Synthesis and Comparison of the Reactivity of Allyl Fluorides and Allyl Chlorides

Thesis submitted for the degree of

Doctor of Philosophy

at the University of Leicester

By

Kirandeep Rakkar MChem (Hons.)

Department of Chemistry

University of Leicester

September 2009

University of Leicester

Synthesis and Comparison of the Reactivity of Allyl Fluorides and Allyl Chlorides

Kirandeep Rakkar

Abstract

A small library of novel allylic fluorides were synthesised *via* a two-step process, involving the cross-metathesis of allyltrimethylsilane with varying olefinic partners, followed by fluorodesilylation of the corresponding allylsilane with Selectfluor. Their structures were determined by NMR spectroscopy and mass spectrometry. The analogous novel allylic chlorides were also formed and successfully separated from their rearranged products by column chromatography and characterised fully by NMR spectrometry and mass spectroscopy.

A series of novel Pd(II) chloride-bridged dimers were synthesised from the corresponding allylic chlorides and purified by column chromatography. Their structures were determined by NMR spectroscopy, mass spectrometry and single crystal X-ray crystallography. New palladium cationic complexes were synthesised from their preceding allylic fluorides by reaction with $Pd(dba)_2$ and PPh_3 in $CDCl_3$, but not isolated. Their structures were determined by NMR spectroscopy and mass spectrometry. It was observed that the allylic chloride, 2-chlorobut-3-enyl benzoate and allylic fluoride, 2-fluorobut-3-enyl benzoate both oxidatively added to Pd(0) in the same manner. However, with 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione, although the cationic species was formed, due to the electron-withdrawing property of the nitro group, the protons alpha to nitrogen were susceptible to elimination by fluoride acting as a base to form 2-(buta-1,3-dienyl)isoindoline-1,3-dione.

The novel Pd(II) chloride-bridged dimers and the palladium cationic complexes on reaction with the sodium salt of dimethyl malonate afforded nucleophilically substituted products in moderate yields. However, it was also found that the substituents on allyl substrates influenced the site of nucleophilic attack. In contrast, reactions with a variety of sources of fluoride were unsuccessful.

A series of related allylic difluorides were also synthesised by reaction of 2,2-difluoro but-3-en-1-ol in DCM solution with derivatised benzoyl chlorides. Attempts to activate these difluoroallyl compounds with $Pd(dba)_2$ and $Pd(PPh_3)_4$ were unsuccessful. However, the reaction of 3-bromo-3,3-difluoropropene with $Pd(PPh_3)_4$ formed the corresponding novel π-allyl complex and was identified by mass spectrometry.

Acknowledgements

Firstly, I would like to thank my family for their love and support over the many years I have been at the University of Leicester, especially my brother Rohit, whose help in sorting all of my stacks of spectra over the course of the Ph.D. has been invaluable! I also wish to thank my partner John, whose unwavering belief in me has helped me continue through the many problems inherent in a Ph.D.

Next, I would like to thank my supervisor Prof. Eric Hope for his help, support and enthusiasm throughout the three years. I would also like to thank Dr Alison Stuart, for her help with random NMR questions.

I give thanks to everyone I have had the pleasure of knowing and working with whilst I have been at the University of Leicester, with special thanks to Dr Carla Jones, Michal Fornalczyk, Becky Williams, Alex Goddard and Ann Beresford.

I give a huge thank you to Dr Daniel Duncan for proofreading my thesis and his continued friendship. I would also like to thank Kerry Willis, Raminder Shergill and Chris Whyte for helping me take my mind off work occasionally with trips to the pub and quizzing.

I would like to thank Toni Wilkes, Benjamin Ho and Pradeep Chenna for their contributions to Chapter Five.

I would also like to thank Dr Graham Eaton, Dr Gerry Griffiths and Kuldip Singh for all their technical support over the years.

Finally, I must also thank the University of Leicester and EPSRC for funding throughout my Ph.D.

Contents

Abstract		**i**
Acknowledgements		**ii**
Contents		**iii**
List of Abbreviations		**x**
Chapter One - Introduction		**1**
1.1	Types of Fluorination	1
1.1.1	Electrophilic Fluorination	1
1.1.2	Nucleophilic Fluorination	2
1.2	Chiral Fluorinating Reagents	4
1.2.1	$[N\text{-}F]^+$ Reagents	8
1.2.2	Asymmetric Catalysis	11
1.3	Enantioselective Nucleophilic Fluorination	16
1.4	Building Block Approach to Organofluorine Compounds	19
1.5	C-F Activation	23
1.5.1	Aromatic Fluorides	23
1.5.2	Alkenyl Fluorides	25
1.5.3	Aliphatic Fluorides	27
1.6	Thesis Outline	30
1.7	References	31
Chapter Two – Synthesis of Allylic Fluorides and Allylic Chlorides		**35**
2.1	Introduction	35
2.1.1	Synthesis of Allylic Fluorides *via* Nucleophilic Fluorination	35
2.1.2	Synthesis of Allylic Fluorides *via* Electrophilic Fluorination	39
2.1.3	Allylic Chlorides from Allylic Alcohols	42
2.2	Results and Discussion	49
2.2.1	Synthesis of Allyl Fluorides	49
2.2.1.2	Synthesis of Derivatised Allyl Benzoates	52
2.2.1.3	Synthesis of Silyl Derivatised Allyl Benzoates	56
2.2.1.4	Synthesis of Fluorinated Derivatised Allyl Benzoates	58
2.2.2	Synthesis of Allylic Chlorides	59
2.2.2.1	Synthesis of Allyl Alcohols	60

2.2.2.1.1 Synthesis of 1-(Benzyloxy)but-3-en-2-ol **(98)** 60
2.2.2.2.2 Synthesis of 2-hydroxybut-3-enyl benzoate and related Allylic Alcohols 60
2.2.3 Synthesis of Allylic Chlorides 64
2.2.3.1 Synthesis of ((2-chlorobut-3-enyloxy)methyl)benzene **(107)** 64
2.2.3.2 Synthesis of 2-chlorobut-3-enyl benzoate **(108)** and related Allylic Chlorides 65
2.3 Conclusions 67
2.4 References 68

Chapter Three - Activation of Allylic Fluorides and Chlorides by Palladium 71
3.1 Introduction 71
3.1.1 Reactions of Allyl chlorides with Palladium 71
3.1.2 Reactions of Allyl fluorides with Palladium 74
3.2 Results and discussion 78
3.2.1 Reactions of Allyl chlorides with Palladium 78
3.2.2 Reactions of Allyl fluorides with Palladium 83
3.2.2.1 Initial Studies – Activation of Allylic Fluorides with Pd(0) 83
3.2.2.2 Activation of Allylic Fluoride with Pd(0) in the Presence of a Nucleophile – Trapping the Allyl Pd Intermediate 88
3.3 Conclusions 93
3.4 References 94

Chapter Four - Reactions of Palladium Allyl Complexes with Nucleophiles 96
4.1 Introduction 96
4.1.1 Reactions of π-Allyl Complexes with Nucleophiles 96
4.2 Results and Discussion 99
4.2.1 Reactions of Palladium Chloro-bridged Complexes with Nucleophiles 100
4.2.2 Reactions of Palladium Cationic Complexes with dimethyl malonate anion 103
4.2.3 Reactions of Pd cationic complexes with other carbon based nucleophiles
4.2.4 Reactions with Fluoride 107
4.3 Conclusions 110
4.4 References 112

Chapter Five - Synthesis and Reactions of Difluoroallylic Compounds **114**
5.1 Introduction 114
5.1.1 Difluoromethylene Synthons 114
5.1.2 Difluoroallylanions 116
5.2 Results and discussion 119
5.2.1 Synthesis of 2,2-difluoro-1-phenylbut-3-en-1-ol **(158)** 119
5.2.2 Synthesis of difluoroallylic esters 120
5.2.3 Synthesis of Derivatised Difluoro phenyl alcohols 123
5.2.4 Synthesis of Allylic Difluorides 126
5.2.5 Metal-Mediated Synthesis of 3,3-difluoro-2-phenylpent-4-en-2-ol **(181)** 128
5.2.6 Reactions of Difluoroallylic Products with Palladium(0) 129
5.3 Conclusions 131
5.4 References 133

Chapter Six- Experimental Details **135**
6.1 General Experimental Procedures **135**
6.1.1 Nuclear Magnetic Resonance Spectroscopy 135
6.1.2 Mass spectroscopy 136
6.1.3 Infrared Spectroscopy 136
6.1.4 Elemental Analysis 136
6.1.5 X-Ray Crystallography 136
6.1.6 Starting materials 136

6.2 Experimental Details for Chapter 2 **137**
6.2.1 Preparation of 2-Allyl-isoindole-1,3-dione **(66)** 137
6.2.2 Preparation of Allyl Benzoate **(67)** 137
6.2.3 Preparation of allyl 4-methylbenzoate **(85)** 138
6.2.4 Preparation of allyl 4-fluorobenzoate **(81)** 138
6.2.5 Preparation of allyl 3-fluorobenzoate **(82)** 138
6.2.6 Preparation of allyl 2-fluorobenzoate **(83)** 140
6.2.7 Preparation of allyl 4-(trifluoromethyl)benzoate **(84)** 141
6.2.8 Preparation of But-3-en-2-yl benzoate **(87)** 141
6.2.9 Preparation of 2-methylbut-3-en-2-yl benzoate **(86)** 142
6.2.10 Preparation of (3-[1,3]Dioxalan-2-yl-allyl)trimethylsilane **(69)** 143
6.2.11 Preparation of (4-Benzyloxy-but-2-enyl)-trimethylsilane **(68)** 143

6.2.12 Preparation of 2-(4-trimethylsilanyl-but-2-enyl)isindole-1,3-dione **(70)** 144
6.2.13 Preparation of Benzoic acid 4-trimethylsilanyl-but-2-enyl ester **(71)** 144
6.2.14 Preparation of 4-(trimethylsilyl)but-2-enyl 4-methylbenzoate **(92)** 145
6.2.15 Preparation of 4-(trimethylsilyl)but-2-enyl 4-(trifluoromethyl) benzoate **(91)** 146
6.2.16 Preparation of 4-(trimethylsilyl)but-2-enyl 4-fluorobenzoate **(88)** 146
6.2.17 Preparation of 4-(trimethylsilyl)but-2-enyl 3-fluorobenzoate **(89)** 147
6.2.18 Preparation of 4-(trimethylsilyl)but-2-enyl 2-fluorobenzoate **(90)** 148
6.2.19 Preparation of (2-Fluoro-but-3-enyloxymethyl)-benzene **(73)** 149
6.2.20 Preparation of 2-(2-Fluoro-but-3-enyl)-isoindole-1,3-dione **(74)** 149
6.2.21 Preparation of 2-fluorobut-3-enyl benzoate **(75)** 150
6.2.22 Preparation of 2-fluorobut-3-enyl 4-methylbenzoate **(97)** 151
6.2.23 Preparation of 2-fluorobut-3-enyl 4-fluorobenzoate **(93)** 151
6.2.24 Preparation of 2-fluorobut-3-enyl 3-fluorobenzoate **(94)** 152
6.2.25 Preparation of 2-fluorobut-3-enyl 2-fluorobenzoate **(95)** 153
6.2.26 Preparation of 2-fluorobut-3-enyl 4-(trifluoromethyl)benzoate **(96)** 153
6.2.27 Preparation of 1-(Benzyloxy)but-3-en-2-ol **(98)** 154
6.2.28 Preparation of 2-hydroxybut-3-enyl benzoate **(100)** 155
6.2.29 Preparation of *p*-methyl-2-hydroxybut-3-enyl benzoate **(105)** 155
6.2.30 Preparation of 2-hydroxybut-3-enyl 4-fluorobenzoate **(101)** 156
6.2.31 Preparation of 2-hydroxybut-3-enyl 3-fluorobenzoate **(102)** 157
6.2.32 Preparation of 2-hydroxybut-3-enyl 2-fluorobenzoate **(103)** 158
6.2.33 Preparation of 2-hydroxybut-3-enyl 4-(trifluoromethyl)benzoate **(104)** 158
6.2.34 Preparation of ((2-chlorobut-3-enyloxy)methyl)benzene **(106)** 159
6.2.35 Preparation of ((4-chlorobut-2-enyloxy)methyl)benzene **(107)** 160
6.2.36 Preparation of 2-chlorobut-3-enyl benzoate **(108)** 160
6.2.37 Preparation of 2-chlorobut-3-enyl 4-fluorobenzoate **(109)** 161
6.2.38 Preparation of 2-chlorobut-3-enyl 3-fluorobenzoate **(110)** 161
6.2.39 Preparation of 2-chlorobut-3-enyl 2-fluorobenzoate **(111)** 162
6.2.40 Preparation of 2-chlorobut-3-enyl 4-(methyl)benzoate **(113)** 163
6.2.41 Preparation of 2-chlorobut-3-enyl 4-(trifluoromethyl)benzoate **(112)** 163

6.3 Experimental Details for Chapter 3 164
6.3.1 Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)-benzoate]dipalladium **(125)** 164

6.3.2	Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)oxy)methyl)benzene] dipalladium **(126)**	165
6.3.3	Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)-4-methylbenzoate] dipalladium **(131)**	165
6.3.4	Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)-4-(trifluoromethyl) benzoate] dipalladium **(130)**	166
6.3.5	Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)-4-fluorobenzoate] dipalladium **(127)**	167
6.3.6	Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)-3-fluorobenzoate] dipalladium **(128)**	167
6.3.7	Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)-2-fluorobenzoate] dipalladium **(129)**	168
6.3.8	Preparation of ((butenyl-(1,2,3-η)-isoindoline-1,3-dione)bis(triphenyl-phosphine)palladium fluoride **(132)**	169
6.3.9	Experimental Data for 2-(buta-1,3-dienyl)isoindoline-1,3-dione **(133)**	170
6.3.10	General procedure for NMR experiments following reactions of allyl halides with palladium (0)	172
6.4	**Experimental Details for Chapter 4**	**174**
6.4.1	Preparation of Acetylacetonato[(butenyl-(1,2,3-η)-benzoate]palladium **(145)**	174
6.4.2	Preparation of Acetylacetonato[(butenyl-(1,2,3-η)-oxy)methyl)benzene] palladium **(146)**	174
6.4.3	Preparation of dimethyl 2-(1-(benzoyloxy)but-3-en-2-yl)malonate **(148)**	175
6.4.4	Preparation of Dimethyl 2-(4-(benzyloxy)but-2-enyl)malonate **(147)**	176
6.4.5	Preparation of dimethyl 2-(1-(4-fluorobenzoyloxy)but-3-en-2-yl) malonate **(150)**	176
6.4.6	Preparation of dimethyl 2-(1-(4-(trifluoromethyl)benzoyloxy)but-3-en-2-yl)malonate **(149)**	177
6.4.7	Preparation of 1-fluoro-bis(phenylsulfonyl)methane **(140)**	177
6.4.8	Preparation of Dimethyl 2-(4-(benzoyloxy)but-2-enyl)malonate **(151)**	178
6.4.9	Preparation of Dimethyl 2-(4-(benzoyloxy)but-2-enyl)malonate **(151)**	179
6.4.10	Preparation of Dimethyl 2-(4-(benzoyloxy)but-2-enyl)malonate **(151)**	179
6.4.11	Preparation of Dimethyl 2-(4-(benzoyloxy)but-2-enyl)malonate **(152)**	180

