose form inhibited the requisite phosphorylation step.
Therefore, the complete failure to inhibit the growth of \textit{E.coli} was not surprising. However, 1-deoxy-1,1-difluoro-D-xylulose-5-phosphate (1-F$_2$-1-DXP, 174) may very well show some interesting behaviour. Any identification of the biosynthesis of fluorinated vitamin B$_6$ would also confirm the incorporation of the entire xylulose backbone into the metabolite (Scheme 100).

\begin{center}
\includegraphics[width=\textwidth]{scheme100.png}
\end{center}

\textbf{Scheme 100:} Possible incorporation of 1-F$_2$-1-DXP into unnatural PNP

\textit{Retrosynthetic analysis}

Disconnection of the target xylulose 173 reveals enetriol 175 as a key intermediate. This material should be available from coupling product 176 (Scheme 101).

\begin{center}
\includegraphics[width=\textwidth]{scheme101.png}
\end{center}

\textbf{Scheme 101:} Retrosynthetic analysis of target sugar 173

Initial work (see Section 2.2.1) has shown that dienes of type 176 exhibit very low reactivities to dihydroxylation. In order to make progress, it was necessary to find a means to increase the reactivity of the olefin to the AD reagents.
Enhanced AD reactivity of para-methoxybenzoate (pMBz) esters of allylic alcohols

The work of Corey has demonstrated that the use of certain hydroxyl protecting groups for allylic alcohols can dramatically improve their reaction with the AD-mixes. After examining several protecting groups, the para-methoxybenzoyl (pMBz, p-MeOC₆H₄) group was found to give the highest ee’s and the lowest degree of acyl transfer during the reaction. Corey postulated that the ligand forms a binding pocket in which the osmium reagent docks preferentially onto one of the nitrogen centres, affording a catalyst within a well-defined chiral environment (Figure 16).

Figure 16: Binding model explaining enhanced reactivity of para-methoxybenzoate esters of allylic alcohols to AD reagents

One can perceive that the substrate enters the cavity, reacts with the complexed osmium reagent to form the osmate ester, which undergoes either intra- or extracavity hydrolysis (assisted by methanesulfonamide) to the diol. The recycled osmium reagent then re-enters the cavity and re-forms the activated osmium catalyst. It is therefore important that the ratio of ligand to osmium catalyst is greater than one.

125
(2-3 fold in general) in order to guarantee a complexed osmium catalyst. Of course, the whole idea relies on the premise that the substrate can enter the cavity and that the olefin reacts immediately, before having an opportunity to diffuse. If the second case is false, then the reactivity will be extremely low requiring a higher catalyst concentration and/or longer reaction times.

Corey suggested that if one could attach a group to the substrate with the ability to participate in π-π stacking with the 4-methoxyquinoline “walls” of the ligand, one would increase its reactivity, presumably by increasing the longevity of the olefin within the vicinity of the osmium catalyst.

In order to test this theory, iodoester 181 was synthesised in four steps from propiolic acid 177 (Scheme 102).

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \rightarrow \quad \text{I} \quad \rightarrow \quad \text{I} \quad \rightarrow \quad \text{I} \\
177 & \quad 178 & \quad 179 & \quad 180
\end{align*}
\]

Reagents and Conditions: i) 1.5 eq. HI (57% w/w in water), 90°C, 21 h, 94%; ii) EtOH (abs.), 1.0 eq. H$_2$SO$_4$ (conc.), reflux, 24 h, 65%; iii) 2.2 eq. dibal-H, -78°C, DCM, 50%; iv) 1.1 eq. 4-anisoyl chloride, pyr., DMAP (cat.), DCM, rt, 24 h, 97%

Scheme 102: Synthesis of iodoester 181

Addition of aqueous hydriodic acid across the acetylene unit occurred smoothly upon heating in an Ace® tube at 90-95°C for 21 hours. Washing with water and then with light petroleum afforded the corresponding (E)-3-iodopropenoic acid 178 as white
needles in 94% yield.\textsuperscript{213} Fischer esterification using ethanol and concentrated sulfuric acid afforded the corresponding ethyl ester 179,\textsuperscript{213a} which underwent a double reduction to the alcohol 180 using diisobutylaluminium hydride.\textsuperscript{214} Esterification to the target vinyl iodide 181 was achieved using 4-anisoyl chloride with pyridine or 2,6-lutidine as a base in the presence of 4-(dimethylamino)pyridine as a nucleophilic catalyst.

Coupling with stannane 81 was attempted using the previously optimised conditions, and gratifyingly ester 182 could be isolated in good (83%) yield (Scheme 103).

\begin{center}
\begin{tikzpicture}
  \node[draw] (N1) {81};
  \node[draw, right of=N1, xshift=1cm] (N2) {181, 2.5\% Pd(OAc)\textsubscript{2}};
  \node[draw, right of=N2, xshift=1cm] (N3) {20\% CuI, 10\% PPh\textsubscript{3}};
  \node[draw, right of=N3, xshift=1cm] (N4) {DMF, 50\degree C, 83\%};
  \node[draw, right of=N4, xshift=1cm] (N5) {182};

  \draw[->] (N1) -- (N2);
  \draw[->] (N2) -- (N3);
  \draw[->] (N3) -- (N4);
  \draw[->] (N4) -- (N5);

\end{tikzpicture}
\end{center}

\textbf{Scheme 103:} Synthesis of AD substrate bearing a \( p\text{-}MBz \) group

Subjecting 182 to the usual buffered AD conditions led to an immediate difference in colour of the AD mix, as previously observed with the pentyl derivative. After stirring for 5 days, TLC indicated near complete consumption of the starting material and the production of a more polar compound. \textsuperscript{19}F NMR indicated that most of the starting material had been consumed, but no signals corresponding to the expected diol 183 were present. Instead, several sets of AB signals were observed indicating that any diol intermediate formed had undergone transacylation under the basic (pH 10.3) conditions to afford a mixture of difluoromethyl ketones 184 (Scheme 104).
It was deduced that the $p$MBz group had indeed increased the reactivity of the olefin, though it is still extremely unreactive.\textsuperscript{215} The presence of several ketones indicates that the resultant enantiomerically enriched ketone also underwent partial epimerisation at the $\alpha$-carbon, and scrambling of the $N,N$-diethylcarbamoyl group had also occurred, leading to at least four ketones.

Unfortunately, all attempts to curtail the side-reaction failed; an increase in sodium bicarbonate buffer had no effect while an increase in osmium loading led to a slightly faster reaction, though ketones still predominated. The use of 3 mol\% catalyst (in conjunction with 1 mol\% chiral ligand), with interruption of the reaction allowed the observation of diol, though ketone contamination was still significant. It was apparent that the diol underwent transacylation at a much faster rate than it underwent dihydroxylation, meaning that the desired diol would never be isolated in good yield by this method.
Attempts to trap the diol intermediate

In order to be able to secure the diol intermediate, a method was required that could trap the diol in situ. Narasaka has described the use of boronic acids as trapping reagents during dihydroxylation reactions. The method uses Upjohn conditions (NMO as re-oxidant) with phenylboronic acid in slight excess (Scheme 105).\textsuperscript{216}

\[ \text{Scheme 105: Formation of a boronate ester in situ from indene} \]

Crystalline boronate ester products of this type are able to undergo deborylation using sodium peroxide or more interestingly glycol exchange using neopentyl glycol in DCM under neutral conditions. Nicolaou and co-workers described the synthesis of boronate ester 185 which underwent glycol exchange with neopentyl glycol to form diol 186 in situ, which rearranged to bicyclic lactone 187.\textsuperscript{217} This was used to construct the C ring of Taxol 188 (Scheme 106).
Subjecting ester 182 to Narasaka’s modified dihydroxylation conditions (1.5 eq. phenylboronic acid present) cleanly transformed the intermediate racemic diol 183 to a product consistent with the boronate ester 189 by $^{19}\text{F} \text{NMR}$ and $^1\text{H} \text{NMR}$ (Appendix XIII). This material, however, could not be purified by chromatographic methods (Scheme 107).

**Scheme 106: Glycol exchange of a boronate ester**

**Scheme 107: Trapping of the diol unit as a boronate ester**

*Reagents and Conditions: i) $3.0\% \text{K}_2\text{SO}_2\text{(OH)}_4$, 2.0 eq. NMO, 1.5 eq. PhB(OH)$_2$, acetone-water (4:1), rt*
When the presumed boronate ester 189 was treated with one equivalent of neopentyl glycol (2,2-dimethylpropane-1,3-diol) in DCM at ambient temperature for one hour, NMR indicated only the presence of the boronate ester 189. Upon turning to more forcing conditions (at reflux overnight), NMR indicated the successful conversion through to diol 183 (\(^{19}\text{F}\) NMR signals agreed with those observed earlier), without any trace of ketone by-products (Scheme 108).

**Scheme 108:** Glycol exchange with neopentyl glycol to afford diol 183

Although diol can be accessed, this line of work appeared unpromising, so it was abandoned, in favour of pursuing the use of MEM as a protecting group.

**Application of a MEM protecting group strategy**

Coupling of iodoalkene 181 with stannane 118 with a Pd(II)/CuI/PPh\(_3\) catalyst system led to the formation of diene 190 by \(^{19}\text{F}\) and \(^1\text{H}\) NMR. Trace amounts of alkene 162 and dimer 191 were also usually observed (Scheme 109).

**Scheme 109:** Stille coupling of MEM-derived difluorovinyl-stannane 118 with iodoester 181
Dimer 191 results from reduction of the Pd(II) complex by the stannane to Pd(0). Diene 190 proved to be difficult to purify and unstable to storage. However, purification by column chromatography through a short plug of alumina afforded diene 190 in moderate (45-55%) yield. A highly coloured impurity was observed by $^1$H and $^{13}$C NMR, and isolation by fortuitous crystallisation from a chloroform solution identified the red material as the known palladium(II) complex, Pd(PPh$_3$)$_2$I$_2$.

With diene 190 in hand, exposure to AD mix-$\beta$ (0.4% Os) using methanesulfonamide in a $^t$BuOH-water mixed solvent led to the very slow conversion to diol 192 (Scheme 110). Several minor unidentified impurities were also observed in the crude $^{19}$F NMR.

Scheme 110: AD of MEM-derived dienyl ester 190

Analysis by NMR indicated that the conversion reached its maximum at ca. 85% after 4 days, with no change after a further 4 days. It has been noted that long reactions using the K$_3$Fe(CN)$_6$-K$_2$CO$_3$ oxidant can often stop due to ‘deactivation’, and that re-addition is required.

In order to reduce the reaction time, increases in the loading of osmium catalyst were investigated. Use of 1 mol% Os (by addition of 0.6 mol% K$_2$OsO$_2$(OH)$_4$) led to no significant increase in rate. Attempts with higher loadings were carried out by addition of the individual reagents, so as to allow an addition of extra chiral ligand and because it has also been noted that the individual reagents can out-perform the pre-
mixes. Use of 5 mol% catalyst (with 8 mol% ligand) led to high (86%) conversion after only 48 hours.

It was also noted that the presence of tributyltin halides (impurities in substrate) totally deactivated the osmium and led to the precipitation of the osmium catalyst, affording black reaction mixtures. Purification of the diol product is reasonably facile due to the polarity of this material, though methanesulfonamide must be removed prior to chromatography. Washing of the crude material with ice-cold 2M KOH removes this material as the water-soluble potassium salt. The sulfonamide can otherwise be removed by cooling the purified diol, whereby the sulfonamide crystallises out and can be removed by filtration.

Although diol 192 could be isolated, the requirement for large amounts of catalyst was undesirable due to its high cost and toxicity. Furthermore, the rate of reaction is still low (ca. 3 days for near complete reaction) which could possibly lead to slow decomposition of the substrate and/or product.

In order to optimise the reaction further, the first goal was to attain complete conversion of the starting material. As described above, it was found that the reaction stopped at ca. 90% conversion in all circumstances. However, readdition of the reoxidant combination successfully promoted the complete conversion of the remaining diene to the diol product.

At this stage, Beller and co-workers reported a paper describing a pH effect. Under the present conditions, the overall reaction of a diene can be described using the following redox equation (Scheme 111).
The desired diene 193 undergoes an overall double addition of hydroxide, mediated by osmium tetroxide, to afford the desired diol 194. Ferricyanide (Fe$^{3+}$) is used as the oxidant.

As written, two hydroxide ions are consumed per turnover during the reaction. The consequence of this is that the pH drops during the reaction causing a reduction in the rate of recycling of the osmium. The authors showed how the pH dropped rapidly from 12.2 to ca. 11.0 with a concomitant 40% conversion within one hour (using trans-5-decene), before the rate of change of pH lowered significantly, requiring a further 33 hours to reach 100% conversion. The same reaction was complete within 1.7 hours when the pH was maintained at 12.0 throughout.

In order to study this dramatic effect more closely for our system, the pH was monitored during an attempted racemic dihydroxylation. Aqueous sodium hydroxide (1M) was added at such time that the pH had dropped below ca. 11.0. A representation of the data obtained is shown below and qualitatively confirms Beller’s quantitative observations (Figure 17).
Clearly, the pH begins to drop immediately, but at a shallower gradient than usual due to the lower reactivity of the diene. At ca. pH 11.0, the reaction begins to slow considerably. On the addition of aqueous NaOH, the required pH level is re-established and the pH begins to drop at a similar rate as previously observed. If left for a long period, the pH slowly reduces down to pH 9.0, at which point the reaction rate would be deemed to be very slow. This crude experiment therefore clearly demonstrates that pH indeed plays a vital role in determining the overall rate of reaction.

When this method was used under asymmetric conditions, complete consumption of the starting diene could be achieved in several hours if the pH was maintained in the range 11.0-12.0. Maintaining the pH at near 12.0 at all times allowed complete reaction in 30 minutes, with confirmation coming from TLC and $^{19}$F NMR (Scheme 112).
It was noted that the pH should not be taken above 12.0 since decomposition of the starting material began to occur, presumably due to either ester cleavage or attack of hydroxide at the difluoromethylene centre.

\[
\begin{array}{c}
\text{MEMO} \\
\begin{array}{c}
\text{F} \\
\text{F} \\
\text{OH} \\
\text{F} \\
\text{OH} \\
\end{array}
\end{array}
\xrightarrow{i) \text{ 55\%}}
\begin{array}{c}
\text{MEMO} \\
\begin{array}{c}
\text{F} \\
\text{F} \\
\text{OH} \\
\text{F} \\
\text{OH} \\
\end{array}
\end{array}
\]

Reagents and Conditions: i) K₂OsO₄·2H₂O (2 mol%), (DHQD)₂PHAL (5 mol%), K₂CO₃ (300 mol%), K₃Fe(CN)₆ (300 mol%), tBuOH-H₂O (1:1 v/v), pH 12.0, rt, 30 min

Scheme 112: pH-controlled synthesis of diol 192

In order to determine the degree of asymmetric induction, samples of diol obtained from AD-mix-β (not pH-controlled) and racemic dihydroxylation (pH-controlled) were both obtained by preparative HPLC. Both samples were then subjected to chiral HPLC on a Chiralcell OD column using a 10% isopropanol/hexane mobile phase. Unfortunately, no separation of the enantiomeric diols was observed under these conditions, with both samples affording a single peak.

This was a disappointing result since this column has been successfully used to determine the ee’s of diols. Two other column types commonly used (Chiralpak AS and Welkmann (S,S)-0.1) were unavailable, so an NMR method was pursued.

NMR can be used to resolve enantiomers by employing a chiral derivatising agent, thus forming diastereoisomers with different physical properties. A common method for analysing alcohols is to generate Mosher (MTPA) esters. It was decided to synthesise a bis-Mosher ester 195 and to analyse the product by \(^{19}\text{F}\) NMR, in which the difluoromethylene unit can be used as a second reporter centre. Reaction of pure
chiral diol with (R)-Mosher’s acid chloride under typical esterification conditions afforded a crude material 195 showing a single set of fluorine signals (Scheme 113). Close monitoring of the reaction was essential in order to prevent the attack of DMAP on the difluoromethylene centre with carboxylate expulsion, affording 196 (identified by $^{19}$F NMR$^{219}$ and MS).

![Scheme 113: Formation of bis-Mosher ester 195](image)

The reaction was then repeated using pure racemic diol 192. In the first trial, there was insufficient acid chloride to drive the second esterification. However, the result clearly indicated the reactivity difference between the two hydroxyl groups (the allylic hydroxyl being less reactive) and that the diastereoisomers had different $^{19}$F NMR shifts for the difluoromethylene centre. Repetition of the reaction using fresh acid chloride allowed the clean conversion to the racemic bis-Mosher ester 195 as judged by TLC. Analysis by $^{19}$F NMR clearly indicated the presence of two diastereoisomers in both fluorine environments (CF$_3$ and $\equiv$CF$_2$) in a 1:1 ratio, as expected.

This result, in conjunction with that obtained with the chiral diol, indicated an excellent ee, greater than 95%. The reaction with the chiral diol was repeated and subjected to
high resolution $^{19}$F NMR at 300 MHz (4096 scans and 512K data points) allowing an estimation of the ee to be greater than 99.5%. The partial $^{19}$F NMR spectra are depicted below (Figure 18).

![Partial $^{19}$F NMR spectra](image)

**Figure 18**: Partial NMR of *bis*-Mosher esters of diol 192

Attempts to make crystalline derivatives, which could be analysed by X-ray crystallography to confirm the connectivity and relative stereochemistry were unsuccessful. Though boronate ester 197 could be prepared cleanly by $^{19}$F NMR (Appendix XIV), the material proved difficult to purify. On the other hand, triester 198 was successfully prepared but existed as an oil.
Completion of the synthesis of the target xylulose 173 is shown in Scheme 114.

Reagents and Conditions: i) 2.0 eq. CuSO₄, pTSA (cat.), acetone, rt, 48 h, 68%; ii) 4.0 eq. H₂O₂ (30% w/w in water), 2.1 eq. LiOH.H₂O, THF-H₂O (3:1 v/v), rt, 140 h, 61%; iii) 1.1 eq. Me₃SiCl, MeOH, rt, 88%

Scheme 114: Synthesis of target sugar 173 from diol 192

Protection of the diol 192 as the acetonide 199 was accomplished using acetone and an acid catalyst, using anhydrous copper(II) sulfate as a dehydrating agent. Attempts to use Amberlyst-15 and 2,2-dimethoxypropane resulted in the desired product on a 0.5 mmol scale, but returned starting material on scaling up. The acetonide was unstable on silica gel and purification was achieved by chromatography on basic alumina.

Saponification of the ester to alcohol 200 was successful using lithium hydroperoxide, prepared in situ from hydrogen peroxide and lithium hydroxide. Dual cleavage of the MEM enol ether and acetal linkages occurred in methanol containing chlorotrimethylsilane and the target sugar 173 could be isolated in
excellent (88%) yield as a 3:1 mixture of $\alpha$ and $\beta$ anomers. Both anomers could be converged into a single acetonide derivative 201 by treatment with acetone and an acid catalyst.\textsuperscript{221}

The D-xylulose 173 was characterised by 2D NMR techniques, in order to distinguish the two anomers. The connectivity was confirmed by COSY, HSQC and HMBC experiments (\textit{Appendices XV-XXVI}). The relative configuration at the anomeric centre was confirmed by a 1D-GOESY experiment, in which the major ($\alpha$) anomer showed a positive NOE between the H-3, H-5b and H-1 protons (\textbf{Figure 19}).

\begin{center}
\textbf{Figure 19}: Assignment of anomeric configuration by 1D-GOESY
\end{center}

Accurate measurement of the optical rotation gave a value comparable with that reported by O'Hagan, thereby confirming the absolute stereochemistry of the $\alpha$-anomer as that shown. The observed sense of enantioselection is also consistent with that predicted using the Sharpless model.
2.2.4 Evaluation of one carbon extension strategies

The successful completion of a synthesis of a 2-deoxy-2,2-difluorohexose requires the addition of a hydroxymethyl equivalent to the difluoromethylene centre (Scheme 115).

Scheme 115: Two generic strategies to formylation of diol 192

Analysis of the desired target indicated that several methods could potentially install the key formyl component (or equivalent) to the difluoromethylene centre. Several possible methods have been studied only briefly due to a lack of laboratory time.

Radical additions

At the outset it was realised that although =CF₂ centres are electrophilic, the most common pathway was via addition-elimination, leading to monofluorinated materials.²²² Therefore, if such a process is to be used, a good leaving group at the allylic centre is required. Disconnection readily shows that this requires the loss of a chiral centre, painstakingly installed through a dihydroxylation reaction. This option was therefore ruled out.

A more profitable solution was deemed to be the addition of a nucleophilic radical, since the loss of a highly energetic fluorine atom is very unfavourable. In addition, the
neighbouring chiral centre may control the facial reduction of the intermediate radical, leading to control of the relative stereochemistry between C-3 and C-4.

Motherwell and Bumgardner have both described the addition of nucleophilic and electrophilic radicals to vinylic CF₂ centres.

Motherwell²²³ showed how difluoroenol ethers, derived from sugar lactones, showed significant reactivity towards nucleophilic radicals, such as those derived from cycloalkanes and sugars (Scheme 116).

![Scheme 116: Addition of a nucleophilic radical to a difluoroenol ether](image)

Bumgardner²²⁴ also showed how β,β-difluoroacrylates are susceptible to the addition of nucleophilic radicals, derived from cyclic ethers or aldehydes (Scheme 117).

![Scheme 117: Addition of cyclic ether radicals to a difluoroalkenoate](image)

Initial attempts in this research concerned the attempted addition of carbon-centred radicals derived from cyclic ethers, namely tetrahydrofuran and 1,3-dioxolane to
Based upon the above protocol, azobisisobutyronitrile (AIBN) and benzoyl peroxide (BPO) were used as a combined radical initiator system. Runs employing THF and 1,3-dioxolane with acetonide 199 uniformly gave discouraging results. Starting material was present in all cases (Scheme 118).

![Scheme 118: Failure to add a cyclic acetal radical to acetonide 199](image)

In order to test the initiator system, difluoroalkenoate 94 was used in direct analogy to the work of Bumgardner, which strongly suggested that reaction should be feasible. Indeed, heating a solution of 94 in refluxing THF in the presence of AIBN (4.7 mol%) and BPO (6.5 mol%) successfully promoted the addition of a THF radical with the formation of diastereoisomeric esters 202 and 203 in good (82%) isolated yield after column chromatography (Scheme 119).

![Scheme 119: Successful addition of a THF radical to difluoroalkenoate 94](image)

Okano et al. have published work regarding the successful addition of 1,3-dioxolane and 2,2-dimethyl-1,3-dioxolane to enol carbamate 98. Reaction with 1,3-dioxolane
afforded a 73:27 mixture of acetals 204 and 205. However, the 1,3-dioxolane unit in 204 could not be deprotected, even with concentrated HCl, due to the development of positive charge alpha to the CF₂ centre. The poor regioselectivity in hydrogen atom abstraction from tetrahydrofuran is also much lower than expected. However, reaction with 2,2-dimethyl-1,3-dioxolane afforded acetonide 206 (no problem of regioselectivity) which could be deprotected with acid, and converted through to the alcohol 207 via oxidative cleavage to the aldehyde by sodium periodate and subsequent reduction with sodium borohydride (Scheme 120).

Scheme 120: Addition of cyclic acetal linkages to enol carbamate 98

The stability of acetal 204 to acid is a major problem. The poor regioselectivity is also a concern. Of more concern is the compatibility of the MEM acetal linkage to radical conditions using 2,2-dimethyl-1,3-dioxolane. Malatesta and Ingold²²⁶ have studied stereoelectronic effects in hydrogen atom abstraction from various cyclic and acyclic ethers using electron paramagnetic
resonance (EPR) spectroscopy. Table 14 shows the experimental $\rho$ values (relative reactivities per equivalent hydrogen type) for key ethers toward $t$-butoxyl radical at -60°C.

<table>
<thead>
<tr>
<th>Ether</th>
<th>H</th>
<th>$\rho$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$H_a (4)$</td>
<td>(1.0)</td>
</tr>
<tr>
<td>2</td>
<td>$H_a (2)$</td>
<td>8.8</td>
</tr>
<tr>
<td></td>
<td>$H_b (4)$</td>
<td>0.32</td>
</tr>
<tr>
<td>3</td>
<td>$H_b (4)$</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>$H_a (1)$</td>
<td>5.2</td>
</tr>
<tr>
<td>4</td>
<td>$H_a (2)$</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>$H_b (4)$</td>
<td>0.11</td>
</tr>
<tr>
<td>5</td>
<td>$H_b (6)$</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Entry 2 indicates that an $H_a$ in a 1,3-dioxolane unit is much more easily abstracted than either an $H_a$ of tetrahydrofuran or an $H_b$ of a 1,3-dioxolane. Entry 3 indicates that an $H_b$ of 2,2-dimethyl-1,3-dioxolane is comparable to that of an $H_b$ in 1,3-dioxolane. Of most importance is that entries 4 and 5 indicate that the ease of abstraction of an $H_a$ in an acyclic acetal (such as MEM) is comparable to that of an $H_b$ in 1,3-dioxolanes. This would suggest that the MEM protecting group is incompatable with
the use of 2,2-dimethyl-1,3-dioxolane as a formyl radical equivalent. An alternative formyl equivalent would therefore have to be found.

**O to C protecting group transfer**

During studies by Thomas on the application of 1-bromo-2,2-difluoro-1-(2-methoxyethoxymethoxy)-ethene 208 as a substrate for styrene synthesis via palladium-catalysed cross-coupling, it was discovered that this material was prone to acid-catalysed (CDCl$_3$ from NMR solvent) rearrangement to acid bromide 209 (trapped by MeOH to form ester 210), resulting from transfer of the MEM group (Scheme 121).$^{169}$

![Scheme 121: Observed migration of a MEM group in vinyl bromide 208](image)

Indeed, during these studies, certain styrene derivatives also underwent rearrangement if left at ambient temperature for extended periods. No detailed studies have been performed on this intriguing reaction, so it was decided to use styrene 121e to test conditions to promote such a rearrangement. Initially, a sample was stirred with Amberlyst-15 for 18 hours in deuterated chloroform. NMR analysis indicated, however, the absence of any ketone 211 (Scheme 122).
The use of trifluoroacetic acid led, conversely, to a multitude of fluorinated products, none of which could be properly assigned, although signals consistent with ketone 211 could be seen.

On the other hand, treatment of styrene 121e with trimethylsilyl triflate successfully promoted the formation of ketone 211 (δ_F -107.40, t, 3_J_HF 14.0 Hz) as well as difluoromethylketone 213 (δ_F -122.25, d, 2_J_HF 53.4 Hz), resulting from hydrolysis of the intermediate TMS enol ether 212 (Scheme 123).

Having established a protocol to induce the desired O to C protecting group transfer, incorporation into aldohexose synthesis was attempted. The diol 192 was protected as the carbonate 214 using triphosgene, so as to tie up the diol unit as a Lewis-acid-stable protecting group (Scheme 124).
Scheme 124: Conversion of diol 192 to cyclic carbonate 214

Attempts to use 1,1-carbonyldiimidazole also led to carbonate 214. $^{19}$F NMR and mass spectral analysis also detected traces of the addition of imidazole to the difluoromethylene centre. Treatment with ethylene carbonate only returned starting material. Carbonate 214 was found to be unstable for long periods.

When carbonate 214 was treated with tert-butyldimethylsilyl trifluoromethanesulfonate in the presence of 2,6-lutidine (to scavenge traces of acid), a 14:86 mixture of starting material 214 and a new difluoroolefin was observed, as indicated by the new chemical shifts at -99 and -114 ppm. None of the desired ketone 216 was observed. The shifts correlated very well with those expected for silyl difluoroenol ethers, suggesting that cleavage had occurred, but that the TBDMS enol ether 215, under these conditions, was insufficiently reactive to trap the resulting MEM cation. Unfortunately, attempted column chromatography failed to afford silyl difluoroenol ether 215 to confirm its identity (Scheme 125).
However, this is an important observation since silyl difluoroenol ethers are useful species and a Mukaiyama aldol process may be applicable (using paraformaldehyde) to install the required hydroxymethyl group.\textsuperscript{228}
Chapter Three

Conclusions
The Stille coupling of a range of difluorovinyl C-stannanes with aryl, vinyl, heteroaryl and allyl halides has been developed. It was also possible to employ a difluorovinyl iodide to access the same targets, giving scope to the synthesis of certain styrene derivatives. It was also possible to generate biarylethenes through coupling of aryl triflates under Stille and Suzuki-Miyaura conditions. Sonogashira coupling was also possible. With the correct choice of enol protecting group, these materials could be cleaved under mild electrophilic conditions with a range of electrophiles. The methodology developed offers the possibility of generating a diverse array of aryl difluoromethyl ketones for the first time.

Limitations to the methodology are that a stannane is required as the metal, leading to toxicity issues. In addition, the MEM enol ethers are fairly labile and are therefore difficult to purify and cannot be stored for long periods. Also, the first coupling protocol is only amenable to aryl iodides as the organic electrophiles, although it should be stressed that only a small range of commonly used palladium catalysts were studied.

Future work in this area could look at the possibility of using either a difluorovinylzinc reagent or a difluorovinylsilane as the coupling component. Early indications are that couplings, in one pot from the MEM ether of trifluoroethanol, using a zinc reagent are feasible. The extension to the use of bromo- and chloroarenes could also be studied. Although the range of electrophiles studied is fairly extensive, it would be instructive to further probe the possibility of using an aldol reaction to construct β-hydroxy-α,α-difluoroketones.

It has been demonstrated, for the first time, that fluorinated 1,4-dienes and 1,3-dienes are useful precursors to the synthesis of fluorinated carbohydrate analogues.
The Sharpless Asymmetric Dihydroxylation of a limited range of 1,1-difluoro-1,3-dienes has been studied and it has been found that the reaction is highly dependent upon the electronic nature of the olefinic substituents. Through the use of a special protecting group (pMBz) and controlled pH conditions, it has been possible to dihydroxylate a 1,1-difluoro-1,3-dien-5-ol with high levels of regio- and enantioselection. This sequence has afforded an intermediate with high synthetic potential for the synthesis of enantiomerically enriched oxygenated fluorine-containing materials. Its use was exemplified in the short asymmetric synthesis of a fluorinated deoxyxylulose of current interest.

Possible future work could look at the use of a difluorozinc reagent to form the key diene 190 in order to be able to allow telescoping of the reaction. It may also be beneficial to use a PMB group for allylic alcohol protection to possibly increase the stability of both the diene and the diol product to the basic reaction conditions (Scheme 126).

![Scheme 126: Possible future developments using a MEM protecting group](image)

A successful outcome to this initial work would see the synthesis of a difluorinated hexose analogue. This requires a more thorough study of the use of an enol
protecting group transfer strategy. The use of a benzyloxymethyl protecting group could be beneficial to allow easier deprotection strategies to be employed.

Possible targets using the methodology developed could be 2,2-difluorinated analogues of oleandrose and fucose (Scheme 127).

Scheme 127: Possible targets using the methodology developed to date
**General Procedures:**

**NMR Spectroscopy:**

All NMR spectra were recorded on Bruker AC-300, AV-300, AMX-400 or DRX-500 spectrometers. $^1$H NMR and $^{13}$C NMR were recorded using deuterated solvent as the lock and residual protic solvent as the internal standard. $^{13}$C NMR were recorded using the PENDANT pulse sequence unless otherwise stated. The central peak of the CDCl$_3$ resonance ($\delta$ 77.0) was used as an external reference. The multiplicities of the signals have been indicated as Cq, CH, CH$_2$ and CH$_3$. $^{19}$F NMR spectra were recorded relative to chlorotrifluoromethane as the internal standard over the range -40 to -180 ppm. Multiplicities are represented in the following manner: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets etc., envelope=overlapping multiplets of different nuclei. All coupling constants are recorded in hertz (Hz). $J$ (italic) represents homonuclear coupling (i.e H-H or F-F). Square brackets ([ ]) represent groups of resonances for a single nucleus resulting from rotamers. The numbering used to aid interpretation of NMR data does not necessarily correlate with the IUPAC numbering in the given name.

**Mass Spectrometry:**

Chemical ionisation (CI) and Electron Impact (EI) mass spectra were recorded on a VG Prospec or Kratos MS-80 mass spectrometer with a DS-90 data system. Chemical ionisation methods used ammonia as the carrier gas. Fast Atom Bombardment (FAB) mass spectra were recorded using a VG Zabspec instrument. A micromass LCT mass spectrometer was used for both low-resolution (ES-TOF) mass spectra (using methanol as the mobile phase) and HRMS measurements (using a
lock mass incorporated into the mobile phase). HRMS measurements were also obtained from either the VG Prospec spectrometer or a VG autospec instrument.

Chromatography:

Thin layer chromatography was performed on either pre-coated aluminium-backed silica gel plates (E.Merck, A.G.Darmstadt, Germany. Silica gel 60 F$_{254}$, thickness 0.2 mm), pre-coated aluminium-backed alumina gel plates (E.Merck, A.G.Darmstadt, Germany. Alumina gel 60 F$_{254}$, thickness 0.2 mm) or plastic-backed RP-C18 plates. Visualisation was achieved using potassium permanganate staining, ammonium molybdate staining and UV detection at 254 nm.

Column chromatography was performed on silica gel (E.Merck, A.G. Kieselgel 60, Art. 9385), alumina (pH 9-11, Brockmann 1, Fisher) or florasil. Column fractions were collected and monitored by thin layer chromatography upon the appropriate plates.

GC analysis was carried out on a Carlo Erba GC 8000 Series with Flame Ionisation Detection (FID). An SPE BPX-5 Megabore column (15 m × 0.53 mm ID/Split Mode 20:1) was used with helium as the carrier gas. Chromcard was used as the software.

Analytical HPLC analysis was performed on a Dionex Summit HPLC system with chromeleon software using a Summit P580 quaternary low-pressure gradient pump with built-in vacuum degasser. A Summit UVD 170s UV/VIS multi-channel detector with an analytical flow cell was used for detection. A Luna 10μ C18(2) column (250 mm × 4.6 mm) was used as the stationary phase unless otherwise stated. Semi-preparative HPLC of diols 192 was performed on an identical system accept that a Prep flow cell was used in conjunction with a Luna 10μ C18(2) column (250 mm × 10
Chiral HPLC of alcohols 157 and 159 was performed on a Chiralcel OD column (0.46 cm × 25 cm) using a 90% hexane: 10% isopropanol eluent.

Elemental analyses were performed on a Carlo Erba 1110 CHNS microelemental analysis machine. Optical rotations were performed on a PolAAr 2001 optical activity Ltd automatic polarimeter using 0.25 dm (1 ml) cells. IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer using sodium chloride plates. Melting points were recorded on a Stuart scientific SMP1 melting point apparatus and are uncorrected. UV spectra were recorded on a ThermoScientific UV 500 UV-Vis spectrometer using 10.00 mm quartz glass cuvettes.

Solvents and Reagents:

Tetrahydrofuran was dried by heating under reflux with sodium metal and benzophenone, under dry nitrogen, until a deep purple colour persisted. The solvent was then collected by syringe as required. DMF was distilled from barium oxide under reduced pressure and stored under nitrogen. Dioxane was distilled from diphosphorous pentoxide. DCM was distilled from calcium hydride. Diisopropylamine was distilled from calcium hydride and stored over 4Å molecular sieves. Dichloromethane was distilled from calcium hydride. 2,6-Lutidine was distilled from KOH and stored over KOH pellets. pH Measurements were taken using a pH tester (‘Checker’, Hanna instruments) available from Fisher chemicals. Degassing of solvents for couplings was performed by purging with dry nitrogen or dry argon for 20 min prior to use. n-Butyllithium was titrated against either 4-benzylidene benzylamine or N-pivaloyl-o-toluidine before use.
Zinc(II) bromide was dried by powdering using a pestle and mortar, followed by heating at 200°C under high vacuum (0.1 mmHg). All crude coupling products were diluted with diethyl ether and aqueous KF (1 M, > 3 molar equivalents) added and stirred rapidly for 30 minutes. The solution was then filtered and extracted with the appropriate solvent.

All materials were purchased from Aldrich, Lancaster, Acros (Fisher) or Avocado and used as received unless otherwise stated. 

(R)-(−)-α-(Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (Chiraselect, >99%) was purchased from the Aldrich chemical company PLC and stored in a dri-kold freezer whilst not in use. 4-Iodoanisole was recrystallised from ethanol prior to use. Copper(I) iodide was recrystallised from potassium iodide according to the method of Taylor et al. Allyl bromide was distilled prior to use. Tris(dibenzyldieneacetone)dipalladium(0)-chloroform adduct was prepared according to the method of Cotton. 5-Bromo-2-iodopyridine was prepared according to the method of Song. 1-(N,N-Diethylcarbamoyloxy)-2,2,2-trifluoroethane was prepared according to the method of Howarth. 1-(N,N-Diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene was prepared according to the method of Haworth. N-Pivaloyl-o-toluidine was prepared according to the method of Suffert. (E)-2-[3-(Tributylstannyl)-prop-2-enyloxy]-tetrahydropyran was prepared according to the method of Corey.
n-Butyllithium (24.6 ml of a 2.0 M solution in pentane, 49.2 mmol) was added dropwise over 20 min to a –78°C solution of diisopropylamine (6.8 ml, 51.1 mmol) in THF (45 ml) to afford a pale yellow solution. The solution was allowed to warm slightly by removal from the Dewar flask for 5 min, then re-cooled to –78°C. 2,2,2-Trifluoroethyl N,N-diethylcarbamate 96 (4.0 ml, 24.6 mmol) was added over 25 min and the mixture was stirred for a further 30 min. During this time the colour of the mixture changed from yellow through red to a deep blue. Tributyltin chloride (7.5 ml, 27.6 mmol) was added in one portion and the reaction mixture stirred for 1 h at –78°C, before being allowed to warm to room temperature, affording a yellow solution. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (100 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 50 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (5% diethyl ether in light petroleum) afforded enol stannane 81 as a colourless oil (10.75 g, 93%); R_f (5% diethyl ether in light petroleum) 0.48; \( \delta_H \) (300 MHz, CDCl_3) 3.29 (4H, q, \( ^3J \ 7.4 \), N(CH_2CH_3)_2), 1.54-1.43 (6H, m), 1.35-1.23 (6H, m), 1.15-1.09 (6H, m, N(CH_2CH_3)_2), 1.01-0.96 (6H, m), 0.88 (9H, t, \( ^3J \ 7.4 \), Sn(CH_2CH_2CH_2CH_3)_3); \( \delta_F \) (282 MHz, CDCl_3) 157
-83.64 (1F, d, $^2J$ 64.1), -110.27 (1F, d, $^2J$ 64.1, satellite peaks due to Sn coupling were also observed). NMR Data agreed with those reported by Howarth. 99

4-[1-(N,N-Diethylcarbamoyloxy)-2,2-difluoro-vinyl]-1-methoxybenzene 95a

\[
\text{A mixture of copper(I) iodide (27 mg, 0.14 mmol), triphenylphosphine (53 mg, 0.20 mmol), 4-iodoanisole (286 mg, 1.22 mmol) and tris(dibenzylideneacetone) dipalladium(0)-chloroform adduct (27 mg, 52 \mu\text{mol Pd}) in dry, degassed DMF (8 ml) was heated to 50} ^\circ \text{C. A solution of stannane 81 (514 mg, 1.10 mmol) in DMF (2 ml) was added and the reaction mixture heated at 50-65} ^\circ \text{C for 16 h under a nitrogen atmosphere. After cooling, the mixture was diluted with diethyl ether (10 ml) and water (20 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 \times 15 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a brown oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded anisole 95a as a pale yellow oil (261 mg, 83%); Rf (20% diethyl ether in light petroleum) 0.24; $\nu$ (film/cm$^{-1}$) 1729 s (C=O), 1611 m, 1515 m, 1425 m, 1269 s, 1147 s, 1035 m, 983 m, 838 w, 824 w, 786 w, 756 w; $\lambda_{\text{max}}$ 250.2 nm (10$^{-4}$ M in MeOH), (log $\varepsilon$ = 4.24); $\delta$$_H$ (300 MHz, CDCl$_3$) 7.34 (2H, d, $^3J$ 8.8, ArH), 6.90 (2H, d, $^3J$ 8.8, ArH), 3.80 (3H, s, OCH$_3$), 3.42 (2H, q, $^3J$ 7.2, CH$_2$NCH$_2$), 3.34 (2H, q, $^3J$ 7.2, CH$_2$NCH$_2$), 1.24 (3H, t, $^3J$ 7.2, CH$_2$NCH$_2$)
7.2, EtNCH₂Me), 1.16 (3H, t, 3 J 7.2, MeCH₂NEt); δC (75 MHz, CDCl₃) 159.4 (t, 6 JCF 1.6, Cq-OMe), 154.5 (dd, 2 JCF 290.5, 287.7, CF₂), 152.9 (dd, 4 JCF 3.2, 2.0, CO), 127.0 (dd, 4 JCF 6.0, 3.7, CH), 122.4 (dd, 3 JCF 6.3, 0.6, Cq), 113.9 (CH), 112.1 (d, 2 JCF 39.2, 19.3, C=CF₂), 55.1 (OCH₃), [42.4, 41.8] (CH₂), [14.1, 13.2] (CH₃); δF (282 MHz, CDCl₃) -95.78 (1F, d, 2 J 53.9), -105.85 (1F, d, 2 J 53.9); [HRMS (ES-TOF, M+Na)] Found: 308.1078; Calc. for C₁₄H₁₇NO₃F₂Na: 308.1074; m/z (EI) 285 (53%, M), 186 (18%), 169 (21%, M-ODEC), 135 (62%), 108 (33%), 100 (100%, CONEt₂), 92 (34%), 77 (36%), 72 (88%), 56 (37%), 44 (74%). Data are in agreement with those reported by Thomas.¹⁶⁹

3-[1-(N,N-diethylcarbamoyloxy-2,2-difluoro-vinyl)-1-methoxybenzene 95b

Anisole 95b was prepared as for 95a using palladium(II) acetate (13 mg, 58 μmol), Cul (21 mg, 0.11 mmol), triphenylarsine (69 mg, 0.23 mmol), 3-iodoanisole (253 mg, 1.08 mmol) and stannane 81 (549 mg, 1.17 mmol) in DMF (5 ml) at 100°C. After 2 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded anisole 81 as a colourless oil (152 mg, 49%); Rf (20% diethyl ether in light petroleum) 0.22; ν (film/cm⁻¹) 1733 s, 1602 m, 1581 s, 1422 s, 1382 m, 1270 s, 1219 m, 1142 s, 1096 m, 1043 m, 1007 m, 952 m, 931 m, 843 m, 782 m, 755 m, 690 m; δH (300 MHz, CDCl₃)
7.29 (1H, t, $^{3}J 8.1$, ArH), 7.01 (1H, d, $^{3}J 7.7$, ArH), 6.95 (1H, s, ArH), 6.84 (1H, dd, $^{3}J 8.5$, $^{4}J 2.6$, ArH), 3.79 (3H, s, OCH$_3$), 3.44 (2H, q, $^{3}J 7.2$, NCH$_2$Me), 3.35 (2H, q, $^{3}J 7.2$, NCH$_2$Me), 1.26 (3H, t, $^{3}J 7.2$, NCH$_2$CH$_3$), 1.17 (3H, t, $^{3}J 7.2$, NCH$_2$CH$_3$); $^{13}$C (75 MHz, CDCl$_3$) 159.6 (Cq-OMe), 154.9 (t, $^{1}J_{CF}$ 289.9, CF$_2$), 152.8 (t, $^{4}J_{CF}$ 2.8, CO), 131.5 (dd, $^{3}J_{CF}$ 6.8, 1.1, Cq), 129.6 (CH), 117.8 (dd, $^{4}J_{CF}$ 6.8, 3.4, CH), 113.6 (CH), 112.0 (dd, $^{2}J_{CF}$ 37.3, 18.1, C=CF$_2$), 111.2 (dd, $^{4}J_{CF}$ 6.2, 3.4, CH), 55.1 (OCH$_3$), [42.5, 41.9] (CH$_2$), [14.1, 13.2] (CH$_3$); $^{19}$F (282 MHz, CDCl$_3$) -93.39 (1F, d, $^{2}J$ 48.0), -103.00 (1F, d, $^{2}J$ 48.0); [HRMS (ES-TOF, [M+Na])] Found: 308.1059; Calc. for C$_{14}$H$_{17}$NO$_3$F$_2$Na: 308.1074; m/z (CI) 303 (100%, M$+$NH$_4$), 286 (48%, M$+$H), 74 (53%, H$_2$NEt$_2$), 72 (20%), 52 (9%), 44 (16%). Data are in agreement with those reported by Thomas.$^{169}$

[1-(N,N-Diethylcarbamoyloxy-2,2-difluoro)-vinyl]-benzene 95d

Method A:

Styrene 95d was prepared as for 95a using tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (25 mg, 48 μmol Pd), triphenylphosphine (53 mg, 0.20 mmol), Cul (24 mg, 0.13 mmol), iodobenzene (240 mg, 1.17 mmol) and stannane 81 (517 mg, 1.10 mmol). After 20 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded
styrene 95d as a pale yellow oil (225 mg, 80%); R\textsubscript{f} (20% ether in light petroleum) 0.32; ν (film/cm\textsuperscript{-1}) 1732 s, 1424 m, 1382 w, 1269 s, 1224 w, 1148 s, 1098 w, 1077 w, 1036 w, 984 m, 951 w, 928 w, 788 w, 759 m, 693 m; δ\textsubscript{H} (300 MHz, CDCl\textsubscript{3}) 7.44-7.25 (5H, m, ArH), 3.44 (2H, q, 3\textsuperscript{J} 7.0, NCH\textsubscript{2}CH\textsubscript{3}), 3.40 (2H, q, 3\textsuperscript{J} 7.0, NCH\textsubscript{2}CH\textsubscript{3}), 1.26 (3H, t, 3\textsuperscript{J} 7.0, NCH\textsubscript{2}CH\textsubscript{3}), 1.17 (3H, t, 3\textsuperscript{J} 7.0, NCH\textsubscript{2}CH\textsubscript{3}); δ\textsubscript{C} (75 MHz, CDCl\textsubscript{3}) 154.9 (t, 1\textsuperscript{J}CF 289.9, CF\textsubscript{2}), 152.9 (CO), 130.1 (d, 3\textsuperscript{J}CF 6.8, Cq), 128.5 (CH), 128.1 (t, 5\textsuperscript{J}CF 1.7, CH), 125.4 (dd, 4\textsuperscript{J}CF 6.2, 3.4, CH), 112.4 (dd, 2\textsuperscript{J}CF 37.9, 19.2, C=CF\textsubscript{2}), [42.5, 41.9] (CH\textsubscript{2}), [14.1,13.2] (CH\textsubscript{3}); δ\textsubscript{F} (282 MHz, CDCl\textsubscript{3}) -93.66 (1F, d, 2\textsuperscript{J} 49.1), -103.73 (1F, d, 2\textsuperscript{J} 49.1); m/z (Cl) 273 (32%, M+NH\textsubscript{4}), 256 (100%, M+H), 100 (19%, CONEt\textsubscript{2}). Data are in agreement with those reported by Thomas.\textsuperscript{169}

**Method B:**

A flask containing tetrakis(triphenylphosphine)palladium(0) (54 mg, 47 \textmu mol) and copper(I) iodide (179 mg, 0.94 mmol) was pump-purged with nitrogen. Dry, degassed THF (3 ml) was added followed by iodobenzene (210 mg, 1.03 mmol). The reaction mixture was stirred and warmed to 30°C. A solution of stannane 81 (477 mg, 0.94 mmol based on 92% purity) in THF (1 ml) was added and the heterogeneous reaction mixture heated under reflux for 18 h. The resulting black reaction mixture was allowed to cool to ambient temperature and diluted with diethyl ether (10 ml). This mixture was transferred to a conical flask and an aqueous solution of KF (10 ml of a 1 M soln) added with vigorous stirring. After 25 min, the grey solids were removed by suction filtration. The ethereal layer was separated and the aqueous phase extracted with diethyl ether (3 × 10 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford an orange oil, in addition to
some solids. This crude material was taken up in acetone (ca. 15 ml) and concentrated onto silica gel to afford an orange powder. Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded styrene 95d as a pale yellow oil (182 mg, 76%); 98% by GC; Rf (20% diethyl ether in hexanes) 0.28. NMR data (19F and 1H) were in agreement with those reported by Thomas.169

Methyl 2-[(1-(N,N-diethylcarbamoyloxy)-2,2-difluoro-vinyl)benzenecarboxylate 95f

Ester 95f was prepared as for 95a using tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (26 mg, 50 μmol Pd), Cul (19 mg, 0.10 mmol), triphenylarsine (63 mg, 0.21 mmol), methyl 2-iodobenzoate (641 mg, 2.44 mmol) and stannane 81 (476 mg, 1.02 mmol) in DMF (10 ml) at 100°C. After 1.5 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (15% diethyl ether in light petroleum ⇒ 20% ethyl acetate in light petroleum) afforded ester 95f as a pale orange oil (174 mg, 55%); Rf (20% ethyl acetate in light petroleum) 0.38; ν (film/cm−1) 1758 m, 1729 s, 1599 w, 1575 w, 1423 s, 1382 m, 1271 s, 1146 s, 1088 m, 1042 w, 984 m, 954 w, 929 w, 768 m, 712 m; δH (300 MHz, CDCl3) 7.87 (1H, dd, 3J 7.4, 4J 1.5, ArH), 7.60-7.57 (1H, m, ArH), 7.52 (1H, td, 3J 7.4, 4J 1.5, ArH), 7.42 (1H, td, 3J 7.4, 4J 1.5, ArH), 3.89 (3H, s, OCH3), 3.28 (2H, q, 3J 7.0, NCH2Me), 3.24
(2H, q, \(^3J\) 7.0, NCH\(_2\)Me), 1.12 (3H, t, \(^3J\) 7.0, NCH\(_2\)CH\(_3\)), 1.08 (3H, t, \(^3J\) 7.0, NCH\(_2\)CH\(_3\)); \(\delta\)\(_C\) (75 MHz, CDCl\(_3\)) 167.4 (CO ester), 154.5 (t, \(^1J\)\(_{CF}\) 283.1, CF\(_2\)), 153.5 (CO carbamate), 131.9 (CH), 131.6 (t, \(^4J\)\(_{CF}\) 2.8, CH), 130.3 (CH), 129.3 (CH), 52.2 (OCH\(_3\)), [42.3, 41.7] (CH\(_2\)), [13.9 13.2] (CH\(_3\)). 2 × Cq too weak to assign with confidence and C=CF\(_2\) too weak to assign; \(\delta_F\) (282 MHz, CDCl\(_3\)) -96.57 (1F, d, \(^2J\) 53.9), -106.73 (1F, d, \(^2J\) 53.9); [HRMS (ES-TOF, M+Na) Found: 336.1012; Calc. for C\(_{15}\)H\(_{17}\)NO\(_4\)F\(_2\)Na: 336.1023]; \(m/z\) (Cl) 314 (100 %, M+H), 216 (10%), 198 (7%), 74 (84 %, H\(_2\)CONEt\(_2\)), 72 (67%), 52 (12%), 44 (22%).

4-[(1-(N,N-Diethylcarbamoyloxy)-2,2-difluoro-vinyl]-phenyl trifluoromethane-sulfonate 95e

Triflate 95e was prepared as for 95a using tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (109 mg, 210 μmol Pd), triphenylphosphine (263 mg, 1.00 mmol), CuI (102 mg, 0.54 mmol), 4-iodophenyl trifluoromethanesulfonate 120a (1.98 g, 5.62 mmol) and stannane 81 (2.61 g, 5.57 mmol) in DMF (10 ml). After 16 h, the usual work-up afforded a red oil. Purification by column chromatography over silica gel (5% diethyl in light petroleum ⇒ 10% diethyl ether in light petroleum) afforded triflate 95e as a pale yellow oil (1.79 g, 82%); 69% by GC; R\(_f\) (10% diethyl ether in light
petroleum) 0.17; ν (film/cm⁻¹) 2982 w, 1736 sm, 1598 wm, 1426 m, 1275 m, 1216 sm, 1146 sm, 989 w, 888 m, 849 w, 826 sm, 786 w, 759 w; δ_H (300 MHz, CDCl₃) 7.50-7.46 (2H, m, ArH), 7.30-7.25 (2H, m, ArH), 3.40 (2H, q, 3J 7.2, NCH₂CH₃), 3.32 (2H, q, 3J 7.2, NCH₂CH₃), 1.21 (3H, t, 3J 7.2, NCH₂CH₃), 1.13 (3H, t, 3J 7.2, NCH₂CH₃); δ_C (75 MHz, CDCl₃) 155.0 (dd, 1J_CF 292.7, 291.6, Cq, CF₂), 152.5 (dd, 4J_CF 3.3, 2.1, Cq, CO), 148.7 (t, 6J_CF 2.3, Cq), 130.7 (dd, 3J_CF 6.9, 1.1, Cq), 127.2 (dd, 4J_CF 7.1, 3.4, CH), 121.5 (CH), 118.6 (q, 1J_CF 321.0, Cq, CF₃), 111.2 (dd, 2J_CF 37.9, 20.3, Cq, C=CF₂), [42.6, 41.9] (CH₂), [14.0, 13.0] (CH₃); δ_F (282 MHz, CDCl₃) -72.92 (3F, s), -91.75 (1F, d, 2J 45.2), -101.98 (1F, d, 2J 45.2); [HRMS (ES-TOF, M+Na) Found: 426.0413; Calc. for C₁₄H₁₄NO₅F₅NaS: 426.0411]; m/z (ES-TOF) 426.0 (100%, M+Na).

4-[1-(N,N-Diethylcarbamoyloxy)-2,2-difluoro-vinyl]-1-nitrobenzene 95g

Nitrobenzene 95g was prepared as for 95a using palladium(II) acetate (22 mg, 98 µmol), triphenylphosphine (105 mg, 0.40 mmol), Cul (38 mg, 0.20 mmol), 1-iodo-4-nitrobenzene (498 mg, 2.00 mmol) and stannane 81 (936 mg, 2.00 mmol) in DMF (5 ml). After 3 h, the usual work-up afforded orange crystals in addition to a supernatant orange oil. Purification by column chromatography over silica gel (20% diethyl ether in hexanes ⇒ 60% diethyl ether in light petroleum) afforded nitrobenzene 95g as a
orange semi-solid (99 mg, 18%); 92% by GC; mp 40°C; Rf (20% diethyl ether in hexanes) 0.16;ν (film/cm\(^{-1}\)) 1731 s, 1600 m, 1476 m, 1460 m, 1427 m, 1383 m, 1350 s, 1332 m, 1270 s, 1223 m, 1151 s, 988 m, 951 w, 928 w, 854 m, 826 w, 788 w, 753 m, 693 w; δ\(_H\) (300 MHz, CDCl\(_3\)) 8.23-8.18 (2H, m, ArH), 7.57-7.51 (2H, m, ArH), 3.44 (2H, q, \(^3\)J 7.1, CH\(_2\)NCH\(_2\)), 3.33 (2H, q, \(^3\)J 7.1, CH\(_2\)NCH\(_2\)), 1.25 (3H, t, \(^3\)J 7.1, NCH\(_2\)CH\(_3\)), 1.15 (3H, t, \(^3\)J 7.1, NCH\(_2\)CH\(_3\)); δ\(_C\) (75 MHz, CDCl\(_3\)) 155.5 (dd, \(^1\)J\(_{CF}\) 294.5, 293.3, Cq, CF\(_2\)), 152.4 (dd, \(^4\)J\(_{CF}\) 3.2, 2.0, Cq, CO), 146.9 (t, \(^6\)J\(_{CF}\) 2.0, Cq-NO\(_2\)), 136.8 (dd, \(^3\)J\(_{CF}\) 7.5, 1.7, Cq), 125.9 (dd, \(^4\)J\(_{CF}\) 7.5, 3.7, CH), 123.8 (d, \(^5\)J\(_{CF}\) 0.7, CH), 111.5 (dd, \(^2\)J\(_{CF}\) 36.9, 20.4, C=CF\(_2\)), [42.8, 42.1] (CH\(_2\)), [14.1, 13.2] (CH\(_3\)); δ\(_F\) (282 MHz, CDCl\(_3\)) -88.51 (1F, d, \(^2\)J 36.9), -98.54 (1F, d, \(^2\)J 36.9); [HRMS (ES-TOF, M+Na) Found: 323.0830; Calc. for C\(_{13}\)H\(_{14}\)N\(_2\)O\(_4\)F\(_2\)Na: 323.0819]. A satisfactory mass spectrum (ES) could not be obtained.

2-[1-(N,N-Diethylcarbamoyloxy)-2,2-difluoro)- vinyl]-thiophene 99a

![Thiophene 99a](image)

Thiophene 99a was prepared as for 95a using tris(dibenzylideneacetone)-dipalladium(0)-chloroform adduct (25 mg, 48 μmol Pd), CuI (23 mg, 0.12 mmol), triphenylphosphine (53 mg, 0.20 mmol), 2-iodothiophene (232 mg, 1.10 mmol) and stannane 81 (539 mg, 1.15 mmol). After 45 h, the usual work-up afforded an orange oil. Purification by column chromatography over alumina (10% diethyl ether in light
petroleum) afforded thiophene **99a** as a colourless oil (127 mg, 44%); R_f (20% diethyl ether in light petroleum) 0.30; ν (film/cm\(^{-1}\)) 1732 s, 1423 s, 1304 m, 1260 s, 1222 m, 1149 s, 1098 m, 1033 m, 965 m, 913 m, 850 m, 821 m, 786 m, 753 m, 700 m; δ\(_{\text{H}}\) (300 MHz, CDCl\(_3\)) 7.28 (1H, dd, \(^3\)J 4.8, \(^4\)J 1.1, H-α), 7.06-7.05 (1H, m, H-β), 7.01-6.99 (1H, m, H-γ), 3.39 (2H, q, \(^3\)J 7.2, NCH\(_2\)Me), 3.32 (2H, q, \(^3\)J 7.2, NCH\(_2\)Me), 1.22 (3H, t, \(^3\)J 7.2, NCH\(_2\)C\(_3\)H\(_3\)), 1.15 (3H, t, \(^3\)J 7.2, NCH\(_2\)C\(_3\)H\(_3\)); δ\(_{\text{C}}\) (75 MHz, CDCl\(_3\)) 154.1 (dd, \(^1\)J\(_{\text{CF}}\) 292.2, 289.9, CF\(_2\)), 152.4 (CO), 132.5 (Cq), 127.5 (CH), 125.7 (dd, \(^1\)J\(_{\text{CF}}\) 5.1, 3.4, CH), 124.8 (dd, \(^1\)J\(_{\text{CF}}\) 6.2, 5.1, CH), [42.7, 42.1] (CH\(_2\)), [14.2, 13.3] (CH\(_3\)), C=CF\(_2\) too weak to assign; δ\(_{\text{F}}\) (282 MHz, CDCl\(_3\)) -95.77 (1F, d, \(^2\)J 45.5), -101.04 (1F, d, \(^2\)J 45.5); m/z (CI) 279 (94%, M+NH\(_4\)), 262 (38%, M+H), 100 (12%), 74 (100%, H\(_2\)N\(_2\)Et), 72 (29%), 58 (20%), 52 (16%). This material decomposed to the [2+2] dimer before a HRMS measurement could be obtained.

**{(Z)}-[4-(N,N-Diethylcarbamoyloxy)-5,5-difluoro-penta-2,4-dienyl] (benzyloxy)-acetate 99b**

![Chemical Structure]

**Method A:**

Ester **99b** was prepared as for **95a** using tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (26 mg, 50 \(\mu\)mol Pd), Cul (19 mg, 0.10 mmol), triphenylarsine (63 mg, 0.21 mmol), (Z)-3-iodopropen-2-yl benzyloxyacetate (271 mg, 0.81 mmol) and
stannane 81 (463 mg, 0.99 mmol). After 18.5 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (20% diethyl in light petroleum) afforded pentadienyl ester 99b as a pale orange oil (145 mg, 46%); R_f (10% ethyl acetate in light petroleum) 0.15; ν (film/cm^{-1}) 1732 s, 1476 m, 1456 m, 1428 m, 1383 m, 1267 s, 1194 s, 1128 s, 1085 s, 1030 m, 752 m, 700 m; [Found: C, 59.22; H, 6.04; N, 3.48; Calc. for C_{19}H_{23}O_5NF_2: C, 59.52; H, 6.05; N, 3.65%]; δ_H (300 MHz, CDCl_3) 7.35-7.25 (5H, m, ArH), 6.00 (1H, ddt, 3_J 12.2, 4_J_{HF} 3.7, 4_J 2.4, H-3), 5.59 (1H, dtdd, 3_J 12.1, 6.3, 5_J_{HF} 1.5, 0.8, H-2), 4.85 (2H, ddd, 3_J 6.2, 4_J 2.4, 6_J_{HF} 1.5, H-1), 4.61 (2H, s, CH_2OBn), 4.09 (2H, s, OCH_2Ph), 3.37 (2H, q, 3_J 7.2, NCH_2Me), 3.32 (2H, q, 3_J 7.0, NCH_2Me), 1.18 (3H, t, 3_J 7.2, NCH_2Me), 1.15 (3H, t, 3_J 7.2, NCH_2Me); δ_C (75 MHz, CDCl_3) 169.9 (CO ester), 154.6 (dd, 1_J_{CF} 295.0, 293.3, CF_2), 152.2 (d, 4_J_{CF} 2.3, CO carbamate), 136.9 (Cq), 128.4 (CH), 127.9 (CH), 127.9 (CH), 125.3 (dd, 3_J_{CF} 11.0, 3.7, C-3), 118.4 (d, 4_J_{CF} 4.5, C-2), 111.2 (dd, 2_J_{CF} 39.0, 19.2, C=CF_2), 73.2 (OCH_2), 66.9 (OCH_2), 61.3 (OCH_2), [42.4, 41.8] (CH_2), [13.8, 13.1] (CH_3); δ_F (282 MHz, CDCl_3) -94.18 (1F, d, 2_J 35.7), -102.19 (1F, d, 2_J 35.7); m/z (CI) 401 (56%, M+NH_4), 237 (16%), 218 (49%, M-OCOCH_2OBn), 184 (23%), 106 (28%), 74 (100%, H_2NEt_2), 52 (59%).

Method B:

Ester 99b was prepared as for 95a using tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (27 mg, 52 μmol Pd), Cul (21 mg, 0.11 mmol), triphenylphosphine (55 mg, 0.21 mmol), (Z)-3-iodopropen-2-yl benzyloxyacetate (267 mg, 0.81 mmol) and stannane 81 (519 mg, 1.11 mmol) in DMF (10 ml) at 50°C. After 20 h, the usual work-up afforded a crude orange oil. Purification by column chromatography over
silica gel (20% diethyl ether in light petroleum ⇒ 10% ethyl acetate in light petroleum) afforded dienyl ester 99b as a pale brown oil (192 mg, 62%); Rf (10% ethyl acetate in light petroleum) 0.15. 19F and 1H NMR in agreement with those found for method A.

(E)-2-[4-(N,N-Diethylcarbamoyloxy)-5,5-difluoropenta-2,4-dienyloxy]-tetrahydropyran 99c

Pyran 99c was prepared as for 95a using tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (27.5 mg, 53 μmol Pd), CuI (26 mg, 0.14 mmol), triphenylphosphine (54 mg, 0.21 mmol), (E)-3-iodopropenol THP ether (99 mg, 0.37 mmol) and stannane 81 (519 mg, 1.11 mmol) in DMF (3 ml). After 16 h, the usual work-up afforded a brown solid. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded protected 2,4-dien-1-ol 99c (29 mg, 25%) as a pale yellow oil. NMR data was in close agreement with those obtained from the coupling of iodoalkene 82 and stannane 100b (see pg 172).

2-(N,N-Diethylcarbamoyloxy) -1,1-difluoro-1,4-pentadiene 99d

1,4-Diene 99d was prepared as for 95a using tris(dibenzylideneacetone)-dipalladium(0)-chloroform adduct (26 mg, 50 μmol Pd), CuI (29 mg, 0.15 mmol),...
triphenylphosphine (60 mg, 0.23 mmol), freshly distilled allyl bromide (100 μl, 1.16 mmol) and stannane 81 (519 mg, 1.11 mmol). After 18 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded 1,4-diene 99d as a pale yellow oil (213 mg, 87%); Rf (10% diethyl ether in light petroleum) 0.32; ν (film/cm⁻¹) 3085 w, 1782 s (C=CF₂), 1730 s (C=O), 1643 m (C=C), 1476 m, 1460 m, 1426 s, 1383 m, 1288 s, 1246 s, 1211 s, 1157 s, 1074 s, 1036 m, 992 m, 958 m, 924 m, 785 m, 757 m; δH (300 MHz, CDCl₃) 5.79-5.66 (1H, m, H-4), 5.14-5.04 (2H, m, H-5), 3.30-3.20 (4H, m, CH₂N₂), 3.00-2.95 (2H, m, H-3), 1.10 (6H, t, ³J₇.0, (MeCH₂)₂N); δC (75 MHz, CDCl₃) 154.2 (dd, ¹JC₂ 288.0, C-1), 152.7 (CO), 132.0 (t, ⁴JC₂ 3.0, C-4), 117.6 (C-5), 110.6-109.8 (m, C-2), [42.2, 41.7] (CH₂), 31.2 (d, ³JC₂ 2.3, C-3), [13.7, 13.0] (CH₃); δF (282 MHz, CDCl₃) -99.32 (1F, dt, ²J 63.6, ⁴JHF 2.5), -111.49 (1F, dt, ²J 63.6, ⁴JHF 3.8); [HRMS (EI, M+H) Found: 220.1159; Calc. for C₁₀H₁₆NO₂F₂: 220.1149]; m/z (EI) 237 (35%, M+NH₄⁺), 220 (100%, M+H), 170 (24%), 100 (66%, ODEC), 74 (69%, NH₂Et₂), 58 (23%), 44 (12%). Data are in close agreement with those reported by Howarth.189a

2-(N,N-Diethylcarbamoyloxy)-1,1-difluoro-1,3-butadiene 99e

1,3-Diene 99e was prepared as for 95a, using Cul (94 mg, 0.50 mmol), triphenylarsine (331 mg, 1.08 mmol), palladium(II) acetate (593 mg, 0.26 mmol), 2-
(N,N-diethylcarbamoyloxy)-1,1-difluoro-2-iodoethene **82** (1.56 g, 5.11 mmol) and tributylvinyltin (1.77 g, 5.58 mmol) in dry, degassed DMF (10 ml) at 100°C. The solution had an initial yellow colour, which changed to black after 6 min leaving a Pd black suspension. TLC after 80 min indicated no starting iodoalkene **82**. The mixture was diluted with diethyl ether (10 ml) and decanted from the Pd into a separating funnel. Water (30 ml) was added and the organic phase separated. The aqueous phase was extracted with diethyl ether (3 × 15 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude yellow oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded 1,3-diene **99e** as a pale yellow oil (925 mg, 88%); 88% by G.C;

Rf (10% diethyl ether in light petroleum) 0.29; δH (300 MHz, CDCl3) 6.34 (1H, dddd, 3 Jtrans 17.3, 3 Jcis 11.2, 4 JHF 3.3, 1.8, H-3), 5.21 (1H, d, 3 Jtrans 17.3, H-4a), 5.17-5.12 (1H, m, H-4b), [3.42-3.30] (4H, m, two overlapping q, N(CH2CH3)2), [1.23-1.13] (6H, m, two overlapping t, N(CH2CH3)2); δC (75 MHz, CDCl3) 154.2 (dd, 1 JCF 294.4, 292.2, CF2), 152.3 (CO), 124.1 (d, 3 JCF 5.1, CH=CH2), [113.3, 113.1] (2 × d, 4 JCF 4.5, =CH2), 112.3 (dd, 2 JCF 40.7, 18.1, C=CF2), [42.5, 41.9] (CH2), [14.0, 13.20] (CH3); δF (282 MHz, CDCl3) -95.50 (1F, d, 2 J40.7), -105.50 (1F, dd, 2 J40.7, 4 JHF 3.8); [HRMS (Cl, M+H) Found: 206.0995; Calc. for C9H14NO2F2: 206.0993; m/z (Cl) 223 (47%, M+NH4), 206 (100%, M+H), 100 (11%, CONEt2). This material decomposed before full characterisation could be achieved.
(E)-2-(N,N-Diethylcarbamoyloxy)-1,1-difluoro-1,3-nonadiene and
(Z)-2-(N,N-diethylcarbamoyloxy)-1,1-difluoro-1,3-nonadiene 99f

1,3-Dienes 99f were prepared as for 95a using palladium(II) acetate (12.7 mg, 56.5 μmol), CuI (21.3 mg, 0.11 mmol), triphenylarsine (66 mg, 0.22 mmol), iodoalkene 82 (321 mg, 1.1 mmol) and 1-heptynltributyltin (439 mg, 1.1 mmol, 5:1 E:Z) in dry DMF (5 ml). After 3 h, the usual work-up afforded a pale yellow oil. Purification by column chromatography over silica gel (5% diethyl ether in light petroleum) afforded inseparable 1,3-dienes 99f as pale yellow oils (205 mg, 71%, 5:1 E:Z); Rf (5% diethyl ether in light petroleum) 0.11; δH (300MHz, CDCl3) 6.02-5.94 (0.83H, m, H-3, E-isomer), 5.81-5.74 (0.17H, m, H-3, Z-isomer), 5.70-5.59 (0.83H, unres. dt, H-4, E-isomer), 5.58-5.47 (0.17H, m, H-4, Z-isomer), 3.41-3.31 (4H, m, N(CH2CH3)2 E and Z-isomers), 2.21-2.07 (2H, m, H-5, E and Z isomers), 1.65-1.13 (12H, envelope, H-6, H-7, H-8 and N(CH2CH3)2, E and Z-isomers), 0.94-0.85 (3H, envelope, H-9, E and Z-isomers); δC (75 MHz, CDCl3)(E-isomer only, Z-isomer too weak to assign) 153.8 (t, 1JCF 289.9, Cq, C-1), 152.6-152.5 (m, Cq, CO), 130.6 (dd, 3JCF 11.6, 4.5, CH, C-3), 117.0-116.9 (m, CH, C-4), 112.0 (dd, 2JCF 40.7, 18.1, Cq, C-2), [42.5, 41.9] (CH2, NCH2CH3), 32.5 (CH2), 31.3 (CH2), 28.6 (CH2), 22.4 (CH2), 14.0 (CH3), [14.1, 13.2] (CH3, NCH2CH3); δF (282 MHz, CDCl3) -98.14 (1F, d, 2J 48.3, E and Z isomers), -104.56 to -104.73 (0.17F, m, Z isomer), -107.87 (0.83F, d, 2J 47.0, E isomer);
[HRMS (EI, M) Found: 275.1692; Calc. for $C_{14}H_{23}NO_2F_2$: 275.1697; $m/z$ (EI) 275 (13%, M), 100 (100%, CONEt$_2$), 72 (74%, $H_2$NEt$_2$), 55 (14%), 44 (32%).]