6.4.12 Experimental Data for Dimethyl 2-allylmalonate **(154)** 180
6.4.13 Preparation of dimethyl 2-(1-(3-fluorobenzoyloxy)but-3-en-2-yl) malonate **(153)** 181
6.4.14 Preparation of 5-fluoro-5,5-bis(phenylsulfonyl)pent-2-enyl 4-(trifluoro-methyl) benzoate **(155)** 181
6.4.15 Preparation of Allyl 1-fluoro-bis (phenylsulfonyl)methane **(156)** 182

6.5 Experimental Details for Chapter 5 183
6.5.1 Preparation of 2,2-difluoro-1-phenylbut-3-en-1-ol **(158)** 183
6.5.2 Preparation of 2,2-difluoro-1-phenylbut-3-enyl benzoate **(159)** 183
6.5.3 Preparation of 2,2-difluoro-1-phenylbut-3-enyl 4-fluorobenzoate **(160)** 184
6.5.4 Preparation of 2,2-difluoro-1-phenylbut-3-enyl 3-fluorobenzoate **(161)** 185
6.5.5 Preparation of 2,2-difluoro-1-phenylbut-3-enyl 2-fluorobenzoate **(162)** 186
6.5.6 Preparation of 2,2-difluoro-1-phenylbut-3-enyl 4-(trifluoromethyl) benzoate **(163)** 187
6.5.7 Preparation of 2,2-difluoro-1-phenylbut-3-enyl 4-methylbenzoate **(164)** 188
6.5.8 Preparation of (1-(benzyloxy)-2,2-difluorobut-3-enyl)benzene **(165)** 188
6.5.9 Preparation of 2,2-difluorobut-3-en-1-ol **(174)** 189
6.5.10 Preparation of 2,2-difluorobut-3-enyl benzoate **(175)** 189
6.5.11 Preparation of 2,2-difluorobut-3-enyl 4-fluorobenzoate **(176)** 190
6.5.12 Preparation of 2,2-difluorobut-3-enyl 3-fluorobenzoate **(177)** 191
6.5.13 Preparation of 2,2-difluorobut-3-enyl 2-fluorobenzoate **(178)** 192
6.5.14 Preparation of 2,2-difluorobut-3-enyl 4-methylbenzoate **(180)** 192
6.5.15 Preparation of 2,2-difluoro-1-(4-(trifluoromethyl)phenyl)but-3-en-1-ol **(166)** 193
6.5.16 Preparation of 2,2-difluoro-1-*p*-tolylbut-3-en-1-ol **(167)** 194
6.5.17 Preparation of 2,2-difluoro-1-(4-fluorophenyl)but-3-en-1-ol **(168)** 194
6.5.18 Preparation of 2,2-difluoro-1-(perfluorophenyl)but-3-en-1-ol **(169)** 195
6.5.19 Preparation of 2,2-difluoro-1-*p*-tolylbut-3-enyl 4-fluorobenzoate **(170)** 196
6.5.20 Preparation of 2,2-difluoro-1-(4-(trifluoromethyl)phenyl)but-3-enyl 4-fluoro benzoate **(171)** 197
6.5.21 Preparation of 2,2-difluoro-1-(perfluorophenyl)but-3-enyl 4-fluoro benzoate **(173)** 198
6.5.22 Preparation of 2,2-difluoro-1-(4-fluorophenyl)but-3-enyl 4-fluoro benzoate **(172)** 199

6.5.3	References	200
	Appendix	**I**
A1	Attempted Reactions in Chapter 2	I
A2	Attempted Reactions in Chapter 3	II
A3	Attempted Reactions in Chapter 4	V
A4	Attempted Reactions in Chapter 5	VI
A5	Crystal data and structure refinement for 2-hydroxybut-3-enyl 4-(trifluoromethyl) benzoate **(104)**	IX
A6	Crystal data and structure refinement for 2-hydroxybut-3-enyl 4-methylbenzoate **(105)**	X
A7	Crystal data and structure refinement for 2-hydroxybut-3-enyl 4-fluorobenzoate **(101)**	XI
A8	Crystal data and structure refinement for Bis[μ-chloro-bis(butenyl-(1,2,3-η)-4-fluorobenzoate] dipalladium **(127)**	XII
A9	Crystal data and structure refinement for Bis[μ-chloro-bis(butenyl-(1,2,3-η)-3-fluorobenzoate] dipalladium **(128)**	XIII
A10	Crystal data and structure refinement for 2-(2-fluorobut-3-enyl) isoindoline-1,3-dione **(74)**	XIV
A11	Crystal data and structure refinement for Palladium(II) Acetylacetonate **(144)**	XV
A12	Lecture Courses Attended	XVI
A13	Organic/Inorganic Seminar Programme	XVI
A14	Conferences Attended	XVIII
A15	Presentations	XVIII
A16	References	XIX

Abbreviations

AgF	Silver fluoride
ap	Apparent
Bn	Benzyl
Bz	Benzoate
CsF	Caesium fluoride
d	Doublet
DAST	Diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DCM	Dichloromethane
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1'-*bis*(diphenylphosphino)ferrocene
dppp	1,3-*bis*(diphenylphosphino)propane
EI	Electron Impact
ee	Enantiomeric excess
Et	Ethyl
FAB	Fast atom bombardment
F-TEDA	Selectfluor
Hz	Hertz
J	Coupling Constant
KH	Potassium hydride
KF	Potassium fluoride
LDA	Lithium diisopropylamide
LHMDS	Lithium *bis*(trimethylsilyl)amide
m	Multiplet
Me	Methyl
MeCN	Acetonitrile
mp	Melting point
NaF	Sodium fluoride
NaH	Sodium hydride
NFSI	*N*-Fluorobenzenesulfonimide
NMR	Nuclear magnetic resonance

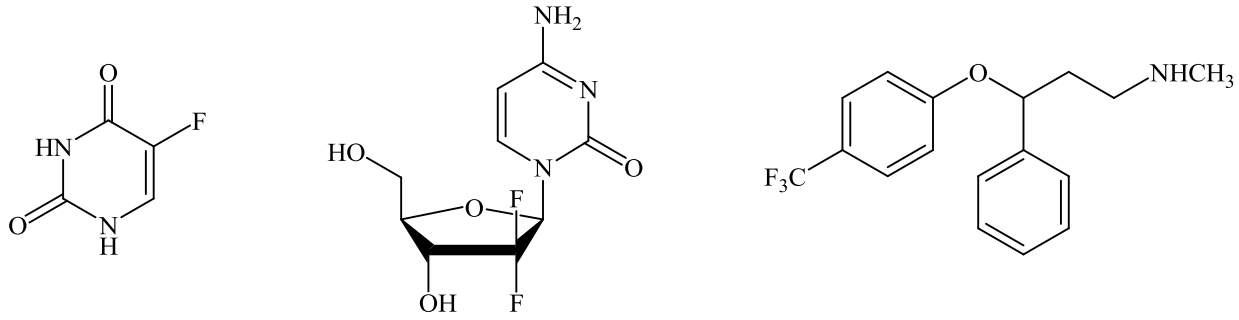
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium(0)
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
ppm	Parts per million
PPh_3	Triphenylphosphine
R	General alkyl or aryl fragment
s	Singlet
t	Triplet
TREAT HF	Triethylamine *tris*(hydrogen fluoride)
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetrabutylammonium fluoride
TBMe	Methyl *tert*-butyl ether
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilane

CHAPTER ONE

1 Introduction

The efficient formation of carbon-fluorine bonds is of widespread interest to synthetic and medicinal chemists. Organofluorine compounds have extensive applications, such as lubricants,[1] refrigerants,[2] fire extinguisher agents,[3] inhalation anaesthetics,[4] coatings for cooking utensils[5] and in the production of agrochemicals.[3, 6] They are also utilised extensively in the pharmaceutical industry, with many drugs now containing one or more fluorine atoms (Figure 1.1). The presence of fluorine often leads to increased lipophilicity, greater activity and inhibition of oxidative metabolism of drug molecules within the body. However, organofluorine compounds can be difficult to prepare, fluorine being both reactive and difficult to control.

There are two possible strategies for synthesising a fluorinated molecule; the first is to insert the carbon-fluorine bond at a convenient stage using a fluorinating agent, whilst the second employs the "building block approach", using a starting material already containing the carbon-fluorine bond required. These are considered separately below.



5-Fluorouracil Gemcitabine Fluoxetine (Prozac)

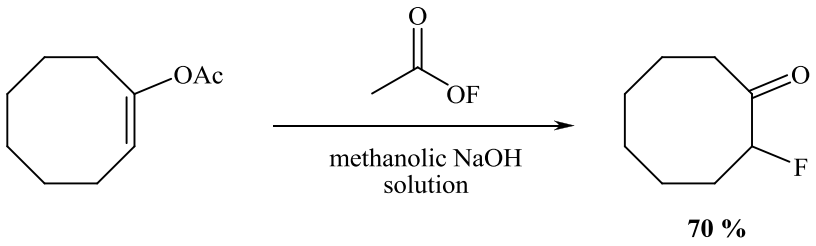
Figure 1.1 *Fluorine containing pharmaceuticals*

1.1. Types of Fluorination

1.1.1. Electrophilic Fluorination

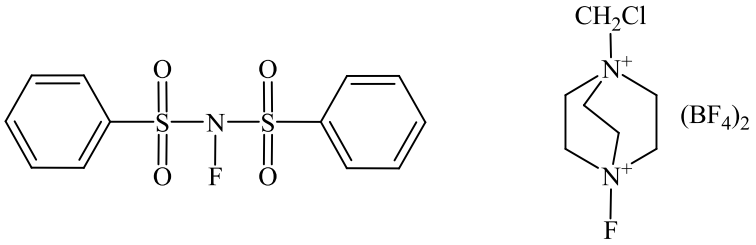
Fluorine is the most electronegative element, however, it can be utilised as an electrophilic source, F^+, in several ways. Elemental fluorine is a highly reactive fluorinating agent, however its use is restricted to reactions that can be controlled by dilution with inert gases (N_2, Ar, He *e.g.* 5-10 % F_2/N_2).[7] Alternatively, F_2 can be used to synthesise compounds containing an X-F moiety, where X is a highly electronegative atom or group (O, Cl, N). These compounds, which can be used as electrophilic fluorinating reagents, fall into two groups, the hypofluorites and fluoraza reagents. Here, electronic charge is withdrawn from fluorine through inductive effects. Hypofluorites, such as acetyl hypofluorite can be used *in situ* without isolation (Scheme 1.1).[8] However, all hypofluorites are dangerous and

potentially explosive reagents. One example being alkali metal fluoroxysulfates, which although relatively stable anionic hypofluorites, decompose or explode on contact with metals.



Scheme 1.1 *Fluorination using acetyl hypofluorite*

The fluoraza reagents consist of two classes, the neutral compounds (R_2NF), of which the most commonly used is *N*-Fluorobenzenesulfonimide (NFSI) and the quaternary compounds ($R_3N^+FX^-$), such as the widely used Selectfluor (F-TEDA) (Figure 1.2). The fluoraza reagents have many advantages over other electrophilic reagents. They are less hazardous than elemental fluorine or hypofluorites and they can be easily stored and handled as they are stable solids. They are also more selective fluorinating reagents and have been used successfully for electrophilic fluorination of a number of organic substrates including aromatics, carbonyl compounds, enol acetates and olefins.[9, 10] However, one of the disadvantages is that they are synthesised using elemental fluorine. They are also expensive reagents that contain only a small amount of active fluorine per mole of reagent.



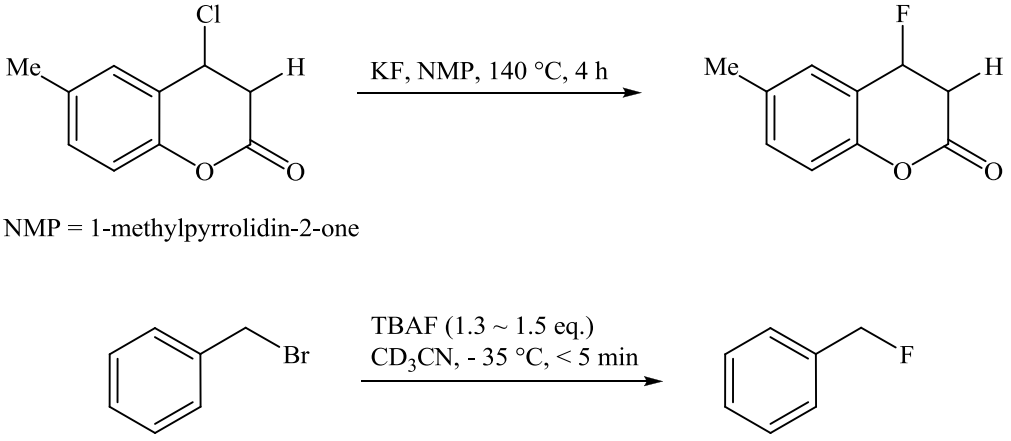
N-Fluorobenzenesulfonimide (NFSI) Selectfluor (F-TEDA)

Figure 1.2 *The two main Fluoraza reagents.*

1.1.2. Nucleophilic Fluorination

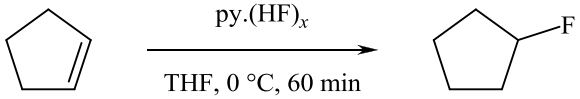
The fluoride ion, with its small size and low polarizability often behaves as a base rather than a nucleophile, hence its use as such in organic synthesis.[11] However, nucleophilic substitution of a halogen with fluoride was first achieved in 1863 by Borodine,[12] and since then fluoride sources have been continually developed in order to increase their stability, lower their toxicity and surmount solubility problems.[13] There are numerous nucleophilic fluorinating reagents, for example the alkali metal fluorides. This group, often regarded as the "classical" fluorinating reagents, are utilised in halogen substitutions of a range of substrates, such as alkyl halides and aromatic halides (Scheme 1.2).[14] Fluorinations are

frequently conducted in either high boiling solvents, which aid solubility of the ionic fluorides, or in anhydrous solvents, which diminish the chances of stray hydrogen bonds forming, which occur due to the high hydration energy (123 kcal/mol) of fluoride.[13] Alternatively, TBAF (tetrabutylammonium fluoride) is often used as it provides a soluble source of the fluoride ion, with nucleophilicity enhanced by the presence of the bulky organic cation (Scheme 1.2). One disadvantage is the extreme hydroscopic nature of the fluorinating agent, which may consequently lead to inconsistent results if water is present.



Scheme 1.2 *Fluorinations using KF and TBAF*

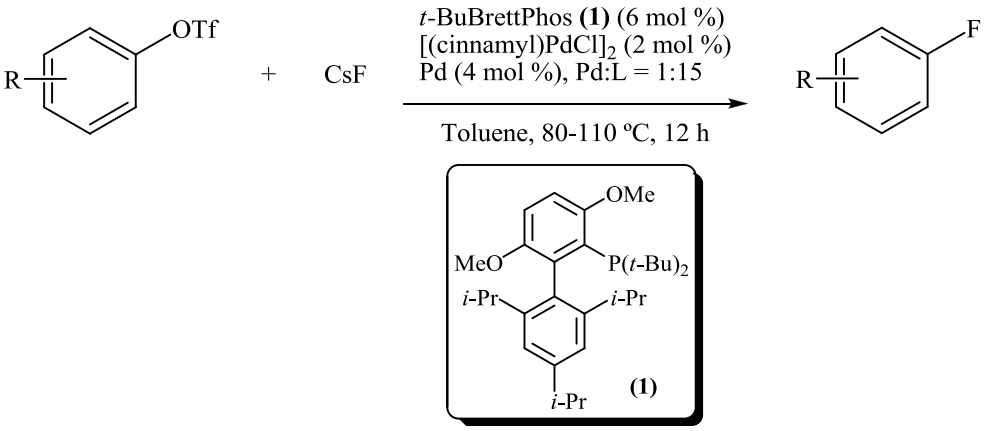
Another source of fluoride is anhydrous HF. However, HF has a low boiling point, high vapour pressure and is corrosive and toxic, therefore, HF/base complexes, such as pyridinium poly(hydrogen fluoride)[15] and triethylamine *tris*(hydrogen fluoride)[16] have been developed as safer alternatives (Scheme 1.3).