(E)-2-[4-(N,N-Diethylcarbamoyloxy)-5,5-difluoropenta-2,4-dienyloxy]-tetrahydropyran 99c

Pyran 99c was prepared as for 95a using palladium(II) acetate (12.8 mg, 57.0 μmol), triphenylarsine (68 mg, 0.22 mmol), Cul (22.3 mg, 0.12 mmol), iodoalkene 82 (340 mg, 1.11 mmol based upon 81% purity (enol carbamate 98 impurity)) and (E)-2-[3-(tributylstannyl)-prop-2-enyloxy]-tetrahydropyran (460 mg, 1.07 mmol) in DMF (10 ml). After 6.5 h, the usual work-up afforded a yellow oil. Purification over silica gel (20% diethyl ether in light petroleum) afforded 1,3-diene 99c as a pale yellow oil (90 mg, 31%); $R_f$ (20% diethyl ether in light petroleum) 0.05; $\delta_H$ (300 MHz, CDCl$_3$) 6.31-6.22 (1H, dm, H-8), 5.74 (1H, dt, $^3J$ 15.4, 5.9, H-7), 4.62 (1H, t, $^3J$ 3.3, H-1), 4.34-4.26 (1H, dm, H-6), 4.08-4.00 (1H, dm, H-6'), 3.87-3.80 (1H, m, H-5), 3.52-3.45 (1H, m, H-5'), 3.40-3.29 (4H, m, N(CH$_2$CH$_3$)$_2$), 1.87-1.45 (6H, envelope, H-2, H-2', H-3, H-3', H-4, H-4'), 1.21-1.13 (6H, envelope, N(CH$_2$CH$_3$)$_2$); $\delta_C$ (75 MHz, CDCl$_3$) 154.2 (dd, $^1J_{CF}$ 293.9, 291.6, Cq, C-10), 152.3 (Cq, CO), 125.6 (dd, $^3J_{CF}$ 11.9, 4.3, CH, C-8), 119.0 (d, $^4J_{CF}$ 5.1, CH, C-7), 111.7 (dd, $^2J_{CF}$ 40.7, 18.6, Cq, C-9), 97.9 (CH, C-1), 66.7
(CH₂O), 62.1 (CH₂O), [42.5, 41.9] (CH₂), 30.5 (CH₂), 25.3 (CH₂), 19.3 (CH₂), [14.0, 13.2] (CH₃); δF (282 MHz, CDCl₃) -95.66 (1F, d, ²J 41.9), -105.72 (1F, dd, ²J 41.9, ⁴JHF 3.2); [HRMS (ES-TOF, M+Na) Found: 342.1490; Calc. for C₁₅H₂₃NO₄F₂Na: 342.1493]; m/z (Cl) 337.7 (49%, M+NH₄), 319.0 (3%, M), 253.5 (100%, M+NH₄-THP), 218.4 (32%, M-OTHP), 102.3 (13%, OTHP+H).

**Tributyl-(4-methoxyphenyl)-tin 100c**

![Tributyl-(4-methoxyphenyl)-tin 100c](image_url)

4-Iodoanisole (582 mg, 2.0 mmol) was dissolved in dry diethyl ether (20 ml) under a nitrogen atmosphere and the solution cooled to -85°C using a diethyl ether/solid CO₂ bath. After stirring for 5 min, ⁷BuLi (2.6 ml of a 1.6 M solution in hexanes, 4.2 mmol) was dispensed via syringe into the reaction vessel, and the subsequent solution stirred for 30 min at this temperature. Tributyltin chloride (0.4 ml, 1.8 mmol) was then added and the solution allowed to stir for 1 h, then allowed to warm to room temperature overnight. The reaction was quenched by the addition of a saturated solution of ammonium chloride (20 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 20 ml). The combined organic
extracts were dried and concentrated under reduced pressure to afford a crude yellow oil. Purification by column chromatography over alumina (100% toluene) afforded aryl stannane \textbf{100c} as a pale yellow oil (555 mg, 76%); est. 90% purity by $^1$H NMR; R$_f$ (100% toluene) 1.00; $\delta$$_H$ (300 MHz, CDCl$_3$) 7.45-7.30 (2H, m, ArH, weak satellite peaks due to Sn coupling were also observed), 6.94-6.88 (2H, m, ArH), 3.81 (3H, s, OCH$_3$), 1.58-1.48 (6H, m), 1.39-1.27 (6H, m), 1.07-0.98 (6H, m), 0.89 (9H, t, $^3$J 7.4, Sn(CH$_2$CH$_2$CH$_2$CH$_3$)$_3$); $\delta$$_C$ (75 MHz, CDCl$_3$) 159.7 (Cq-OMe), 137.5 (CH), 132.0 (Cq), 113.9 (CH), 55.0 (OCH$_3$), 29.1 (CH$_2$), 27.4 (CH$_2$), 13.7 (CH$_3$), 9.6 (CH$_2$); m/z (El) 397 (13%, M($^{118}$Sn)+1), 341 (73%, M($^{120}$Sn)-Bu), 285 (46%, M($^{120}$Sn)-2Bu+1), 227 (84%, M($^{120}$Sn)-3Bu), 135 (26%), 108 (77%, M+1-SnBu$_3$), 91 (26%), 78 (39%), 65 (38%), 56 (73%), 41 (100%), 32 (88%). This material was used without further characterisation.

\textbf{4-[1-(N,N-Diethylcarbamoyloxy-2,2-difluoro)-vinyl]-1-methoxybenzene 95a from iodoalkene 82}

Anisole \textbf{95a} was prepared using \textit{tris}(dibenzylideneacetone)dipalladium (0)-chloroform adduct (25 mg, 48.3 $\mu$mol Pd), Cul (22 mg, 0.12 mmol), triphenylphosphine (51 mg, 0.19 mmol), (4-methoxyphenyl)tributyltin \textbf{100c} (487 mg, 1.2 mmol) and iodide \textbf{82} (305 mg, 1.0 mmol) in DMF (10 ml). After 45 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded anisole \textbf{95a} as a pale yellow oil (99 mg, 35%); R$_f$ (20% ether in light petroleum) 0.19. NMR data were in agreement with those found for the Stille coupling protocol from stannane \textbf{81} (see pg 158).
A mixture of copper(I) iodide (23 mg, 0.12 mmol), triphenylarsine (68 mg, 0.22 mmol), palladium(II) acetate (15 mg, 67 μmol) and iodoalkene 82 (280 mg, 0.93 mmol) in dry, degassed DMF (10 ml) was stirred at ambient temperature for 2 min under nitrogen. 2-(Tributylstannyl)furan (370 mg, 1.04 mmol) was added and the reaction heated at 100°C for 16 h. The solution had an initial orange colour, which changed to straw yellow upon stannane addition. The reaction mixture was allowed to cool to ambient temperature and diluted with diethyl ether (10 ml) and water (30 ml). The ethereal phase was separated and the aqueous phase extracted with diethyl ether (3 × 15 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford an orange oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded furan 99g as a pale yellow oil (180 mg, 81%); Rf (10% diethyl ether in light petroleum) 0.23; ν (film/cm⁻¹) 1741 m, 1610 m, 1562 s, 1423 w, 1269 w, 1171 m, 982 s; δH (300 MHz, CDCl₃) 7.43 (1H, d, 3J 1.5, H-α), 6.43 (1H, dd, 3J 3.3, 1.5, H-β), 6.37 (1H, d, 3J 3.3, H-γ), 3.43-3.32 (4H, two overlapping q, 3J 7.0, CH₂NCH₂), 1.25-1.15 (6H, two overlapping t, 3J 7.0, N(CH₂CH₃)₂); δC (75 MHz, CDCl₃) 154.6 (t, 1J₉ 291.0, CF₂), 152.8 (CO), 144.0 (d, 3J₉ 10.2, Cq), 142.9 (HetArH), 111.5 (HetArH), 111.2-111.0 (m, C=CF₂), 108.6-108.4
(m, HetArCH), [42.9, 42.2] (CH$_2$), [14.2, 13.5] (CH$_3$); $\delta$F (282 MHz, CDCl$_3$) -95.94 (1F, d, $^2$J 44.5), -101.38 (1F, d, $^2$J 44.5); [HRMS (ES-TOF, M+Na) Found: 268.0761; Calc. for C$_{11}$H$_{13}$NO$_3$F$_2$Na: 268.0761]; m/z (ES-TOF) 268.1 (100%, M+Na).

2-[1-(N,N-Diethylcarbamoyloxy)-2,2-difluoro-vinyl]-thiophene 99a from iodoalkene 82

Thiophene 99a was prepared as for 99g using tris(dibenzylideneacetone)-dipalladium(0)-chloroform adduct (26 mg, 49.1 $\mu$mol Pd), Cul (26 mg, 0.14 mmol), triphenylphosphine (53 mg, 0.20 mmol), iodoalkene 82 (308 mg, 1.01 mmol) and 2-(tributylstannyl)thiophene (421 mg, 1.13 mmol) in DMF (10 ml), except that the stannane was added over 1 h via a syringe pump. After 30 h, the usual work-up afforded an orange oil (1.17 g). Purification by column chromatography over alumina (10 % diethyl ether in light petroleum) afforded thiophene 99a as a colourless oil (94 mg, 36%); R$_f$ (10 % ether in light petroleum) 0.31. NMR data were in agreement with those found using the Stille protocol from stannane 81 (see pg 166).
Attempted preparation of 1-[1-(N,N-diethylcarbamoyloxy-2,2-difluoro)-vinyl]-3-(1,3-dioxacyclopent-2-yl)-furan 99k

A mixture of CuI (240 mg, 0.13 mmol), triphenylarsine (70 mg, 0.23 mmol), palladium (II) acetate (12.5 mg, 56 μmol Pd) and 1-(N,N-diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene 82 (341 mg, 0.92 mmol based on 82% purity (enol carbamate 98 impurity)) in dry DMF (10 ml) was stirred at ambient temperature for 2 min under nitrogen. 5-(Tributylstannyl)-2-(2,5-dioxacyclopentyl)-furan 100f (614 mg, 1.03 mmol based on 72% purity) was added and the reaction mixture heated at 100°C for 16 h. The solution had an initial orange colour which changed to straw yellow upon addition of the stannane. A black mixture was observed by the end of the reaction, leaving a palladium black deposit. The mixture was diluted with diethyl ether (10 ml), decanted from the Pd and washed with water (20 ml), allowing the DMF to enter the aqueous phase. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 15 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford an orange oil. Analysis by 19F NMR indicated the presence of furan 99k (61%), enol carbamate 98 (28%) and dimer 97 (11%), in addition to several baseline fluorinated products, including those resulting from [2+2] cycloaddition reactions. Attempted purification by column chromatography
over silica gel (20% diethyl ether in light petroleum) failed to afford any of the desired product.

Data for crude 99k; $\delta_F$ (282 MHz, CDCl$_3$) -95.96 (1F, d, $^2J$ 43.2), -101.66 (1F, d, $^2J$ 43.2). Shifts are in agreement with those found for furan 99g and thiophene 99a.

Procedure for Negishi coupling of 1-(N,N-diethylcarbamoyloxy)-2,2-difluorovinylzinc halides:

[1-(N,N-Diethylcarbamoyloxy)-2,2-difluorovinyl]-benzene 95d

$n$-Butyllithium (0.84 ml of a 2.38 M solution in hexanes, 2.0 mmol) was added dropwise by syringe to a −78°C solution of diisopropylamine (0.28 ml, 2.0 mmol) in THF (3 ml). The pale yellow solution was warmed to −30°C for 5 min to allow complete LDA formation, then re-cooled to −78°C. Trifluoroethyl N,N-diethylcarbamate 96 (0.16 ml, 0.99 mmol) was added dropwise over 15 min to afford an orange solution. After stirring for a further 20 min, a deep red solution was observed which changed to light orange upon addition of a solution of vacuum-dried zinc bromide (230 mg, 1.02 mmol) in THF (2 ml). After stirring for 1 h at −78°C, the solution was allowed to warm to room temperature, with no loss of the pale orange colour. Iodobenzene (0.12 ml, 1.07 mmol) was added in one portion, followed by triphenylphosphine (26.8 mg, 0.26 mmol) and tris(dibenzylideneacetone)-dipalladium(0)-chloroform adduct (11.5 mg, 22.1 μmol Pd). The resulting heterogeneous mixture was stirred for 48 h at ambient temperature under a nitrogen atmosphere. Diethyl ether (5 ml) was added, followed by water (10 ml). The organic
phase was separated and the aqueous phase extracted with diethyl ether (3 × 5 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded styrene 95d as a colourless oil (134 mg, 54%); R$_f$ (20% diethyl ether in light petroleum) 0.36. The data obtained agreed with those found for the Stille coupling, but the sample was found to be slightly cleaner by $^1$H NMR owing to the absence of tin residues.

(E)-4-(1-(N,N-Diethylcarbamoyloxy)-2-fluoro-prop-1-enyl)-1-methoxybenzene

Methyllithium (2.8 ml of a 1.29 M solution in hexanes, 3.61 mmol) was added to a –78°C solution of styrene 95a (338 mg, 1.19 mmol) in THF (15 ml) to afford a brown solution. After stirring for 1 h at this temperature, TMEDA (0.7 ml, 4.62 mmol) was added and the resulting solution stirred for 15 min. Chlorotrimethylsilane (0.5 ml, 3.94 mmol) was added and the reaction allowed to warm to ambient temperature over 1 h. A saturated solution of ammonium chloride (10 ml) was added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 10 ml). The combined organic extracts were consecutively washed with brine (15 ml) and a saturated solution of sodium bicarbonate (15 ml), then dried and concentrated under
reduced pressure to afford an orange oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded fluoroalkene 104 as pale yellow crystals (213 mg, 64%); 86% by GC; 97% by HPLC at 225 nm; HPLC t; (20% water in MeCN, 1ml/min) 4.83 min; Rf (20% diethyl ether in light petroleum) 0.14; mp. 57-60°C; [Found: C, 64.11; H, 7.05; N, 4.76; Calc. for C_{15}H_{20}FNO_3: C, 64.04; H, 7.17; N, 4.98%]; ν (nujol mull/cm\(^{-1}\)) 1730 w, 1610 w, 1514 w, 1294 w, 1262 w, 1221 w, 1126 w, 1076 w, 936 w, 922 w; δ_H (300 MHz, CDCl\(_3\)) 7.31 (2H, d, \(^3\)J 9.2, ArH), 6.87 (2H, d, \(^3\)J 9.2, ArH), 3.78 (3H, s, OCH\(_3\)), [3.39-3.26] (4H, two overlapping q, CH\(_2\)NCH\(_2\)), 2.07 (3H, d, \(^3\)J\(_{HF}\) 17.7, =CFCH\(_3\)), [1.21-1.10] (6H, two overlapping t, N(CH\(_2\)CH\(_3\))\(_2\)); δ_C (75 MHz, CDCl\(_3\)) 159.3 (Cq-OMe), 153.5 (d, \(^4\)J\(_{CF}\) 1.7, CO), 148.9 (d, \(^1\)J\(_{CF}\) 252.1, CF), 130.4 (d, \(^2\)J\(_{CF}\) 17.5, C=CF), 129.6 (d, \(^4\)J\(_{CF}\) 2.8, CH), 125.7 (d, \(^3\)J\(_{CF}\) 2.8, Cq), 113.6 (CH), 55.1 (OCH\(_3\)), [42.1, 41.7] (NCH\(_2\)), 14.9 (d, \(^2\)J\(_{CF}\) 27.1, =CFCH\(_3\)), [14.0, 13.2] (NCH\(_2\)CH\(_3\)); δ_F (282 MHz, CDCl\(_3\)) -113.45 (q, \(^3\)J\(_{HF}\) 17.8); [HRMS (ES-TOF, M+Na) Found: 304.1331; Calc. for C\(_{15}\)H\(_{20}\)FNO\(_3\)Na: 304.1325]; m/z (EI) 281 (18%, M), 153 (4%), 151 (4%), 135 (16%), 100 (100%, CONEt\(_2\)), 72 (39%, H\(_2\)NEt\(_2\)), 44 (8%); m/z (ES) 304.1 (100%, M+Na).
A mixture of copper(I) iodide (21 mg, 0.11 mmol), triphenylphosphine (54 mg, 0.21 mmol) and tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (25 mg, 48 μmol Pd) was pump-purged twice with argon, then degassed DMF (5 ml) was added. A solution of allyl bromide (90 μl, 1.08 mmol) in DMF (2 ml) was added and the mixture heated to 50°C under an argon atmosphere. A solution of 1,1-difluoro-2-[(N-isopropyl-N-(tert-butyldiphenylsilyloxyethyl))-carbamoyloxy]-1-(tributylstannyl)-ethene (660 mg, 0.91 mmol) in DMF (2 ml) was added in one portion and the reaction mixture heated at 50-65°C until TLC indicated consumption of starting material. The reaction was diluted with diethyl ether (10 ml) and water (20 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 10 ml). The combined organic extracts were dried and concentrated under reduced pressure. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded a yellow oil (230 mg, 73%) consisting of an inseparable mixture of 1,4-diene 108 (60%) and enol carbamate (13%). Purification by preparative HPLC afforded diene 108 as a colourless oil; Rf (20% diethyl ether in light petroleum) 0.66; δH (300 MHz, CDCl3) 7.67 (4H, d, J 6.2, ArH), 7.44-7.36 (6H, m, ArH), [5.81-5.69,
5.67-5.54 (1H, 3:7, m, H-4), [5.16-4.95] (2H, m, H-5), [4.21-4.12, 4.09-4.00] (1H, 7:3, m, NCH\textsubscript{Me\textsubscript{2}}), 3.78-3.69 (2H, m, NCH\textsubscript{2}CH\textsubscript{2}O), [3.38-3.33, 3.30-3.25] (2H, 3:7, m, NCH\textsubscript{2}CH\textsubscript{2}O), [3.05-3.01, 2.95-2.89] (2H, 3:7, m, H-3), 1.12-1.09 (6H, m, NCH\textsubscript{Me\textsubscript{2}}), 1.06 (9H, s, \textsuperscript{1}Bu-Si); \(\delta\textsubscript{\text{c}}\) (75 MHz, CDCl\textsubscript{3}) 154.3 (dd, \textsuperscript{1}J\textsubscript{CF} 288, 287, C-1), [152.9, 152.8] (CO), 135.5 (ArCH), 133.4 (Cq), 132.1 (ArCH), 129.8 (CH), 127.7 (ArCH), 117.8 (CH\textsubscript{2}), 110.5-109.9 (m, \textsuperscript{2}J\textsubscript{CF} 46.8, C-2), 62.7 (CH\textsubscript{2}O, major rotamer), 62.0 (CH\textsubscript{2}O, minor rotamer), 49.0 (Me\textsubscript{2}CHN, minor rotamer), 48.7 (Me\textsubscript{2}CHN, major rotamer), 46.0 (CH\textsubscript{2}N, minor rotamer), 44.7 (CH\textsubscript{2}N, major rotamer), 31.4 (CH\textsubscript{2}, C-3), 26.8 (CH\textsubscript{3}, C(CH\textsubscript{3})\textsubscript{3}), 20.9 (CH\textsubscript{3}, (CH\textsubscript{3})\textsubscript{2}CHN, minor rotamer), 20.2 (CH\textsubscript{3}, (CH\textsubscript{3})\textsubscript{2}CHN, major rotamer), 19.2 (Cq, C(CH\textsubscript{3})\textsubscript{3}); \(\delta\textsubscript{\text{F}}\) (282 MHz, CDCl\textsubscript{3}) major rotamer (66%) -98.8 (1F, m), -111.30 to -111.56 (1F, m, \textsuperscript{2}J\textsubscript{62.3}); minor rotamer (34%) -99.1 (1F, d, \textsuperscript{2}J\textsubscript{64.9}), -111.18 to -111.44 (1F, m, \textsuperscript{2}J ca. 64.0); [HRMS (ES-TOF, M+Na) Found 510.2258; Calc. for C\textsubscript{27}H\textsubscript{35}NO\textsubscript{3}F\textsubscript{2}NaSi: 510.2252]. A satisfactory mass spectrum could not be obtained.

2,2,2-Trifluoroethyl N-ethyl-N-(2-methylallyl)carbamate 109b

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\text{O} \\
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2,2,2-Trifluoroethanol (7.25 ml, 100.4 mmol) was added to a solution of 1,1-carbonyldiimidazole (16.25 g, 100.4 mmol) in DCM (220 ml) at ambient temperature and the resulting solution stirred for 16 h. Imidazole (7.76 g, 114.0 mmol) and N-(2-
methylallyl)-ethylamine (14.5 ml, 110.1 mmol) were added and the resulting solution stirred for a further 16 h. The reaction mixture was concentrated under reduced pressure to half volume. The residual mixture was transferred to a separating funnel and washed twice with HCl (2 × 100 ml of a 0.5M aqueous solution). The organic layer was separated, dried and concentrated under reduced pressure to afford carbamate 109b as a pale yellow oil (21.70 g, 96%). Purification by distillation under reduced pressure afforded 109b as a colourless oil (21.63 g, 96%); 100% by GC; bp. 51°C/ 11 mmHg; [Found: C, 47.97; H, 6.08; N, 6.21; Calc. for C9H14O2NF3: C, 48.00; H, 6.27; N, 6.22%]; ν (film/cm−1) 2979 m, 2941 m, 1720 m, 1659 w, 1476 m, 1432 m, 1381 m, 1290 m, 1254 m, 1170 m, 1099 m, 975 m, 903 w, 763 w; δH (300 MHz, CDCl3) 4.85 (1H, bd s, =CCHaHb), [4.78, 4.76] (1H, =CHaHb), [4.53-4.41] (2H, two overlapping q of two rotamers, CH2CF3), 3.80 (2H, d, 2J 12.0, NCH2vinyl), [3.27-3.23] (2H, two overlapping q, NCH2Me), 1.66 (3H, s, =C(CH3)vinyl), [1.10-1.09] (3H, two overlapping t, NCH2Me); δc (75 MHz, CDCl3) [154.6, 154.1] (CO), 140.8 (Cq), 123.3 (q, 1JC 277.5, CF3), [112.4, 112.3] (=CH2), 61.3 (q, 2JC 36.1, CH2CF3), [52.9, 52.1] (CH2), [42.0, 41.2] (CH2CH3), 19.7 (CH3), [13.1, 12.6] (CH2CH3); δF (282 MHz, CDCl3) [-74.39, -74.46] (3F, t, 3JHF 8.9); [HRMS (ES-TOF, M+Na) Found: 248.0866; Calc. for C9H14O2NF3Na: 248.0874]; m/z (El) 225 (100%, M), 210 (50%, M-Me), 184 (61%, M-MeC=CH2), 170 (12%), 156 (17%), 142 (10%, 126 (16%), 110 (5%), 98 (46%, N(Et)CH2C(Me)=CH2), 92 (11%), 83 (41%, CH2CF3), 55 (75%, CH2C(Me)=CH2).
n-Butyllithium (2.8 ml of a 2.4 M solution in pentanes, 6.8 mmol) was added over 20 min to a -78°C solution of diisopropylamine (0.9 ml, 6.8 mmol) in dry THF (5 ml). The pale yellow solution was allowed to warm slightly by removal from the Dewar flask for 5 min then re-cooled to -78°C. Carbamate 109b (759 mg, 3.4 mmol) was added over 25 min, affording a brown solution, which was left to stir at this temperature for 2 h. Tributyltin chloride (1.0 ml, 3.6 mmol) was added in one portion and the reaction mixture stirred for 1 h at -78°C, before being allowed to warm to room temperature, affording a yellow solution. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (15 ml), then diluted with diethyl ether (30 ml) and water (30 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude orange oil. Diethyl ether (10 ml) was added followed by KF (10 ml of a 1 M aqueous soln) and the resulting mixture stirred rapidly for 30 min. The suspension was filtered and the filtrate extracted with diethyl ether (3 × 10 ml). The combined organic extracts were dried
and concentrated under reduced pressure. Purification by column chromatography over silica gel (5% diethyl ether in light petroleum) afforded stannane 112 as a colourless oil (1.27 g, 76%); 88% by GC; Rf (5% diethyl ether in light petroleum) 0.68; ν (film/cm\(^{-1}\)) 3081 w, 2925 s, 1705 s, 1462 s, 1425 s, 1378 m, 1259 s, 1193 m, 1151 s, 1108 m, 1003 m, 966 w, 900 w, 797 w, 761 w; δ\(_{\text{H}}\) (300 MHz, CDCl\(_3\)) 4.86 (1H, s, =CH\(_a\)H\(_b\)), 4.80 (1H, s, =CH\(_a\)H\(_b\)), 3.82 (2H, s, NCH\(_2\)vinyl), [3.30-3.20] (2H, m, NCH\(_2\)CH\(_3\)), 1.69 (3H, s, C(CH\(_3\))=CH\(_2\)), 1.55-1.44 (6H, m, 3 \times CH\(_2\)), 1.36-1.24 (6H, m, 3 \times CH\(_2\)), 1.14-0.97 (9H, envelope, 3 \times CH\(_2\), NCH\(_2\)CH\(_3\)), 0.88 (9H, t, \(^3\)J 7.4, 3 \times CH\(_3\)); δ\(_C\) (75 MHz, CDCl\(_3\)) 162.1-155.0 (triplet of multiplets, centred around 158.5, CF\(_2\)), 157.9-157.9 (m, CO), 154.6-154.3 (doublet of multiplets, C=CF\(_2\)), 140.9 (=CH\(_2\)), [112.4, 112.1] (C=CH\(_2\)), [52.5, 52.2] (NCH\(_2\)C(Me)=CH\(_2\)), [41.7, 41.0] (NCH\(_2\)CH\(_3\)), 28.8 (CH\(_2\), satellite peaks due to Sn coupling were also observed), 27.2 (CH\(_2\), satellite peaks due to Sn coupling were also observed), 19.8 (C(CH\(_3\))=CH\(_2\)), 13.7 (CH\(_3\)), [13.1, 12.7] (CH\(_3\)), 11.4 (CH\(_2\)); δ\(_F\) (282 MHz, CDCl\(_3\)) [-83.13, -83.18] (1F, d, \(^2\)J 63.6), [-110.07, -110.13] (1F, d, \(^2\)J 63.6; satellite peaks due to Sn coupling were also observed); [HRMS (ES-TOF, M(\(^{120}\)Sn)+Na) Found: 518.1874; Calc. for C\(_{21}\)H\(_{39}\)NO\(_2\)F\(_2\)Na\(^{120}\)Sn: 518.1869]; \(m/z\) (ES-TOF) 550.3 (6%, M(\(^{120}\)Sn)+Na+MeOH), 518.2 (100%, M(\(^{120}\)Sn)+Na), 517.2 (19%, M(\(^{119}\)Sn)+Na), 516.2 (67%, M(\(^{118}\)Sn)+Na), 515.2 (23%, M(\(^{117}\)Sn)+Na), 514.2 (34%, M(\(^{116}\)Sn)+Na).
(3RS)-2-(N-Ethyl-N-2-methallylcarbamoyloxy)-1,1-difluoro-pent-1-en-3-ol 113

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\begin{align*}
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\text{N} & \text{O} \\
\text{F} & \text{OH} \\
\text{F} & \text{1 2 3} \\
\text{4 5} & \text{}
\end{align*}
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\(n\)-Butyllithium (6.30 ml of a 1.6 M in hexane, 10.08 mmol) was added dropwise to a -78°C solution of diisopropylamine (1.33 ml, 10.23 mmol) in THF (20 ml). Following the addition, the solution was removed from the Dewar for 5 min to complete LDA formation, before being recooled to -78°C. 2,2,2-Trifluoroethyl N-ethyl-N-2-methallylcarbamate 109b (1.1 ml, 5.0 mmol) was added dropwise via syringe over 25 min. During this period, the solution changed from pale yellow, through to a deeper yellow colour. After stirring for 30 min, freshly distilled propanal (0.4 ml, 5.51 mmol) was added in one-portion and the resulting pale yellow solution maintained at -78°C for 1 h, affording a pale orange solution. After this period, boron trifluoride-diethyl ether complex (0.70 ml, 5.52 mmol) was added, which immediately discharged the orange colour, affording a pale yellow solution. The solution was allowed to warm to 0°C by use of an ice bath, then stirred for a further 1 h at this temperature. The pale yellow solution was then quenched with a saturated aqueous solution of ammonium chloride (50 ml). Diethyl ether (50 ml) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 40 ml) and the combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil (1.6 g). Purification by column chromatography over silica gel (20% ethyl acetate in light petroleum) afforded allylic alcohol 113 as a colourless oil (858
mg, 65%); 98% by GC; Rf (20% ethyl acetate in light petroleum) 0.33; ν (film/cm⁻¹) 3450 bd (OH), 3082 w, 2974 m, 2941 m, 2881 m, 1770 s (C=CF₂), 1712 s (C=O), 1460 m, 1427 m, 1381 m, 1297 m, 1231 m, 1134 m, 1071 m, 1016 m, 972 w, 897 m, 838 w, 797 w, 756 w, 735 w; δH (300 MHz, CDCl₃) 4.88 (1H, s, =CH₃-Hₐ), 4.80 (1H, s, =CH₃-Hₐ), 4.33-4.21 (1H, m, CH₃OH), 3.82 (2H, s, NCH₂All), [3.59, 3.55] (1H, d, 3J 5.4, OH), 3.28 (2H, q, 3J 7.1, NCH₂Me), [1.69, 1.67] (3H, 2 × s, C(CH₃)=CH₂), 1.24-1.09 (5H, envelope, CHCH₂Me, NCH₂CH₃), [0.90, 0.87] (3H, t, 3J 6.7, CH₂CH₃); δC (300 MHz, CDCl₃) 155.4 (CO), 154.8 (dd, 1J CF 295.9, 287.4, C-1), 154.7 (dd, 1J CF 291.4, 286.8, C-1 rotamer), [140.4, 140.2] (C(Me)=CH₂), 113.2-113.0 (m, C-2), [112.7, 112.3] (=CH₂), 68.4-68.3 (m, C-3), [53.1, 52.7] (NCH₂C(Me)=CH₂), [42.4, 41.8] (NCH₂Me), [26.7, 26.6] (C-4), [19.7, 19.7] (C(CH₃)=CH₂) [13.2, 12.4] (NCH₂CH₃), 9.7 (C-5); δF (282 MHz, CDCl₃) [-95.52, -95.94] (1F, d, 2J 52.8), -106.17 (1F, d, 2J 52.8); [HRMS (ES, M+Na) Found: 286.1235; Calc. for C₁₂H₁₉O₃NF₂Na: 286.1231]; m/z (ES-TOF) 286.1 (100%, M+Na).