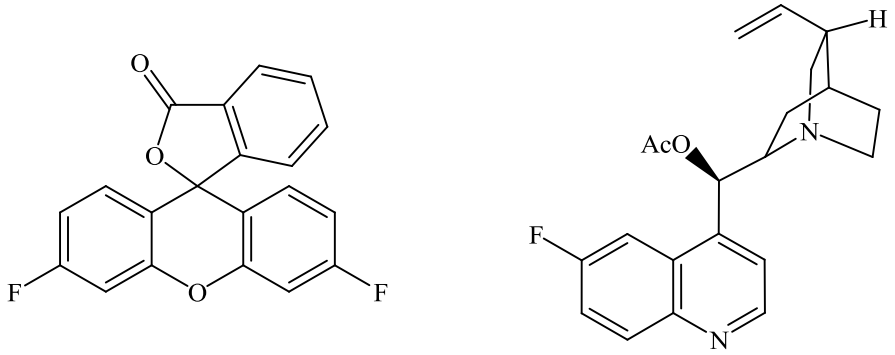
Scheme 1.3 *Fluorination using pyridinium poly(hydrogen fluoride)*

Recent work by Buchwald[17] has demonstrated that aryl fluorides, which are important in a number of pharmaceutical and agrochemical products, can be synthesised using CsF in a palladium catalysed reaction from aryl triflates. Initial work was conducted using aryl bromides and AgF, however, these were limited to electron poor substrates with ortho directing substituents. Therefore, aryl triflates were used with AgF. Only trace amounts of fluorinated product were obtained, however, with CsF, yields increased. Therefore reaction conditions were honed and it was found that the reaction proceeded best with CsF, $[(\text{cinnamyl})\text{PdCl}]_2$ (2 mol %) and *t*-BuBrettPhos **(1)** (6 mol %) in toluene. The use of *t*-BuBrettPhos **(1)** as a ligand was integral in the reaction as it was found to promote reductive-elimination of the Ar-F due to its size, as well as prevent formation of unwanted dimeric $[\text{LPdAr(F)}]_2$ complexes (Scheme 1.4). A variety of aryl triflates were evaluated,

ortho-biphenyl triflates, heterocyclic triflates and more importantly complex aryl triflates derived from fluorescein **(2)** and quinine **(3)**, demonstrating that the method could be applied to the synthesis of pharmaceutically important compounds to afford the desired fluorinated products in good yields (57-84 %).



Scheme 1.4 *Fluorination of aryl triflates*



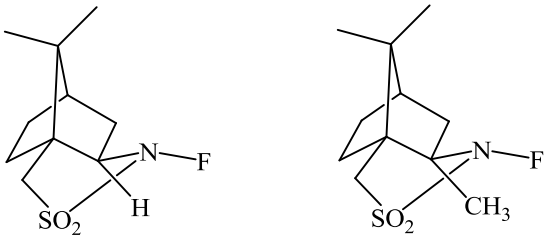
(2) **(3)**

Figure 1.3 *Structures of products derived from fluorescein* ***(2)*** *and quinine* ***(3)***

The nucleophilic and electrophilic fluorinating reagents described previously, though useful, are unable to fluorinate compounds in an enantioselective manner without the addition of a chiral catalyst. Subsequently, the development of fluorinating agents with inbuilt chirality has received considerable attention in the literature.

1.2 Chiral Electrophilic Fluorinating Reagents

The first enantioselective fluorination reaction was carried out in 1988 by Differding and Lang,[18] who synthesised *N*-fluoro sultams **(4)** and **(5)**, the first examples of enantioselective fluorinating reagents (Scheme 1.5).



(4) **(5)**

Scheme 1.5 *N-fluoro sultams **(4)** and **(5)***

Fluorination experiments using the *N*-fluoro sultams **(4)** and **(5)** showed them to react with various metal enolates generated under standard reaction conditions to give the anticipated α-fluoro carbonyl compounds with the *ee* depending strongly on the structure of the metal enolate (Table 1.1). *N*-fluoro sultam **(4)** was found to give greater enantiomeric excesses in comparison with **(5)**; the best result observed with ethyl cyclopentanone-2-carboxylate (70 % *ee*). However, the main secondary reaction of *N*-fluoro sultam **(4)** was HF elimination from the *N*-fluoro sultam by the metal enolate to give the starting imine and carbonyl compounds. *N*-fluoro sultam **(5)**, although designed to prevent HF elimination from the fluorinating reagent, gave poor results possibly as a result of steric hindrance.

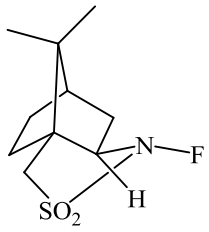
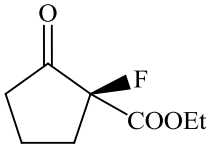
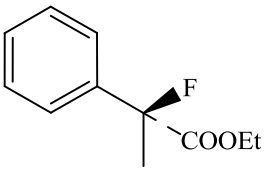
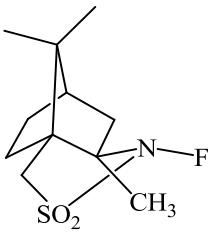
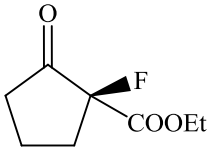
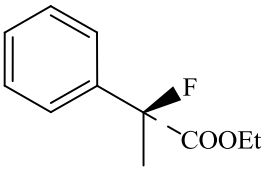
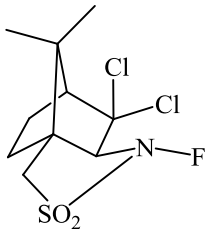
***N*-fluoro sultam**	**Product**	**Reaction Conditions**	***ee* (%)**	**Yield (%) [a]**
 **(4)**		NaH; Et_2O; 0 °C - r.t. 1.5 equiv. **(4)**	70	63 (63)
		LDA; THF; -78 °C - r.t. 1.2 equiv. **(4)**	35	27 (30)
 **(5)**		KH; Toluene/THF (2:1), 0 °C - r.t. 1.3 equiv. **(5)**	<10	<5
		LDA; THF; -78 °C - r.t. 1.2 equiv. **(5)**	<10	34 (47)

Table 1.1 *Enantioselective fluorination reactions using N-fluoro sultams **(4)** and **(5)**.*

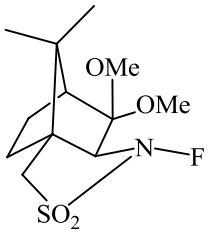
[a] Isolated yields (based on recovered starting material).

Davis,[19, 20] following on from the pioneering work by Differding and Lang, reported closely related structures in 1993 and 1998, and synthesised both enantiomers of *N*-fluoro-

2,10 (3,3-dichlorocamphorsultam) **(6)**, *N*-fluoro-2,10-(3,3-dimethoxycamphorsultam) **(7)** in addition to *N*-fluoro-2,10-(camphorsultam) **(4)**.



(6)

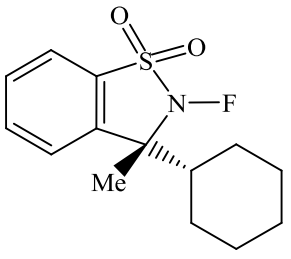


(7)

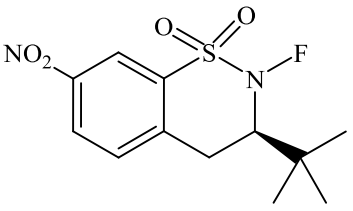
Figure 1.4 *N-fluoro-2,10-(3,3-dichlorocamphorsultam)* ***(6)*** *and N-fluoro-2,10-(3,3dimethoxycamphorsultam)* ***(7)****.*

N-fluoro-2,10-(3,3-dichlorocamphorsultam) **(6)** was found to give greater yields and enantioselectivities than *N*-fluoro-2,10-(camphorsultam) **(4)** and this was attributed to the greater reactivity of **(6)** in comparison with that of **(4)**, with fluorinations occurring at lower temperatures (-78 ºC *vs.* r.t. for **(4)**). Since the reactions occur at -78 ºC with **(6)**, the rate of HF elimination is decreased, which in turn increases the yield of the fluorinated product. The best result observed for *N*-fluoro-2,10-(3,3-dichlorocamphorsultam) **(6)** was the fluorination of the sodium enolate of 2-methyl-1-tetralone**,** affording the product 2-fluoro-2-methyl-1-tetralone in 53 % yield with 76 % *ee*. However, with fluorinations of β-ketone ester enolates, enantiomeric excesses were in the range of 34-46 %. The only secondary enolate studied, the enolate of propiophenone, gave a moderate yield but racemic product, due to base-catalysed epimerisation under the reaction conditions, owing to the enhanced acidity of the α-fluoro proton. Fluorination yields for *N*-fluoro-2,10-(3,3-dimethoxy-camphorsultam) **(7)** were good (55-83 %), however, the enantiomeric excesses were very low (< 5 %).

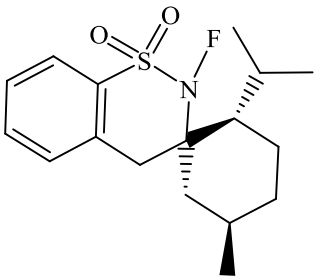
Takeuchi and Shibata synthesised three enantiomeric *N*-fluorosulfonamides, **(8, 9, 10)**, which comprised of a stable but reactive N-F bond and also steric factors that were expected to favour asymmetric induction (Figure 1.5).[21-23]



(8)



(9)

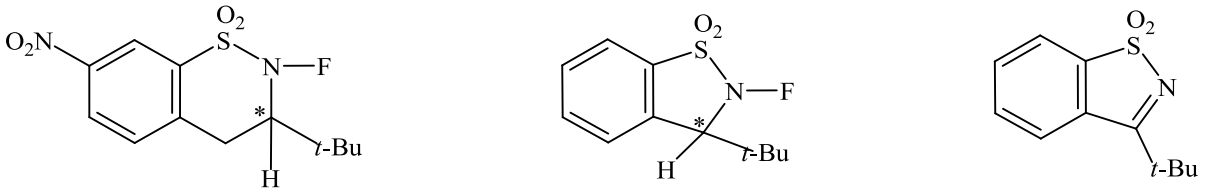


(10)

Figure 1.5 *The three N-Fluorosulfonamides synthesised by Takeuchi and Shibata*

The first *N*-fluorosulfonamide synthesised by Takeuchi and Shibata was *N*-fluoro-3-cyclohexyl-3-methyl-2,3-dihydrobenzo[1,2-*d*]-isothiazole-1,1-dioxide (CMIT-F) **(8)**.[21] This was prepared in five steps, with fluorination in the final step proceeding *via* 15 % F_2/He affording the product in a 65 % yield. CMIT-F **(8)** was reacted with various ketones to evaluate its enantioselective fluorinating ability, with reactions carried out using 1.1-1.3 equivalents of LDA and 1.1-1.3 equivalents of fluorinating agent in THF solution. The optimal result was obtained with 2-benzyl-1-tetralone, which yielded the fluorinated product in 79 % and 88 % *ee*. However, all other enantioselectivities were moderate ranging from 18-74 %.

After developing CMIT-F **(8)** it was evident that the enantioselectivity of the fluorination reaction was dependent on the difference in steric bulk of the two substituents at the chiral centre. Therefore, *N*-fluoro sultam **(11)** was synthesised, however, under reaction conditions with lithium enolates the corresponding imine was formed **(12)**. This was attributed to the acidity of the proton at the chiral centre which leads to HF elimination. (*R*)- and (*S*)-*N*-fluoro-3-tert-butyl-7-nitro-3,4-dihydro-2H-benzo[e][1,2]-thiazine-1,1-dioxides (BNBT-F) **(9)**, were designed with the proton at the chiral centre to be significantly less acidic, but with the differential bulk of the two substituents at the chiral centre to be sufficient to induce high enantioselection (Figure 1.6). The electron-withdrawing nitro group was introduced into the aromatic ring to increase the fluorinating ability of the reagent.[22]



(9) **(11)** **(12)**

Figure 1.6 *The structures of (BNBT-F)* ***(9), (11) and (12)***

The two enantiomers of BNBT-F **(9)** were prepared in three steps, with fluorination in the final step proceeding with $FClO_3$ in THF to afford (*R*) and (S)-**(9)** in 66 % and 83 % yields respectively. Once synthesised their fluorinating ability was tested with a series of tetralones and indanones. Enantioselectivities were moderate to high, ranging from 42-69 %.

The third *N*-fluorosulfonamide, synthesised by Takeuchi and Shibata, was 2-fluoro-14-methyl-11-(methylethyl)-spiro[4*H*-benzo[e]-1,2-thiazine-3,2'-cyclohexane]-1,1-dione **(10)**,

both enantiomers were isolated **(10a** and **10b)**.[23] Asymmetric enolate fluorinations were conducted at -50 ºC, by the addition of 1.2 equivalents of **10a/10b** to the preformed enolates, generated by treatment of 1.5 equivalents of LHMDS with the corresponding ketones. The 11*S*,12*R*,14*R* isomer **(10a)** was found to give modest enantioselectivities ranging from 33-70 % *ee*. The enantioselective fluorination of the lithium enolate of 2-methyl-1-tetralone, exhibited the highest asymmetric induction with 70 % *ee*, 65 % yield. However, 11*S*,12*S*,14*R* **(10b)** was very poor in comparison, with enantioselectivities only ranging from 13-24 % *ee*. Overall, the enantioselectivities obtained were comparable to those obtained by the *N*-fluorocamphorsultams synthesised by Differding[18] and Davis.[20]

1.2.1 $[N\text{-}F]^+$ Reagents

The development of quaternary *N*-fluoro ammonium salts based on the cinchona alkaloids as electrophilic fluorinating agents, was a key development in the area of asymmetric fluorination, and was independently reported by the groups of Cahard and Takeuchi.[24, 25] These are charged $[N\text{-}F]^+$ reagents and have several advantages over neutral N-F reagents. Cinchona alkaloids are readily available and can be fluorinated without the need for highly reactive elemental F_2 or $FClO_3$, previously required for the synthesis of *N*-fluoro-sultams, -camphorsultams and –amines. Cahard initially synthesisied four $[N\text{-}F]^+$ reagents, using the naturally occurring cinchona alkaloids cinchonidine, cinchonine, quinine and quinidine (Figure 1.7).