[((1-(N-Ethyl-N-2-methylallyl)-carbamoyloxy)-2,2-difluoro-vinyl]-benzene 114

Styrene 114 was prepared as for 95a using palladium(II) acetate (61 mg, 273 μmol), Cul (426 mg, 2.23 mmol), triphenylphosphine (265 mg, 1.03 mmol), iodobenzene
(1.2 ml, 10.7 mmol) and stannane 112 (4.94 g, 8.78 mmol based on 88% purity) in
DMF (20 ml). After 16 h, the usual work-up afforded an orange oil. Flash column
chromatography over silica gel (15% diethyl ether in light petroleum) removed
baseline colour to afford a colourless oil (2.30 g). Purification by distillation under
reduced pressure (60°C/11 mmHg ⇒ 95°C/13 mmHg ⇒ 95°C/2 mmHg ⇒
104°C/0.03 mmHg) afforded styrene 114 as a colourless oil (1.85 g, 72%); 95% by
GC; bp. 104°C/0.03 mmHg; ν (film/cm⁻¹) 3081 w, 1736 s, 1658 w, 1422 m, 1275 s,
1147 s, 1130 m, 982 s; δH (300 MHz, CDCl₃) 7.44-7.27 (5H, m, ArH), [4.95, 4.90,
4.90, 4.88] (2H, s, =CH₂), [3.97, 3.88] (2H, s, NCH₂), [3.42, 3.34] (2H, q, ³J 7.1,
NCH₂Me), [1.78, 1.71] (3H, s, C(CH₃)=CH₂), [1.24, 1.15] (3H, t, ³J 7.2, NCH₂CH₂);
δC (75 MHz, CDCl₃) 155.0 (t, ¹JCF 289.9, CF₂ of rotamer), 155.0 (t, ¹JCF 289.5, CF₂ of
rotamer), 153.7 (CO of rotamer), 153.1 (CO of rotamer), 140.8 (CMe=CH₂ of
rotamer), 140.6 (CMe=CH₂ of rotamer), [130.2, 130.1] (C₃), [128.6, 128.6] (CH),
128.2 (CH), 125.7-125.4 (m, CH), [112.7, 111.9] (=CH₂), [53.0, 52.4] (CH₂ of allyl),
[42.4, 41.5] (NCH₂Me), [20.0, 19.7] (CH₃), [13.5, 12.7] (CH₂CH₃); δF (282 MHz,
CDCl₃) [-93.39, -93.70] (1F, d, ²J 49.6), [-103.72, -103.77] (1F, d, ²J 49.6); [HRMS
(ES-TOF, M+Na) Found: 304.1134; Calc. for C₁₅H₁₇NO₂F₂Na: 304.1125]; m/z (ES)
304.1 (100%, M+Na).
[4-((1-(N-Ethyl-N-2-methylallyloxy)-2,2-difluoro-vinyl)-phenyl] trifluoromethane-sulfonate 115

\[
\text{N} - \text{C(C(H}_2)_3 = \text{CH}_2) - \text{O} - \text{CF}_2 \text{OSO}_2 \text{CF}_3
\]

Trflate 115 was prepared as for 114 using tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (48 mg, 92 μmol Pd), triphenylphosphine (107 mg, 0.41 mmol), Cul (42 mg, 0.22 mmol), trflate 120a (792 mg, 2.00 mmol) and stannane 112 (960 mg, 2.10 mmol) in DMF (5 ml). After 16 h, the usual work-up afforded a yellow oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded trflate 115 as a colourless oil (490 mg, 59%); 100% by GC; Rf (10% diethyl ether in light petroleum) 0.23; ν (film/cm\(^{-1}\)) 3083 w, 2981 m, 2936 m, 1738 s, 1505 m, 1426 s, 1281 s, 1251 s, 1216 s, 1145 s, 1019 w, 987 m, 889 s, 847 m, 791 w, 756 w, 607 m; δ\(_H\) (300 MHz, CDCl\(_3\)) [7.50, 7.49] (2H, 2 × d, \(^3\)J 8.8, ArH), [7.31-7.26] (2H, m, ArH), [4.95, 4.91, 4.87, 4.84] (2H, 4 × s, =CH\(_a\)H\(_b\)), [3.95, 3.88] (2H, 2 × s, NCH\(_2\)C(Me)=CH\(_2\)), [3.45-3.30] (2H, m, NCH\(_2\)CH\(_3\)), [1.77, 1.70] (3H, 2 × s, C(CH\(_3\))=CH\(_2\)), [1.23, 1.16] (3H, 2 × t, \(^3\)J 7.4, NCH\(_2\)CH\(_3\)); δ\(_C\) (75 MHz, CDCl\(_3\)) 159.0-151.2 (triplet of multiplets, centred at 155.1, CF\(_2\)), [153.3-152.7] (m, CO), 148.8 (t, \(^3\)J\(_{CF}\) 2.3, Cq), 140.4 (=CH\(_2\)), 130.7-130.6 (m, Cq), [127.4-127.2] (m, CH), [121.6, 121.5] (CH), 118.7 (q, \(^1\)J\(_{CF}\) 321.0, CF\(_3\)), [112.7, 111.7] (C(Me)=CH\(_2\)), [53.0, 52.4] (CH\(_2\)), [42.6, 41.6] (CH\(_2\)), [19.9, 19.7] (CH\(_3\)), [13.5, 12.6] (CH\(_3\)). C=CF\(_2\) too weak to
assign; $\delta_F$ (282 MHz, CDCl$_3$) -72.75 (3F, s, CF$_3$), [-91.18, -91.54] (1F, d, $^2J$ 44.4), -101.72 (1F, d, $^2J$ 44.4); [HRMS (ES-TOF, M+H) Found: 430.0755; Calc. for C$_{16}$H$_{16}$NO$_5$F$_5$S: 430.0748]; m/z (ES-TOF) 452.1 (30%, M+Na), 430.1 (100%, M+H).

2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-1-(tributylstanny)-ethene 118

\[
\begin{array}{c}
\text{O} \\
\text{F} \\
\text{F} \\
\text{Sn} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\]

$n$-Butyllithium (16.8 ml of a 2.38 M solution in hexanes, 40.0 mmol) was added to a $-78^\circ$C solution of diisopropylamine (5.4 ml, 40.0 mmol) in THF (30 ml). The flask was removed from the dewar for 5 min to complete LDA formation, then recooled to $-78^\circ$C. 1,1,1-Trifluoro-2-(2-methoxy-ethoxymethoxy)ethane 119 (3.2 ml, 20.0 mmol) was added dropwise over 10 min to afford a pale yellow solution. The reaction mixture was then allowed to stir for a further 20 min to afford a thick brown solution. Tributyltin chloride (5.6 ml, 20.0 mmol) was added in one portion and the reaction allowed to warm to ambient temperature over 3 h. The reaction was quenched with a saturated solution of ammonium chloride (50 ml), then diethyl ether (50 ml) added. The organic phase was separated and the aqueous phase extracted with diethyl ether ($3 \times 20$ ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a yellow oil. Diethyl ether (20 ml) was added followed by KF (15 ml of a 1 M solution in water) and the resulting solution stirred rapidly for 30
min. The suspension was filtered using suction filtration and the organic phase separated. The ether phase was dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by flash column chromatography over a 5 cm pad of silica gel (5% diethyl ether in light petroleum) afforded stannane 118 as a colourless oil (8.12 g, 89%); R_f (5% diethyl ether in light petroleum) 0.50; δ_H (300 MHz, CDCl_3) 4.74 (2H, s, OCH_2O), 3.76-3.74 (2H, m, CH_2O), 3.56-3.53 (2H, m, CH_2O), 3.38 (3H, s, OCH_3), 1.55-1.44 (6H, m), 1.37-1.24 (6H, m), 1.04-0.99 (6H, m), 0.88 (9H, t, J 7.4, Sn(CH_2CH_2CH_2CH_3)_3); δ_C (75 MHz, CDCl_3) 159.7 (dd, J_CF 317.2, 267.5, CF_2), 96.2-96.1 (m, OCH_2O), 71.6 (CH_2O), [67.7, 67.7] (CH_2O), 59.0 (OCH_3), 28.7 (s, satellite peaks due to Sn coupling were also observed, CH_2), 27.2 (s, satellite peaks due to Sn coupling were also observed, CH_2), 13.6 (CH_3), 10.2 (dd, J_CF 2.0, 1.1, CH_2), C=CF_2 too weak to assign; δ_F (282 MHz, CDCl_3) -84.96 (1F, d, J_F 66.1, satellite peaks due to Sn coupling were also observed), -109.34 (1F, d, J_F 66.1, satellite peaks due to Sn coupling were also observed). NMR data were in close agreement with those reported by Patel.\textsuperscript{101}

4-Iodophenyl trifluoromethanesulfonate 120a

\[
\begin{align*}
\text{I} & \quad \text{SO}_2\text{CF}_3
\end{align*}
\]

4-Iodophenol (7.80 g, 35.5 mmol) was dissolved in pyridine (20 ml) and cooled to 0°C under a nitrogen atmosphere. Trifluoromethanesulfonic anhydride (6.0 ml, 35.5 mmol) was added dropwise and the resulting solution allowed to warm to room
temperature. The solution was stirred overnight until TLC indicated complete consumption of starting iodophenol. The mixture was quenched with water (30 ml) and diluted with diethyl ether (50 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 20 ml). The combined organic extracts were sequentially washed with water (30 ml), 3M HCl (30 ml) and brine (30 ml), then dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (100% light petroleum) afforded triflate 120a as a colourless oil (11.60 g, 93%); 100% by GC; \( R_f \) (100% light petroleum) 0.30; \( \nu \) (film/cm\(^{-1}\)) 1479 m, 1427 m, 1396 w, 1251 m, 1214 m, 1179 w, 1141 m, 1957 w, 1010 m, 885 m, 829 m, 747 m; \( \delta_H \) (300 MHz, CDCl\(_3\)) 7.75 (2H, d, 3\( J \) 8.5, ArH), 7.01 (2H, d, 3\( J \) 8.5, ArH); \( \delta_C \) (75 MHz, CDCl\(_3\)) 149.4 (Cq), 139.4 (ArCH), 123.4 (ArCH), 118.7 (q, 1\( J_{CF} \) 320.8, CF\(_3\)), 93.2 (Cq); \( \delta_F \) (282 MHz, CDCl\(_3\)) -72.7 (3F, s). NMR data were in agreement with those reported by Qing et al.\(^{179}\)

3-Iodophenyl trifluoromethanesulfonate 120b

![3-Iodophenyl trifluoromethanesulfonate 120b](image)

Triflate 120b was prepared as for 120a, using 3-iodophenol (5.17 g, 23.5 mmol), pyridine (13 ml) and trifluoromethanesulfonic anhydride (5 ml, 29.7 mmol). After the usual work-up, a crude yellow oil was isolated. Purification by column chromatography over silica gel (100% light petroleum) afforded triflate 120b as a
colourless oil (7.85 g, 95%); 100% by GC; Rf (100% light petroleum) 0.47; ν (film/cm\(^{-1}\)) 1588 m, 1574 s, 1465 s, 1428 s, 1249 s, 1214 s, 1169 m, 1142 s, 1089 w, 1060 w, 999 w, 893 s, 792 s, 753 m, 679 w, 606 s, 569 s; [Found: C, 23.99; H, 1.00; Calc: C, 23.88; H, 1.15%]; δ\(^1\)H (300 MHz, CDCl\(_3\)) 7.73 (1H, dd, \(^3\)J 7.7, \(^4\)J 1.1, ArH), 7.63 (1H, t, \(^4\)J 2.0, ArH), 7.29-7.24 (1H, m, ArH), 7.18 (1H, t, \(^3\)J 8.1, ArH); δ\(^13\)C (75 MHz, CDCl\(_3\)) 149.2 (Cq), 137.6 (CH), 131.4 (CH), 130.4 (d, \(^3\)J 0.6, CH), 120.8 (d, \(^4\)J 0.6, CH), 118.6 (q, \(^1\)J\(_{CF}\) 320.7, CF\(_3\)), 93.8 (Cq); δ\(^19\)F (282 MHz, CDCl\(_3\)) -72.55 (3F, d, \(^3\)J 3.8).

NMR data were in agreement with those reported by Qing et al.\(^{179}\)

2-Iodophenyl trifluoromethanesulfonate 120c

![2-Iodophenyl trifluoromethanesulfonate 120c](image)

Triflate 120c was prepared as for 120a, using 2-iodophenol (5.15 g, 23.4 mmol), pyridine (13 ml) and trifluoromethanesulfonic anhydride (4.0 ml, 23.8 mmol). After the usual work-up, a crude yellow oil was isolated. Purification by column chromatography over silica gel (100% light petroleum) afforded triflate 120c as a colourless oil (7.77 g, 94%); 100% by GC; Rf (100% light petroleum) 0.24; ν (film/cm\(^{-1}\)) 1573 w, 1463 m, 1427 s, 1248 s, 1213 s, 1167 m, 1138 s, 1118 w, 1042 w, 1022 w, 946 w, 886 s, 780 m, 765 m, 739 m, 702 w; [Found: C, 23.82; H, 1.16; S, 9.26; Calc: C, 23.88; H, 1.15; S, 9.11%]; δ\(^1\)H (300 MHz, CDCl\(_3\)) 7.91 (1H, dd, \(^3\)J 7.9, \(^4\)J 1.7, ArH), 7.42 (td, \(^3\)J 7.8, \(^4\)J 1.7, ArH), 7.32 (1H, dd, \(^3\)J 8.2, \(^4\)J 1.4, ArH), 7.11 (1H, td,
$^3 J 7.7, ~^4 J 1.5, \text{ArH})$; $\delta_C$ (75 MHz, CDCl$_3$) 150.2 (Cq), 140.8 (ArCH), 130.0 (ArCH), 129.6 (ArCH), 122.1-122.0 (m, ArCH), 118.7 (q, $^1 J_{CF} 320.7$, CF$_3$), 89.0 (Cq); $\delta_F$ (282 MHz, CDCl$_3$) -73.14 (3F, s, CF$_3$). NMR data were in agreement with those reported by Qing et al.$^{179}$

**4-[(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy))-vinyl]-phenyl] trifluoromethane-sulfonate 121a**

A mixture of copper(I) iodide (756 mg, 3.97 mmol), triphenylphosphine (469 mg, 1.79 mmol) and palladium(II) acetate (107 mg, 0.48 mmol) was pump-purged twice with argon, then dry, degassed DMF (45 ml) added. A solution of 4-iodophenyl triflate 120a (6.53 g, 18.54 mmol) in DMF (2 ml) was added and the mixture heated to 50°C. Stannane 118 (8.12 g, 17.76 mmol) was subsequently added and the mixture stirred for 16 h at this temperature. The mixture was allowed to cool to ambient temperature and diluted with diethyl ether (20 ml) and water (100 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether ($3 \times 25$ ml). The combined organic extracts were dried and concentrated under reduced pressure. Purification by column chromatography over silica gel (5% diethyl ether in light petroleum $\Rightarrow$ 20% ethyl acetate in light petroleum) afforded triflate 121a as a pale orange oil (6.32 g, 96%); 97% by GC; $R_f$ (20% ethyl acetate in light petroleum) 0.44;
ν (film/cm⁻¹) 1731 m, 1504 m, 1428 s, 1251 s, 1215 s, 1179 m, 1142 s, 1103 m, 984 m, 941 m, 889 s, 847 m, 783 w, 758 w; δ_H (300 MHz, CDCl₃) 7.50 (2H, d, 3J 8.9, ArH), 7.24 (2H, d, 3J 8.9, ArH), 4.82 (2H, s, OCH₂O), 3.80-3.77 (2H, m, OCH₂CH₂O), 3.49-3.46 (2H, m, OCH₂CH₂O), 3.31 (3H, s, OCH₃); δ_C (75 MHz, CDCl₃) 155.8 (t, 1J_CF 292.0, CF₂), 148.9 (t, 6J_CF 2.3, Cq), 130.7 (dd, 3J_CF 4.7, 1.7, Cq), 128.5 (dd, 4J_CF 6.2, 3.4, CH), 121.6 (CH), 118.7 (q, 1J_CF 320.0, CF₃), 114.6 (dd, 2J_CF 34.4, 19.5, C=CF₂), 95.8 (t, 4J_CF 3.0, OCH₂O), 71.5 (OCH₂), 68.7 (OCH₂), 59.0 (OCH₃); δ_F (282 MHz, CDCl₃) -73.0 (3F, s, CF₃), -95.79 (1F, d, 2J 51.5), -104.51 (1F, d, 2J 51.5); [HRMS (ES-TOF, M+Na) Found: 415.0247; Calc. for C₁₃H₁₃O₆F₅SNa: 415.0251]; m/z (Cl) 410 (100%, M+NH₄), 361 (12%), 346 (43%), 317 (10%), 287 (25%, M-OMEM), 253 (41%), 223 (12%), 189 (8%), 171 (6%), 154 (19%); m/z (ES-TOF) 415.1 (100%, M+Na).

3-[(2,2-Difluoro-1-(2-methoxyethoxymethoxy))-vinyl]-phenyl trifluoromethanesulfonate 121b

![Chemical Structure](image)

Triflate 121b was prepared as for 121a using copper(I) iodide (440 mg, 2.3 mmol), triphenylphosphine (270 mg, 1.0 mmol), palladium(II) acetate (60 mg, 0.27 mmol), 3-iodophenyl triflate 120b (3.52 g, 10.0 mmol) and stannane 118 (4.58 g, 10.0 mmol) in DMF (28 ml). After 16 h, the usual work-up afforded an orange oil. Purification by
column chromatography over silica gel (5% diethyl ether in light petroleum ⇒ 20% diethyl ether in light petroleum) afforded triflate **121b** as an orange oil (3.24 g, 86%); 91% by GC; R_f (20% diethyl ether in light petroleum) 0.27; ν (film/cm^{-1}) 2931 m, 2888 m, 1729 s, 1612 m, 1577 m, 1489 m, 1426 s, 1369 w, 1272 s, 1246 s, 1215 s, 1027 m, 1009 m, 946 s, 896 s, 804 s, 762 m, 608 s; δH (300 MHz, CDCl_3) 7.52-7.43 (2H, envelope, ArH), 7.38 (1H, t, 4J 1.8, ArH), 7.20 (1H, dt, 3J 7.4, 4J 2.2, ArH), 4.88 (2H, s, OCH_2O), 3.86-3.83 (2H, m, CH_2O), 3.54-3.51 (2H, m, CH_2O), 3.36 (3H, s, OCH_3); δC (75 MHz, CDCl_3) 155.8 (t, 1J_CF 292.2, CF_2), 149.7 (Cq), 133.1 (dd, 3J_CF 6.9, 2.0, Cq), 130.4 (CH), 126.3 (dd, 4J_CF 7.2, 3.2, CH), 120.9-120.8 (m, CH), 119.3 (dd, 4J_CF 5.8, 3.7, CH), 118.7 (q, 1J_CF 320.7, CF_3), 114.5 (dd, 2J_CF 34.2, 19.8, C=CF_2), 96.0 (t, 4J_CF 2.9, OCH_2O), 71.5 (CH_2O), 68.7 (d, 6J_CF 1.7, CH_2O), 58.9 (OCH_3); δF (282 MHz, CDCl_3) -72.83 (3F, s, CF_3), -94.59 (1F, d, 2J 49.4), -103.09 (1F, d, 2J 49.4); [HRMS (M+Na) Found: 415.0244; Calc. for C_{13}H_{13}O_6F_5SNa: 415.0251]; m/z (ES) 414.9 (100%, M+Na).

2-[(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy))-vinyl]-phenyl trifluoromethane-sulfonate **121c**

![Structure of 121c](image)

Triflate **121c** was prepared as for **121a** using palladium(II) acetate (65 mg, 0.29 mmol), triphenylphosphine (266 mg, 1.02 mmol), Cul (433 mg, 2.28 mmol), 2-
iodophenyl triflate 120c (3.53 g, 10.03 mmol) and stannane 118 (4.58 g, 10.02 mmol). After 16 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded triflate 121c as an orange oil (810 mg, 21%); 97% by GC; Rf (10% diethyl ether in light petroleum) 0.15; ν (film/cm⁻¹) 2932 m, 2898 m, 1748 s, 1612 w, 1490 m, 1426 s, 1279 s, 1248 s, 1215 s, 1179 s, 1141 s, 1102 s, 986 s, 949 s, 886 s, 783 s, 779 s; δH (300 MHz, CDCl₃) 7.57-7.30 (4H, envelope, ArH), 4.79 (2H, s, OCH₂O), 3.81-3.78 (2H, m, OCH₂CH₂O), 3.53-3.50 (2H, m, OCH₂CH₂O), 3.36 (3H, s, OCH₃); δC (75 MHz, CDCl₃) 154.9 (dd, 1JCF 292.2, 286.2, CF₂), 147.3 (dd, 4JCF 3.1, 1.7, Cq), 132.3 (t, 4JCF 2.9, CH), 131.3 (CH), 128.3 (CH), 123.5 (dd, 3JCF 4.8, 2.8, Cq), 122.0 (dd, 5JCF 2.3, 1.1, CH), 118.5 (q, 1JCF 319.9, CF₃), 110.8 (dd, 2JCF 40.7, 21.5, C=CF₂), 94.8 (t, 4JCF 2.6, OCH₂O), 71.4 (CH₂O), 68.2 (d, 6JCF 1.7, CH₂O), 59.0 (OCH₃); δF (282 MHz, CDCl₃) -73.85 (3F, s, CF₃), -97.28 (1F, d, 2J 52.1), -104.94 (1F, d, 2J 52.1); [HRMS (ES-TOF, M+Na) Found: 415.0263; Calc. for C₁₃H₁₃O₆F₅Na S: 415.0251]; m/z (ES) 415 (100%, M+Na).
Benzyl 5-[(2,2-difluoro-1-(2-methoxy-ethoxymethoxy))-vinyl]-2-trifluoromethanesulfonoxy-benzenecarboxylate 121d

Triflate 121d was prepared as for 121a using palladium(II) acetate (17 mg, 76 μmol), Cul (12 mg, 63 μmol), triphenylphosphine (75 mg, 292 μmol), benzyl 5-iodo-2-(trifluoromethanesulfonoxy)-benzene-carboxylate (1.30 g, 2.68 mmol) and stannane 118 (1.25 g, 2.74 mmol) in DMF (8 ml) at 50°C. After 16 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (30% diethyl ether in light petroleum) afforded triflate 121d as a pale yellow oil (986 mg, 70%); 96% by GC; R_f (30% diethyl ether in light petroleum) 0.21; ν (film/ cm^{-1}) 2930 m, 2891 m, 1733 s (CO), 1607 w, 1588 w, 1491 m, 1429 s, 1248 s, 1213 s, 1178 s, 1141 s, 1103 m, 1072 s, 1026 w, 945 m, 894 m, 758 w, 699 w; δ_H (300 MHz, CDCl_3) 8.18 (1H, d, 3^J 2.5, H-c), 7.71 (1H, ddd, 3^J 8.8, 3^J 2.5, 5^J_HFa 1.1, H-a), 7.47-7.44 (2H, envelope, ArH), 7.40-7.29 (4H, envelope, ArH), 5.41 (2H, s, CH_2Ph), 4.87 (2H, s, OCH_2O), 3.84-3.79 (2H, m, OCH_2C, 3.50-3.44 (2H, m, OCH_2CH_2O), 3.33 (3H, s, OCH_3); δ_C (75 MHz, CDCl_3) 163.1 (CO ester), 156.0 (t, 1^J_CF 293.0, CF_2), 147.5 (Cq-OTf), 135.1 (Cq of Bn), 132.0 (dd, 4^J_CF 7.2, 3.4, CH), 131.3 (dd, 3^J_CF 7.1, 1.5, Cq), 130.7 (dd, 4^J_CF 6.2, 4.0, CH), 128.8 (CH), 128.6 (CH), 128.6 (CH), 124.9 (Cq-CO), 123.2 (d, 5^J_CF 1.1, CH), 118.7 (q, 1^J_CF 320.8, CF_3), 114.3 (dd, 2^J_CF 33.9, 19.8, C=CF_2),
96.2 (t, J_{CF} 2.8, OCH_2O), 71.5 (OCH_2), 68.8 (d, J_{CF} 2.3, OCH_2), 67.8 (OCH_2Ph), 59.0 (OCH_3); δ_F (282 MHz, CDCl_3) -73.41 (s, CF_3), -94.18 (d, J_F 49.4), -103.06 (d, J_F 49.7); [HRMS (ES-TOF, M+Na) Found: 549.0605; Calc. for C_{21}H_{19}O_8F_5NaS: 549.0619]; m/z (ES-TOF) 549.1 (100%, M+Na).

2-[(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy))-vinyl]-benzene 121e

Styrene 121e was prepared as for 121a using palladium(II) acetate (25 mg, 0.11 mmol), triphenylphosphine (107 mg, 0.41 mmol), CuI (172 mg, 0.90 mmol), iodobenzene (0.45 ml, 4 mmol) and stannane 118 (1.83 g, 4 mmol) in DMF (9 ml) at 50°C. After completion of the reaction as judged by TLC (2.5 h) the reaction mixture was allowed to cool to ambient temperature and diluted with diethyl ether (10 ml), followed by KF (6 ml of a 0.91 M aqueous solution). The mixture was stirred rapidly for 30 min, then filtered under suction to remove the grey precipitate. Usual work-up from this stage afforded a crude brown oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded styrene 121e as a colourless oil (427 mg, 44%); 100% by GC; R_f (20% diethyl ether in light petroleum) 0.27; [Found: C, 58.93; H, 5.97; Calc. for C_{12}H_{14}O_3F_2: C, 59.01; H, 5.78%]; ν (film/cm⁻¹) 2929 m, 2884 m, 1735 s, 1498 w, 1449 m, 1265 s, 1201 m, 1177 s, 1153 s, 1103 s, 1070 s, 1032 m, 980 s, 948 s, 850 w, 767 s, 715 s, 697 s; δ_H (300 MHz,
CDCl₃) 7.47-7.42 (2H, envelope, ArH), 7.39-7.32 (2H, envelope, ArH), 7.31-7.24 (1H, m, H-4), 4.86 (2H, s, OCH₂O), 3.86-3.82 (2H, m, OCH₂CH₂O), 3.54-3.51 (2H, m, OCH₂CH₂O), 3.35 (3H, s, OMe); δC (75 MHz, CDCl₃) 155.4 (dd, ¹JCF 289.9, 289.0, CF₂), 129.8 (dd, ³JCF 6.3, 1.7, C-1), 128.4 (C-4), 128.3 (t, ⁵JCF 1.4, C-3, C-3'), 126.7 (dd, ⁴JCF 5.6, 3.4, C-2, C-2'), 115.5 (dd, ²JCF 35.2, 18.1, C=CF₂), 95.2 (t, ⁴JCF 2.9, OCH₂O), 71.4 (CH₂O), 68.3 (d, ⁶JCF 2.0, CH₂O), 58.8 (OCH₃); δF (282 MHz, CDCl₃) -97.85 (1F, d, ²J 55.9), -106.34 (1F, d, ²J 55.9); [HRMS (ES-TOF, M+Na) Found: 267.0814; Calc. for C₁₂H₁₄O₃F₂Na: 267.0809]; m/z (ES-TOF) 267.0 (100%, M+Na).

4-[2,2-Difluoro-1-(2-methoxyethoxymethoxy)-vinyl]-1-methoxybenzene 121f

Anisole 121f was prepared as for 121a using palladium(II) acetate (24 mg, 0.11 mmol), triphenylphosphine (105 mg, 0.40 mmol), copper(I) iodide (170 mg, 0.89 mmol), 4-idoanisole (936 mg, 4.0 mmol) and stannane 118 (1.83 g, 4.0 mmol) in DMF (5 ml). After 1.5 h, the usual work-up afforded an orange oil containing a red sediment. Purification by column chromatography over silica gel (20 % diethyl ether in hexanes ⇒ 20% ethyl acetate in hexanes) afforded anisole 121f as a pale yellow oil (761 mg, 71%); 100% by GC; Rf (20% diethyl ether in hexanes) 0.12; ν (film/cm⁻¹) 2936 m, 1737 m, 1611 m, 1576 w, 1515 m, 1465 m, 1257 s, 1179 m, 1151 m, 1035 m, 979 m, 950 m, 836 m; δH (300 MHz, CDCl₃) 7.39-7.33 (2H, m, ArH), 6.92-
8.86 (2H, m, ArH), 4.83 (2H, s, OCH₂O), 3.85-3.82 (2H, m, CH₂O), 3.79 (3H, s, ArOMe), 3.55-3.52 (2H, m, CH₂O), 3.36 (3H, s, CH₂OCH₃); δ_C (75 MHz, CDCl₃) 159.5 (t, 6_J_CF 1.3, Cq-OMe), 155.0 (dd, 1_J_CF 288.5, 286.5, CF₂), 128.2 (dd, 4_J_CF 5.2, 3.4, CH), 121.9 (dd, 3_J_CF 6.0, 1.4, Cq), 115.2 (dd, 2_J_CF 36.1, 18.4, C=CF₂), 113.9 (CH), 94.9 (t, 4_J_CF 2.9, OCH₂O), 71.5 (CH₂O), [68.3, 68.2] (CH₂O), [58.8, 58.8] (CH₂OCH₃), [55.1, 55.1] (ArOCH₃); δ_F (282 MHz, CDCl₃) -100.38 (1F, d, 2_J 61.0), -108.94 (1F, d, 2_J 61.0); [HRMS (ES-TOF) Found: 297.0901; Calc. for C₁₃H₁₆O₄F₂Na: 297.0914]; m/z (ES-TOF) 297.1 (100%, M+Na).

2,4-Difluoro-1-[(2,2-difluoro-1-(2-methoxy-ethoxymethoxy))-vinyl]-benzene 121g

Styrene 121g was prepared as for 121a using palladium(II) acetate (3 mg, 13.4 μmol), triphenylphosphine (14 mg, 53.4 μmol), Cul (20 mg, 0.11 mmol), 2,4-difluoro-1-iodobenzene (120 mg, 0.5 mmol) and stannane 118 (274 mg, 0.6 mmol) in DMF (3 ml) at 50°C. After 3.7 h, the usual work-up afforded a yellow oil. Purification by column chromatography over silica gel (10% ethyl acetate in hexanes) afforded styrene 121g as a colourless oil (77 mg, 55%); 99% by GC; R_f (10% ethyl acetate in hexanes) 0.34; ν (film/cm⁻¹) 2898 m, 1754 m, 1615 m, 1596 m, 1508 s, 1456 w, 1427 m, 1369 w, 1344 w, 1276 s, 1243 s, 1155 s, 1105 s, 988 s, 969 m, 947 m, 853 m, 821 m; δ_H (300 MHz, CDCl₃) 7.38 (1H, dt, 3_J_HF 8.1, 4_J 6.6, ArH), 6.94-8.81 (2H,
envelope, ArH), 4.78 (2H, s, OCH$_2$O), 3.80-3.77 (2H, m, CH$_2$O), 3.53-3.50 (2H, m, CH$_2$O), 3.36 (3H, s, OCH$_3$); $\delta$C (75 MHz, CDCl$_3$) 165.3-158.6 (unresolved 2 $\times$ Cq-F), 158.6-150.8 (m, CF$_2$), 132.0-131.7 (m, ArCH), 111.8-111.5 (m, ArCH), 104.5 (t, $^2$J$_{CF}$ 25.6, ArCH), 94.7 (t, $^4$J$_{CF}$ 2.6, OCH$_2$O), 71.5 (CH$_2$O), 68.2 (d, $^6$J$_{CF}$ 1.4, CH$_2$O), 59.0 (OCH$_3$). Cq and C=CF$_2$ too weak to assign due to multiple F-coupling; $\delta$F (282 MHz, CDCl$_3$) -98.33 (1F, d, $^2$J 54.7), -105.90 (1F, dd, $^2$J 54.0, $^5$J 20.3), -107.39 to -107.64 (2F, envelope, ArF); m/z (ES-TOF) 303 (100%, M+Na); m/z (Cl) 298 (100%, M+NH$_4$), 94 (3%), 89 (2%).

2-Benzyleoxy-5-[2,2-difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-3-iodo-benzaldehyde 121h

Benzaldehyde 121h was prepared as for 121a using copper(I) iodide (44 mg, 0.23 mmol), triphenylphosphine (26 mg, 99 $\mu$mol), palladium(II) acetate (6 mg, 27 $\mu$mol), 3,5-diiodo-2-benzyleoxy-benzaldehyde (466 mg, 1.01 mmol) and stannane 118 (461 mg, 1.01 mmol) in DMF (3 ml) at 50°C. Usual KF work-up afforded a pale yellow oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded iodide 121h as a white solid (131 mg, 26%); 98% by HPLC at 225 nm; HPLC $t_r$ (20% water in MeCN, 1ml/min) 7.73 min; $R_f$ (20% diethyl ether in
light petroleum) 0.08; m.p. 90-92°C; [Found: C, 47.83; H, 3.72; Calc. for C20H19O5F2:
C, 47.64; H, 3.80%]; ν (nujol mull/cm⁻¹) 1728 w, 1692 w, 1589 m, 1279 m, 1262 m,
1228 w, 1189 w, 1164 m, 1110 m, 1078 w, 1032 w, 937 m, 911 w, 692 w; δH (300
MHz, CDCl₃) 10.06 (1H, s, CHO), 8.17 (1H, s, H-4), 7.89 (1H, s, H-6), 7.50-7.38 (5H,
envelope, OCH₂Ph), 5.08 (2H, s, CH₂Ph), 4.87 (2H, s, OCH₂O), 3.87-3.84 (2H, m,
CH₂O), 3.57-3.53 (2H, m, CH₂O), 3.37 (3H, s, OCH₃); δC (75 MHz, CDCl₃) 188.0
(CO), 160.4 (t, 6JC₅F 1.6, C-2), 155.6 (dd, ¹JC₅F 292.2, 291.1, CF₂), 143.1 (dd, ⁴JC₅F 6.6,
3.4, C-4), 134.9 (Cq of Ph), 130.5 (C-1), 129.0 (CH of Ph), 128.8 (CH of Ph), 128.7
(CH of Ph), 127.1 (dd, ⁴JC₅F 6.0, 3.7, C-6), 113.7 (dd, ²JC₅F 34.8, 19.5, C=CF₂), 95.9 (t,
⁴JC₅F 2.9, OCH₂O), 93.6 (C-3), 78.4 (OCH₂Ph), 71.5 (OCH₂), [68.7, 68.7] (OCH₂), 59.0
(OCH₃), C-5 not observed as a distinct resonance and possibly lies under the signal
at 129.0; δF (282MHz, CDCl₃) -95.11 (1F, d, ²J 51.1), -103.78 (1F, d, ²J 51.4); [HRMS
(ES-TOF, M+Na) Found: 527.0133; Calc. for C₂₀H₁₉O₅F₂Na: 527.0143]; m/z (ES)
559.1 (42%, M+Na+MeOH), 527.1 (100%, M+Na).