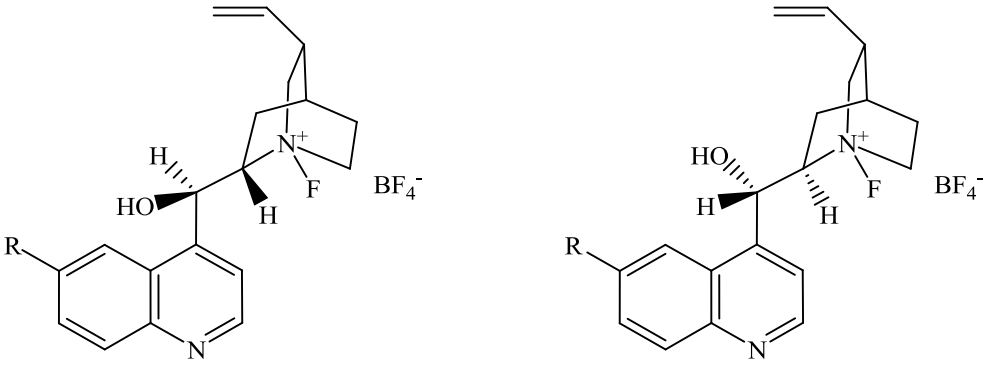
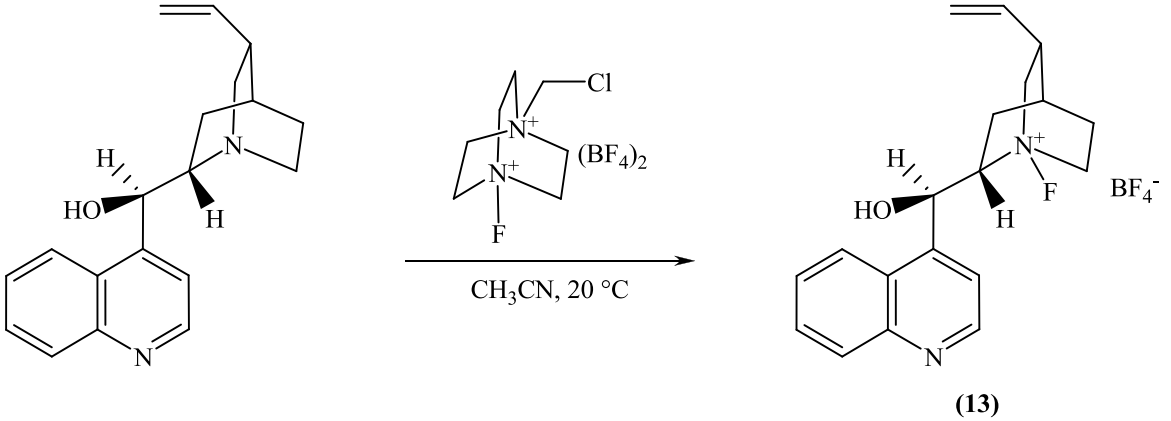


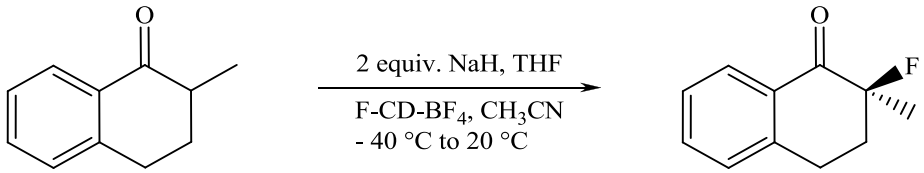
Figure 1.7 *$[N\text{-}F]^+$ Enantiopure fluorinating reagents*

A one step fluorination based on previous work by Banks[26] was conducted; an equimolar mixture of the cinchona alkaloid was stirred with Selectfluor in MeCN at 20 °C, with complete transfer occurring in 20 minutes according to ^{19}F NMR spectroscopy, and workup yielding the desired fluorinated product (Scheme 1.6).



Scheme 1.6 *Synthesis of F-CD-BF_4* ***(13)***

The enantioselective fluorinating ability of the new $[N\text{-}F]^+$ reagents was tested with 2-methyl-1-tetralone. Initially, only moderate yields (40–50 %) were obtained of the 2-fluoro compound, due to the protonation of the enolate by the free hydroxyl group, this was rectified by using two equivalents of base (Scheme 1.7). After which, all four $[N\text{-}F]^+$ reagents afforded the desired fluorinated product in high yield (70–98 %), though moderate enantioselectivities were obtained (20–50 % *ee*), with the highest enantioselectivity induced by F-CD-BF_4 (50 % *ee*).

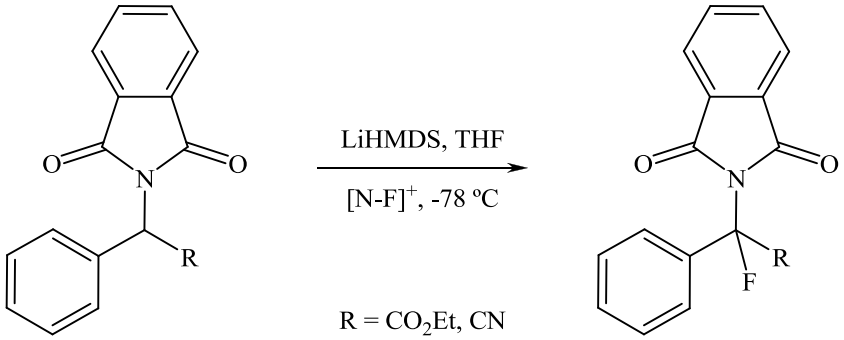


Scheme 1.7 *Fluorination of the Enolate of 2-Methyl-1-tetralone.*

The fluorinating ability of F-CD-BF_4 **(13)** was tested with various substrates. Although the enantioselectivities obtained were moderate and not always an improvement on previous results using neutral [N-F] reagents, the yields were substantially higher (80-98 %), suggesting that charged $[N\text{-}F]^+$ reagents had a greater fluorinating ability. Additionally, $[N\text{-}F]^+$ reagents are less substrate dependent and therefore allow the trimethyl silyl enol ether of 2-methyl-1-tetralone to be fluorinated. Higher enantioselectivity was obtained than that for the fluorination of enolates, with addition of sodium hydroxide to the fluorinating agent aiding reactivity and stereoselectivity. F-CD-BF_4 afforded the fluorinated product in a 93 % yield and 61 % *ee* which was the highest of the $[N\text{-}F]^+$ reagents.

In 2001, Cahard further utilised the $[N\text{-}F]^+$ reagents by achieving the first enantioselective α-fluorination of α-amino acid derivatives. The synthesis was based upon reacting the preformed ester enolate or nitrile anion with the modified *N*-fluoro cinchona alkaloids. However, the $[N\text{-}F]^+$ reagents based upon naturally occurring cinchona alkaloids afforded

poor to moderate enantioselectivities (7-48 %), attributable to the unprotected hydroxyl group. Therefore, a new range of $[N\text{-}F]^+$ reagents were synthesised, where the hydroxyl group on the alkaloid was protected using acetyl and benzoyl groups. These were used to fluorinate a range of imido-protected (phthaloyl, tetrachlorophthaloyl, succinoyl, dimethylmaleoyl) phenylglycine esters (methyl, ethyl, benzyl), phenylglycinonitrile, and phenylglycine *N,N*-diethylamides. Work was concentrated on *N*-phthaloyl-α-aminophenyl glycine ethyl ester and phenyl glycinotrile, as the phthaloyl amino protecting group induced a higher degree of enantioselectivity than the succinoyl and dimethylmaleoyl protected compounds.

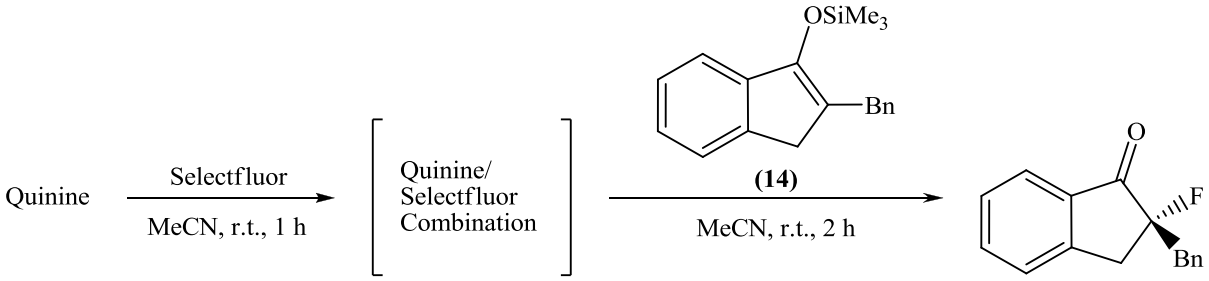


Scheme 1.8 *Enantioselective electrophilic fluorination of N-phthaloylphenylglycine derivatives using various $[N\text{-}F]^+$ cinchona alkaloids*

The enantioselectivities obtained were higher for *N*-phthaloylphenylglycinonitrile than those for *N*-phthaloylphenyl glycine ethyl ester. It was also observed that enantioselection was greater when quinine and quinidine fluorinating agents were used, suggesting that methoxy substituents on quinoline participate in the stereoselection. Another important factor in obtaining high enantioselectivities was protection of the hydroxyl group. For the ester derivatives, acetyl protection yielded higher enantioselectivities than the benzoyl, however, the opposite was true in the case of the nitrile derivatives. No improvement was found in the enantioselectivity by modifying the nature of the *para* substituents on the benzoyl protecting group. Fluorination of *N*-phthaloyl phenylglycinonitrile with O-(*p*-methoxybenzoyl)-*N*-fluoroquinium tetrafluoroborate afforded the highest enantioselectivity, 94 % *ee*.

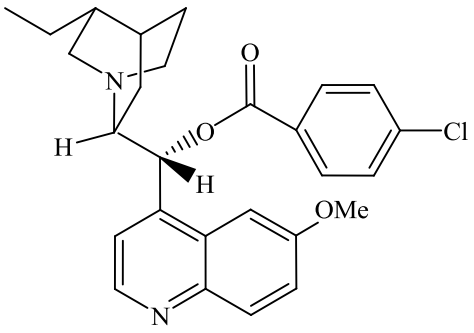
Shibata's group also synthesised $[N\text{-}F]^+$ reagents using cinchona alkaloid derivatives such as dihydroquinine 4-chlorobenzoate (DHQB) and dihydroquinidine acetate (DHQDA).[25, 27] However, they were only used *in situ* and synthesised by stirring Selectfluor (1.2 equivalents) and the cinchona alkaloid (1.2 equivalents) in anhydrous MeCN with 3 Å molecular sieves at room temperature for 1 hour. Firstly the fluorination of 2-benzyl-3H-inden-1-yloxy-trimethyl-silane was attempted with the fluorinating reagent prepared *in situ*

from quinine and Selectfluor. The product was obtained in an 80 % yield and moderate 40 % *ee* (Scheme 1.9).



Scheme 1.9 *Fluorination of* ***(14)*** *by Quinine/Selectfluor combination*

In order to improve upon this, numerous commercially available cinchona alkaloids were screened. Both DHQB **(16)** and hydroquinine 1,4-phthalazinediyl diether ((DHQ)$_2$PHAL) were found to yield the desired fluorinated product as the (*R*) stereoisomer, with enantioselectivities greater than 80 % in MeCN at 0 °C. DHQB **(16)** was used for further fluorinations simply because it was the cheaper reagent. Various silyl enol ethers were tested affording the corresponding 2-fluoro indanones and 2-fluoro tetralones in high yields (71-99 %) and moderate enantioselectivities (42-73%).

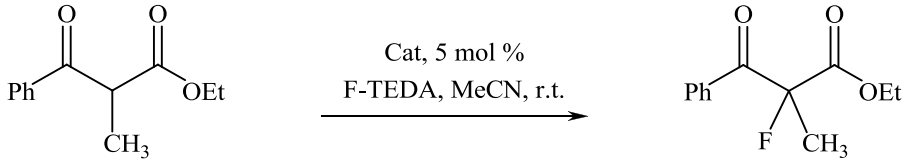


(16)

Figure 1.8 *DHQB* ***(16)***

1.2.2 Asymmetric Catalysis

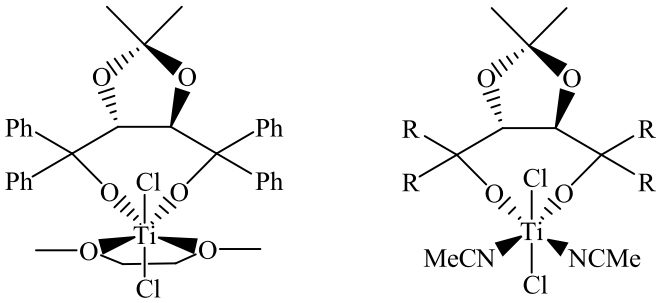
In 2000 the first example of a catalytic asymmetric fluorination of β-ketoesters was reported by Togni.[28] This work was based on previous studies by Umemoto[29] that had shown that the reactivity of 1,3-dicarbonyls in the presence of [N-F]$^+$ reagents was increased by the addition of stoichiometric amounts of a Lewis acid, such as zinc chloride. The Lewis acid significantly accelerated product formation, attributed to the triggering of the enolisation process. Togni's group therefore intended to use a chiral non-racemic transition-metal Lewis acid to promote the enolisation process enabling production of optically active α-fluorinated 1,3-dicarbonyl compounds.



(17) **(18)**

Scheme 1.10 *Fluorination of (17)*

The monosubstituted β-ketoester **(17)** was found to be unreactive with a saturated solution of Selectfluor in MeCN at room temperature. A range of Lewis acids were evaluated, including $ZnCl_2$, HCl and BF_3, however, the titanium-based Lewis acids ($TiCl_4$, [$CpTiCl_3$]), previously synthesised by Seebach,[30] were found to be the most effective. Therefore, after screening a vast quantity of known chiral enantiopure Lewis acidic Ti complexes, it was found that with 5 mol % of *in situ* prepared [$TiCl_2$(*R,R*-TADDOLato)] a swift reaction of racemic β-ketoester **(17)** with Selectfluor took place yielding the fluoro- β-ketoester **(18)** in good yield and with a 28 % *ee*. Two catalysts were tested **(19)** and **(20)**, isolated in high yields (85-90%) as air-stable DME **(19)** and MeCN **(20)** crystalline adducts. In both cases the isolated catalysts gave more consistent results than the *in situ* generated species previously described.



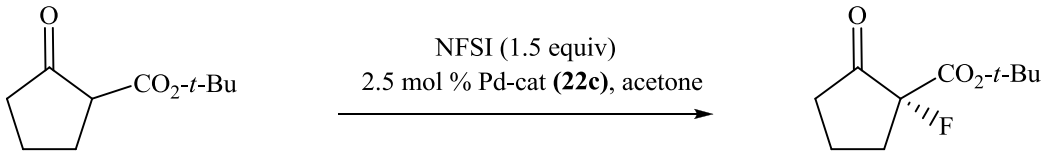
R = naphthyl

(19) **(20)**

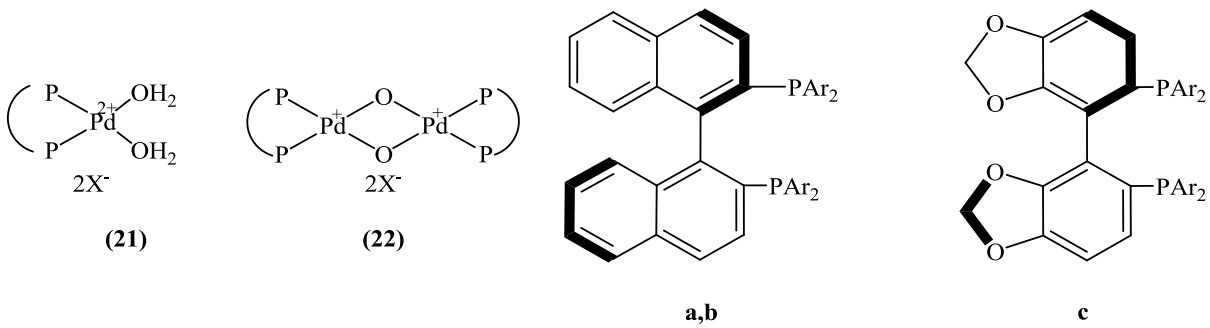
Figure 1.8 *Catalysts (19) and (20)*

The catalytic enantioselective fluorination reactions using isolated [$TiCl_2$(TADDOLato)] complexes were conducted at room temperature in a closed vessel with a slight excess of saturated Selectfluor solution in MeCN, products were obtained in high yield (80- 95 %). The results also indicated that the steric bulk of the catalyst was important, as all substrates gave higher enantioselectivities when reacted with **(20)**. It is assumed that interaction of the β-ketoester with the catalyst triggers an enolisation reaction and that the coordinated enol/enolate is the reactive form of the substrate susceptible to external electrophilic attack by the fluorinating agent. Hence, the role of the Lewis acid is to activate the nucleophile and not to enhance the electrophilicity of the coordinated carbonyl group.