2-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-thiophene 121j

A flask containing palladium(II) acetate (24 mg, 0.11 mmol), triphenylphosphine (105
mg, 0.40 mmol) and copper(I) iodide (170 mg, 0.89 mmol) was pump-purged twice
with argon. Dry, degassed DMF (3 ml) was added followed by 2-iodothiophene (0.44
ml, 4.0 mmol). The mixture was heated to 30°C, then stannane 118 (1.83 g, 4.0 mmol) was added as a solution in DMF (1 ml). After stirring at 50°C for 2 h, the dark red mixture was allowed to cool to ambient temperature, then diluted with diethyl ether (5 ml). The mixture was transferred to a conical flask and aqueous KF (15 ml of a 1 M soln) was added. The resulting mixture was stirred rapidly for 30 min, then filtered to remove the cream precipitate. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude reddish oil containing a red sediment. Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded thiophene 121j as a pale yellow oil (430 mg, 45%); 96% by GC; Rf (20% diethyl ether in hexanes) 0.23; ν (film/cm⁻¹) 3108 w, 2925 m, 1730 s, 1453 w, 1436 w, 1354 s, 1292 m, 1256 s, 1228 w, 1201 w, 1175 m, 1152 s, 1102 s, 1045 w, 1029 w, 962 m, 911 m; δH (300 MHz, CDCl₃) 7.31 (1H, dd, 3J 5.1, 4J 1.1, H- ), 7.10 (1H, d, 3J 3.7, H- ), 7.03-7.00 (1H, m, H- ), 4.97 (2H, s, OCH₂O), 3.88-3.85 (2H, m, CH₂O), 3.57-3.54 (2H, m, CH₂O), 3.37 (3H, s, OCH₃); δC (300 MHz, CDCl₃) 154.6 (dd, 1J CF 291.6, 290.2, CF₂), 132.7 (dd, 3J CF 8.6, 1.4, Cq), 127.3 (d, 6J CF 0.6, C-α), 125.9 (dd, 5J CF 4.9, 2.9, C-β), 125.4 (dd, 4J CF 6.6, 4.9, C-γ), 112.5 (dd, 2J CF 38.2, 22.2, C=CF₂), 96.1 (dd, 4J CF 3.2, 2.7, OCH₂O), 71.5 (CH₂O), 68.6 (d, 6J CF 2.0, CH₂O), 58.9 (OCH₃); δF (282 MHz, CDCl₃) -98.79 (1F, dd, 2J 51.5, 5JHF 3.2), -102.43 (1F, dd, 2J 52.1, 5JHF 3.8); [HRMS (ES-TOF, M+Na) Found: 273.0366; Calc. for C₁₀H₁₂O₃F₂NaS: 273.0373; m/z (ES) 273.0 (100%, M+Na).
2-Iodobenzoxazole 124

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\(n\)-Butyllithium (6.25 ml of a 1.6 M solution in hexanes, 10.0 mmol) was added dropwise to a solution of benzoxazole (1.19 g, 10.0 mmol) in THF (30 ml) at -78°C to afford a deep orange solution. After stirring for 15 min, with thickening of the solution, zinc chloride (20 ml of a 0.5 M solution in THF, 10.0 mmol) was added and the resulting brown solution stirred for 15 min before being allowed to warm to 0°C over 20 min. A solution of iodine (2.79 g, 11.0 mmol) in THF (10 ml) was added in one portion and the reaction stirred for a further 2 h whilst warming to room temperature. The reaction was quenched with a saturated aqueous solution of ammonium chloride (20 ml). The contents were transferred to a separating funnel and washed with a saturated solution of sodium thiosulfate (60 ml). Diethyl ether (50 ml) was added and the organic phase separated. The aqueous phase was extracted with diethyl ether (3x 30 ml) and the combined organic extracts dried and concentrated under reduced pressure to afford a deep red solid. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded 2-iodobenzoxazole 124 (CAUTION: severe irritant to eyes and skin) as a sand-textured solid (1.79 g, 73%), in addition to colourless crystals which collected on the rims of the tubes (240 mg, 10%). The sand-textured solid was triturated with hexane (3 \times 10 ml) to afford a light brown solid (1.68 g, 69%, total = 2.03 g, 79%). Recrystallisation by vapour diffusion (acetone/hexane) afforded further 2-iodobenzoxazole as colourless crystals; [Found: C, 34.23; H, 1.44; N, 5.55; Calc. for C₇H₄NOI: C, 34.31; H, 1.65; N, 5.72%]; Rf (20%
diethyl ether in light petroleum) 0.50; δ_H (300 MHz, CDCl_3) 7.74-7.67 (1H, m, ArH), 7.57-7.51 (1H, m, ArH), 7.34-7.27 (2H, envelope, ArH); δ_C (75 MHz, CDCl_3) 154.0 (Cq), 142.6 (Cq), 125.3 (CH), 124.7 (CH), 119.3 (CH), 110.1 (CH), 108.1 (Cq); m/z (Cl) 247 (6%, M^{13}C+H), 246 (100%, M+1), 245 (1%, M), 135 (4%), 120 (24%, M+2H^{127}I), 80 (4%). This material was found to be relatively unstable, even in a refrigerated (-5°C) environment and should therefore be used immediately.

5-Bromo-2-[2,2-difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-pyridine 121m

Bromopyridine 121m was prepared as for 121a using palladium(II) acetate (34 mg, 0.15 mmol), Cul (14 mg, 80 μmol), triphenylphosphine (118 mg, 0.45 mmol), 2,5-dibromopyridine (640 mg, 2.70 mmol) and stannane 118 (1.36 g, 2.98 mmol) in DMF (4 ml) at 50°C. After 16 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (30% diethyl ether in light petroleum) afforded pyridine 121m as a pale yellow oil (290 mg, 33%); R_f (30% diethyl ether in light petroleum) 0.19; δ_H (300 MHz, CDCl_3) 8.66 (1H, d, 4J 2.2, H-6), 7.80 (1H, dd, 3J 8.5, 4J 2.2, H-4), 7.36 (1H, d, 3J 8.5, H-3), 4.96 (2H, s, OCH_2O), 3.85 (2H, t, 3J 4.8, OCH_2CH_2O), 3.52 (2H, t, 3J 4.8, OCH_2CH_2O), 3.35 (3H, s, OCH_3); δ_C (75 MHz, CDCl_3) 157.1 (dd, 1J_CF 297.3, 293.3, CF_2), 150.7 (C-6), 148.5 (dd, 3J_CF 7.9, 4.0, C-2), 139.1 (C-4), 123.1 (dd, 4J_CF 8.2, 3.7, C-3), 119.5 (t, 5J_CF 2.3, C-5), 115.3 (dd, 2J_CF 206
30.8, 18.9, C=CF), 96.4 (t, \(^4\)J\(^{\text{CF}}\) 2.8, OCH\(_2\)O), 71.5 (OCH\(_2\)), 68.7 (d, \(^6\)J\(^{\text{CF}}\) 2.3, OCH\(_2\)), 59.0 (OCH\(_3\)); \(\delta\)\(^{\text{F}}\) (282 MHz, CDCl\(_3\)) -91.69 (d, \(^2\)J 38.2), -99.03 (d, \(^2\)J 38.2); HRMS [ES-TOF (M+Na) Found: 345.9861; Calc. for C\(_{11}\)H\(_{12}\)O\(_3\)NBrF\(_2\)Na: 345.9866]; \(m/z\) (ES) 348 (100%, M\(^{(81}\text{Br})+}\text{Na}) , 346 (100%, M\(^{(79}\text{Br})+}\text{Na}). This material decomposed before full characterisation could be achieved.

4-(2,2-Difluoroacetyl)-phenyl trifluoromethanesulfonate 132

Chlorotrimethylsilane (0.15 ml, 1.17 mmol) was added to a solution of enol acetal 121a (249 mg, 630 \(\mu\)mol) in methanol (5 ml) at 0°C. The solution was allowed to warm to ambient temperature and the colourless solution stirred for 18 h, with monitoring by TLC. The reaction mixture was concentrated under reduced pressure to afford a mixture of the ketone 132 and its methanol hemiketal. Toluene (5 ml) was added and the methanol removed by azeotropic distillation with toluene, affording the ketone 132 as the sole fluorinated product. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded ketone 132 as a colourless oil (42 mg, 22%); 98% by GC; \(R_f\) (20% diethyl ether in light petroleum) 0.14; \(\nu\) (film/cm\(^{-1}\)) 1715 s, 1600 s, 1502 s, 1430 s, 1348 m, 1291 m, 1252 s, 1219 s, 1141 s, 1067 s, 1017 m, 983 w, 889 s, 781 w, 750 w; \(\delta\)\(^{\text{H}}\) (300 MHz, CDCl\(_3\)) 8.20 (2H, d, \(^3\)J 9.0, ArH), 7.45 (2H, d, \(^3\)J 9.0, ArH), 6.24 (1H, t, \(^3\)J\(^{\text{HF}}\) 53.5, HCF\(_2\)); \(\delta\)\(^{\text{C}}\) (75 MHz,
Sulfuryl chloride (80 μl, 1 mmol) was added to a solution of styrene 121e (244 mg, 1 mmol) in DCM (3 ml) at ambient temperature. An intense red colouration was observed for a few seconds, before being discharged with the evolution of a gas (SO\(_2\)) to afford a pale yellow solution. After stirring for 2.5 h, with monitoring by TLC, the reaction mixture was concentrated under reduced pressure to afford a pale green oil. This material was diluted with acetone (10 ml) and concentrated on to silica gel. Purification by flash column chromatography over silica gel (100% light petroleum) afforded chlorodifluoromethyl ketone 133b as a colourless oil (68 mg, 60%) 97% by GC; \(R_f\) (100% light petroleum) 0.22; \(\delta_H\) (300 MHz, CDCl\(_3\)) 8.13-8.10 (2H, m, ArH), 7.69 (1H, tt, \(^3\)J 7.5, \(^4\)J 1.3, ArH), 7.56-7.50 (2H, m, ArH); \(\delta_C\) (75 MHz, CDCl\(_3\)) 135.2 (CH), 130.5 (t, \(^4\)J\(_{CF}\) 2.3, CH), 129.3 (Cq), 128.9 (CH), 120.1 (t, \(^1\)J\(_{CF}\) 304.9, CF\(_2\)); CO too weak to assign; \(\delta_F\) (282 MHz, CDCl\(_3\)) -60.79 (s); \(m/z\) (EI) 193 (<1%, M(\(^{37}\)Cl)+1), 192 (<1%, M(\(^{37}\)Cl)), 191 (<1%, M(\(^{35}\)Cl)+1), 192 (<1%, M(\(^{35}\)Cl)), 155
(<1%, M-Cl), 106 (7%), 105 (100%, COPh), 77 (57%, Ph), 51 (24%), 50 (11%). $^{19}$F and $^1$H NMR data in agreement with those reported by Kuroboshi.\textsuperscript{239}

2,2-Difluoro-2-iodo-1-(4'-methoxyphenyl)-ethanone 133c

A solution of iodine (550 mg, 2.18 mmol) in DCM (5 ml) was added to a solution of anisole 121f (570 mg, 2.08 mmol) in DCM (3 ml) at ambient temperature. The intense violet colour of the iodine solution was quenched upon initial addition, ultimately affording a red solution. The reaction was stirred in the absence of light for 18 h and monitored by TLC. The reaction mixture was washed with 10% sodium thiosulfate solution (20 ml) to afford a pale yellow solution. The organic phase was separated and the aqueous phase extracted with DCM ($3 \times 10$ ml). The combined organic extracts were dried concentrated under reduced pressure to afford a brown oil. Purification by column chromatography over silica gel (in the dark; 20% diethyl ether in hexanes) afforded iodoketone 133c as a colourless oil that partly solidified on standing (420 mg, 65%); 98% by GC on mixture; $R_f$ (20% diethyl ether in hexanes) 0.40; mp 35-38°C; $\nu$ (nujol mull/cm\textsuperscript{-1}) 1682 m, 1601 m, 1572 m, 1511 m, 1463 m, 1425 m, 1378 m, 1318 m, 1263 m, 1184 m, 1122 m, 957 m, 942 m, 860 m, 732 m, 686 m, 637 m; $\delta$\textsubscript{H} (300 MHz, CDCl\textsubscript{3}) 8.16-8.13 (2H, m, ArH), 7.00-6.94 (2H, m, ArH), 3.90 (3H, s, OCH\textsubscript{3}); $\delta$\textsubscript{C} (75 MHz, CDCl\textsubscript{3}) 164.9 (Cq), 133.4 (d, $^4$J\textsubscript{CF} 13.2, CH), 121.4
(Cq, coupling unresolved), 114.3 (CH), 95.9 (t, $^1J_{CF}$ 325.8, CF$_2$), 55.7 (OCH$_3$), CO too weak to assign; δ$_F$ (282 MHz, CDCl$_3$) -53.52 (2F, s); m/z (Cl) 330 (81%, M+NH$_4$), 313 (7%, M+1), 204 (100%, COCF$_2$I), 186 (24%, M+1-I), 169 (9%), 152 (14%), 135 (45%, M-CF$_2$I).

2-Chloro-2,2-difluoro-1-(thien-2-yl)-ethanone 133d

![Chemical Structure](image)

Sulfuryl chloride (91 μl, 1.1 mmol) was added to a solution of thiophene 121j (282 mg, 1.1 mmol) in DCM (4 ml) at ambient temperature. An intense red colour was observed upon the addition of the first few drops, which then dissipated to afford a pale yellow solution. The resulting solution was stirred for 18 h until TLC indicated the consumption of starting material. The reaction mixture was concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (100% hexanes) afforded volatile ketone 133d as a colourless oil (80 mg, 36%); 99% by GC; R$_f$ (100% hexanes) 0.13; ν (film/cm$^{-1}$) 3110 m, 1686 bds, 1514 s, 1411 s, 1358 s, 1287 m, 1244 m, 1223 m, 1168 s, 1066 s, 1048 m, 1021 s, 964 s, 874 s, 853 m, 825 s, 770 s, 725 s, 674 s, 617 s; δ$_H$ (300 MHz, CDCl$_3$) 8.00-7.98 (1H, m, H-α), 7.88 (1H, dd, $^3J$ 5.1, $^4J$ 1.0, H-γ), 7.23 (1H, dd, $^3J$ 4.8, 4.0, H-β); δ$_C$ (75 MHz, CDCl$_3$) 174.8-174.8 (m, CO), 137.7 (d, $^5J_{CF}$ 0.9, C-β), 136.5 (t, $^4J_{CF}$ 3.7, C-γ), 135.3 (t, $^3J_{CF}$ 0.9, Cq), 129.0 (C-α), 119.9 (t, $^1J_{CF}$ 304.0, CF$_2$); δ$_F$ (282 MHz,
CDCl₃ -61.88 (2F, s); m/z (Cl) 216 (6%, M(37Cl)+NH₄), 214 (17%, M(37Cl)+NH₄), 145 (19%), 128 (10%), 111 (100%, M-CF₂Cl).

2-Bromo-2,2-difluoro-1-(2,4-difluorophenyl)-ethanone 133f

Bromine (1 ml of a 0.98 M solution in DCM, 1.02 mmol) was added dropwise to a solution of styrene 121g (282 mg, 1.0 mmol) in DCM (3 ml) at 0°C under a dry nitrogen atmosphere. The intense colour of bromine was initially quenched upon addition. The reaction was allowed to warm to ambient temperature and stirred for 22 h, with monitoring by TLC. The reaction mixture was concentrated under reduced pressure to afford a pale brown oil. Purification by column chromatography over silica gel (10% ethyl acetate in hexanes) afforded bromodifluoromethyl ketone 133f as a colourless oil (98 mg, 36%); 97% by GC; Rₙ (10% ethyl acetate in hexanes) ~0.30 (streaks); ν (film/cm⁻¹) 1715 s, 1612 s, 1502 s, 1432 s, 1312 m, 1272 s, 1230 m, 1156 s, 1101 s, 986 s, 859 s, 814 m, 734 m, 685 w; δₕ (300 MHz, CDCl₃) 7.96 (1H, dd, 3JHF 14.7, 3J 8.5, ArH), 7.04-6.90 (2H, envelope, ArH); δₖ (75 MHz, CDCl₃) 179.1-179.0 (m, CO), 166.9 (dd, 1JCF 260.9, 3JCF 12.4, ArCF), 162.9 (dd, 1JCF 266.0, 3JCF 12.7, ArCF), 133.8 (ddt, 3JCF 10.9, 2.6, 4JCF 2.6, ArCH), 115.8-115.6 (m, Cq), 113.2 (t, 1JCF 318.1, BrCF₂), 112.4 (dd, 2JCF 21.8, 4JCF 3.7, CH), 105.8 (t, 2JCF 25.6,
CH); $\delta_F$ (282 MHz, CDCl$_3$) -60.75 (2F, d, $^2J_{HF}$ 15.6), -97.62 to -97.75 (1H, m), -99.75 to -99.96 (1F, m); m/z (EI) 140 (100%, M-1-BrCF$_2$), 112 (24%), 63 (17%).

(E)-[2-Fluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-benzene and (Z)-[2-fluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-benzene 134

\[
\begin{align*}
&\text{(E):} \\
&\text{(Z):}
\end{align*}
\]

Sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al®, 0.38 ml of a 65% w/w solution in toluene, 1.2 mmol) was added to a solution of styrene 121e (244 mg, 1.0 mmol) in hexane (5 ml). The resulting solution was heated under reflux for 3 h, with monitoring by TLC. Upon consumption of styrene 121e, the solution was cooled to ambient temperature and poured into a conical flask containing ice-water (20 ml). The solution was transferred to a separating funnel and ethyl acetate (10 ml) and Rochelle’s salt (20 ml of a 20% w/w aqueous solution) added. The organic phase was separated and the aqueous phase extracted with ethyl acetate ($3 \times 10$ ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a colourless oil. Crude $^{19}$F NMR indicated the presence of styrenes 134 in a 1:1 ratio, in addition to a trace of residual styrene 121e. Purification by column chromatography over silica gel (25% diethyl ether in light petroleum) afforded inseparable monofluoroethenes 134 (48:52 E:Z) as colourless oils (170 mg, 75%); $R_f$ (25% diethyl ether in light petroleum) 0.31; $\delta_F$ (282 MHz, CDCl$_3$) -153.7 (d, $^2J_{HF}$ 77.4,
Z-isomer), -162.8 (d, $\text{J}_{\text{HF}}$ 79.1, $E$-isomer). Stereochemistry has been assigned based upon the work of Patel.$^{102a}$ Due to the unstable nature of this material, the MEM enol ether was cleaved using sulfuryl chloride as the electrophile, without further characterisation (see 133g).

2-Chloro-2-fluoro-1-phenyl-ethanone 133g

![Chemical Structure](image)

Sulfuryl chloride (22 μl, 0.27 mmol) was added to a solution of monofluoroethenes 134 (48:52, $E$:$Z$) (67 mg, 0.27 mmol) in DCM (3 ml) at ambient temperature. The resulting solution was stirred for 48 h, then concentrated to afford a colourless oil. Purification by column chromatography over silica gel (15% diethyl ether in light petroleum) afforded chlorofluoromethyl ketone 133g as a colourless oil (36 mg, 76%); 100% by GC; $R_f$ (15% diethyl ether in light petroleum) 0.55; $\delta_{\text{H}}$ (300 MHz, CDCl$_3$) 8.08-8.04 (2H, m, H-4, H-4'), 7.68-7.62 (1H, m, H-6), 7.54-7.48 (2H, m, H-5, H-5'), 6.83 (1H, d, $\text{J}_{\text{HF}}$ 50.7, H-1); $\delta_{\text{C}}$ (75 MHz, CDCl$_3$) 134.7 (CH), 129.6 (d, $\text{J}_{\text{CF}}$ 2.8, C-4, C-4'), 128.9 (CH), 95.1 (d, $\text{J}_{\text{CF}}$ 256.6, C-1), C-2 and C-3 too weak to assign; $\delta_{\text{F}}$ (282 MHz, CDCl$_3$) -146.58 (d, $\text{J}_{\text{HF}}$ 50.8); $m/z$ (EI) 105 (100%, COPh), 77 (60%, Ph), 51 (24%). $^1$H NMR data is in close agreement with those reported by Normant.$^{240}$
2,2-Difluoro-1-phenyl-2-(phenylsulfanyl)-ethanone 137a

Method A:

Phenylsulfenyl chloride (30 μl, 0.25 mmol) was added dropwise to a solution of styrene 121e (61 mg, 0.25 mmol) in DCM (5 ml) at 0°C. After warming to ambient temperature, the reaction was stirred for 16 h. The reaction mixture was concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded (phenylthio)difluoromethyl ketone 137a as a colourless oil (42 mg, 64%); Rf (20% diethyl ether in light petroleum) 0.68; δH (300 MHz, CDCl3) 8.15-8.10 (2H, m, ArH), 7.68-7.58 (3H, m, ArH), 7.52-7.35 (5H, m, ArH); δC (75 MHz, CDCl3) 184.6 (t, 2JCF 2.0, CO), 136.7 (CH), 136.6 (CH), 134.6 (CH), 131.0 (Cq), 130.3 (t, 4JCF 1.4, CH), 129.2 (CH), 128.6 (CH), 124.6 (t, 3JCF 2.3, Cq), 123.6 (t, 1JCF 290.8, CF2); δF (282 MHz, CDCl3) -77.14 (s); m/z (CI) 282 (48%, M+NH4), 264 (1%, M), 242 (10%), 154 (3%, M-SPh-1), 105 (100%, PhCO), 94 (7%). 1H and 19F NMR data are in close agreement with those reported by Brigaud and Laurent.57

Method B:

Sulfuryl chloride (40 μl, 0.5 mmol) was added to a solution of diphenyl disulfide (110 mg, 0.5 mmol) in DCM (1 ml) at ambient temperature. An orange colouration
appeared immediately, which intensified to a near red solution after 30-40 min of stirring. This solution was added to a solution of styrene 121e (108 mg, 0.44 mmol) in DCM (1 ml) at 0°C and allowed to warm to ambient temperature overnight. Concentration of the reaction mixture afforded an orange oil. Purification by column chromatography over silica gel (5% diethyl ether in light petroleum) afforded ketone 137a (91 mg, 78%) as a colourless oil. Data were in agreement with those previously found above.

2,2-Difluoro-1-phenyl-2-(pyridin-2'-ylsulfanyl)-ethanone 137b

Sulfuryl chloride (40 μl, 0.5 mmol) was added to a stirred solution of 2,2'-dipyridyl disulfide (110 mg, 0.5 mmol) in DCM (4 ml) at ambient temperature under a nitrogen atmosphere. Pyridine (5 μl, 61.3 μmol) was added and the resulting yellow/orange solution heated under reflux for 1 h. Styrene 121e (244 mg, 1.0 mmol) was added and the resulting solution heated under reflux for 48 h. The reaction mixture was concentrated under reduced pressure to afford an orange oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded (arylthio)difluoromethyl ketone 137b as a colourless oil (64 mg, 48%); 100% by GC; Rf (20% diethyl ether in light petroleum) 0.15; ν (film/cm\(^{-1}\)) 1705 s (C=O), 1598 m, 1574 s, 1564 m, 1450 s, 1422 s, 1269 s, 1136 s, 1094 m, 1074 m, 1034 m, 989 s,
889 m, 826 m, 765 m, 734 m, 711 s, 687 m, 669 m, 643 m); δ_H (300 MHz, CDCl_3) 8.50 (1H, dd, ^3_J 4.7, ^4_J 1.4, H-11), 8.12 (2H, dd, ^3_J 8.4, ^4_J 0.8, H-2 and H-2'), 7.69-7.56 (3H, envelope, H-4, H-8, H-9), 7.51-7.45 (2H, m, H-3 and H-3') 7.23 (1H, ddd, ^3_J 7.3, 4.7, ^4_J 1.1, H-10); δ_C (75 MHz, CDCl_3) 150.6 (t, ^3_J CF 2.8, C-7), 150.4 (CH), 137.4 (CH), 134.6 (CH), 131.4 (t, ^3_J CF 1.4, C-1), 130.4 (t, ^4_J CF 2.8, CH), 128.7 (CH), 128.5 (t, ^4_J CF 2.0, CH), 124.3 (t, ^1_J CF 291.6, C-6), 123.4 (CH), C-5 too weak to assign; δ_F (282 MHz, CDCl_3) -76.78 (s); [HRMS (ES-TOF, M+H) Found: 266.0443; Calc. for C_{13}H_{10}NOF_2S: 266.0451]; m/z (EI) 265 (0.4%, M), 245 (9%), 237 (3%), 198 (3%), 182 (5%), 155 (3%, M-SPy), 105 (100%, COPh), 77 (59%, Ph), 51 (23%), 39 (8%).

2-(Benzothiazol-2'-ylsulfanyl)-2,2-difluoro-1-phenyl-ethanone 137c

Sulfuryl chloride (80 μl, 0.99 mmol) was added to a yellow heterogeneous solution of benzothiazol-2-yl disulfide (305 mg, 0.91 mmol) and pyridine (10 μl, 0.12 mmol) in DCM (5 ml) at ambient temperature. The mixture began to clear upon the addition of sulfuryl chloride and became a homogeneous orange solution after 5 min. This solution was heated under reflux for 1 h to ensure complete formation of (benzothiazol-2-yl)sulfenyl chloride. A solution of styrene 121e (443 mg, 1.81 mmol) in DCM (2 ml) was added to afford a yellow solution. The solution was heated under
relux for 21 h, with monitoring by TLC. The reaction mixture was allowed to cool to ambient temperature and then concentrated under reduced pressure to afford an orange solid. Trituration with hexane (3 × 10 ml) afforded orange crystals (542 mg) as a single fluorinated material (by $^{19}$F NMR) corresponding to ketone 137c. Mass spectral analysis (ES) indicated only the presence of ketone 137c; however, analysis by $^1$H NMR showed the presence of the desired material in addition to some unidentified impurities. A small sample of the crude material (ca. 100 mg) was triturated with ethyl acetate to afford a pale yellow solid (ca. 30 mg) which appeared as a single streaking spot by TLC. This material gave satisfactory mass and elemental analyses. The remainder of the crude material was placed in a flask fitted with an air condenser. Hexane (10 ml) was added and the mixture heated gently with a heat gun until it began to boil. The hot hexane solution was decanted on to a petri dish and allowed to evaporate to afford yellow crystals. The brown residue was treated as above twice more. The resulting yellow crystals were dried under vacuum (2.0 mbar) for 5 h to afford a yellow solid (284 mg, 49%). This material proved to still have several minor impurities both by $^1$H and $^{13}$C NMR. This material could not be analysed by GC or by HPLC to give an indication of purity (est. by $^{13}$C NMR: 90-95%); $R_f$ (20% diethyl ether in hexanes) 0.42; mp 90-94°C; [Found: C, 55.85; H, 2.71; N, 4.28; Calc. for C$_{15}$H$_9$NOF$_2$S$_2$: C, 56.06; H, 2.82; N, 4.36%]; ν (nujol mull/cm$^{-1}$) 1694 m, 1595 m, 1578 m, 1552 m, 1410 w, 1311 w, 1282 m, 1235 w, 1188 w, 1169 w, 1136 m, 1049 s, 988 m, 822 m, 763 m, 710 m, 692 m, 677 m, 650m; δ$_H$ (300 MHz, CDCl$_3$) 8.12 (2H, d, $^3$J 7.7, ArH, H-4, H-4'), 8.07 (1H, d, $^3$J 8.1, ArH, H-12), 7.85 (1H, d, $^3$J 8.1, ArH, H-9), 7.64 (1H, t, $^3$J 7.4, ArH, H-6), 7.52-7.39 (4H, envelope, ArH, H-5, H-5', H-10, H-11); δ$_C$ (75 MHz, CDCl$_3$) 184.4 (t, $^2$J$_{CF}$ 27.6, Cq, C-2), 153.5 (t, $^3$J$_{CF}$ 1.9,
Cq, C-7), 153.0 (Cq, C-13), 137.8 (Cq, C-8), 135.1 (CH, C-6), 130.3 (t, $^4J_{CF}$ 2.9, CH, C-4), 130.2 (t, $^3J_{CF}$ 2.3, Cq, C-3), 128.8 (CH, C-5), 126.6 (CH, C-10), 126.2 (CH, C-11), 124.8 (t, $^1J_{CF}$ 297.1, Cq, C-1), 123.7 (CH, C-9), 121.1 (CH, C-12); $\delta_F$ (282 MHz, CDCl$_3$) -72.61 (s); [HRMS (ES-TOF, M+Na) Found: 343.9982; Calc. for C$_{15}$H$_9$NOF$_2$S$_2$Na: 343.9991]; $m/z$ (ES-TOF) 376.0 (3%, M+Na+MeOH), 344.0 (100%, M+Na).

2,2-Difluoro-3-(2-methoxy-ethoxymethoxy)-1,3-diphenyl-propanone 139

Titanium(IV) chloride (1.0 ml of a 1 M soln in DCM, 1.0 mmol) was added to a –20°C solution of styrene 121e (122 mg, 0.5 mmol) and benzaldehyde (50 µl, 0.5 mmol) in DCM (2 ml). The resulting brown solution was stirred at –20°C for 18 h. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (5 ml) and diluted with DCM (3 ml). The organic phase was separated and the aqueous phase extracted with DCM (3 × 5 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude yellow oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded MEM-protected aldol 139 as a colourless oil (31 mg, 24%); R$_f$ (20% diethyl ether in light petroleum) 0.13; $\delta_H$ (300 MHz, CDCl$_3$) 8.08-8.04 (2H, m, ArH), 7.65-7.59 (1H, m, ArH), 7.51-7.45 (4H, m, ArH), 7.41-7.36 (3H, m, ArH), 5.63
(1H, dd, 3\textsubscript{J} \text{HF} 18.9, 6.5, CHCF\textsubscript{2}), 4.70-4.61 (2H, m, OCH\textsubscript{2}O), 3.51-3.44 (2H, m, CH\textsubscript{2}O), 3.40-3.30 (2H, m, CH\textsubscript{2}O), 3.29 (3H, s, OCH\textsubscript{3}); \(\delta\)c (75 MHz, CDCl\textsubscript{3}) 134.1 (CH), 130.1 (central resonance for CF\textsubscript{2}), 130.0 (dd, 4\textsubscript{J} \text{CF} 4.5, 2.8, ArCH), 129.2 (ArCH), 129.1 (ArCH), 128.6 (ArCH), 128.3 (ArCH), 93.3 (OCH\textsubscript{2}O), 76.4 (dd, 2\textsubscript{J} \text{CF} 30.5, 22.6, CHCF\textsubscript{2}), 71.3 (CH\textsubscript{2}O), 67.4 (CH\textsubscript{2}O), 58.9 (OCH\textsubscript{3}), CO and 2 \times Cq too weak to assign due to weak sample; \(\delta\)\text{F} (282 MHz, CDCl\textsubscript{3}) -104.04 (1F, dd, 2\textsubscript{J} 273.4, 3\textsubscript{J} \text{HF} 6.3), -115.99 (1F, dd, 2\textsubscript{J} 273.4, 3\textsubscript{J} \text{HF} 19.1); [HRMS (ES-TOF, M+Na) Found: 373.1224; Calc. for C\textsubscript{19}H\textsubscript{20}O\textsubscript{4}F\textsubscript{2}Na: 373.1227]; \textit{m/z} (ES-TOF) 373.1 (100%, M+Na).

\[2\text{-}[4\text{-}[2,2\text{-Difluoro}\text{-1-(N,N-diethylcarbamoyloxy)}\text{-vinyl}]\text{-phenyl}]\text{-furan} \text{138}\]

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A flask containing triflate 95e (283 mg, 0.72 mmol) and \textit{tetrakis}(triphenylphosphine)-palladium(0) (42 mg, 36 \textmu mol) was pump-purged with nitrogen. Dry, degassed DMF (4 ml) was added and the reaction heated to 50°C. A solution of 2-(tributylstannylfuran) (0.34 ml, 1.08 mmol) in DMF (1 ml) was added to the green/yellow solution and the reaction heated at 80°C for 2.7 h. The dark reaction mixture was cooled to ambient temperature and partitioned between diethyl ether (10 ml) and water (10 ml). The organic phase was separated and the aqueous phase
extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude red oil containing a red sediment. Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded furan 138 as a pale yellow oil which solidified upon standing to afford an off-white solid (140 mg, 60%); 100% by GC; Rf (20% diethyl ether in hexanes) 0.32; mp. 55-57°C; ν (nujol mull/cm⁻¹) 1725 bd, 1461, 1376, 1269, 1150, 1039, 981, 851, 820, 786, 734, 663; [Found: C, 63.36; H, 5.44; N, 4.18; Calc. for C₁₇H₁₇NO₃F₂: C, 63.54; H, 5.33; N, 4.36%]; δH (300 MHz, CDCl₃) 7.69-7.64 (2H, m, ArH), 7.46-7.39 (3H, envelope, ArH + H-α), 6.65 (1H, d, 3J 3.3, H-γ), 6.45 (1H, dd, 3J 3.3, 1.8, H-β), 3.44 (2H, q, 3J 7.2, N(CH₂CH₃)₂), 3.35 (2H, q, 3J 7.2, N(CH₂CH₃)₂); δC (75 MHz, CDCl₃) 155.0 (t, 1JCF 291.0, Cq, CF₂), 153.4 (Cq), 152.9 (Cq), 142.4 (CH), 130.5 (d, 6JCF 1.7, Cq), 129.0 (d, 3JCF 6.8, Cq), 125.7 (dd, 4JCF 6.5, 3.7, CH), 123.9 (CH), 112.4 (dd, 2JCF 38.4, 19.6, Cq, C=CF₂), 111.8 (CH), 105.7 (CH), [42.7, 42.0] (CH₂N), [14.2, 13.3] (CH₃); δF (282 MHz, CDCl₃) -93.23 (1F, d, 2J 47.8), -103.04 (1F, d, 2J 47.8); [HRMS (ES-TOF, M+Na) Found: 344.1066; Calc. for C₁₇H₁₇NO₃F₂Na: 344.1074]; m/z (ES-TOF) 344.1 (100%, M+Na).
2-{4-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-phenyl}-furan 139a

A flask containing dichlorobis(triphenylphosphine)palladium(II) (36 mg, 51.3 μmol) was pump-purged twice with nitrogen, then dry, degassed DMF (3 ml) added to afford a green heterogeneous solution. The mixture was warmed to 60°C and a solution of triflate 121a (398 mg, 1.02 mmol) in DMF (1 ml) was added in one portion to afford a yellow heterogeneous solution. A solution of 2-(tributylstannyl)furan (362 mg, 1.02 mmol) in DMF (1 ml) was added in one portion at 60°C to afford a deep red solution, which was heated at 60-70°C for 48 h. After cooling to ambient temperature, diethyl ether (5 ml) was added followed by water (10 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 5 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude red oil. Purification by column chromatography over silica gel (5% diethyl ether in light petroleum ⇒ 20% diethyl ether in light petroleum ⇒ 20% ethyl acetate in light petroleum) afforded furan 139a as a pale orange oil (270 mg, 86%); Rf (20% diethyl ether in light petroleum) 0.19; δH (300 MHz, CDCl3) 7.67 (2H, d, 3J 8.5, ArH), 7.47 (2H, d, 3J 8.5, ArH), 7.35-7.34 (1H, m, H-α), 6.67-6.65 (1H, m, H-β), 6.46-6.44 (1H, m, H-γ), 4.89 (2H, s, OCH2O), 3.87-3.84 (2H, m, CH2O), 3.56-3.52 (2H, m, CH2O), 3.36 (3H, s, OCH3); δF (282 MHz, CDCl3) -97.29 (1F, d, 2J 54.6), 221
Due to the unstable nature of this material, the MEM enol ether was cleaved under protic conditions without further characterisation (see pg 234).

2-{3-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-phenyl}-thiophene 139b

Thiophene 139b was prepared as for 139a using dichlorobis(triphenylphosphine)-palladium(II) (41 mg, 58.6 μmol), triflate 121b (393 mg, 1.00 mmol) and 2-(tributylstannyl)thiophene (423 mg, 1.13 mmol) in DMF (3 ml). The reaction was carried out at 60°C for 47 h with TLC indicating a single product spot. After the usual work-up, crude 19F NMR indicated an 89% conversion to a new product. The crude orange oil was diluted with acetone and concentrated on to silica gel to afford an orange powder. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded thiophene 139b as a colourless oil (230 mg, 71%); 99% by 19F NMR (contamination with triflate 121b); Rf (10% diethyl ether in light petroleum) 0.11; δH (300 MHz, CDCl3) 7.69 (1H, s), 7.52-7.48 (1H, m), 7.35-7.31 (2H, m), 7.29-7.25 (1H, m), 7.25-7.20 (1H, m), 7.04-7.00 (1H, m), 4.87 (2H, s, OCH2O), 3.85-3.81 (2H, m, CH2O), 3.52-3.49 (2H, m, CH2O), 3.32-3.31 (3H, m, OCH3); δc (75 MHz, CDCl3) 155.6 (dd, 3JCF 290.5, 289.3, CF2), 143.6 (Cq), 134.7 (Cq), 130.6 (dd, 3JCF 6.2, 1.7, Cq), 129.1 (CH), 128.0 (CH), 125.8 (t, 5JCF 1.4, CH), 125.7 (dd, 4JCF 5.9,
3.4, CH), 125.1 (CH), 124.1 (dd, $^4J_{CF}$ 5.5, 3.4, CH), 123.5 (CH), 115.3 (dd, $^2J_{CF}$ 35.0, 18.7, C=CF$_2$), 95.4 (t, $^4J_{CF}$ 2.5, OCH$_2$O), 71.5 (CH$_2$O), [68.4, 68.4] (CH$_2$O), 59.0 (CH$_3$); $\delta_F$ (282 MHz, CDCl$_3$) -97.13 (1F, d, $^2J$ 54.7), -105.55 (1F, d, $^2J$ 54.7). Due to the unstable nature of this material, the MEM enol ether was cleaved to 140c under protic conditions without further characterisation (see pg 235).

**Benzyl 5-[(2,2-difluoro-1-(2-methoxy-ethoxymethoxy))-vinyl]-2-furan-2'-yl benzenecarboxylate 139d**

A flask containing dichloro bis(triphenylphosphine)palladium(II) (12 mg, 17 $\mu$mol) was pump-purged twice with argon. Dry, degassed DMF (4 ml) was added, followed by a solution of triflate 121d (184 mg, 0.35 mmol) in DMF (1 ml). The resulting yellow solution was warmed to 40°C. 2-(Tributylstannyl)furan (138 mg, 0.39 mmol) was added yellow solution heated for 3 min to 55°C. TLC indicated the consumption of starting material with the formation of a highly UV active material. The resulting colourless solution, containing palladium black was diluted with diethyl ether (5 ml), then an aqueous solution of KF added (5 ml of a 1 M solution). After stirring for 30 min, the grey precipitate was removed by suction filtration. Diethyl ether (5 ml) was
added and the phases were separated. The aqueous phase was extracted with
diethyl ether (3 × 5 ml) and the combined organic extracts were dried and
concentrated under reduced pressure to afford a colourless oil. Purification by flash
column chromatography over silica gel (40% diethyl ether in light petroleum) afforded
furan 139d as a colourless oil (156 mg, 96%); Rf (20% ethyl acetate in light
petroleum) 0.28; δH (300 MHz, CDCl3) 7.70-7.69 (1H, m, H-α), 7.61-7.50 (2H, m,
ArH), 7.30-7.28 (6H, bd. s, envelope, ArH), 6.52 (1H, dd, 3J 3.3, 4J 0.7, H-γ), 6.36
(1H, dd, 3J 3.3, 3J 1.8, H-β), 5.26 (2H, s, CH₂Ph), 4.84 (2H, s, OCH₂O), 3.82-3.79
(2H, m, OCH₂CH₂O), 3.50-3.47 (2H, m, OCH₂CH₂O), 3.32 (3H, s, OCH₃); δC (75
MHz, CDCl3) 168.6 (CO ester), 155.8 (t, 1JCF 291.4, CF₂), 151.7 (C-δ), 143.1 (C-α),
135.4 (Cq of Ph), 130.3 (C-2), 129.6 (dd, 3JCF 6.8, 1.7, C-5), 129.3 (t, 5JCF 1.4, C-1),
128.7 (dd, 4JCF 6.5, 3.4, CH), 128.6 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.0
(dd, 4JCF 5.8, 3.8, CH), 114.7 (dd, 2JCF 35.9, 16.7, C=CF₂), 111.7 (C-β), 108.7 (C-γ),
95.9 (t, 4JCF 2.8, OCH₂O), 71.6 (CH₂O), [68.7, 68.7] (CH₂O), 67.4 (OCH₂Ph), 59.1
(OCH₃); δF (282 MHz, CDCl3) -95.66 (1F, d, 2J 52.1), -104.11 (1F, d, 2J 52.1); [HRMS
(ES-TOF, M+Na) Found: 467.1287; Calc. for C₂₄H₂₂O₆F₂Na: 467.1282]; m/z (ES-
TOF) 467.1 (100%, M+Na).

2-{4-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-phenyl}-furan 139a
A mixture of dichlorobis(triphenylphosphine)palladium(II) (20 mg, 28 μmol) and
benzeneboronic acid (117 mg, 0.96 mmol) was pump-purged twice with nitrogen,
then dry, degassed DMF (2 ml) added. The mixture was then warmed towards 90°C.
Triethylamine (0.28 ml, 1.99 mmol) was added at 30°C, followed by a solution of
triflate 121a (205 mg, 0.52 mmol) in DMF (1 ml). The resulting dark red solution was heated at 90°C for 90 h, then cooled to ambient temperature. Diethyl ether (5 ml) and water (10 ml) were added. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 5 ml). The combined organic extracts were washed with water (10 ml), then dried and concentrated under reduced pressure to afford a brown oil. This oil was diluted with acetone and silica gel added. Concentration under reduced pressure afforded a brown powder. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded furan 139a as a colourless oil (76 mg, 49%); Rf (20% diethyl ether in light petroleum) 0.21; δF (282 MHz, CDCl3) -97.29 (1F, d, 2J 54.6), -105.52 (1F, d, 2J 54.6). 19F NMR data is identical to that obtained via a Stille coupling. This material was also cleaved to 140b without further characterisation.

5-{4-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-phenyl}-2,3-benzofuran 139f

A flask containing 2-benzofuranboronic acid (520 mg, 3.2 mmol), potassium phosphate (685 mg, 3.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (210 mg, 0.18 mmol) was pump-purged with nitrogen. Dry, degassed DMF (6 ml) was
added followed by a solution of triflate **121a** (837 mg, 2.1 mmol) in DMF (2 ml). The heterogeneous yellow mixture was warmed to 85°C with darkening. The reaction mixture was allowed to stir for 4 h before being cooled to ambient temperature. The reddish reaction mixture was partitioned between diethyl ether (10 ml) and water (10 ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were dried and concentrated to afford a dark red oil, which solidified upon cooling. The crude material was dissolved with acetone and concentrated on to silica gel to afford a brown powder. Purification by column chromatography (20% diethyl ether in hexanes) afforded benzofuran **139f** as yellow flakes (616 mg, 80%); mp 48-49°C; ν (nujol mull/cm⁻¹) 1722 s, 1455 s, 1413 m, 1270 s, 1196 m, 1182 m, 1156 m, 1119 m, 1077 m, 1036 m, 982 m, 934 m, 847 m, 800 m, 752 m, 742 m, 726 m; δH (300 MHz, CDCl3) 7.87 (2H, d, 3J 8.5, ArH), 7.59-7.52 (4H, envelope, ArH), 7.33-7.21 (2H, envelope, ArH), 7.04 (1H, s, ArH), 4.92 (2H, s, OCH₂O), 3.90-3.87 (2H, m, CH₂O), 3.59-3.55 (2H, m, CH₂O), 3.39 (3H, s, OCH₃); δC (75 MHz, CDCl3) 155.6 (t, 1JCF 290.8, CF₂), 155.1 (Cq), 154.9 (Cq), 130.1 (t, 6JCF 1.4, Cq), 130.0 (dd, 3JCF 6.6, 1.4, Cq), 129.0 (Cq), 129.9 (dd, 4JCF 6.2, 3.7, ArCH), 124.9 (ArCH), 124.5 (ArCH), 123.0 (ArCH), 120.9 (ArCH), 115.4 (dd, 2JCF 34.8, 3.7, ArCH), 111.1 (ArCH), 101.9 (ArCH), 95.6 (t, 4JCF 2.6, OCH₂O), 71.5 (CH₂O), [68.5, 68.5] (CH₂O), 58.9 (OCH₃); δF (282 MHz, CDCl₃) -96.44 (1F, d, 2J 53.4), -104.64 (1F, dd, 2J 53.4); [HRMS (ES-TOF, M+Na) Found: 383.1086; Calc. for C₂₀H₁₈O₄F₂Na: 383.1071]; m/z (ES) 383.1 (100%, M+Na).
A mixture of tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (7 mg, 6.6 μmol), triphenylphosphine (13 mg, 49.6 μmol), potassium orthophosphate (159 mg, 0.75 mmol) and phenylboronic acid (7 mg, 0.57 mmol) was pump-purged twice with nitrogen. Degassed dioxane (1 ml) was added, followed by a solution of triflate 121a (210 mg, 0.51 mmol) in dioxane (1 ml). The mixture was stirred at 85°C for 16 h, then allowed to cool to ambient temperature. The reaction mixture was diluted with diethyl ether (5 ml) and partitioned between water (10 ml) and diethyl ether (10 ml). The organic layer was separated and the aqueous phase extracted with diethyl ether (3 × 5 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a brown oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded biphenyl 139g as a pale yellow oil (109 mg, 67%); 100% by GC; Rf (20% diethyl ether in light petroleum) 0.30; ν (film/cm⁻¹) 1732 m (C=CF₂), 1600 w, 1558 w, 1489 m, 1450 m, 1408 m, 1266 m, 1027 m, 980 m, 945 m, 768 m, 732 m, 698 m; δH (300 MHz, CDCl₃) 7.64-7.53 (6H, envelope, ArH), 7.48-7.43 (2H, m, ArH), 7.39-7.34 (1H, m, ArH), 4.92 (2H, s, OCH₂O), 3.91-3.88 (2H, m, CH₂O), 3.59-3.56 (2H, m, CH₂O), 3.39 (3H, s, OCH₃); δC (75 MHz, CDCl₃) 155.5 (dd, ¹J_CF 290.2, 289.6, CF₂), 141.0 (t, ⁶J_CF 1.7, Cq), 140.3 (Cq), 128.9
(d, $^3J_{CF}$ 1.4, Cq), 128.8 (CH), 127.5 (CH), 127.2 (CH), 127.1 (dd, $^4J_{CF}$ 5.8, 3.4, CH), 127.0 (CH), 115.5 (dd, $^2J_{CF}$ 35.1, 18.7, C=CF$_2$), 95.4 (t, $^4J_{CF}$ 2.9, OCH$_2$O), 71.6 (CH$_2$O), [68.5, 68.5] (CH$_2$O), 59.0 (OCH$_3$); $\delta_F$ (282 MHz, CDCl$_3$) -97.33 (1F, d, $^2J$ 55.9), -105.72 (1F, d, $^2J$ 55.9); [HRMS (ES-TOF, M+Na) Found: 343.1137; Calc. for C$_{18}$H$_{18}$O$_3$F$_2$Na: 343.1122]; m/z (El) 321 (1%, M+H), 215 (5%), 181 (7%), 152 (10%), 89 (37%), 59 (100%)

4-[(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-3’-methoxy-biphenyl 139h

A flask containing 3-methoxyphenylboronic acid (230 mg, 1.5 mmol), potassium phosphate (320 mg, 1.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (100 mg, 86 $\mu$mol) was pump-purged with nitrogen. Dry, degassed DMF (3 ml) was added followed by a solution of triflate 121a (392 mg, 1.0 mmol) in DMF (1 ml). The heterogeneous yellow mixture was warmed to 85°C with darkening. The reaction mixture was allowed to stir for 45 min, with monitoring by TLC, before being cooled to ambient temperature. The reddish reaction mixture was partitioned between diethyl ether (10 ml) and water (10 ml). The organic layer was separated and the aqueous phase extracted with diethyl ether (3 $\times$ 10 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a brown oil. Purification by
column chromatography over silica gel (20% diethyl ether in hexanes) afforded anisole 139h as a pale yellow oil (263 mg, 73%); 97% by GC; Rf (20% diethyl ether in hexanes) 0.13; ν (film/cm⁻¹) 1729 m, 1600 m, 1584 m, 1558 w, 1482 m, 1436 w, 1402 w, 1296 m, 1266 s, 1177 m, 1152 s, 1034 m, 981 s, 947 m, 839 m, 781 m, 696 w; δH (300 MHz, CDCl₃) 7.63-7.52 (4H, AB quartet, ArH), 7.36 (t, 3J 7.9, ArH), 7.21-7.12 (2H, envelope, ArH), 6.94-6.89 (1H, m, ArH), 4.92 (2H, s, OCH₂), 3.91-3.88 (2H, m, CH₂O), 3.86 (3H, s, ArOCH₃), 3.60-3.56 (2H, m, CH₂O), 3.39 (3H, s, CH₂OCH₃); δC (75 MHz, CDCl₃) 159.9 (Cq-OMe), 155.5 (t, 1JCF 289.3, CF₂), 141.8-141.7 (m, Cq), 140.8-140.8 (m, Cq), 129.7 (ArCH), 128.9-128.8 (m, Cq), 127.1 (ArCH), 127.0 (dd, 4JCF 5.9, 3.4, ArCH), 119.4 (ArCH), 115.4 (dd, 2JCF 35.1, 18.7, C=CF₂), 112.9 (ArCH), 112.7 (ArCH), 95.5-95.3 (m, OCH₂O), 71.5 (CH₂O), [68.4, 68.4] (CH₂O), 58.9 (CH₂OCH₃), 55.1 (ArOCH₃); δF (282 MHz, CDCl₃) -97.28 (1F, d, 2J 56.0), -105.66 (1F, d, 2J 54.7); [HRMS (ES-TOF, M+Na) Found: 373.1243; Calc. for C₁₉H₂₀O₄F₂Na: 373.1227]; m/z (ES) 373.1 (100%, M+Na).

4-[(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-2'-methyl-biphenyl 139j

A flask containing o-tolylboronic acid (208 mg, 1.5 mmol), potassium phosphate (320 mg, 1.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (100 mg, 86 μmol) was
pump-purged with nitrogen. Dry, degassed DMF (3 ml) was added followed by a solution of triflate 121a (398 mg, 1.02 mmol) in DMF (1 ml). The heterogeneous yellow mixture was warmed to 85°C with darkening. The reaction mixture was allowed to stir for 2 h, with monitoring by TLC, before being cooled to ambient temperature. The reddish reaction mixture was partitioned between diethyl ether (10 ml) and water (10 ml). The organic layer was separated and the aqueous phase extracted with diethyl ether (3 × 10 ml). The combined organic extracts were dried and concentrated to afford a brown oil. Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded biphenyl 139j as a colourless oil (222 mg, 65%); 97% by GC; Rf (20% diethyl ether in hexanes) 0.33; ν (film/cm⁻¹) 1922 w, 1736 s, 1484 s, 1457 s, 1402 m, 1266 s, 1177 s, 1153 s, 1101 s, 1029 m, 980 s, 949 s, 846 s, 765 s; δH (300 MHz, CDCl₃) 7.54-7.51 (2H, m, ArH), 7.38-7.35 (2H, m, ArH), 7.29-7.23 (4H, envelope, ArH), 4.95 (2H, s, OCH₂O), 3.93-3.90 (2H, m, CH₂O), 3.61-3.58 (2H, m, CH₂O), 3.41 (3H, s, OCH₃), 2.30 (3H, s, ArCH₃); δC (75 MHz, CDCl₃) 155.5 (t, 1JCF 290.2, CF₂), 141.9-141.9 (m, Cq), 141.1 (Cq), 135.2 (Cq), 130.3 (ArCH), 129.6 (ArCH), 129.3 (ArCH), 128.35-128.2 (m, Cq), 127.4 (ArCH), 126.5-126.3 (m, 2 overlapping dd, ArCH), 125.8 (ArCH), 115.9-115.1 (m, C=CF₂), 95.4 (t, 4JCF 2.6, OCH₂O), 71.6 (CH₂O), [68.4, 68.4] (CH₂O), 58.9 (OCH₃), 20.4 (CH₃); δF (282 MHz, CDCl₃) -97.56 (1F, d, 2J 55.9), -105.98 (1F, d, 2J 55.9); [HRMS (ES-TOF, M+Na) Found: 357.1284; Calc. for C₁₉H₂₀O₃F₂Na: 357.1278]. A satisfactory mass spectrum could not be obtained.
3-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-biphenyl 139n

A mixture of dichlorobis(triphenylphosphine)palladium(II) (80 mg, 0.11 mmol) and benzeneboronic acid (509 mg, 4.18 mmol) was pump-purged twice with nitrogen, then dry, degassed DMF (4 ml) added. The mixture was then warmed towards 70°C. Triethylamine (1.1 ml, 7.8 mmol) was added at 30°C, followed by a solution of triflate 121b (0.79 g, 2.01 mmol) in DMF (1 ml). The resulting dark black solution was heated at 70°C for 70 h, with monitoring by TLC and GLC. GLC indicated an 86% conversion after this initial reaction period. Palladium catalyst (40 mg) was re-added and the reaction continued for a further 96 h (total 166 h) to give a 97% conversion by GLC. The reaction mixture was allowed to cool to ambient temperature, then diluted with diethyl ether (10 ml). The contents were added to a saturated aqueous solution of sodium bicarbonate (10 ml). The phases were separated and the aqueous phase extracted with diethyl ether (3 × 20 ml). The combined organic extracts were washed with water (10 ml) and brine (15 ml). The organic extracts were then dried and concentrated under reduced pressure to afford a brown oil. Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded biphenyl 139n as a colourless oil (401 mg, 62%); 98% by GC; [Found: C, 67.47; H, 5.75; Calc. for C_{18}H_{18}F_{2}O_{3}: C, 67.49; H, 5.66%]; ν (film/cm⁻¹) 1952 w, 1886 w, 1732 s, 1600 w, 1481 m, 1453 m, 1414 w, 1278 s, 1241 s, 1176 s, 1152 s, 1030 m, 988 s, 950 s, 760 s, 701 s; δH (300 MHz, CDCl₃) 7.68-7.66 (1H, m, ArH), 7.57-7.54 (2H, m,
ArH), 7.53-7.48 (1H, m, ArH), 7.45-7.38 (4H, envelope, ArH), 7.36-7.30 (1H, m, ArH), 4.89 (2H, d, \(^5J_{HF}\) 0.7 Hz, OCH\(_2\)O), 3.87-3.84 (2H, m, CH\(_2\)O), 3.54-3.51 (2H, m, CH\(_2\)O), 3.34 (3H, s, OCH\(_3\)); δ \(_C\) (75 MHz, CDCl\(_3\)) 154.0 (t, \(^1J_{CF}\) 289.7, CF\(_2\)), 140.0 (Cq), 139.0 (Cq), 128.8 (dd, \(^3J_{CF}\) 6.3, 1.4, Cq), 127.4 (CH), 127.2 (CH), 126.0 (CH), 125.5 (CH), 124.1 (dd, \(^4J_{CF}\) 5.9, 3.3, CH), 123.9 (dd, \(^4J_{CF}\) 5.5, 3.5, CH), 93.7 (t, \(^4J_{CF}\) 2.7, OCH\(_2\)O), 70.0 (CH\(_2\)O), [66.8, 66.8] (CH\(_2\)O), 57.4 (OCH\(_3\)); δ \(_F\) (282 MHz, CDCl\(_3\)) -97.96 (1F, d, \(^2J\) 55.6), -106.47 (1F, d, \(^2J\) 55.6); [HRMS (ES-TOF, M+Na) Found: 343.1127; Calc. for C\(_{18}\)H\(_{18}\)F\(_2\)O\(_3\)Na: 343.1122]; \(m/z\) (ES) 343.0 (100%, M+Na).

1-Dec-1'-ynyl-4-[2,2-difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-benzene 139p

[Chemical Structure Image]

A flask containing dichlorobis(triphenylphosphine)palladium(II) (12 mg, 34.2 μmol) was pump-purged twice with argon. Triethylamine (0.56 ml, 3.98 mmol) and a solution of triflate 121a (205 mg, 0.52 mmol) in DMF (1 ml) were added and the orange solution stirred at ambient temperature for 2 min. 1-Decyne (0.1 ml, 0.55 mmol) was then added via syringe, and the resulting brown mixture heated at 90°C, with darkening, for 1 h. The resulting black solution was cooled to ambient temperature and ethyl acetate (5 ml) and water (5 ml) added. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 5 ml). The
combined organic extracts were washed once with brine (5 ml), then dried and concentrated under reduced pressure to afford a brown oil, which was diluted with acetone and concentrated onto silica gel to afford a brown powder. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded alkyne 139p as a pale yellow oil (82 mg, 41%); Rf (10% diethyl ether in light petroleum) 0.21; δH (300 MHz, CDCl3) 7.39-7.32 (4H, m, ArH), 4.83 (2H, s, OCH2O), 3.84-3.80 (2H, m, CH2O), 3.53-3.50 (2H, m, CH2O), 3.35 (3H, s, OCH3), 2.37 (2H, t, 3J 7.0, Ar-C≡C-H2-C7H16), 1.62-1.52 (2H, m), 1.47-1.35 (2H, m), 1.32-1.15 (8H, envelope), 0.89-0.81 (3H, m); δF (282 MHz, CDCl3) -97.48 (1F, d, 2J 53.7), -105.59 (1F, d, 2J 53.7). Due to the unstable nature of this material, the MEM enol ether was cleaved to 140a under protic conditions without further characterisation (vide infra).

1-[(4-Decen-1'-yl)-phenyl]-2,2-difluoro-ethanone 140a

Acetophenone 140a was prepared as for 132 using enol acetal 139p (82 mg, 0.21 mmol) and chlorotrimethylsilane (0.1 ml, 0.78 mmol) in methanol (2 ml). Concentration under reduced pressure afforded a brown oil. Acetone (5 ml) was added and the solution concentrated onto silica to afford a brown powder. Purification by column chromatography over silica gel (15% diethyl ether in light petroleum) afforded alkyne 140a as a pale brown oil (46 mg, 78%); 99% by GC; Rf (15% diethyl
ether in light petroleum) 0.70; \( \delta_H \) (300 MHz, CDCl\(_3\)) 7.99 (2H, d, \(^3J 8.4\), ArH), 7.50 (2H, d, \(^3J 8.3\), ArH), 6.26 (1H, t, \(^2J_{HF} 53.5\), CF\(_2\)H), 2.43 (2H, t, \(^3J 7.0\), C≡CH\(_2\)), 1.61 (2H, tt, \(^3J 7.3\), 7.3, C≡CCH\(_2\)CH\(_2\)), 1.49-1.39 (2H, m, C≡CCH\(_2\)CH\(_2\)H), 1.37-1.23 (8H, envelope, C≡C(CH\(_2\))\(_2\)(CH\(_2\))\(_4\)), 0.88 (3H, t, \(^3J 6.5\), CH\(_3\)); \( \delta_C \) (75 MHz, CDCl\(_3\)) 132.0 (CH), 131.3 (Cq), 129.9 (t, \(^3J_{CF} 2.0\), Cq), 129.5 (t, \(^4J_{CF} 2.3\), CH), 111.3 (t, \(^1J_{CF} 254.1\), CF\(_2\)H), 96.3 (C≡C), 80.0 (C≡C), 31.9 (CH\(_2\)), 29.2 (CH\(_2\)), 29.1 (CH\(_2\)), 29.0 (CH\(_2\)), 28.5 (CH\(_2\)), 22.7 (CH\(_2\)), 19.6 (CH\(_2\)), 14.1 (CH\(_3\)), CO too weak to assign; \( \delta_F \) (282 MHz, CDCl\(_3\)) -122.0 (d, \(^2J 51.1\)); [HRMS (EI, M) Found: 292.1637; Calc. for C\(_{18}\)H\(_{22}\)OF\(_2\): 292.1639]; m/z (EI) 292 (13%, M), 241 (100%, M-CF\(_2\)H), 221 (10%), 185 (8%), 157 (8%), 142 (13%), 129 (17%), 115 (17%), 55 (25%), 43 (43%), 41 (63%).

2,2-Difluoro-1-(4-furan-2-yl-phenyl)-ethanone 140b

Chlorotrimethylsilane (0.2 ml, 1.58 mmol) was added dropwise to a solution of enol acetal 139a (270 mg, 0.87 mmol) in methanol (6 ml) at 0°C. The resulting solution was allowed to warm to ambient temperature, and stirred overnight. Evaporation of the solution afforded crude difluoroketone 140b as a dark green solid. This material was dissolved in acetone (10 ml) and concentrated onto silica gel to afford a green powder. Purification by flash column chromatography over silica gel (15% diethyl
ether in light petroleum) afforded difluoromethyl ketone 140b as an amorphous white solid (120 mg, 60%); 100% by HPLC at 225 nm; HPLC t (5% EtOAc in hexanes, 3 ml/min) 2.51 min; mp 113-114°C; Rf (15% diethyl ether in light petroleum) 0.58; ν (nujol mull/cm\(^{-1}\)) 1695 w, 1608 w, 1256 w, 1223 w, 1057 w, 1021 w, 906 w, 876 w, 825 w, 746 w, 720 w, 670 w; [Found: C, 64.87; H, 3.75; Calc. for C\(_{12}\)H\(_8\)F\(_2\)O\(_2\): C, 64.66; H, 3.63%]; δ\(_H\) (300 MHz, CDCl\(_3\)) 8.06 (2H, d, 3\(\text{J}\) 8.5, ArH), 7.87 (2H, d, 3\(\text{J}\) 8.5, ArH), 7.70-7.69 (1H, m, H-α), 7.09-7.08 (1H, m, H-γ), 6.84 (1H, t, 2\(\text{J}\)\(_{HF}\) 53.1, CF\(_2\)H), 6.59-6.57 (1H, m, H-β); δ\(_C\) (75 MHz, CD\(_3\)COCD\(_3\)) 157.4 (C-δ), 149.5 (C-α), 141.3 (Cq), 135.7 (Cq), 135.1 (CH), 128.8 (CH), 117.6 (C-β), 115.2 (t, 1\(\text{J}\)\(_{CF}\) 248.0, CF\(_2\)H), 114.1 (C-γ), CO too weak to assign; δ\(_F\) (282 MHz, CDCl\(_3\)) -121.71 (d, 2\(\text{J}\)\(_{HF}\) 47.4); [HRMS (EI, M) Found: 222.0495; Calc. for C\(_{12}\)H\(_8\)F\(_2\)O\(_2\): 222.0492]; m/z (EI) 222 (42%, M), 171 (100%, M-CF\(_2\)H), 143 (17%, M-COCF\(_2\)H), 115 (53%), 89 (13%), 63 (12%), 51 (21%), 39 (12%).

2,2-Difluoro-1-(3-thien-2-yl-phenyl)-ethanone 140c

Thiophene 140c was prepared as for 140b using enol acetal 139b (230 mg, 0.7 mmol) and chlorotrimethylsilane (0.2 ml, 1.56 mmol) in methanol (3 ml). Evaporation of the solution afforded a colourless oil and white needles. Diethyl ether (5 ml) was
added and the white needles removed by filtration. The filtrate was concentrated under reduced pressure to afford a colourless oil. Acetone was added and the solution concentrated onto silica gel to afford a white powder. Purification by column chromatography over silica gel (15% diethyl ether in light petroleum ⇒ 20% ethyl acetate in light petroleum) afforded difluoromethyl ketone 140c as a colourless oil (103 mg, 62%); 100% by GC; Rf (20% ethyl acetate in light petroleum) 0.55 (streaks); ν (film/cm⁻¹) 2925 w, 1709 s (C=O), 1600 m, 1580 m, 1482 w, 1442 w, 1422 w, 1345 w, 1299 w, 1275 m, 1247 w, 1232 w, 1205 w, 1136 s, 1067 s, 866 w, 852 w, 792 w, 709 m; δH (300 MHz, CDCl₃) 8.23 (1H, s, H-5), 7.91 (1H, br. d, 3J 7.9, H-2 or H-4), 7.48 (1H, t, 3J 7.9, H-3), 7.34 (1H, d, 3J 4.4, H-6), 7.30 (1H, d, 3J 5.1, H-8), 7.08-7.04 (1H, m, H-7), 6.27 (1H, t, 2JHF 53.7, H-1); δC (75 MHz, CDCl₃) 187.7 (t, 2JCF 25.6, CO), 142.7 (Cq), 135.8 (Cq), 132.4 (t, 3JCF 1.9, Cq), 132.3 (CH), 129.8 (CH), 128.6 (t, 4JCF 2.7, CH), 128.6 (CH), 126.9 (t, 4JCF 2.0, CH), 126.2 (CH), 124.5 (CH), 111.4 (t, 1JCF 253.8, CF₂H); δF (282 MHz, CDCl₃) -122.29 (d, 2JHF 53.7); [HRMS (EI, M) Found: 238.0265; Calc. for C₁₂H₈OSF₂: 238.0264]; m/z (El) 239 (11%, M+H), 238 (71%, M), 187 (100%, M-CF₂H), 159 (44%, M-HF₂CO), 115 (66%), 79 (8%, HF₂CO).
Biphenyl ketone \(140d\) was prepared as for \(140b\) using enol acetal \(139n\) (153 mg, 0.48 mmol), chlorotrimethylsilane (0.2 ml, 1.58 mmol) in MeOH (2 ml). Evaporation of the solution afforded a crude brown oil. This material was diluted with acetone and concentrated onto silica gel to afford a brown powder. Purification by column chromatography over silica gel (15% diethyl ether in light petroleum ⇒ 20% ethyl acetate in light petroleum) afforded ketone \(140d\) as a colourless oil (589 mg, 48%); 100\% by GC; \(R_f\) (20\% ethyl acetate in light petroleum) 0.55 (streaks); \(\nu\) (film/cm\(^{-1}\)) 3036, 1711, 1600, 1586, 1481, 1455, 1347, 1319, 1257, 1222, 1138, 1070, 909, 735, 699; \(\delta_H\) (300 MHz, CDCl\(_3\)) 8.29 (1H, bd s, ArH), 8.05 (1H, d, \(^3J \approx 8.1\), ArH), 7.90 (1H, dd, \(^3J \approx 7.9\), J 0.9, ArH), 7.63-7.58 (3H, envelope, ArH), 7.51-7.38 (3H, envelope, ArH), 6.33 (1H, t, \(^2J_{HF} \approx 53.5\), COCF\(_2\)H); \(\delta_C\) (75 MHz, CDCl\(_3\)) 142.2 (Cq), 139.6 (Cq), 133.5 (CH), 132.0-132.0 (m, Cq), 133.5 (CH), 129.4 (CH), 129.0 (CH), 128.4 (t, \(^4J_{CF} \approx 2.5\) Hz, CH), 128.3 (t, \(^4J_{CF} \approx 2.1\) Hz, CH), 128.1 (CH), 127.2 (CH), 111.3 (t, \(^1J_{CF} \approx 253.8\) Hz, CF\(_2\)), CO too weak to assign; \(\delta_F\) (282 MHz, CDCl\(_3\)) -122.11 (d, \(^2J_{HF} \approx 52.6\)) [HRMS (El, M) Found: 232.0691; Calc. for \(C\(_{14}\)H\(_{10}\)OF\(_2\): 232.0700]; \(m/z\) (El) 232 (28\%, M), 181 (50\%, M-CF\(_2\)H), 153 (30\%, M-COCF\(_2\)H), 152 (33\%, M-1-COCF\(_2\)H), 51 (74\%, CF\(_2\)H), 40 (100\%).
Benzyl 5-[(2,2-difluoro-2-phenylsulfanyl)-acetyl]-2-furan-2' -yl benzenecarboxylate 143

Phenylsulfenyl chloride (40 μl, 0.34 mmol) was added to a solution of furan 139d (156 mg, 0.34 mmol) in DCM (4 ml) at ambient temperature. After 16 h, the reaction was concentrated under reduced pressure to afford a crude yellow oil. Purification by flash column chromatography over silica gel (30% diethyl ether in light petroleum) afforded ketone 143 as a bright yellow oil (126 mg, 80%); 71% by HPLC at 225 nm; HPLC tᵫ (20% water in MeCN, 1 ml/min) 11.84 min; minor impurities were observed by ¹⁹F, ¹H and ¹³C NMR; Rᵢ (20% ethyl acetate in light petroleum) 0.44 (streaks); ν (film/cm⁻¹) 1734 m, 1730 m, 1700 m, 1696 m, 1600 m, 1499 w, 1474 w, 1454 w, 1441 w, 1372 w, 1306 w, 1265 m, 1239 m, 1136 m, 1095 m, 1034 m, 1012 m, 737 m, 699 m; δH (300 MHz, CDCl₃) 8.34 (1H, d, ⁴J 1.9, H-6), 8.20-8.17 (1H, m, H-4), 7.75 (1H, d, ³J 8.5, H-3), 7.58-7.55 (2H, m, ArH), 7.48-7.26 (9H, envelope, ArH + H-α), 6.74 (1H, d, ³J 3.7, H-γ), 6.45 (1H, dd, ³J 3.7, ⁴J 1.9, H-β), 5.36 (2H, s, OCH₂Ph); δC (75 MHz, CDCl₃) 183.8 (t, ³Jₐ 2.0, CF₂CO), 168.0 (CO ester), 150.7 (Cq, C-δ), 144.3 (CH, C-α), 136.8 (CH), 135.2 (Cq of benzyl), 134.4 (Cq, C-2), 132.3 (t, ³Jₐ 2.8, CH, C-4), 131.5 (t, ⁴Jₐ 2.8, CH, C-6), 130.7 (CH), 129.4 (CH), 128.7 (CH), 128.7 (CH), 128.5 (CH), 127.4 (CH), 124.5 (t, ³Jₐ 1.4, Cq of PhS), 123.6 (t, ¹Jₐ 290.5, CF₂), 112.2 (CH, C-γ), 111.3 (CH, C-β), 67.7 (OCH₂Ph), C-1 and C-5 obscured by aryl CH
resonances in δ127-132 range; δF (282 MHz, CDCl3) -77.62 (s); [HRMS (ES-TOF, M+Na) Found: 487.0789; Calc. for C_{26}H_{18}O_4SF_2Na: 487.0792]; m/z (ES-TOF) 519.3 (29%, M+Na+MeOH), 487.2 (100%, M+Na), 465.2 (13%, M+1).