Sodeoka also focused on the enantioselective fluorination of β-ketoesters, reporting an efficient catalytic system for enantioselective electrophilic fluorination based on palladium complexes (Figure 1.9).[31] Recent findings had shown that a chiral palladium enolate could be formed directly from β-ketoesters using palladium complexes **(21)**/**(22)** (Figure 1.9) and reacted with enone to give a highly optically active Michael product.[32] Therefore, the reaction of *t*-butyl 2-oxo-cyclopentanecarboxylate was examined under various conditions. NFSI was the most effective of the fluorinating reagents tested, and its reaction with *t*-butyl-2-oxo-cyclopentanecarboxylate and 5 mol % **(21a)** in THF gave the desired product in 72 % yield, with 79 % *ee*. The palladium complex retained its catalytic activity, despite the formation of a sulfonimide [$(PhSO_2)_2NH$] during the reaction. In order to improve the enantioselectivity a series of chiral phosphine ligands were studied and substituents at the *meta* positions of the aryl group on the phosphine were found to be important. Enantioselectivities increased to 88 and 80 % when R = DM-BINAP and R = DTBM-SEGPHOS were used. The reaction was also found to proceed more rapidly in polar solvents, with the yield improving in acetone (Scheme 1.11), and the reaction accelerating in ethanol with completion in 18 hours without any loss of enantioselectivity.



Scheme 1.11 *Formation of* ***(23)***

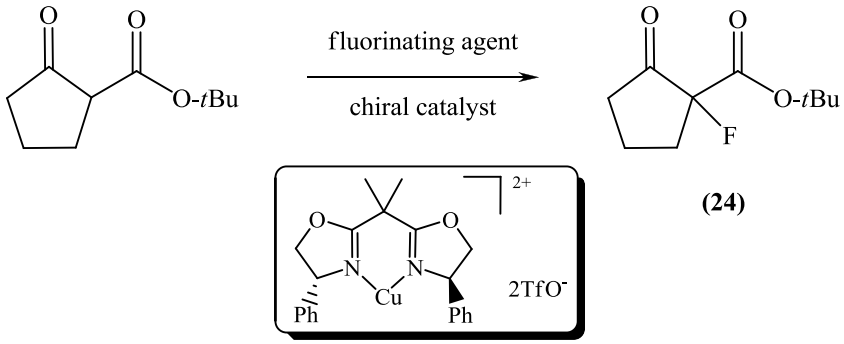


a: Ar = Ph: (*R*)-BINAP
b: Ar = 3,5-$Me_2C_6H_3$: (*R*)-DM-BINAP
c: Ar = 3,5-$Me_2C_6H_3$: (*R*)-DM-SEGPHOS

Figure 1.9 *Palladium catalysts* ***(21)*** *and* ***(22)***

More recently Ma and Cahard have utilised enantiopure *bis*oxazoline-copper (II) complexes as catalysts in the enantioselective electrophilic fluorination of β-ketoesters.[33] Various

fluorine donors, Lewis acids and chiral ligands were screened in order to optimise reaction conditions for the enantioselective fluorination of 1-fluoro-2-oxo-cyclopentanecarboxylic acid *tert*-butyl ester **(24)** which was used as a model compound (Scheme 1.12).



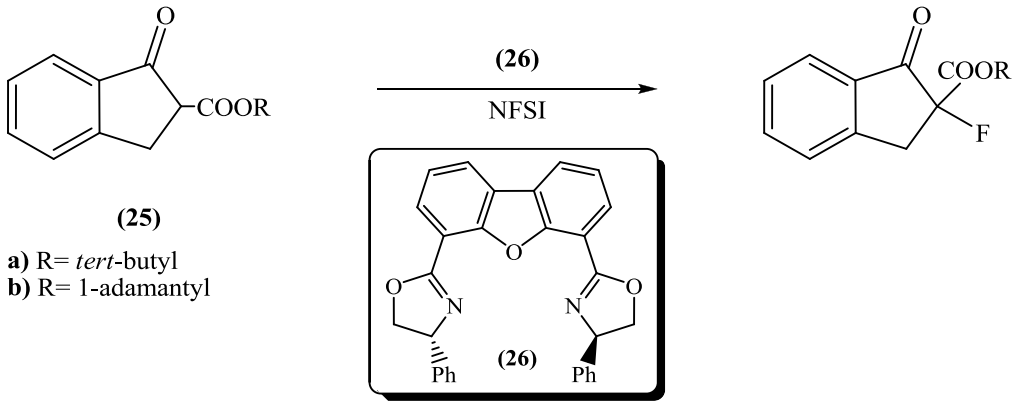
Scheme 1.12 *Formation of* ***(24)***

NFSI was found to be the best fluorine source, while the use of toluene and diethyl ether as solvents resulted in higher enantioselectivities. The metal ion was also important in order for the reaction to work, with both Cu(II) and Zn(II) possessing the properties necessary for both *in situ* generation of the enolate species and the stereoselectivity of the reaction. Stereoselectivity was also found to be independent of the reaction temperature. In order to increase enantioselectivities achiral additives were screened, with the addition of one equivalent of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) increasing enantioselectivities to 85 %. The role of HFIP was to promote the release of fluorinated product from the catalyst, in order to assist catalyst turnover.

After optimising reaction conditions, the enantioselective fluorination of a range of cyclic and acyclic β-ketoesters was carried out, to afford the corresponding fluorinated adducts in good to excellent yields (56-96 %) and enantioselectivities (35-85 %).

Recent work by Shibata demonstrated that (*S*, *S*)-*bis*(oxazoline)-Ph **(26)** can be used to synthesise both enantiomers of target fluorinated compounds, when the metal coordinated is altered.[34] The Cu(II) and Ni(II) bisoxazoline complexes were tested with NFSI in fluorination reactions, using the model compounds *t*-butyl 1-indanone-2-carboxylate **(25a)** and 1-adamantyl 1-indanone-2-carboxylate **(25b)**. The configuration of the major product was (*S*) when the chiral ligand was coordinated to Cu(II), however, when Ni(II) was used the (*R*) configuration was obtained. The enantioselectivities were found to be dependent on the solvent used, especially in the case of Ni(II)-catalysed reactions. Substrate **(25a)** afforded the fluorinated product in a 71 % *ee* when DCM was the solvent, however this

dropped dramatically to 1 % *ee* when THF was used. Conversely, the enantioselectivity was found to improve substantially (93 % *ee*) when the reaction was conducted in the presence of 4 Å molecular sieves, and the temperature increased to 20 °C. Substrate **(25b)** gave moderate enantioselectivities and yields for both Ni(II) and Cu(II)-catalysed reactions. The best result achieved for Cu(II) was 84 % *ee*, obtained at 20 °C with TBMe, 79 % *ee* was afforded for Ni(II) at 20 °C in DCM.

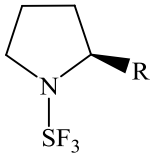


Scheme 1.13 *Fluorination of* ***(25a)*** *and* ***(25b)****, with (S, S)-Bis(oxazoline)-Ph* ***(26)***

Shibata has also utilised the Dbfox-Ph ligand coordinated to a Ni(II) centre to fluorinate carbonyl compounds capable of two-point binding.[35] Previous work by the group had found the Dbfox-Ph ligand to be highly effective in asymmetric Diels-Alder and Michael addition reactions.[36] Reactions were conducted by treating a solution of the β-ketoester in DCM with 1.2 equivalents of NFSI in the presence of a catalytic amount of dbfox-Ph/Ni(ClO_4).6H_2O at room temperature, to afford the α-fluoro compound in good yield (76 %) and high enantioselectivity (99 %). A variety of β-ketoesters were examined, all affording the fluorinated product in good yields and excellent enantioselectivities. The dbfox-Ph/Ni^{II} catalyst exhibited excellent enantioselectivity in comparison to previously reported procedures; this is attributable to the control of the enantioface of enolates by the dbfox-Ph/Ni^{II} complex. However, the fluorination reaction only occurred with high enantioselectivity for the substrates containing sterically bulky substituents located on the ester side. For the β-keto esters with methyl or cyclohexyl ester groups, slightly lower enantioselectivities were obtained (R= Me, 65 % *ee*; R= c-C_6H_{11}, 91 % *ee*). It was also found that the catalyst loading could be lowered to 2 mol % without loss of enantioselectivity. To further investigate the potential efficacy of the dbfox-Ph/Ni^{II} fluorination system, pharmaceutically important fluorooxindoles were also tested. Maxipost (used to treat ischemic stroke) was obtained in a good 71 % yield and excellent 93 % ee. This was the first example of a catalytic enantioselective preparation of Maxipost.

1.3 Enantioselective Nucleophilic Fluorination

Enantioselective nucleophilic fluorination was first attempted in 1989 by Hann and Sampson.[37] Their aim was to develop homochiral aminofluorosulphuranes as potential enantioselective fluorinating agents. A homochiral anologue of DAST was therefore synthesised where R= CH_2OMe **(27)** (Scheme 1.14).

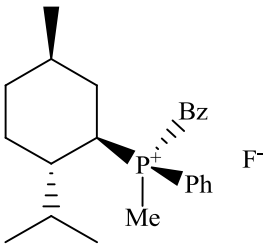


(27) R = CH_2OMe

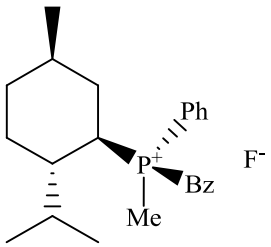
Scheme 1.14 *Homochiral anologue of DAST* ***(27)***

Fluorination of racemic 2-(trimethylsiloxy)octane using 1.1 equivalents of **(27)** in DCM for 5 hours at -78 °C, yielded a 74/26 mixture of 2-fluorooctane and alkenes. In order to evaluate the enantiodiscriminating ability of **(27)**, kinetic resolution studies were conducted. The reaction of 2-(trimethylsiloxy)octane with 0.5 equivalents of **(27)**, afforded an 8 % kinetic resolution. Whilst the reaction of racemic ethyl-2-(trimethylsiloxy)propanoate with 0.5 equivalents of **(27)** at 0 °C for 4 hours afforded ethyl 2-fluoropropanoate in a disappointing 16 % *ee*.

Beaumont *et al.* took a similar approach and synthesised two chiral quaternary phosphonium fluorides with chiral alkyl groups and asymmetric phosphonium centres in 2000 (Figure 1.11).[38] It was proposed that chiral quaternary ammonium and phosphonium fluorides would have interesting properties as novel reagents for simple asymmetric nucleophilic fluorination. Initial studies showed that the phosphonium compounds were more effective reagents than the ammonium salts and were therefore considered in more detail.



(28)

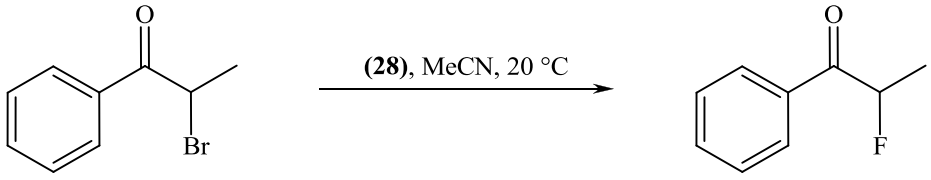


(29)

Figure 1.11 *Diastereomeric benzylmenthylmethylphenylphosphonium fluorides* ***(28)*** *&* ***(29)***

Diastereomeric benzylmenthylmethylphenylphosphonium fluorides **(28)** and **(29)**, with *R* and *S* configuration at phosphorus were synthesised from the diastereomers of menthyl-methylphenylphosphine. In order to test the abilities of **(28)** and **(29)** as asymmetric nucleophilic fluorinating reagents, a two-fold excess of **(28)** was reacted with racemic 2-

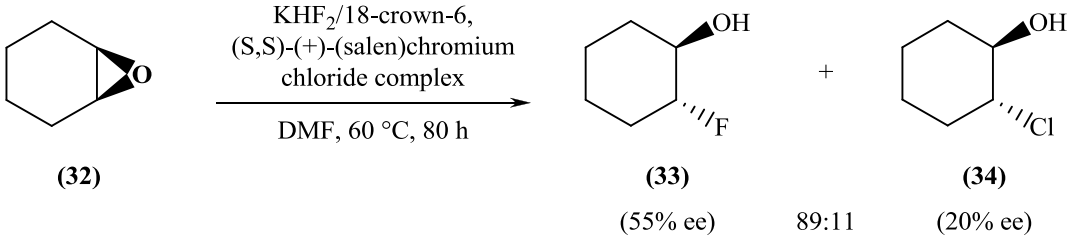
bromopropiophenone **(30)** in MeCN at room temperature (Scheme 1.15). The reaction was followed by gas chromatography and after 38 hours, conversion to 2-fluoropropiophenone **(31)** had occurred in a 40 % yield. The reaction was then quenched and the product isolated, an excess of the (+) enantiomer had formed by kinetic resolution of racemic starting material.