(2R)- 4-(N,N-Diethylcarbamoyloxy)-5,5-difluoro-pent-4-en-1,2-diol 156

![Chemical structure](image)

A solution of AD-mix-β (11.7 g, 1.41 g/mmol) and sodium hydrogencarbonate (1.8 g, 21.4 mmol) in tBuOH:H2O (82 ml, 1:1 v/v) was stirred vigorously at ambient temperature until the phases became clear. Diene 99d (1.82 g, 8.32 mmol) was added in one portion and the slurry stirred vigorously at 0°C until TLC indicated the consumption of starting material. The yellow mixture was quenched with sodium sulfite (12 g) then stirred for 30 min to afford a grey solution. The reaction mixture was diluted with DCM (5 ml) and the layers were separated. The aqueous phase was extracted with DCM (3 × 20 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a yellow oil. Purification by column chromatography over silica gel (60% ethyl acetate in light petroleum) afforded diol 156 as a colourless oil (1.85 g, 88%); Rf (60% ethyl acetate in light petroleum) 0.25; [Found: C, 47.14; H, 6.77; N, 5.53; Calc. for C_{10}H_{17} NO_4F_2: C, 47.43; H, 6.77; N, 5.53%]; ν (film/cm⁻¹) 3600-3100 bd, 1780 m (C=CF₂), 1706 s (C=O), 1476 m, 1429 s,
1382 m, 1291 s, 1217 s, 1158 m, 1115 s, 1047 m, 956 w, 935 w, 785 w, 757 w; δ_H (300 MHz, CDCl_3) 3.80-3.72 (1H, m, H-2), 3.65 (1H, dd, ^2J_11.4, ^3J_3.3, H-1a), 3.50 (1H, dd, ^2J_11.4, ^3J_6.6, H-1b), 3.30 (2H, q, ^3J_7.0, CH_2NCH_2), 3.29 (2H, q, ^3J_7.0, CH_2NCH_2), 2.40 (1H, ddd, ^2J_15.1, ^3J_9.9, ^4J_{HF} 3.7, H-3a), 2.27-2.18 (1H, m, H-3b), 1.14 (3H, t, ^3J_7.0, (MeCH_2)NEt), 1.13 (3H, t, ^3J_7.0, EtNCH_2Me); δ_C (75 MHz, CDCl_3) 155.6 (dd, ^1J_{CF} 289.0, 288.0, C-5), 154.4 (d, ^4J_{CF} 2.3, CO), 109.0 (dd, ^2J_{CF} 44.7, 16.0, C-4), 67.8 (t, ^4J_{CF} 2.8, C-2), 65.8 (C-1), [42.7, 42.1] (CH_2), 31.9 (d, ^3J_{CF} 2.8, C-3), [13.9, 13.2] (CH_3); δ_F (282 MHz, CDCl_3) -96.40 (1F, dd, ^2J 59.8, ^4J_{HF} 5.1), -109.98 (1F, dt, ^2J 59.8, ^4J_{HF} 3.7); [HRMS (ES-TOF, M+Na) Found: 276.1034; Calc. for C_{10}H_{17}NO_4F_2Na: 276.1023]; m/z (CI) 254 (100%, M+H), 100 (20%, CONEt_2); m/z (ES) 276 (100%, M+Na). Stereochemical assignment is based upon the Sharpless model.²⁰⁴

(2R)-4-(N,N-Diethylcarbamoyloxy)-5,5-difluoro-1-(triisopropylsilyloxy)-pent-4-en-2-ol 157

Chlorotriisopropylsilane (0.22 ml, 1.05 mmol) was added to a solution of diol 156 (266 mg, 1.05 mmol) in DCM (2 ml) containing imidazole (170 mg, 2.50 mmol) and DMAP (cat.). The mixture was stirred at ambient temperature for 48 h, then diluted with DCM (2 ml). The organic layer was washed consecutively with water (10 ml), a saturated solution of ammonium chloride (10 ml) and brine (10 ml). The organic
extracts were dried and concentrated under reduced pressure to afford alcohol 157 as a colourless oil (430 mg, 100%); 99% by GC; Rf (25% diethyl ether in light petroleum) 0.27; αD -2.1° (c=18.4, 21°C, MeOH, est. error = ± 0.4°); δH (300 MHz, CDCl3) 3.78-3.61 (3H, m, H-1, OH), 3.44 (1H, dd, 3J 7.0, 3J 7.0 H-2), 3.35-3.26 (4H, m, CH2NCH2), 2.53-2.44 (1H, m, H-3a), 2.37-2.28 (1H, m, H-3b), 1.19-1.01 (27H, m, (MeCH2)2N), Si(CHMe2)3; δC (75 MHz, CDCl3) 155.4 (t, 1JCF 288, C-5), 153.9 (CO), 109.4 (dd, 2JCF 45.8, 15.8, C-4), 68.3 (t, 4JCF 2.5, C-2), 66.6 (C-1), [42.6, 42.0] (CH2), 32.1 (d, 3JCF 2.8, C-3), 17.9 (CH3), [13.9, 13.2] (CH3), 11.9 (CH); δF (282 MHz, CDCl3) -96.91 (1F, dd, 2J 61.0, 4JHF 3.8), -110.51 (1F, dd, 2J 61.0, 4JHF 3.8); [HRMS (ES-TOF, M+Na) Found: 432.2344; Calc. for C19H37NO4F2NaSi: 432.2358]; m/z (ES-TOF) 432.4 (100%, M+Na); Chiral HPLC tR (Chiralcel OD, 10% isopropanol in hexane, 1 ml/min) 6.53 min; 95:5 er.

(2RS)-4-(N,N-Diethylcarbamoyloxy)-5,5-difluoro-pent-4-en-1,2-diol 158

A solution of potassium osmate dihydrate (9 mg, 24.5 μmol), potassium ferricyanide (3.03 g, 9.20 mmol), potassium carbonate (1.32 g, 9.54 mmol), quinuclidine (13 mg, 119 μmol) and sodium hydrogen carbonate (260 mg, 3.09 mmol) in tBuOH-H2O (15 ml, 1:1 v/v) was stirred vigourously at ambient temperature until the phases became clear. Diene 99d (669 mg, 3.05 mmol) was added in one portion and the slurry stirred
vigorously at ambient temperature for 16 h. The yellow mixture was quenched with sodium sulfite (3 g) and then stirred for 30 min to afford a grey solution. The reaction mixture was diluted with DCM (10 ml) and the layers were separated. The aqueous phase was extracted with DCM (3 × 20 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (80% ethyl acetate in light petroleum) afforded diol 158 as a colourless oil (368 mg, 48%); R$_f$ (80% ethyl acetate in light petroleum) 0.38; $\delta_F$ (282 MHz, CDCl$_3$) -96.91 (1F, dd, $^2$J 61.0, $^4$J$_{HF}$ 3.8), -110.51 (1F, dd, $^2$J 61.0, $^4$J$_{HF}$ 3.8). This material was taken on without further characterisation.

(2RS)-4-(N,N-Diethylcarbamoyloxy)-5,5-difluoro-1-(triisopropylsilyloxy)-pent-4-en-2-ol 159

Chlorotriisopropylsilane (0.31 ml, 1.45 mmol) was added to a solution of diol 158 (368 mg, 1.45 mmol) in DCM (3 ml) containing imidazole (220 mg, 3.24 mmol) and DMAP (cat.). The mixture was stirred at ambient temperature for 96 h, then diluted with DCM (3 ml). The organic layer was washed consecutively with water (10 ml), a saturated solution of ammonium chloride (10 ml) and brine (10 ml). The organic extracts were dried and concentrated under reduced pressure to afford crude alcohol
159 as a colourless oil (570 mg, 96%); Chiral HPLC t<sub>r</sub> (Chiralcel OD, 20% IPA in hexane, 0.5 ml/min) 6.16 and 6.72 mins; 50:50 er.

1,1-Difluoro-2-(2-methoxy-ethoxymethoxy)-penta-1,4-diene 161

![Chemical structure of 1,1-Difluoro-2-(2-methoxy-ethoxymethoxy)-penta-1,4-diene 161]

1,4-Diene 161 was prepared as for 99d using palladium(II) acetate (70 mg, 0.31 mmol), Cul (460 mg, 2.43 mmol), triphenylphosphine (320 mg, 1.22 mmol), allyl bromide (1.5 ml, 17.3 mmol) and stannane 118 (6.86 g, 12.15 mmol based on 81% purity) in DMF (10 ml). After 18 h, the usual work-up afforded a yellow oil (3.25 g). Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded 1,3-diene 161 as a pale yellow oil (1.48 g, 62%); R<sub>f</sub> (20% diethyl ether in hexanes) 0.32; ν (film/ cm<sup>-1</sup>) 2929 s, 2896 s, 2822 m, 1765 s, 1717 w, 1643 w, 1456 m, 1431 m, 1416 w, 1368 w, 1274 s, 1250 s, 1212 s, 1160 s, 1111 s, 1053 s, 994 s, 974 s, 923 s, 887 w, 851 m, 773 m; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 5.88-5.71 (1H, m, H-4), 5.21-5.08 (2H, m, H-5c, H-5t), 4.88 (2H, s, OCH<sub>2</sub>O), 3.80-3.77 (2H, m, CH<sub>2</sub>O), 3.57-3.54 (2H, m, CH<sub>2</sub>O), 3.38 (3H, s, OCH<sub>3</sub>), 2.97-2.89 (2H, m, H-3); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 132.8 (C-4), 117.4 (C-5), 94.7-94.6 (m, OCH<sub>2</sub>O), 71.5 (CH<sub>2</sub>O), [68.1, 68.0] (CH<sub>2</sub>O), 59.0 (OCH<sub>3</sub>), 30.4 (C-3), C-1 and C-2 too weak to assign due to weak sample; δ<sub>F</sub> (282 MHz, CDCl<sub>3</sub>) -102.50 (1F, dt, <sup>2</sup>J 71.2, <sup>4</sup>J<sub>HF</sub> 2.5), -113.14 (1F, dt, <sup>2</sup>J 70.6, <sup>4</sup>J<sub>HF</sub> 3.8). A satisfactory mass spectrum could not be obtained. This material was taken on without further characterisation.
(2R)-5,5-Difluoro-4-(2-methoxy-ethoxymethoxy)-pent-4-en-1,2-diol 163

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{F} & \quad \text{F} \\
5 & \quad 4 \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

A solution of AD-mix-\(\beta\) (10.00 g, 1.4g/mmol) in tBuOH/H\(\text{2}O\) (76 ml, 1:1 v/v) was stirred vigourously until the phases became clear. Diene 162 (1.48 g, 6.23 mmol based upon 85% purity, enol carbamate 162 impurity) was added to this solution and the resulting heterogenous mixture stirred vigourously for 21 h. TLC indicated the slow formation of diol 163, confirmed by \(^{19}\text{F} \text{NMR}\). The reaction was quenched with sodium sulfite (11 g) and the reaction stirred for 1 h. DCM (30 ml) was added and the organic layer separated. The aqueous phase extracted with DCM (3 \times 30 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil (950 mg). Purification by column chromatography over silica gel (40% ethyl acetate in light petroleum \(\Rightarrow\) 100% ethyl acetate in light petroleum) afforded diol 163 as a colourless oil (145 mg, 10%); \(R_f\) (80% ethyl acetate in light petroleum) 0.13; \(\nu\) (film/cm\(^{-1}\)) 3414 bd s (OH), 1767 s, 1709 w, 1643 w, 1457 m, 1368 m, 1274 s, 1241 s, 1202 s, 1113 bd s, 1027 s, 963 s, 889 m, 850 m, 769 w; \(\delta\)\(H\) (300 MHz, CDCl\(_3\)) 4.92 (2H, s, OCH\(_2\)O), 3.97-3.88 (1H, m, H-2), 3.82-3.78 (2H, m, OCH\(_2\)CH\(_2\)O), 3.65 (1H, dd, one half of an ABX, \(^2\)J 11.2, \(^3\)J 2.9, H-1a), 3.58-3.54 (2H, m, OCH\(_2\)CH\(_2\)O), 3.50 (1H, dd, one half of an ABX, \(^2\)J 11.2, \(^3\)J 6.6, H-1b), 3.49 (3H, s, OCH\(_3\)), 3.17-3.02 (1H, bd s, OH), 2.57-2.42 (1H, bd s, OH), 2.37-2.30 (2H, m, H-3); \(\delta\)\(C\) (75 MHz, CDCl\(_3\)) 155.2 (dd, \(^1\)J\(_{CF}\) 287.7, 280.9, C-5), 113.1 (dd, \(^2\)J\(_{CF}\) 41.3, 14.1, C-4), 95.6 (t, \(^4\)J\(_{CF}\) 2.8, OCH\(_2\)O), 71.6 (CH\(_2\)O), 69.3 (dd, \(^4\)J\(_{CF}\) 3.4, 2.3, C-2), [68.2, 68.2]
(CH$_2$O), 66.0 (C-1), 59.1 (OCH$_3$), 30.6 (d, $^3$J$_{CF}$ 2.8, C-3); $\delta$F (282 MHz, CDCl$_3$) - 100.24 (1F, d, $^2$J 68.6), -112.31 (1F, dt, $^2$J 68.6, $^4$J$_{HF}$ 4.4); [HRMS (ES-TOF, M+Na) Found: 265.0865; Calc. for C$_9$H$_{16}$O$_5$F$_2$: 265.0864]; m/z (ES-TOF) 265.1 (100%, M+Na). Stereochemistry is assigned on the basis of the Sharpless model.$^{204}$ Degree of asymmetric induction has not been determined.

1,3-Dideoxy-1,1-difluoro-$\alpha$-D-glycero-pent-2-ulofuranose and 1,3-dideoxy-1,1-difluoro-$\beta$-D-glycero-pent-2-ulofuranose 155

Chlorotrimethylsilane (63 $\mu$l, 0.5 mmol) was added dropwise to a solution of diol 163 (145 mg, 0.5 mmol) in methanol (5 ml) at 0°C. The resulting colourless solution was allowed to warm to ambient temperature and stirred for 18 h. The reaction mixture was concentrated under reduced pressure to afford a pale yellow oil. Acetone (5 ml) was added and the solution concentrated onto silica gel to afford a pale yellow powder. Purification by column chromatography over silica gel (60% ethyl acetate in hexanes) afforded pentuloses 165 as clear oils (50 mg, 65%, ~1:1 $\alpha$:\$\beta$); R$_f$ (60% ethyl acetate in hexanes) 0.31; $\nu$ (film/cm$^{-1}$) 3400 bd s (OH), 2963 m, 2894 m, 2520 bd s (OD), 1704 w, 1471 w, 1437 m, 1372 w, 1076 s; $\delta$H (300 MHz, CD$_3$OD) 5.68 (0.5H, t, $^2$J$_{HF}$ 55.9, H-1$\alpha$), 5.59 (0.5H, t, $^2$J$_{HF}$ 56.3, H-1$\beta$), 4.58-4.50 (0.5H, m, H-4$\alpha$), 4.44-4.37 (0.5H, m, H-4$\beta$), 4.11 (0.5H, dd, $^2$J 9.4, $^3$J 4.8, H-5b$\alpha$), 3.96-3.93 (1H, m, envelope,
H-5αβ, H-5ββ), 3.75 (0.5H, dd, 2 J 9.3, 3 J 3.1, H-5αα), 2.43-2.36 (0.5H, m, H-3ββ), 2.17-2.11 (1H, m, envelope, H-3αα, H-3βα), 1.92-1.85 (0.5H, m, H-3αβ); δC (126 MHz, CD3OD) 115.4 (t, 1 JCF 246.0, C-1, α and β), 104.8-104.2 (m, C-2, α and β), 76.8 (C-5β), 76.0 (C-5α), 71.2 (C-4, α or β), 71.2 (C-4, α or β), 42.6 (C-3α), 41.1 (C-3β); δF (282 MHz, CD3OD) -130.22 (dd, 2 J 283.7, 3 JHF 56.1, α isomer), -134.01 (dd, 2 J 283.7, 3 JHF 55.8, α isomer), -132.10 (apparent d, 55.9 Hz separation, highly distorted ABX, β isomer) (1.05:1 α:β after 24 h in CD3OD; 1.35:1 α:β after 2 months in CD3OD); m/z (Cl) 308 (52%, 2M or 2M-H2O+NH4), 290 (28%, 2M-H2O), 194 (29%), 172 (81%, M+NH4), 154 (100%, M).

(E)-3-Iodoacrylic acid 178

A mixture of propiolic acid (18 ml, 3 × 6 ml, 292 mmol) and aqueous HI (66 ml of a 57% w/w (7 M) aqueous solution, 3 × 22 ml, 462 mmol) was heated in three foil-wrapped Ace® tubes at 95°C for 21 h. The resulting mixtures were allowed to cool to ambient temperature to afford a suspension of acid 178 (as large white crystals) in excess aqueous HI. The pressure was released (CARE), then the mixtures were diluted with water (5 ml) and filtered under vacuum, using water to wash out the product from the tube. A final washing of the suspended product with light petroleum (20 ml) followed by drying afforded iodoacid 178 as large white needles (54.32 g, 94%); m.p. 147-149°C (lit. 147-148°C, 144-147°C);213a [Found: C, 18.33; H, 1.36;
Calc. for C₃H₅O₂I; C, 18.20; H, 1.53%; δ_H (300 MHz, CDCl₃) 10.54-8.66 (1H, bd s, OH), 8.08 (1H, d, ³J 14.7, H-2), 6.89 (1H, d, ³J 14.7, H-3). Spectral data were in agreement with those reported both by Takeuchi.²¹³a

(E)-Ethyl 3-iodoacrylate 179

Sulfuric acid (9.0 ml of a 98% aqueous solution) was added to a solution of iodoacid 178 (33.2 g, 168 mmol) in absolute ethanol (200 ml) to afford a colourless solution. This was then heated under reflux, with yellowing, for 23 h before being cooled to ambient temperature. A saturated aqueous solution of sodium bicarbonate (150 ml) was added, then the pH was adjusted to 7.4 by the addition (CARE) of solid sodium bicarbonate (until loss of effervescence). The ethanol was removed under reduced pressure and the residue diluted with ethyl acetate (40 ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 150 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford crude ester 179 as a yellow oil. Filtration through a pad of silica using diethyl ether as eluant afforded an orange oil (28.3 g), after evaporation of solvents. Further purification by distillation under reduced pressure afforded iodoester 179 as a pale yellow oil (24.8 g, 65%); b.p 65°C/~10 mmHg (lit. 74-76°C/9 Torr),²¹³a R_f (15% diethyl ether in hexanes) 0.61; ν (film/cm⁻¹) 3070 w, 2982 m, 1722 s, 1593 s, 1465 w, 1446 w, 1391 w, 1368 m, 1298 s, 1259 s, 1216 s, 1146 s, 1034 s, 949 s; δ_H (300 MHz, CDCl₃) 7.85 (1H, d, ³J 14.7, H-3), 6.84 (1H, d, ³J 14.7, H-2), 4.17 (2H, q, ³J 7.4,
CH₂CH₃), 1.26 (3H, t, 3J 7.4, CH₂CH₃); δC (75 MHz, CDCl₃) 164.2 (C-1), 136.6 (C-2), 99.4 (C-3), 61.0 (CH₂), 14.2 (CH₃). Spectral data were in agreement with those reported by Takeuchi.²¹³a

(E)-3-Iodoprop-2-en-1-ol 180

Diisobutylaluminium hydride (8.84 ml of a 1 M solution in hexanes, 8.84 mmol) was added dropwise to a solution of iodoacrylate 179 (1.00 g, 4.42 mmol) in dry DCM (10 ml) at –75°C under an atmosphere of nitrogen. The addition was controlled so that the temperature did not exceed –70°C. The pale yellow solution was stirred for 45 min at –75°C and then allowed to warm to 0°C. The mixture was quenched at this temperature with methanol (10 ml), methanol/water (20 ml, 3:1 v/v) and water (10 ml) with the formation of a white emulsion. DCM (30 ml) was added followed by Rochelle’s salt (30 ml of a 10% aqueous solution) and the organic layer separated. The aqueous layer was extracted with DCM (3 × 20 ml) and the combined organic extracts dried and concentrated under reduced pressure to afford a runny pale yellow oil (0.76 g). Purification by column chromatography over silica gel (60% diethyl ether in light petroleum) afforded iodoalcohol 180 as a colourless oil (410 mg, 50%); Rf (60% diethyl ether in light petroleum) 0.40; δH (300 MHz, CDCl₃) 6.69 (1H, dt, 3J 14.3, 5.5, H-2), 6.39 (1H, d, 3J 14.7, H-3), 4.09 (2H, dd, 3J 5.2, 1.8, H-1), 1.71 (1H, s, OH); δC (75 MHz, CDCl₃) 144.8 (C-2), 78.1 (C-3), 65.1 (C-1); m/z (EI) 184 (32%, M), 127 (20%, I), 57 (100%, M-I), 39 (17%).
(E)-3-Iodo-2-propenyl 4-methoxybenzenecarboxylate 181

4-Anisoyl chloride (2.02 g, 11.84 mmol) was added to a solution of iodoalcohol 180 (2.00 g, 10.88 mmol), pyridine (0.9 ml, 11.0 mmol) and 4-(dimethylamino)pyridine (78 mg, 0.64 mmol) in DCM (20 ml) at 0°C. The resulting solution was allowed to warm to ambient temperature and then stirred for 18 h. The reaction was quenched with water (10 ml), followed by extraction of the aqueous phase with DCM (3 × 15 ml). The combined organic extracts were washed with 1.0 M HCl (20 ml), before being dried and concentrated under reduced pressure to afford a crude pale yellow oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded iodoester 181 as a colourless oil (3.36 g, 97%); 93% by GC; 98% by HPLC at 225 nm; HPLC t<sub>r</sub> (10% water in MeCN, 1 ml/min) 4.44 min; R<sub>f</sub> (10% diethyl ether in light petroleum) 0.24; ν (film/cm<sup>−1</sup>) 1714 s (C=O), 1607 s (C=C), 1512 m, 1371 w, 1317 m, 1257 s, 1169 s, 1102 m, 1030 m, 847 m, 770 m; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.99 (2H, d, <sup>3</sup>J 8.8, ArH), 6.91 (2H, d, <sup>3</sup>J 8.8, ArH), 6.74 (1H, dt, <sup>3</sup>J 14.7, 5.9, H-2), 6.55 (1H, dt, <sup>3</sup>J, 14.7, <sup>4</sup>J 1.4, H-3), 4.70 (2H, dd, <sup>3</sup>J 5.9, <sup>4</sup>J 1.3, H-1), 3.85 (3H, s, ArOMe); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 165.7 (CO), 163.6 (C<sub>q</sub>-OMe), 140.0 (C-2), 131.8 (ArCH), 122.1 (C<sub>q</sub>-CO), 113.7 (ArCH), 80.8 (C-3), 65.9 (C-1), 55.5 (OCH<sub>3</sub>); [HRMS (ES-TOF, M+Na) Found: 340.9646; Calc. for C<sub>11</sub>H<sub>11</sub>O<sub>3</sub>Na: 340.9651]; m/z (ES-TOF) 341.0 (100%, M+Na).
(E)-[\{4-(N,N-Diethylcarbamoyloxy)-5,5-difluoro\)-penta-2,4-dienyl\} 4-methoxybenzenecarboxylate 182

Ester 182 was prepared as for 95a using tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (23 mg, 22 μmol), triphenylphosphine (58 mg, 0.22 mmol), Cul (26 mg, 0.14 mmol), iodoalkene 181 (359 mg, 1.1 mmol) and stannane 81 (520 mg, 1.11 mmol). Following the usual work-up, a crude brown oil was isolated. Purification by column chromatography over silica gel (15% diethyl ether in light petroleum ⇒ 20% ethyl acetate in light petroleum) afforded pentadienyl ester 182 as a pale orange oil (355 mg, 83%); Rf (20% ethyl acetate in light petroleum) 0.35; ν (film/cm\(^{-1}\)) 1734 bd s, 1606 m, 1511 m, 1421 m, 1381 w, 1251 s, 1168 m, 1097 m, 1031 m, 955 w, 847 w, 770 w; δ\(_\text{H}\) (300 MHz, CDCl\(_3\)) 8.03-7.98 (2H, m, ArH), 6.94-6.89 (2H, m, ArH), 6.38 (1H, ddt, \(^3J\text{CF} 15.5, ^4J\text{H} 1.5, ^4J\text{HF} 2.4, \text{H-3})\), 5.84 (1H, dt, \(^3J\text{H} 15.5, 6.1, \text{H-2}\)), 4.86 (2H, dd, \(^3J\text{H} 6.1, ^4J\text{H} 1.5, \text{H-1}\) 3.86 (3H, s, OCH\(_3\)), 3.42-3.32 (4H, two overlapping q, \(^3J\text{H} 7.0, \text{CH}_2\text{NCH}_2\)), 1.23-1.15 (6H, two overlapping t, \(^3J\text{H} 7.0, \text{N(CH}_2\text{Me})_2\)); δ\(_\text{C}\) (75 MHz, CDCl\(_3\)) 165.7 (CO), 163.3 (Cq-OMe), 154.2 (dd, \(^1J\text{CF} 294.4, 292.2, \text{C-5}\)), 152.1 (t, \(^4J\text{CF} 2.2, \text{CO}\)), 131.5 (CH), 123.0 (dd, \(^3J\text{CF} 11.9, 4.5, \text{C-3}\)), 122.1 (Cq), 120.1 (d, \(^4J\text{CF} 4.5, \text{C-2}\)), 113.5 (CH), 111.6 (dd, \(^2J\text{CF} 40.1, 18.7, \text{C-4}\)), 63.9 (C-1), 55.2 (OCH\(_3\)), [42.4, 41.8] (CH\(_2\)), [13.9, 13.0] (CH\(_3\)); δ\(_\text{F}\) (282 MHz, CDCl\(_3\)) -94.32 (1F, d, \(^2J\text{F} 39.4\)), -104.59 (1F, dd, \(^2J\text{F} 39.4, ^3J\text{HF} 2.5\)); [HRMS (ES-TOF, M+Na) Found: 392.1289; Calc. for
C_{18}H_{21}NO_{5}F_{2}Na: 392.1285; m/z (EI) 369 (27%, M), 269 (11%, M-ODEC), 218 (8%, M-OCOC_{6}H_{4}OMe), 152 (5%), 135 (58%, MeOC_{6}H_{4}CO), 100 (100%, CONEt_{2}), 72 (68%, H_{2}NET_{2}).

**{(E)}-[(5,5-Difluoro-4-(2-methoxy-ethoxymethoxy))-penta-2,4-dienyl] 4-methoxy-benzenecarboxylate 190**

![Chemical Structure](image)

A flask containing palladium(II) acetate (28 mg, 0.13 mmol), copper(I) iodide (199 mg, 1.04 mmol) and triphenylphosphine (136 mg, 0.52 mmol) was evacuated and the vacuum released to a nitrogen inlet. The procedure was repeated twice. Dry, degassed DMF (5 ml) was added and the resulting dark solution warmed to 30°C. Iodoalkene 181 (1.59 g, 5.0 mmol) was added as a solution in DMF (1 ml). The reaction mixture was warmed to 50°C. Stannane 118 (2.76 g, 6.0 mmol) was added at 40°C as a solution in DMF (1 ml). The resulting solution was heated for 3 h at 50°C and monitored by TLC. Upon consumption of the starting material, the solution was diluted with diethyl ether (20 ml), then transferred to a conical flask. An aqueous solution of KF (20 ml of a 0.97 M solution) was added and the resulting mixture stirred rapidly for 1 h. The precipitated solid (Bu_{3}SnF) was filtered under vacuum and washed with ethyl acetate (20 ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were
dried and concentrated under reduced pressure to afford an orange oil, containing a red sediment ([(PPh$_3$)$_2$PdI$_2$]). Purification by column chromatography over alumina (Brockmann 1, pH 9-11, 10% ethyl acetate in hexanes) afforded pentadienyl ester 190 as a pale yellow oil (730 mg, 41%); R$_f$ (20% ethyl acetate in hexanes) 0.32; ν (film/cm$^{-1}$) 1716 s, 1697 s, 1606 s, 1511 s, 1257 bd s, 1168, 910, 848; δ$_H$ (300 MHz, CDCl$_3$) 7.97 (2H, d, $^3$J 8.8, ArH), 6.91 (2H, d, $^3$J 8.8, ArH), 6.24 (1H, br. d, $^3$J 15.6, H-3), 6.03 (1H, dt, $^3$J 15.6, 6.0, H-2), 4.91 (2H, s, OCH$_2$O), 4.84 (2H, br. d, $^3$J 6.3, H-1), 3.82 (3H, s, OCH$_3$), 3.84-3.81 (2H, m, OCH$_2$CH$_2$O), 3.55-3.51 (2H, m, OCH$_2$CH$_2$O), 3.35 (3H, s, CH$_2$OMe); δ$_C$ (75 MHz, CDCl$_3$) 165.9 (CO), 163.5 (C$_q$-OMe), 155.3 (dd, $^1$J$_{CF}$ 295.0, 293.9, C-5), 131.7 (ArCH), 123.8 (dd, $^3$J$_{CF}$ 11.9, 4.5, C-3), 122.4 (C$_q$-CO), 121.3 (d, $^4$J$_{CF}$ 5.1, C-2), 115.2 (dd, $^2$J$_{CF}$ 35.6, 17.5, C-4), 113.6 (ArCH), 96.4 (t, $^4$J$_{HF}$ 2.8, OCH$_2$O), 71.6 (OCH$_2$), 68.7 (OCH$_2$), 64.2 (C-1), 59.0 (CH$_2$OMe), 55.4 (ArOCH$_3$); δ$_F$ (282 MHz, CDCl$_3$) -97.03 (1F, d, $^2$J 45.8), -105.68 (1F, dd, $^2$J 45.8, $^3$J$_{HF}$ 4.0); [HRMS (ES-TOF, M+Na) Found: 381.1134; Calc. for C$_{17}$H$_{20}$O$_6$F$_2$Na: 381.1126]; m/z (ES-TOF) 381.0 (100%, M+Na). This material is unstable (neat) and has a lifetime of ca. 24 hours even in a refrigerated (-5°C) environment and should ideally be used immediately after preparation or stored as a solution in CH$_2$Cl$_2$ under a positive nitrogen atmosphere.
(2R,3S)-[(5,5-Difluoro-2,3-dihydroxy-4-(2-methoxy-ethoxymethoxy)-pent-4-enyl]-4-methoxybenzenecarboxylate 192

Method A (pH control): A three-necked flask was charged with potassium osmate dihydrate (0.11 g, 0.30 mmol), potassium carbonate (6.25 g, 45.2 mmol), potassium ferricyanide (14.88 g, 45.2 mmol) and (DHQD)$_2$PHAL (0.47 g, 0.60 mmol). The mixture was homogenised by the addition of tBuOH/H$_2$O (200 ml, 1:1 v/v) with rapid stirring at ambient temperature. Diene 190 (5.39 g, 15.03 mmol) was added dropwise as a solution in tBuOH/H$_2$O (10 ml, 1:1 v/v). The resulting orange solution was stirred at ambient temperature and the progress of the reaction monitored by TLC and pH measurements made using a pH probe. Aqueous sodium hydroxide (1 M) was added via syringe in order to maintain the pH in the 11.0-12.0 range at all times. pH-Monitoring was continued until a constant pH measurement was recorded over a period of 30 min, with confirmation by TLC (ca. 1-3 h). Sodium sulfite (21 g) was then added and the solution stirred rapidly for 1 h. The tBuOH was removed under reduced pressure and the mixture diluted with ethyl acetate (20 ml). The phases were separated and the aqueous phase extracted with ethyl acetate (6 x 200 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (60% ethyl acetate in hexanes) afforded diol 192 as a colourless oil (3.16 g, 54%);
98% by HPLC at 225 nm; HPLC t_r (40% water in MeCN; 1ml/min) 3.52 min; R_f (60% ethyl acetate in hexanes) 0.18; (film/cm⁻¹) 3430 bd s, 1754 m, 1694 m, 1608 m, 1514 w; δ_H (400 MHz, CDCl₃) 7.96 (2H, d, 3J 8.9, ArH), 6.88 (2H, d, 3J 8.9, ArH), 5.00 (1H, d, one half of an AB, 3J 6.5, H-a), 4.87 (1H, d, one half of an AB, 3J 6.5, H-a), 4.42 (1H, dd, one half of an ABX, 2J 12.0, 3J 3.9, H-1), 4.35-4.30 (1H, m, H-3), 4.27 (1H, dd, one half of an ABX, 2J 11.9, 3J 5.2, H-1‘), 4.13-4.07 (1H, m, H-2), 3.95-3.89 (2H, envelope, m + one half of an ABXY, OH + H-b), 3.83 (3H, s, OMe), 3.77 (1H, dddd, one half of an ABXY, 2J 10.9, 3J 4.8, 2.9, H-b‘), 3.58-3.54 (2H, m, H-c, H-c‘), 3.38 (3H, s, ArOCH₃), 3.28-3.24 (1H, bd s, OH); δ_C (100 MHz, CDCl₃) 166.3 (CO), 163.51 (C₉-OMe), 155.1 (dd, 1J_CF 292.8, 287.7, C-5), 131.7 (C-meta-OMe), 122.1 (C₉-CO), 116.0 (dd, 2J_CF 36.6, 12.2, C-4), 113.6 (Cortho-OMe), 98.2 (OCH₂O), 71.3 (CH₂OMe), 70.8 (C-2), 68.7 (CH₂CH₂OMe), 67.6 (C-3), 64.9 (C-1), 59.0 (CH₂OMe), 55.4 (ArOMe); δ_F (282 MHz, CDCl₃) -97.32 (1F, d, 2J 59.5), -107.93 (1F, dd, 2J 59.5, 4JHF 2.5); [HRMS (ES-TOF, M+Na) Found: 415.1178; Calc. for C₁₇_H₂₂_O₈_F₂ Na: 415.1180]; m/z (ES-TOF) 415.1 (100%, M+Na). See Appendix XXVII for HSQC.