(30) **(31)**

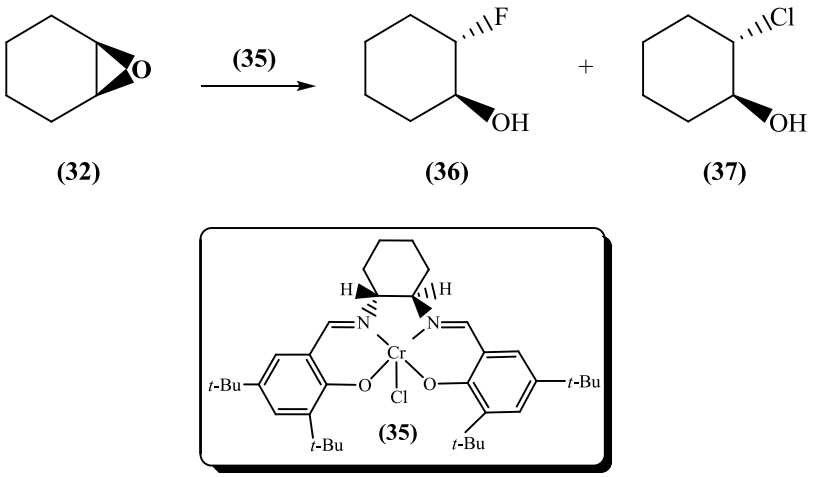
Scheme 1.15 *Asymmetric fluorination of 2-bromopropiophenone by* ***(28)***

Enantioselective ring opening of *meso*- or racemic epoxides by nucleophilic reagents in the asymmetric synthesis of 1,2-disubstituted compounds has been accomplished with many different types of nucleophiles.[39] Examples of which are carbon nucleophiles,[40] thiols,[41] phenols,[42] aromatic amines,[43] azide,[44] cyanide and chloride, bromide or iodide, mediated or catalysed by different Lewis acids[45] although there had been no reports involving the use of fluoride. Drawing on evidence from previous studies where it had been observed that: (i) in order to obtain high enantioselectivity in the ring opening of epoxides an S_N2-like mechanism was desirable,[45] (ii) that Lewis acid activation and nucleophilic attack of the fluoride equivalent should be concerted or direct delivery of a nucleophile should take place from a metal centre; (iii) that Jacobsen's salen complexes were useful catalysts for enantioselective epoxide ring opening with azides,[46-48] Haufe and Bruns were the first to report the asymmetric ring opening of *meso*- and racemic- epoxides by hydrofluorinating reagents mediated by enantiopure Lewis acidic metal complexes.[49] Cyclohexene oxide **(32)** was reacted with KHF_2/18-crown-6 and 100 mol% of (*S,S*)-(+)-(salen)chromium chloride complex in DMF at 60 ºC (Scheme 1.16). After 80 hours, 92 % of the epoxides had been consumed, yielding (*R,R*)-(-)-2-fluorocyclohexanol **(33)** (55 % *ee*) and (*R,R*)-(-)-2-chlorocyclohexanol **(34)** (20 % *ee*) in the crude product mixture. The reaction was repeated with only 10 mol % of (*S,S*)-(+)-(salen)chromium chloride complex, however, the reaction temperature had to be increased to 100 ºC which caused the enantioselectivities to drop, with products **(33)** and **(34)** formed in a 94:6 ratio but **(33)** showing only 11 % *ee*. The formation of the chlorohydrin may be due to partial transfer of chloride directly from the complex to the epoxide (S_N2 reaction).



Scheme 1.16 *Fluorination of* ***(32)***

In 2001 further work was conducted by Bruns and Haufe;[50] reactions of various fluoride sources for the asymmetric ring opening of cyclohexene oxide were examined in order to overcome some of the drawbacks of KHF_2, such as low solubility.[49] However, in this case (*R,R*)-(-)-(salen)chromium chloride complex **(35)** was examined as the catalyst (Scheme 1.17).



Scheme 1.17 *Asymmetric ring opening of cyclohexene oxide* ***(32)***

Initially several different fluorinating reagents were tested such as TREAT HF, Olah's reagent and silver fluoride (AgF). However, after optimisation of reaction conditions in order to lessen the formation of chlorohydrin, which was occurring as a result of direct transfer of chloride from **(35)** to the epoxide, AgF was utilised as the fluoride source with MeCN as the solvent in order to increase the solubility of AgF. The reaction of cyclohexene oxide and other *meso*- and racemic epoxides with AgF in MeCN with varying amounts of catalyst **(35)**, led to the formation of the fluorinated compound as the sole product, in excellent yields (75-90 %) and moderate to good enantioselectivities (44-74 %). Not all of the epoxides tested gave the desired product. Cyclooctene oxide gave no reaction at all, while racemic tetrahydronapthalene oxide formed both the *trans* and *cis* fluorohydrins in a 2:1 ratio. The *trans* product gave 23 % *ee*, whilst the *cis* only 2 % *ee*, this was due to the fact that two competing reaction pathways are occurring; the *cis* product is formed following an S_N1- like reaction path, whilst the *trans* follows the S_N2 process.

1.4 Building Block Approach to Organofluorine Compounds

Fluorinated building blocks are small readily available materials that already contain fluorine atoms, and for this reason they are extremely valuable in synthetic chemistry as they negate the use of hazardous fluorinating reagents such as DAST. There are numerous papers that discuss their uses and a selective review of mono-, di- and tri-fluorinated building blocks will be presented here.

Chlorofluorocarbenes are extremely useful building blocks due to the fact that they react with electron rich alkenes, such as enol ethers and the corresponding products, alkoxycyclopropanes, can undergo solvolysis reactions leading to α-fluoro-*Z*-enals. These are extremely valuable and have been utilised by Johnson *et al.* in the synthesis of steroid analogues.[51-54]

Fluoroalkenes and *gem*-difluoroalkenes are highly reactive towards nucleophilic attack at the fluorinated sp^2 carbon due to 3 factors, i) high electron deficiency on the *gem*-difluoromethylene carbon, ii) thermodynamic instability of sp^2 hybridised fluoroalkenes in comparison with sp^3 hybridised fluoroalkanes and iii) the formation of stable sp^3 hybridised β-fluorocarbanions (Figure 1.10).

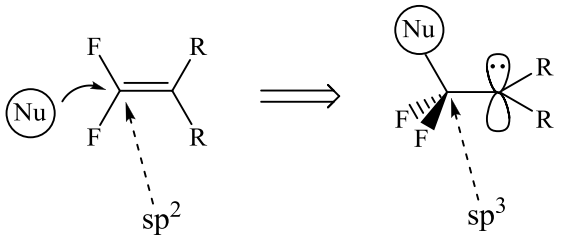


Figure 1.10 *Stable sp^3 hybridised β-fluorocarbanion*

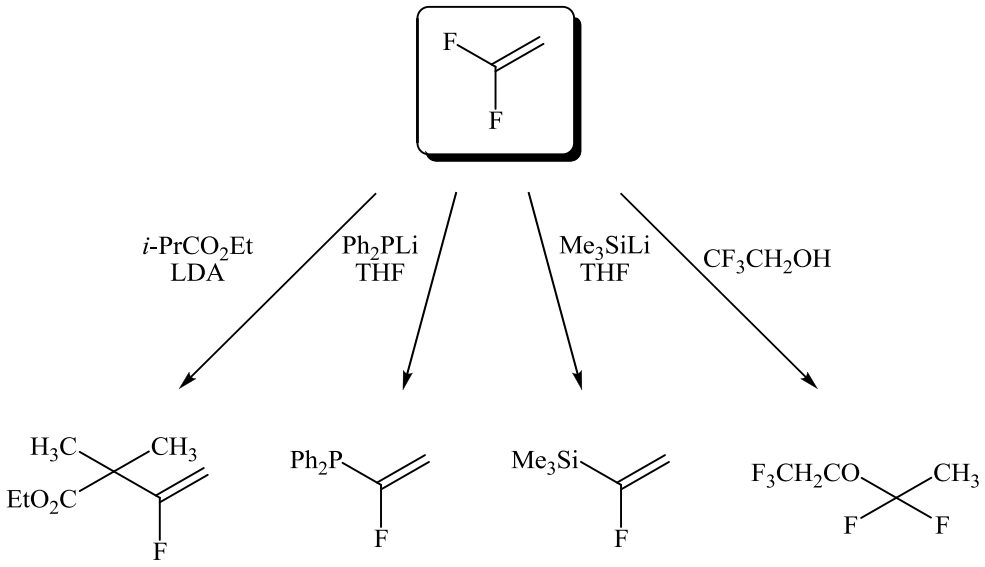
Hence, nucleophiles attack exclusively at the *gem*-difluoromethylene carbon atoms of difluoroalkenes to form the corresponding β-fluorocarbanions. The subsequent reaction pathways can be classified into three groups:

(i) Addition-elimination, which is conducted with metal nucleophiles in aprotic solvents. Here, the carbanion undergoes defluorination affording the product as an α-substituted monofluoroalkene.

(ii) 1,2 addition, which can be conducted with any nucleophile in a protic solvent or with protic nucleophiles (amines and alcohols) or electrophiles in aprotic solvents, where the carbanion can be trapped by either an electrophile or proton in order to yield the addition product.

(iii) S_N2' type substitution. Here, substrates must have a leaving group on the γ-carbon of the carbanion (eg. alkoxy or acyloxy) in order to give the corresponding substituted difluoromethyl ketones.

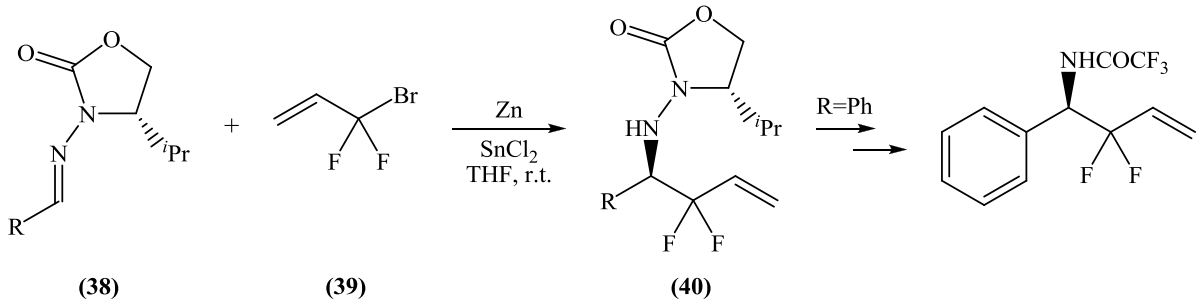
Therefore, 1,1-difluoroethene is an invaluable building block that can react with a variety of nucleophiles as summarised in Scheme 1.18, with the corresponding products obtained in good to excellent yields (56-86 %).[55-58]



Scheme 1.18 *Typical reactions of 1,1-difluoroethane*

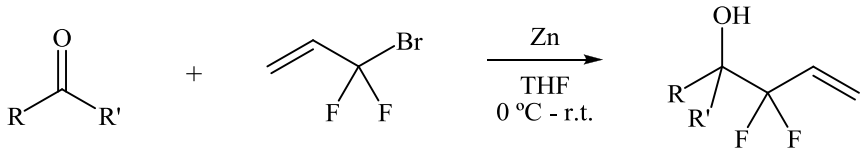
In more recent work Yue *et al.* have developed an efficient route to chiral *gem*-difluorohomoallylic amines by the reaction of *gem*-difluoroallylic zinc with chiral hydrazones in the presence of $SnCl_2$.[59] These are an important series of compounds that are integral in biological chemistry and natural product modification. Previous routes to these compounds have been *via* direct fluorination of allylic ketones with DAST, affording the corresponding products in poor yields,[60] and the conversion of a chiral *gem*-difluorohomoallylic alcohol into an amine.[61] The zinc mediated reaction of **(39)** with **(38)** was screened in the presence of several Lewis acids; the use of 2 equivalents of $SnCl_2$ successfully afforded the desired product in a moderate 41 % yield, with only one diastereoisomer observed in the ^{19}F NMR spectrum. Further optimisation of the reaction conditions found that when the reaction was conducted with 5 equivalents of zinc and 0.4 equivalents of $SnCl_2$ the product was formed in 92 % yield. The reaction conditions were then tested with a variety of chiral hydrazones. It was found that electron-rich aryl hydrazones afforded moderate yields of the product (42-61 %) with high diastereoselectivity (47/1 and 57/1), whilst hydrazones bearing electron-deficient substituents, provided the corresponding products in good yields (70-79 %) with excellent diastereoselectivities (18/1-single). Alkyl substituted hydrazones yielded the product in good yields (67-76 %) and as

single diastereoisomers. Further reaction of **(40)** (R = Ph) with trifluoroacetic anhydride followed by exposure of the resulting *N*-trifluoroacylated hydrazine to SmI_2 yielded the desired *gem*-difluorohomoallylic amine in 55 % with >99 % ee (Scheme 1.19).



Scheme 1.19 *Synthesis of gem-difluorohomoallylic amine*

Previously, 3-bromo-3,3-difluoropropene **(39)** had been utilised by Burton and Yang[62, 63] who had developed a route to the direct allylation of aldehydes and ketones *via* the *in situ* reaction of 3-bromo-3,3-difluoropropene with acid washed zinc powder and carbonyl substrates. This method circumvented issues such as the use of thermally unstable intermediates as well as competitive reactions of the carbonyl substrates with *n*-butyllithium, issues which had previously been a hindrance to Seyferth.[64-66] Products were obtained in moderate to good yields (45-73 %) (Table 1.2).

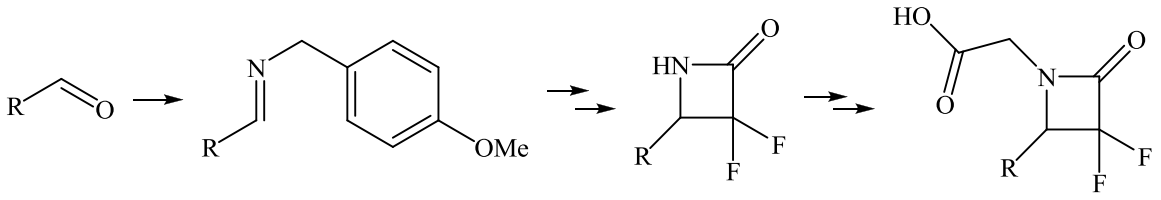


R	R'	Product	Yield (%)
C_6H_5	H	$C_6H_5CH(OH)CF_2CH{=}CH_2$	67
n-C_6H_{13}	H	*n*-$C_6H_{13}CH(OH)CF_2CH{=}CH_2$	53
i-Bu	Me	*i*-$BuC(OH)(Me)CF_2CH{=}CH_2$	55
C_6H_5	Me	$C_6H_5C(OH)(Me)CF_2CH{=}CH_2$	45
C_6H_5	CF_3	$C_6H_5C(OH)(CF_3)CF_2CH{=}CH_2$	73
p-MeC_6H_4	CF_3	*p*-$MeC_6H_4C(OH)\ (CF_3)CF_2CH{=}CH_2$	69

Table 1.2 *Reactions of aldehydes and ketones with Zn activated 3-bromo-3,3-difluoropropene*

Boyer and co-workers utilised ethyl bromodifluoroacetate as a building block in their synthesis of *gem*-difluorinated β-lactams amd *gem*-difluorinated β-amino acids.[67] β-amino acids are pharmacologically important compounds[68, 69] and the presence of the difluoro moiety in β-amino acids has been shown to have positive effects by improving the

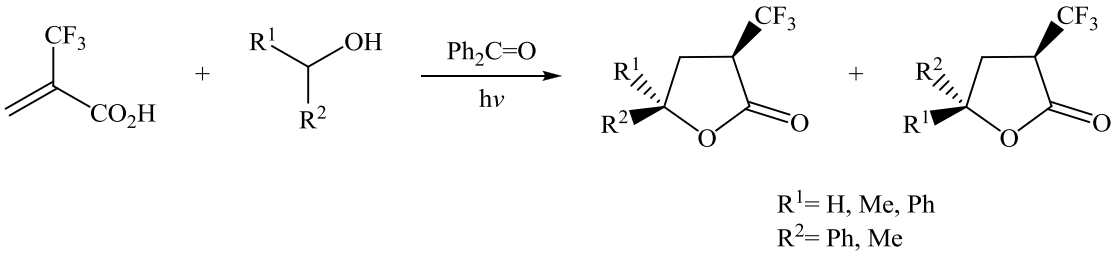
cytotoxicity in the chemotherapy drug Taxotere. Therefore, *gem*-difluorinated β-lactams and β-amino acids, both possessing basic functional groups, were synthesised from ethyl bromodifluoroacetate and their preceding imines (β-lactams) (Scheme 1.20) or *N*-(α-aminoalkyl) benzotriazoles (β-amino esters). After *N*-alkylation of the *gem*-difluoro-β-lactams and *N*-acylation of the *gem*-difluoro-β-amino esters had been conducted the corresponding potential metallocarbopeptidase inhibitors were obtained in moderate to good yields (25-56 %).



Scheme 1.20 *General reaction scheme for synthesis of gem-difluoro-β-lactams*

The substitution of methyl groups by trifluoromethyl groups has become particularly important in the pharmaceutical industry. The strong covalent bonding of the C-F bond in comparison to the C-H bond (116 kcal/mol *vs.* 100 kcal/mol)[70] can ensure that unwanted metabolic transformations are avoided, whilst the C-F bond also increases lipophilicity of the molecule, improving the overall pharmokinetic properties of drug candidates.[71] Additionally, the similarity in size of CF_3 and CH_3 ensures that the activity of a drug is unhindered, *i.e.* a similar drug-protein interaction will occur.

2-(trifluoromethy)acrylic acid was utilised by O'Hagan and co-workers as a building block for the synthesis of 4-substituted 2-trifluoromethyl-γ-butyrolactones (Scheme 1.21).[72] The reaction was conducted by the addition of primary and secondary alcohols to 2-(trifluoromethy)acrylic acid in the presence of benzophenone under UV light, with the corresponding products obtained as diastereoisomers.



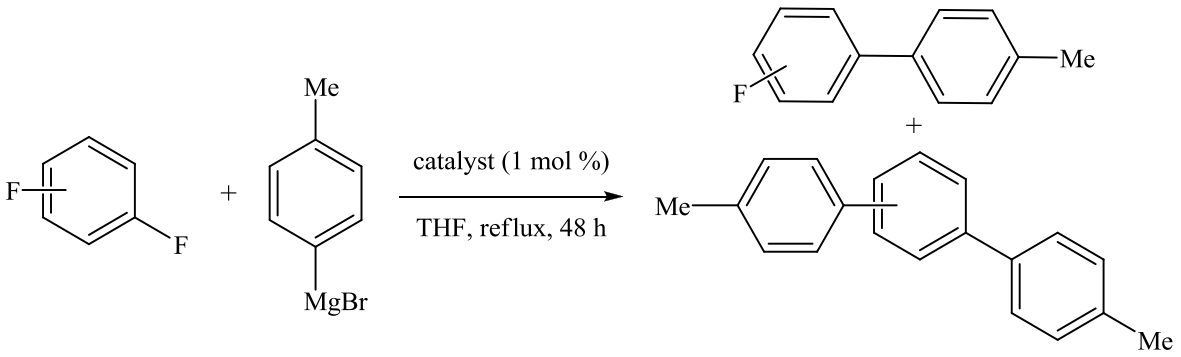
Scheme 1.21 *Synthesis of 4-substituted 2-trifluoromethyl-γ-butyrolactones*

1.5 C-F Activation

Carbon-fluorine bond activation though less explored than carbon-fluorine bond formation is invaluable, especially in the synthesis of partially fluorinated compounds which would be otherwise inaccessible or more difficult to prepare.

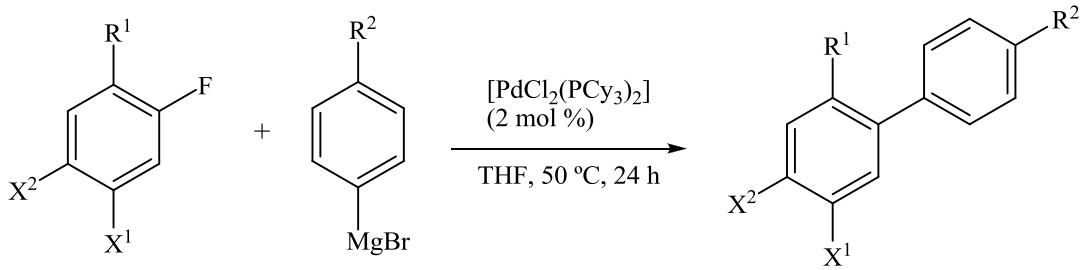
1.5.1 Aromatic Fluorides

The cross-coupling reaction with selective C-F activation of polyfluoroarenes is a useful tool for the synthesis of partially fluorinated aromatics. Recent work by Saeki *et al.*[73] has examined the cross-coupling reaction of 1,2-, 1,3- and 1,4-difluorobenzenes with *p*-tolyl magnesium bromide. Initially the optimised reaction conditions from the reaction of monofluorobenzene were used ([$NiCl_2$(dppp)] (0.01 equivalents) *p*-tolylmagnesium bromide (1.5 equivalents)), however, this afforded a mixture of both the mono-coupled and di-coupled products, whilst increasing the amount of Ni catalyst and *p*-tolylmagnesium bromide simply increased formation of the undesired di-coupled product. Therefore, the catalyst was replaced by [$PdCl_2$(dppf)], which was found to be far more effective, with formation of the mono-coupled product exclusively in 91 % yield. However, this was only in the case of 1,2-difluorobenzene. With 1,3 and 1,4-difluorobenzene, although only the mono-coupled products were formed, the yields obtained were substantially lower 15 % and 6 % respectively (Scheme 1.22). Therefore, it was proposed that the chelating effect of the adjacent fluorine atom in 1,2-difluorobenzene was integral in promoting the oxidative addition of the fluorine bond. Extension of this protocol was also applied to trifluorobenzenes where it was found that [$PdCl_2(PPh_3)_2$] and [$PdCl_2$(dppf)] were better at yielding the desired mono-coupled product than [$NiCl_2$(dppp)]. With 1,2,3-trifluoro benzene, the Pd catalysed reaction afforded the corresponding mono-coupled product in 69 % yield, whilst with the Ni catalyst 41 % of the di-coupled product was afforded, with none of the mono-coupled one. A similar scenario was observed with 2,4,6-trifluorobenzene, where the Pd catalysed reaction afforded the desired mono-coupled product in 60 % yield whilst the Ni catalyst afforded 60 % of the tri-coupled product.



Scheme 1.22 *Cross-coupling reaction of 1,2-, 1,3- & 1,4-difluorobenzenes with p-tolylMgBr*

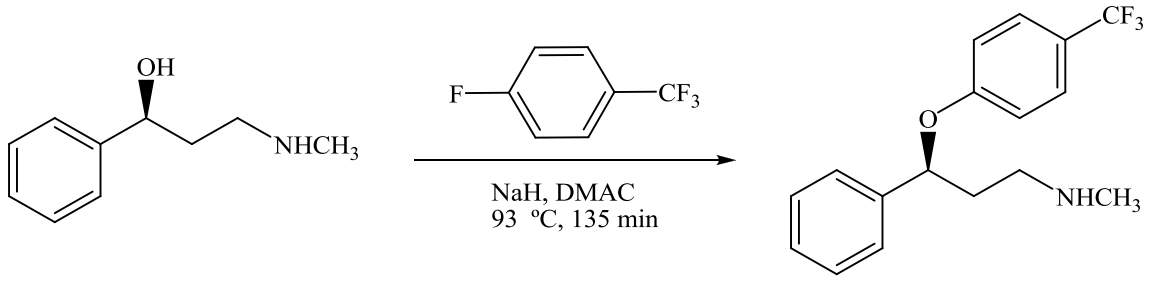
Manabe and Ishikawa[74] reported the first examples of *ortho*-selective cross-coupling reactions of fluorobenzene bearing electron-donating groups. After screening several Pd catalysts, dichloro*bis*(tricyclohexylphosphine) palladium [$PdCl_2(PCy_3)_2$] was found to be the most effective and was utilised in reactions with chlorofluorophenol, difluorophenols and fluorobenzenes bearing hydroxymethyls and amino groups, affording the corresponding products in good to excellent yields (49-85 %). The reaction protocol was also extended to fluorophenylmagnesium bromide with fluorophenol and difluorophenol both affording the corresponding product in excellent yields (74-85%).



R^1= OH, R^2=H - 81 % (X^1=Cl, X^2=H)
R^1= OH, R^2=H - 85 % (X^1=F, X^2=H)
R^1= OH, R^2=CH_3 - 79 % (X^1=H, X^2=F)
R^1= CH_2OH, R^2=OCH_3 - 81 % (X^1=H, X^2=F)
R^1= NH_2, R^2=OCH_3 - 49 % (X^1=Cl, X^2=H)

Scheme 1.23 *Ortho-selective cross-coupling reactions of fluorobenzene*

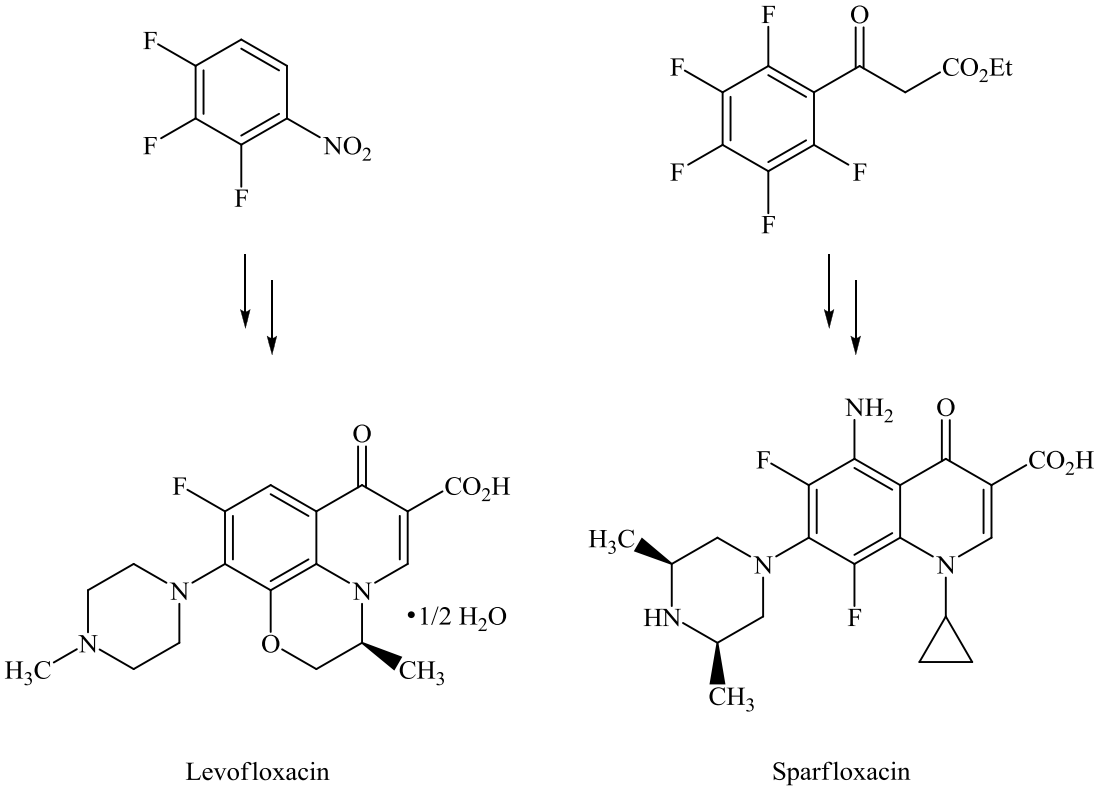
Though electrophilic reagents are most commonly used for the substitution chemistry on aromatic rings, replacement of a fluorine atom can also be conducted with nucleophiles by either nucleophilic substitution or transition metal catalysed coupling with organometallics. This was demonstrated by Robertson[75] where (*S*)-3-(methylamino)-1-phenylpropanol was reacted with NaH in dimethylacetamide (DMAC) in order to generate the alkoxide, and subsequent addition of 4-fluorobenzotrifluoride led to nucleophilic aromatic substitution, affording the desired *(S)*-fluoxetine, an anti-depressant of the selective serotopin reuptake inhibitor.



Scheme 1.24 *Synthesis of (S)-fluoxetine*

Quinoline carboxylic acid derivatives are useful antibacterial agents which can be synthesised by the regioselective nucleophilic displacement of polyfluorinated arenes. This

method is employed by industry in order to synthesise the commercially available Levofloxacin and Sparfloxacin (Figure 1.11).

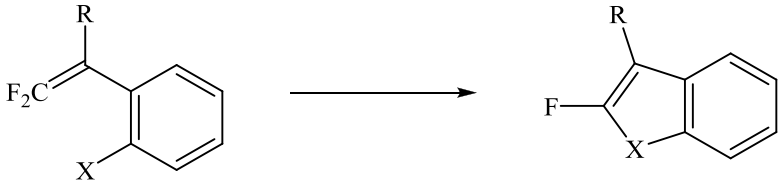


Levofloxacin Sparfloxacin

Figure 1.11 *Levofloxacin and Sparfloxacin*

1.5.2 Alkenyl fluorides

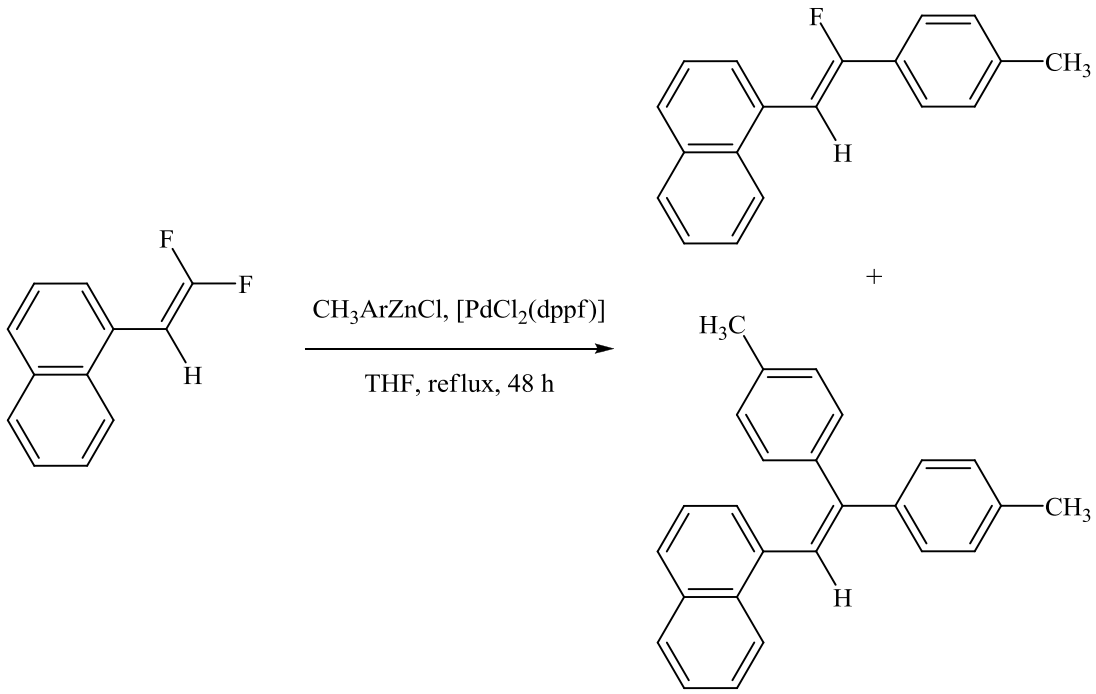
Recently Ichikawa investigated nucleophilic 5-endo-trig cyclisations of 1,1-difluoro-1-alkenes.[76] β,β-difluorostyrene and 1,1-difluoro-1-butene derivatives with a nucleophilic oxygen, nitrogen, sulphur or carbon atom at the ortho/homoallylic position were utilised in order for substitution to proceed in a 5-endo-trig manner. *Para*-toluenesulfonamides when reacted with NaH in DMF afforded the desired cyclic products (**(41)** and **(42)**) in excellent yields (84 and 81 %). Similarly the reaction proceeded equally well with an intramolecular oxygen nucleophile affording the corresponding product **(43)** in 80 % yield, under the same reaction conditions. The utilisation of a sulphur nucleophile was also successful though slightly different reaction conditions were employed, firstly 1-(1,1-difluorohex-1-en-2-yl)-2-(methylsulfinyl)benzene was treated with trifluroacetic anhydride and triethylamine in DCM, followed by reaction with potassium carbonate in methanol to afford the desired product, 2-fluroobenzol[b]thiophene **(44)** in 82 % yield (Scheme 1.25).