Method B (without pH control): As above except that the pH was not monitored and no base was added. Methanesulfonamid was also added (one equivalent) at the start of the reaction. After nine days at ambient temperature, the reaction was worked up in a similar manner, except that the combined organic extracts were washed in triplicate with ice-cold 2 M KOH in order to remove methanesulfonamide as the water-soluble potassium salt. Baseline material was removed by filtration through a plug of silica gel using 100% ethyl acetate. The crude diol was purified by semi-
preparative HPLC (40% water in MeCN; 1ml/min) to afford a pure sample as a colourless oil.

(Rac)-diol 192

Racemic diol 192 was prepared as for chiral diol 192 using potassium osmate dihydrate (10 mg, 28 \( \mu \)mol), potassium ferricyanide (1.36 g, 4.14 mmol), potassium carbonate (0.57 g, 4.14 mmol), quinuclidine (6 mg, 55 \( \mu \)mol), diene 190 (494 mg, 1.38 mmol) in \( \text{tBuOH-H}_2\text{O} \) (18 ml, 1:1 v/v). Sodium hydroxide (1 ml aliquots of a 1.0 M aqueous solution) was added intermittently to keep the pH of the reaction mixture above 11.0 for as long a period as possible. After 22 hours, sodium sulfite (2 g) was added and the reaction stirred for 1 h. \( \text{tBuOH} \) was removed under reduced pressure then ethyl acetate (20 ml) was added. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 \times 20 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a brown oil. Purification by column chromatography over silica gel (60% ethyl acetate in hexanes) afforded racemic diol 192 as a colourless oil (34 mg, 6%); 95% by HPLC at 254 nm; HPLC \( t_r \) (40% water in MeCN, 1 ml/min) 3.52 min; \( R_f \) (60% ethyl acetate in hexanes) 0.18; \( \delta_F \) (282 MHz, CDCl\(_3\)) -97.15 (1F, d, \( ^2J \) 58.5), -107.68 (1F, dd, \( ^2J \) 58.5, \( ^4J_{HF} \) 3.2). This material was further purified by semi-preparative HPLC (40% water in MeCN, 1 ml/min). Chiral HPLC (Chiralcel OD, 10% IPA in hexane, 1 ml/min, 225 nm) gave a single peak (\( t_r \) 25.43 min).
(2R,3S)-5,5-Difluoro-4-(2-methoxy-ethoxymethoxy)-2,3-bis-(2S)-[(3,3,3-trifluoro-2-methoxy-2-phenyl-propionyloxy)]-pent-4-enyl 4-methoxybenzenecarboxylate

(R)-(−)−α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (14 µl, 100 mg/100 µl DCM, 55 µmol) was added to a solution of analytically pure chiral diol 192 (6.0 mg, 15.3 µmol), 2,6-lutidine (20 µl) and 4-(dimethylamino)pyridine (one crystal) in DCM (1 ml) at 0°C. The solution was warmed to ambient temperature and stirred for 4 h and monitored by TLC. Diol 192 was consumed within 1 h, with a concomitant build up of monoester. Bis-esterification was complete within a further 3 h. The reaction was diluted with diethyl ether (3 ml), then poured into a saturated aqueous solution of sodium bicarbonate (5 ml). The phases were separated and the aqueous phase extracted with diethyl ether (2 × 3 ml) and ethyl acetate (2 × 3 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford crude bis-Mosher ester 195 as a colourless oil containing a brown sediment; $\delta_F$ (282 MHz, CDCl$_3$, 4096 scans, 512K data points) -71.23 (3F, s), -71.71 (3F, s), -92.38 (1F, d, $^2$J
47.7), -101.96 (1F, d, $^2J$ 47.7); [HRMS (ES-TOF, M+Na) Found: 847.1977; Calc. for C$_{37}$H$_{36}$O$_{12}$F$_8$Na: 847.1977; R$_f$ (20% ethyl acetate in hexanes) 0.17; Estimated de > 99.5%.

**Bis-MTPA ester 195 of (rac)-diol 192**

(R)-(-)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (14 μl of a 100 mg/100 μl DCM, 55 μmol) was added to a solution of analytically pure racemic diol 192 (7.9 mg, 20.2 μmol), triethylamine (23 μl) and 4-(dimethylamino)pyridine (one crystal) in DCM (1 ml) at 0°C. The solution was warmed to ambient temperature and stirred for 4 h. TLC indicated the presence of products resulting from mono- and bis-esterification. More triethylamine (10 μl) and acid chloride (10 μl) was added and the reaction stirred for a further 2 h. TLC indicated the formation of a single product. The reaction was diluted with diethyl ether (3 ml), then poured into a saturated aqueous solution of sodium bicarbonate (5 ml). The phases were separated and the aqueous phase extracted with ethyl acetate (2 × 3 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford crude bis-Mosher ester 195 as a 1:1 mixture of two diastereoisomers; $\delta$F (282 MHz, CDCl$_3$, 32 scans) -71.22 (3F, s, 2R,3S diastereoisomer), -71.71 (3F, s, 2R,3S diastereoisomer), -71.79 (3F, s, 2S,3R diastereoisomer), -71.86 (3F, s, 2S,3R diastereoisomer), -92.32 (1F, d, $^2J$ 47.0, 2S,3R diastereoisomer), -92.35 (1F, d, $^2J$ 48.3, 2R,3S diastereoisomer), -101.81 (1F, d, $^2J$ 47.0, 2S,3R diastereoisomer), -101.95 (1F, d, $^2J$ 48.3); R$_f$ (40% ethyl acetate in hexanes) 0.75; de 0%. 

257
(2R,3S)-5,5-Difluoro-4-(2-methoxy-ethoxymethoxy)-2,3-bis-(para-nitrobenzoyl-oxy)-pent-4-enyl 4-methoxybenzenecarboxylate 198

\[
\begin{align*}
\text{NO}_2 & \quad \text{NO}_2 \\
\text{O} & \quad \text{O} \\
\text{F} & \quad \text{F} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

\(p\)-Nitrobenzoyl chloride (13 mg, 73 \(\mu\)mol) was added to a solution of diol 192 (13 mg, 33 \(\mu\)mol), 2,6-lutidine (40 \(\mu\)l, 0.34 mmol) and DMAP (1 crystal) in DCM (5 ml) at ambient temperature. The resulting solution was stirred with monitoring by TLC. After 2 h, TLC indicated the presence of both diester and triester, with no further change after a further 1 h. More \(p\)-nitrobenzoyl chloride (6 crystals) was added and the resulting solution allowed to stir for a further 4 h (7 h total), affording a single spot by TLC. Water (5 ml) was added and the phases separated. The aqueous phase was extracted with DCM (3 \(\times\) 5 ml) and the combined organic extracts dried and concentrated under reduced pressure to afford an amorphous yellow solid. Purification by column chromatography over silica gel (40% ethyl acetate in hexanes) afford triester 198 as a colourless oil (22 mg, 96%); \(R_f\) (40% ethyl acetate in
hexanes) 0.36; $\delta_H$ (300 MHz, CDCl$_3$) 8.25-8.18 (4H, envelope, ArH), 8.13-8.08 (4H, envelope, ArH), 8.00-7.95 (2H, m, ArH), 6.96-6.91 (2H, m, ArH), 6.26 (1H, dt, $^3J$ 9.2, $^4J_{HF}$ 2.2, H-3), 6.06 (1H, ddd, $^3J$ 9.2, 4.1, 2.8, H-2), 5.10-5.08 (1H, m, one half of an AB, OCH$_2$H'), 5.04-5.02 (1H, m, one half of an AB, OCHH'O), 4.88 (1H, dd, one half of an AMX, $^2J$ 12.7, $^3J$ 2.8, H-1), 4.53 (1H, dd, one half of an AMX, $^2J$ 12.7, $^3J$ 4.1, H-1'), 3.92-3.78 (2H, m, CH$_2$O), 3.87 (3H, s, ArOCH$_3$), 3.52-3.48 (2H, m, CH$_2$O), 3.32 (3H, s, CH$_2$OCH$_3$); $\delta_C$ (75 MHz, CDCl$_3$) 165.6 (CO of pMBz), 163.8 (CO of pNBz), 163.8 (CO of pNBz), 163.3 (Cq-OMe), 156.3 (dd, $^1J_{CF}$ 295.7, 291.9, CF$_2$), 150.8 (Cq-NO$_2$), 150.8 (Cq-NO$_2$), 134.3 (Cq-CO of pNBz), 134.2 (Cq-CO of pNBz), 131.7 (CH of pNBz), 131.7 (CH of pNBz), 130.8 (CH of pMBz), 123.7 (CH of pNBz), 123.7 (CH of pNBz), 123.7 (CH of pNBz), 121.4 (Cq-CO of pMBz), 113.9 (CH of pMBz), 110.9 (dd, $^2J_{CF}$ 36.5, 16.9, C=CF$_2$), 98.1-98.1 (m, OCH$_2$O), 71.5 (dd, $^3J_{CF}$ 3.2, 2.0, C-2), 71.4 (CH$_2$O), 69.7 (dd, $^3J_{CF}$ 4.9, 2.3, C-3), [68.9, 68.9] (CH$_2$O), 62.0 (C-1), 59.0 (CH$_2$OCH$_3$), 55.5 (ArOCH$_3$); $\delta_F$ (282 MHz, CDCl$_3$) -93.90 (1F, d, $^2J$ 46.8), -102.04 (1F, d, $^2J$ 46.8); [HRMS (ES-TOF, M+Na) Found: 713.1414; Calc. for C$_{31}$H$_{28}$N$_2$O$_4$F$_2$Na: 713.1406]; $m/z$ (ES-TOF) 713.3885 (100%, M+Na). Due to the non-crystalline nature of this material, further characterisation was not pursued.
(2R,3S)-(5-(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl)-2,2-dimethyl-[1,3]dioxalan-4-yl)-methyl 4-methoxybenzenecarboxylate 199

Anhydrous copper(II) sulfate (2.57 g, 16.1 mmol) was added to a solution of diol 192 (3.16 g, 8.05 mmol) in acetone (100 ml) followed by a catalytic amount of pTSA (few crystals). The mixture was stirred at ambient temperature for 42 h, then quenched with brine (50 ml). The residual copper(II) sulfate was removed by filtration and washed with acetone (30 ml). The acetone was removed under reduced pressure, then the mixture diluted with ethyl acetate (20 ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 30 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford the crude acetonide 199 as a pale green oil. Purification by chromatography over alumina (20% ethyl acetate in hexanes) afforded acetonide 199 as a colourless oil (2.38 g, 68%); 99% by HPLC at 225/254/275 nm; HPLC t, (20% water in MeCN; 1 ml/min) 5.19 min; Rf (20% ethyl acetate in hexanes) 0.44; ν (film/cm\(^{-1}\)) 2988 m, 2936 m, 1756 s, 1716 s, 1608 s, 1582 m, 1513 m, 1456 m, 1383 m, 1373 m, 1258 bd s, 1169 s, 1030 s, 951 s, 849 m, 770 m; δ\(_{\text{H}}\) (300 MHz, CDCl\(_3\)) 7.98 (2H, d, \(^3J\) 8.8, ArH), 6.91 (2H, d, \(^3J\) 8.8, ArH), 5.08 (1H, d, one half of an AB, \(^2J\) 5.9, H-a), 5.00 (1H, d, one half of an AB, \(^2J\) 5.9, H-a'), 4.62-4.34 (4H, envelope, H-3, H-2, H-1), 3.95-3.88 (1H,
m, one half of an ABXY, H-b), 3.86 (3H, s, CH$_2$OMe), 3.80-3.73 (1H, m, one half of an ABXY, H-b‘), 3.58-3.55 (2H, m, H-c, H-c‘), 3.38 (3H, s, ArOMe), 1.45 (3H, s, Me), 1.42 (3H, s, Me); $\delta$C (75 MHz, CDCl$_3$) 165.6 (CO), 163.5 (C$_q$-OMe), 156.3 (dd, $^1$JC$_{CF}$ 293.4, 289.3, C-5), 131.6 (ArCH), 121.9 (C$_q$-CO), 113.6 (ArCH), 110.6 (dd, $^2$JC$_{CF}$ 33.8, 14.9, C-4), 110.0 (C$_q$Me$_2$), 98.4 (t, $^4$JC$_{CF}$ 3.4, C-a), 74.5 (t, $^4$JC$_{CF}$ 2.6, C-2), 74.0 (dd, $^3$JC$_{CF}$ 4.3, 2.0, C-3), 71.4 (C-c), 68.5 (d, $^6$JC$_{CF}$ 1.7, C-b), 62.9 (C-1), 58.9 (CH$_2$OMe), 55.3 (ArOMe), 26.8 (Me), 26.5 (Me); $\delta$F (282 MHz, CDCl$_3$) -93.61 (1F, d, $^2$J 54.8), -107.09 (1F, dd, $^2$J 55.5, $^4$J$_{HF}$ 3.0); [HRMS (ES-TOF, M+Na) Found: 455.1481; Calc. for C$_{20}$H$_{26}$O$_8$F$_2$Na: 455.1493]; m/z (ES-TOF) 455.1 (100%, M+Na).

(2R,3S)-(5-(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl)-2,2-dimethyl-[1,3]dioxalan-4-yl)-methanol 200

A solution of ester **199** (2.38 g, 5.5 mmol) in THF/H$_2$O (100 ml, 3:1 v/v) was cooled to 0°C. Hydrogen peroxide (2.6 ml of a 30% w/w aqueous solution (8.8 M), 23 mmol) was added followed by lithium hydroxide monohydrate (0.51 g, 12 mmol). The resulting cloudy solution was stirred for 140 h at ambient temperature and the progress monitored by TLC. Upon completion, the reaction was quenched with sodium sulfite (2.5 g) and the resulting solution stirred rapidly for 1 h. The THF was
removed under reduced pressure, then the mixture diluted with ethyl acetate (20 ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a colourless oil. Purification by column chromatography over alumina (Brockmann 1, pH 9-11, gradient: 40-100% ethyl acetate in hexanes) afforded alcohol 200 as a clear oil (1.00 g, 61%); 96% by HPLC at 245 nm; HPLC t, (Luna 5μ silica (2) 250 mm × 4.6 mm; 100% DCM; 1ml/min) 13.59 min; Rf (40% ethyl acetate in hexanes) 0.33; UV (254 nm) inactive; ν (film/cm⁻¹) 3468 bd s (OH), 1755 s (C≡CF₂), 1456 w, 1373 m, 1291 m, 1247 s; [α]D +80.79° (c=11.63, acetone, 20°C, est. error = ±0.01°); [Found: C, 48.26; H, 6.93; Calc. for C₁₂H₂₀O₆F₂: C, 48.32; H, 6.76%]; δH (300 MHz, CDCl₃) 5.03 (1H, d, one half of an AB, ³J 5.9, H-a), 4.96 (1H, d, one half of an AB, ³J 5.9, H-a'), 4.56 (1H, ddd, ³J 8.9, ⁴JHF 3.7, 2.4, H-3), 4.17 (1H, dt, ³J 8.9, 3.5, H-2), 3.92-3.85 (1H, m, one half of an ABXY, H-b), 3.80 (1H, dd, ³J 12.9, 3.5, H-1), 3.77-3.53 (2H, envelope, m + one half of an ABXY, H-1', H-b'), 3.55 (2H, dd, ³J 5.7, 3.9, H-c, H-c'), 3.36 (3H, s, OMe), 2.32-2.23 (1H, bd s, OH), 2.14 (6H, s, CMe₂); δC (75 MHz, CDCl₃) 156.5 (dd, ¹JC 293.3, 289.9, C-5), 110.9 (dd, ²JC 33.6, 14.1, C-4), 109.7 (CMe₂), 98.5 (dd, ⁴JC 4.0, 2.8, C-a), 77.0 (C-2), 72.8 (dd, ³JC 4.2, 2.3, C-3), 71.6 (C-c), 68.6 (d, ⁶JC 1.7, C-b), 60.6 (C-1), 59.1 (OCH₃), 27.0 (CH₃), 26.7 (CH₃); δF (282 MHz, CDCl₃) -93.65 (1F, d, ²J 56.6), -107.43 (1F, dd, ²J 56.6, ³JHF 3.8); [HRMS (ES-TOF, M+Na) Found: 321.1134; Calc. for C₁₂H₂₀O₆F₂Na: 321.1126]; m/z (ES-TOF) 321.1 (100%, M+Na).
1-Deoxy-1,1-difluoro-α-D-xylulofuranose and 1-deoxy-1,1-difluoro-β-D-xylulofuranose 173

A flask containing alcohol 200 (323 mg, 1.09 mmol) was evacuated and the vacuum released to a nitrogen atmosphere. Methanol (10 ml) was added and the resulting colourless solution cooled to 0°C. Chlorotrimethylsilane (160 μl, 1.26 mmol) was added in one portion and the resulting colourless solution stirred at ambient temperature for 23 h. After consumption of starting material, the reaction was concentrated to afford a pale yellow oil. Purification by flash column chromatography over silica gel (80% ethyl acetate in hexanes) afforded pentuloses 173 as a clear oil (163 mg, 88%, 3:1 α:β); Rf (80% ethyl acetate in hexanes) 0.32; [α]D = -27.66° (c = 14.2, acetone, 20°C, est. error = ±0.6°, α:β = ~3:1), lit (-18.9°, c=0.95, acetone, 25°C);[211] [Found: C, 31.65; H, 5.39; Calc. for C5H8O4F2.H2O: C, 31.92; H, 5.36%]; ν (film/cm⁻¹) 3402 bd s (OH), 2514 bd s (OD), 1470 m, 1401 m, 1347 m, 1204 m, 1078 s; δH (300 MHz, CD3OD) 5.85 (0.23H, dd, 2JHF 55.9, 54.2, H-1β), 5.72 (0.77H, t, 2JHF 55.5, H-1α), 4.30-4.23 (1H, envelope, H-4α, H-5aβ), 4.19-4.12 (1H, envelope, H-5aα, H-4β), 4.08-4.06 (0.23H, m, H-3β), 4.06 (0.77H, bd d, 3J 4.8, H-3α), 3.94 (0.23H, ddd, 2J 9.2, 3J 3.7, 4J 1.5, H-5bβ), 3.62 (0.77H, dd, 2J 9.0, 3J 5.0, H-5bα); δC (100 MHz, CD3OD) 115.2 (t, 1JCF 247.0, C-1α), 114.6 (dd, 1JCF 246.0, 243.0, C-1β), 103.9 (dd, 2JCF 26.2, 20.3, C-2β), 101.3 (t, 2JCF 24.6, C-2α), 82.6 (d, 3JCF 1.8, C-3β), 78.0 (d,
$^4$J$_{CF}$ 1.8, C-4$\beta$), 77.6 (C-3$\alpha$), 77.0 (C-4$\alpha$), 75.1 (C-5$\beta$), 71.9 (C-5$\alpha$); $\delta_F$ (282 MHz, CD$_3$OD) -132.09 (0.23F, dd, one half of an ABX, $^2$J 291.5, $^3$J$_{HF}$ 54.05, $\beta$ isomer), -133.41 (0.77F, dd, one half of a highly distorted ABX, $^2$J 286.1, $^3$J$_{HF}$ 54.7, $\alpha$ isomer), -134.94 (0.77F, dd, one half of a highly distorted ABX, $^2$J 286.1, $^3$J$_{HF}$ 55.95, $\alpha$ isomer), -140.42 (0.23F, dd, one half of an ABX, $^2$J 291.5, $^3$J$_{HF}$ 55.95, $\beta$ isomer)(3.3:1 $\alpha$:$\beta$, CD$_3$OD); $\delta_F$ (282 MHz, D$_2$O) -132.07 (0.25F, dd, $^2$J 293.3, $^3$J$_{HF}$ 53.4, $\beta$ isomer), -133.76 (0.75F, dd, $^2$J 288.6, $^3$J$_{HF}$ 54.8, $\alpha$ isomer), -135.15 (0.75F, dd, $^2$J 288.6, $^3$J$_{HF}$ 54.8, $\alpha$ isomer), -139.77 (0.25F, dd, $^2$J 293.4, $^3$J$_{HF}$ 55.4, $\beta$ isomer)(3:1 $\alpha$:$\beta$, D$_2$O); m/z (CI) 171 (100%, M+1), 153 (8%, M+1-H$_2$O). NMR data is in agreement with those reported by Bouvet.$^{211}$

(3aR,6R,6aS)-3a-Difluoromethyl-2,2-dimethyl-tetrahydrofuro[2,3-d][1,3]-dioxol-6-ol 201

Hydrochloric acid (5 drops of a 12 M soln) was added to a solution of alcohol 200 (30.5 mg, 102 $\mu$mol) in THF (5 ml). The resulting solution was stirred at ambient temperature for 23 h. Sodium bicarbonate (1 microspatula) was added followed by direct concentration of the reaction mixture. The concentrate was taken up in acetone (5 ml) and anhydrous copper(II) sulfate (2 microspatulas) and $p$TSA (1 microspatula) were added consecutively. The resulting heterogenous mixture was stirred for 66 h and monitored by TLC. Brine (5 ml) was added and the acetone removed under
reduced pressure. Ethyl acetate (10 ml) was added and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3 x 5 ml) and the combined organic extracts dried and concentrated under reduced pressure. Purification by column chromatography over silica gel (40% ethyl acetate in hexanes) afforded acetonide 201 as a white solid (14 mg, 66%); mp 77-80°C; [Found: C, 45.87; H, 5.73; Calc. for C₈H₁₂F₂O₄: C, 45.72; H, 5.75%]; Rₚ (40% ethyl acetate in hexanes) 0.33; UV (254 nm) inactive; δ_H (300 MHz, CDCl₃) 5.87 (1H, t, ²J_HF 55.5, H-3a), 4.62 (1H, s, H-6a), 4.32-4.27 (1H, m, H-6), 4.25 (1H, dd, ²J 9.9, ³J 2.9, H-5b), 4.03 (1H, d, ²J 9.9, H-5a), 1.97 (1H, dd, J 8.5, 2.9 Hz, OH), 1.52 (3H, s, H-2), 1.38 (3H, s, H-2'); δ_F (282 MHz, CDCl₃) -128.99 (1F, dd, one half of a highly distorted ABX, ²J 287.5, ²J_HF 55.9), -130.23 (1F, ddd, one half of a highly distorted ABXY, ²J 287.4, ²J_HF 54.7, ⁴J_HF 2.5); m/z (Cl) 211 (100%, M+1), 194 (6%), 178 (29%), 151 (8%), 133 (6%), 116 (6%), 107 (10%), 59 (7%), 47 (9%), 45 (9%). There was an insufficient amount of material to obtain a ¹³C NMR.
Ethyl (syn) 2-(N,N-diethylcarbamoyloxy)-3,3-difluoro-3-(tetrahydrofuran-2'-yl)-propionate 202 and ethyl (anti) 2-(N,N-diethylcarbamoyloxy)-3,3-difluoro-3-(tetrahydrofuran-2'-yl)-propionate 203

![Chemical Structures](syn_202.png) ![Chemical Structures](anti_203.png)

A flask containing AIBN (1.5 mg, 9.1 μmol) and BPO (1.5 mg, 6.2 μmol) was pump-purged with nitrogen. Alkenoate 94 (52 mg, 0.21 mmol) was added as a solution in THF (3 ml). The resulting solution was heated to reflux and stirred for 16 h. The resulting mixture was cooled to ambient temperature and quenched with a saturated aqueous solution of sodium sulfite (3 ml). DCM (5 ml) was added and the organic phase separated. The aqueous phase was extracted with DCM (3 × 5 ml) and the combined organic extracts dried and concentrated under reduced pressure to afford a colourless oil. Purification by column chromatography over silica gel (30% ethyl acetate in light petroleum ⇒ 40% ethyl acetate in light petroleum) afforded an inseparable mixture of syn and anti diastereoisomers 202 and 203 as a colourless oil (56 mg, 82%); 90% by GC; Rf (30% ethyl acetate in light petroleum) 0.43; δH (300 MHz, CDCl3) 5.44 (0.58H, dd, 3JHF 14.7, 7.4, H-2), 5.31 (0.42H, dd, 21.2, 4.6, H-2), 4.42-4.16 (3H, m, envelope, H-2’, OC2H5), 3.89-3.78 (2H, m, envelope, H-5’), 3.38-3.21 (4H, m, envelope, CH2NCH2), 2.21-1.81 (4H, m, envelope, H-3’, H-4’), 1.31-1.09 (9H, m, envelope, CH3CH2NCH2CH3, OCH2CH3); δC (75 MHz, CDCl3)
165.9-165.6 (m, CO ester, both diastereoisomers), 153.8 (Cq, CO carbamate, major),
153.7 (Cq, CO carbamate, minor), 123.2-116.0 (m, Cq, CF$_2$ major and minor), 76.3
(dd, $^2$J$_{CF}$ 32.2, 31.9, CH, C-2 major), 76.1 (dd, $^2$J$_{CF}$ 33.3, 23.2, CH, C-2 minor), 71.6
(dd, $^2$J$_{CF}$ 29.4, 26.0, CH, C-2' major), 71.3 (dd, $^2$J$_{CF}$ 36.7, 24.3, CH, C-2' minor), 69.6
(CH$_2$, C-5' major), 69.6 (CH$_2$, C-5' minor), 61.9 (CH$_2$, CO$_2$CH$_2$Me major), 61.8 (CH$_2$,
CO$_2$CH$_2$Me minor), 42.4 (CH$_2$N), 42.3 (CH$_2$N), 41.7 (CH$_2$, major and minor), 25.8
(CH$_2$, C-4' minor), 25.7 (CH$_2$, C-4' major), 24.9 (dd, 20.1, 4.2, C-3' major and minor),
14.0 (CH$_3$, CO$_2$CH$_2$CH$_3$ minor), 13.9 (CH$_3$, CO$_2$CH$_2$CH$_3$ major), 13.9 (NCH$_2$CH$_3$
major and minor), 13.3 (NCH$_2$CH$_3$ major and minor); $\delta_F$ (282 MHz, CDCl$_3$) major
diastereoisomer (58%) -113.61 (1F, ddd, $^2$J 261.0, $^3$J$_{HF}$ 14.6, 3.8), -121.15 (1F, ddd,
$^2$J 261.0, $^3$J$_{HF}$ 22.3, 7.7) minor diastereoisomer (42%) -116.91 (dd, $^2$J 261.3, $^3$J$_{HF}$
21.6), -123.11 (1F, ddd, $^2$J 261.0, $^3$J$_{HF}$ 22.2, 3.8); [HRMS (ES-TOF, M+Na) Found:
346.1436; Calc. for C$_{14}$H$_{23}$N O$_5$F$_2$Na: 346.1442]; m/z (ES-TOF) 346.2 (100%, M+Na).
(2R,3S)-(5-(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl)-2-oxo-[1,3]dioxalan-4-yl)-methyl 4-methoxybenzenecarboxylate 214

Triphosgene (25 mg, 84 μmol) was added to a solution of diol 192 (33 mg, 84 μmol) in DCM (5 ml) containing 2,6-lutidine (20 μl, 168 μmol) at ambient temperature. The solution was heated at reflux for 20 h, with monitoring by TLC. The reaction mixture was allowed to cool to ambient temperature, then quenched with methanol (5 ml) and water (5 ml) in order to destroy excess phosgene. Extractive work-up with DCM (3 × 5 ml), followed by drying and concentration under reduced pressure afforded crude 214 as a brown oil. Purification by column chromatography over silica gel (60% ethyl acetate in hexanes) afforded carbonate 214 as a colourless oil (23 mg, 66%); Rf (60% ethyl acetate in hexanes) 0.67; δH (300 MHz, CDCl3) 7.90 (2H, d, 3J 8.8, ArH), 6.88 (2H, d, 3J 8.8, ArH), 5.24-5.20 (1H, m, H-5), 5.05-4.94 (3H, envelope, OCH2O and H-4), 4.53 (1H, dd, one half of an ABX, 2J 12.6, 3J 3.1, CHH’OOpMBz), 4.44 (1H, dd, one half of an ABX, 2J 12.6, 3J 3.3, CHH’OOpMBz), 3.87-3.71 (2H, m, CH2O), 3.80 (3H, s, ArOCH3), 3.57-3.49 (2H, m, CH2O), 3.32 (3H, s, CH2OCH3); δC (75 MHz, CDCl3) 165.3 (CO ester), 163.8 (Cq-OMe), 155.4 (dd, 1JCF 292.2, 296.8, CF2), 153.4 (C-2), 131.7 (ArCH), 120.8 (Cq-CO), 113.8 (ArCH), 111.4 (dd, 2JCF 34.6, 16.1, C=CF2), 98.6 (dd, 4JCF 4.6, 1.9, OCH2O), 75.4 (t, 4JCF 2.3, C-4), 73.5 (dd, 3JCF 5.7,
2.0, C-5), 71.3 (CH$_2$O), [69.0, 69.0] (CH$_2$O), 62.5 (CH$_2$OpMBz), 58.8 (ArOCH$_3$), 55.3 (CH$_2$OCH$_3$); $\delta_F$ (282 MHz, CDCl$_3$) -91.28 (1F, dd, $^2J$ 50.9, $^4J_{HF}$ 2.5), -104.89 (1F, dd, $^2J$ 50.9, $^4J_{HF}$ 2.5); $m/z$ (ES-TOF) 441.4 (47%, M+Na), 397.4 (100%, M+Na-CO$_2$). This material decomposed before full characterisation could be achieved.

**Attempted preparation of (2R,3S)-(5-(2,2-difluoro-1-(tert-butyldimethylsilyloxy)-vinyl)-2-oxo-[1,3]dioxalan-4-yl)-methyl 4-methoxybenzenecarboxylate 215**

[Chemical structure image]

tert-Butyldimethylsilyl triflate (12.6 $\mu$l, 55 $\mu$mol) was added dropwise to a solution of carbonate 214 (23 mg, 55 $\mu$mol) and 2,6-lutidine (6.4 $\mu$l, 55 $\mu$mol) in THF (3 ml) at 0°C under a nitrogen atmosphere. After 18 h, TLC indicated the formation of a less polar material. Concentration under reduced pressure and analysis by $^{19}$F NMR indicated an 86:14 mixture of silyl difluoroenol ether 215 and carbonate 214. Attempted purification by flash column chromatography (40% ethyl acetate in light petroleum) failed to afford any of the desired product silyl difluoroenol ether 215.

Crude data for 215; $R_f$ (60% ethyl acetate in light petroleum) 0.65; $\delta_F$ (282 MHz, CDCl$_3$) -99.71 (1F, dd, $^2J$ 71.2, $^4J_{HF}$ 2.5), -114.24 (1F, dd, $^2J$ 71.2, $^4J_{HF}$ 2.5). Chemical
shifts are in agreement for silyl difluoroenol ethers, according to the work of Haworth.\textsuperscript{189}
Chapter Five

References


7) For an example of one such approach, see ref. 144.


286


169) Thomas, A.C., PhD Thesis, Birmingham (UK), **2001**.


180) For an example of a catalyst system capable of mediating the coupling of sterically congested aryl triflates, see Kamikawa, T.; Hayashi, T., *Synlett*, 1997, 163-164.


182) For an example of the generation of this lithium reagent, see Moore, S.S.; Whitesides, G.M., *J. Org. Chem.* 1982, 47, 1489-1493.


191) Formation of the appropriate sulfenyl halide was determined by mixing the two reagents for 1 hour and then adding styrene 121e with stirring for 24 hours. 19F NMR was used to determine the produce distribution.


202) For conditions A, see Chen, Q.-Y.; Yang, Z.-Y., Tetrahedron Lett. 1986, 10, 1171-1174. For conditions C, see ref. 111b. Conditions B are a variant of conditions C.


208) For an example of the synthesis of functionalised gem-difluoro-1,4-pentadienes, see Shen, Y.; Jiang, G.-F.; Wanf, G.; Zhang, Y., J. Fluorine Chem. 2001, 109, 141-144.


219) The $^{19}$F NMR shift is comparable to those described by Röschenthaler and co-workers, see Bissky, G.; Staninets, V.I.; Kolomeitsev, A.A.; Röschenthaler, G.-V., *Synlett* **2001**, 3, 374-378.


241) For contents that have been published, see ref. 164 and Deboos, G.A.; Fullbrook, J.J.; Percy, J.M., *Org. Lett.* **2001**, *18*, 2859-2861.
Chapter Six

Appendices
Appendix I: Chiral HPLC trace of racemic alcohol 159 with shoulder impurity
Appendix II: Chiral HPLC trace of chiral alcohol 157 with ketone impurity
Appendix III: Overlay of Chiral HPLC traces of chiral alcohol 157 and racemic alcohol 159
Appendix IV: $^{19}$F of sugar 155 (282 MHz, CD$_3$OD)
Appendix V: $^1$H of sugar 155 (500 MHz, CD$_3$OD)
Appendix VI: $^{13}$C of sugar 155 (126 MHz, CD$_3$OD)
Appendix VII: COSY90 of sugar 155 (500 MHz, CD$_3$OD)
Appendix VIII: HSQC of sugar 155 (500/126 MHz, CD$_3$OD)
Appendix IX: HMBC of sugar 155 (500/126 MHz, CD$_3$OD)
Appendix X: Partial 1D-GOESY spectrum of sugar 155 (500 MHz, CD$_3$OD)
Appendix XI: Partial 1D-GOESY spectrum of sugar 155 (500 MHz, CD$_3$OD)
Appendix XII: Partial 1D-GOESY spectrum of sugar 155 (500 MHz, CD$_3$OD)
Appendix XIII: Crude $^{19}$F of racemic boronate ester 189 (282 MHz, CDCl$_3$)
Appendix XIV: Crude $^{19}$F of racemic boronate ester 197 (282 MHz, CDCl$_3$)
Appendix XV: $^{19}$F NMR of 173 (282 MHz, CD$_3$OD)
Appendix XVI: $^{19}$F NMR of 173 (282 MHz, D$_2$O)
Appendix XVII: $^1$H NMR of 173 (300 MHz, CD$_3$OD)
Appendix XVIII: $^{13}$C NMR of 173 (100 MHz, CD$_3$OD)
Appendix XIX: COSY90 of 173 (300 MHz, CD$_3$OD)
Appendix XX: HSQC of 173 (75/300 MHz, CD$_3$OD)
Appendix XXI: HMBC of 173 (75/300 MHz, CD$_3$OD)
Appendix XXII: Partial 1D-GOESY of 173 (500 MHz, CD$_3$OD)
Appendix XXIII: Partial 1D-GOESY of 173 (500 MHz, CD$_3$OD)
Appendix XXIV: Partial 1D-GOESY of 173 (500 MHz, CD$_3$OD)
Appendix XXV: Partial 1D-GOESY of 173 (500 MHz, CD$_3$OD)
Appendix XXVI: Partial 1D-GOESY of 173 (500 MHz, CD$_3$OD)
Appendix XXVII: HSQC of diol 192 (400 MHz, CDCl$_3$)