(41) Y= NHTs, R= Bu - 84 %
(42) Y= NHTs, R= *sec*-Bu - 81 %
(43) Y= OH, R= Bu - 80 %
(44) Y= S(O)Me, R= Bu - 82 %

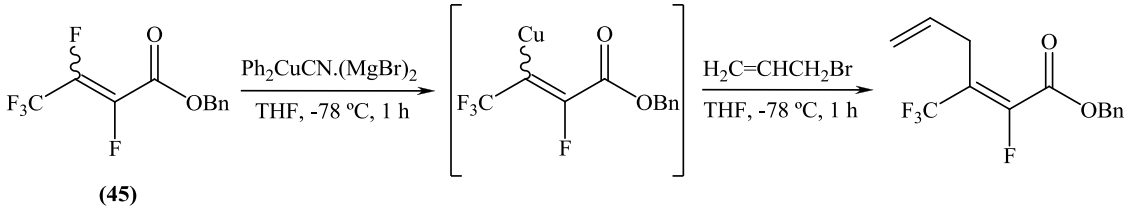
Scheme 1.25 *Synthesis of* ***(41)-(44)***

Saeki *et al.*[73] following on from their work on cross-coupling reactions with fluorobenzenes, applied the same protocol to *gem*-difluoroalkenes, however, in conjunction with the palladium catalyst it was found that the arylzinc reagent was more effective than the Grignard reagent, and reflux for 48 hours in THF afforded the mono-coupled product in 70 % yield, with 23 % of the di-coupled product also forming. When the Ni catalyst [$NiCl_2$(dppp)] was employed with Grignard the di-coupled product was obtained as the major product in 58 % yield (Scheme 1.26).



Scheme 1.26 *Cross-coupling of gem-difluoroalkenes*

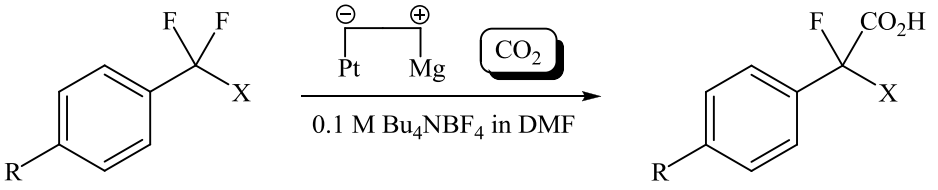
More recently Yamada *et al.* have reported how copper (I) salts promote the fluorine-metal exchange reactions of fluoroalkenes with Grignard reagents, and that the selective replacement of fluorine in **(45)** by the organocuprate takes place efficiently to generate the corresponding β-metallated tetrafluorocuprate intermediate which then reacts with allyl bromide to give (Z)-benzyl 2-fluoro-3-(trifluoromethyl)hexa-2,5-dienoate in 67 % yield as virtually all the *cis* isomer (E/Z = 0:99) (Scheme 1.27).[77]



Scheme 1.27 *Synthesis of (Z)-benzyl 2-fluoro-3-(trifluoromethyl)hexa-2,5-dienoate*

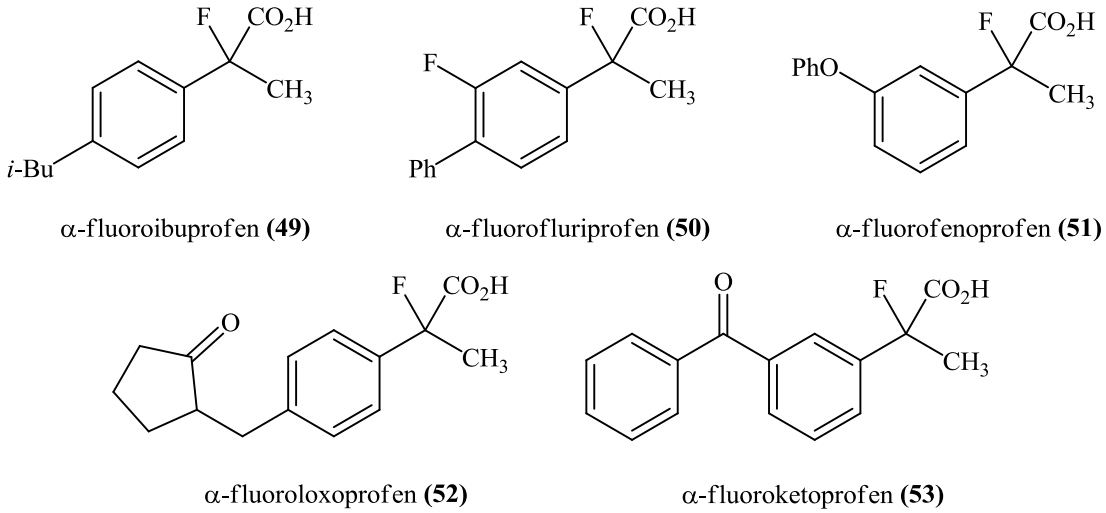
1.5.3 Aliphatic Fluorides

Yamauchi and co-workers have reported the electrochemical carboxylation (EC) of α,α–difluorotoluene derivatives in order to obtain the corresponding α-fluorophenylacetic acids in good yields.[78] This method was also extended to the synthesis of α-fluorinated non-steroidal anti-inflammatory drugs (NSAIDs). Initially reaction conditions were honed with α,α,α-trifluorotoluene where electrochemical reduction in the presence of CO_2 was conducted using a Pt cathode and Mg anode, affording the desired product **(46)** in 87 % yield. The same reaction conditions were then applied to the formation of **(47)** and **(48)** both of which were obtained in good yields (93 and 79 %), (Scheme 1.28). The procedure was extended to the synthesis of α-fluorinated NSAIDs, which were previously synthesised using hazardous fluorinating reagents such as DAST [79, 80] and acetyl hypofluorite.[81] The synthesis of α-fluoroibuprofen **(49)** was conducted in 3 steps, with electrochemical carboxylation in the last step affording the desired product in 82 % yield. The same method was applied to the other NSAIDs **(50) - (53)** (Figure 1.12). All of which were obtained in good yields (61-93 %).



(46) R=H, X= F - 87 %
(47) R=*t*-Bu, X= H - 93 %
(48) R=H, X= Me - 79 %

Scheme 1.28 *Electrochemical carboxylation of benzylic fluorides*

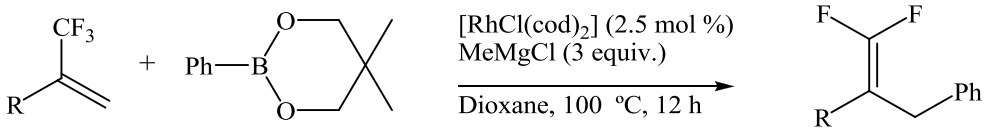


α-fluoroibuprofen **(49)** α-fluorofluriprofen **(50)** α-fluorofenoprofen **(51)**

α-fluoroloxoprofen **(52)** α-fluoroketoprofen **(53)**

Figure 1.12 *α-fluorinated NSAIDs*

Miura and co-workers recently demonstrated that trifluoromethylene alkenes react with organoboron compounds in the presence of Rh complexes.[82] *Gem*-difluoroalkenes were obtained when α-trifluoromethylstyrenes were treated with arylboronic esters and MeMgCl in the presence of a rhodium (I) catalyst. MeMgCl was used as it was thought that the Mg-F interaction activated the C-F bond, promoting the β-fluoride elimination step. Optimised reaction conditions of rhodium (2.5 mol %) and MeMgCl (3 equivalents) in dioxane at 100 ºC were used with a range of arylboronic esters all leading to the formation of the desired *gem*-difluoroalkenes in moderate yields (48-79 %). Varying the substituent on the trifluoromethyl alkene was also found to have an effect and it was observed that the methoxy substrate was more reactive than substrates bearing electron-withdrawing substituents whilst the use of alkyl substrates resulted in no reaction occurring at all (Scheme 1.29).

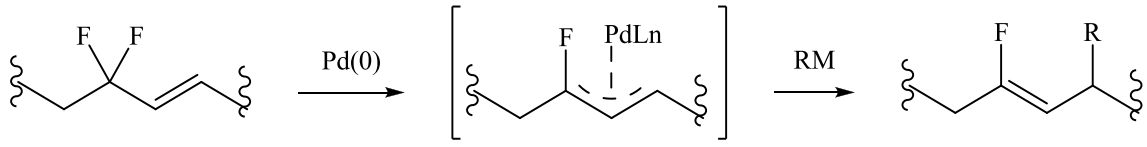


R = 4-MeO-C_6H_4 - 80 %
R = 4-F-C_6H_4 - 60 %
R = 4-Br-C_6H_4 - 61 %
R = 4-CN-C_6H_4 - 54 %
R = 2-naphthyl - 88 %
R = *n*-$C_{10}H_{21}$ - 0 %

Scheme 1.29 *Synthesis of gem-difluoroalkenes*

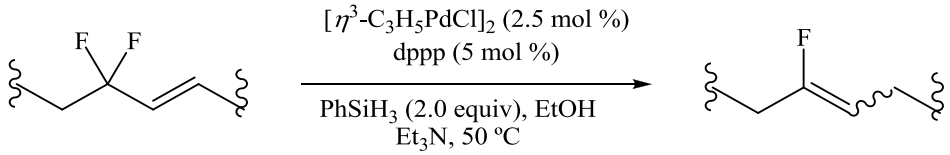
More recently, work by Narumi has shown that selective mono-defluorination of allylic difluorides can be achieved by catalysis with Pd(0). Inspired by the research of Hudlicky,[83] where hydrogenolysis of allyl fluorides in the presence of Pd/C was found to be a convenient route for the replacement of a fluorine atom by hydrogen. Narumi and co-

workers [84] were prompted to react *gem*-difluorides with a Pd catalyst and additives that have an affinity for fluorine in order to promote the elimination of fluorine, leading to the generation of a fluorinated π-allyl Pd intermediates that on reaction with a nucleophile affords a (*Z*)-fluoroalkene. These products are an important class of compounds that can be utilised as peptide isosteres,[85-88] enzyme inhibitors[89] and in liquid crystalline materials.[90]



Scheme 1.30 *Synthesis of fluoroalkene via Pd catalysis*

The reaction was conducted using readily available allylic difluorides. Initially, in order to optimise and hone reaction conditions, γ,γ-difluoro-α−β-enoate was used and reacted with dimethyl sodiomalonate in the presence of the Pd catalyst and dppe. Several additives were screened including TMSCl, Et_4Si, $(EtO)_4Si$ and Me_3Al, however, none promoted the desired defluorination reaction. However, $PhSiH_3$ did promote the formation of the desired product and, after optimisation of solvent and temperatures, it was found that $PhSiH_3$ with NEt_3 in EtOH at 50 ºC yielded the desired product in 96 % yield (Scheme 1.31). These conditions were then used in reactions with different allylic difluorides, all of which were found to be chemoselective with good to excellent yields being obtained of the desired product (64 – 99 %). It was also noted that *N*-Boc amides, esters and substituents such as alkyl and siloxy groups at the δ carbon did not affect the reaction, and that amides, peptides, (Z)-enoates and lactams could all be used to give the desired fluoroalkene. A mechanistic study demonstrated that Et_3N promoted the dehydrogenative coupling of $PhSiH_3$ with EtOH to produce the reactive species.



Scheme 1.31 *Pd and Et_3N catalysed reductive defluorination*

1.6 Thesis Outline

This thesis sets out to examine the synthesis and reactions of allylic fluorides and chlorides with sources of Pd(0). A series of interrelated experimental routes have been followed. In chapter two, the synthesis of a range of analogously functionalised allylic fluorides and allylic chlorides will be described. In chapter three, C-F and C-Cl activation reactions of these allylic halides with Pd(0) starting materials will demonstrate that these reactions lead to the same Pd(II) derivatives. In chapter four, the reactions of these Pd(II) allyls with carbon-based nucleophiles and varying sources of fluoride anions will be outlined. Finally, in chapter five, the synthesis and reaction chemistry with Pd(0) of a related series of allylic difluorides will be discussed. From the synthesis and reactions of allyl halides with Pd(0), it can be concluded that both the C-F and C-Cl bond can be activated in the same manner and subsequently give rise to the same product when reacted with nucleophiles.

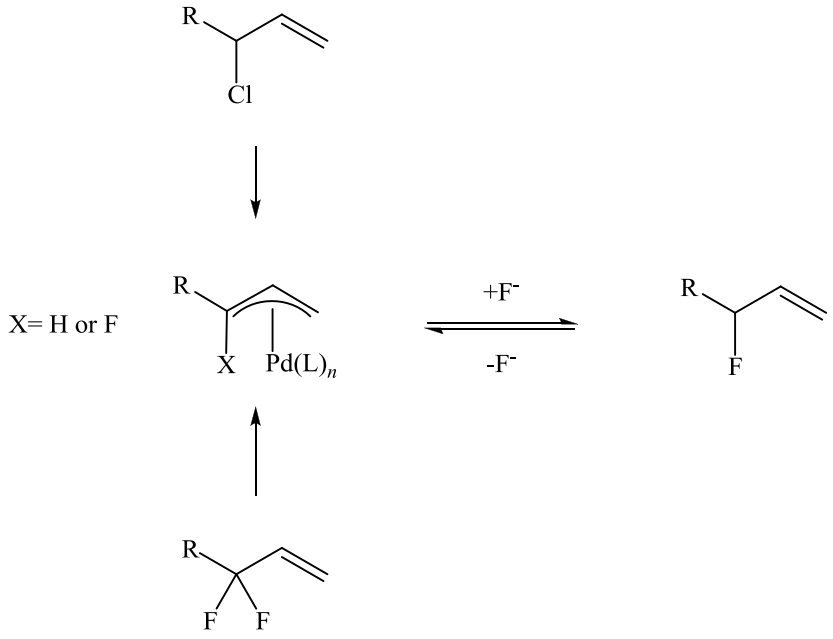


Figure 1.13 *Proposed reaction schemes*

1.7 References

[1] X. Zeng, Y. Wang, X. Wu, T. Ren, Z. He, *J. Synth Lub.* **2006**, *23*, 1.

[2] T. J. Leck, P. J. Fagan, in *PCT Int. Appl.*, Du Pont, US, **2004**, p. 45.

[3] W. R. Dolbier Jr., *J. Fluorine Chem.* **2005**, *126*, 157.

[4] A. Gupta, T. Stierer, R. Zuckerman, N. Sakima, S. D. Parker, L. A. Fleisher, *Anesthesia and Analgesia* **2004**, *98*, 632.

[5] P. R. Resnick, W. H. Buck, *Fluoropolymers* **1999**, *2*, 25.

[6] D. Cartwright, *Recent Developments in Fluorine-Containing Agrochemicals, in Organofluorine Chemistry, Principles and Commercial Applications*, Plenum, New York, **1994**.

[7] C. L. Bumgardner, J. C. Sloop, *J. Fluorine Chem* **1992**, *56*, 141.

[8] S. Rozen, O. Lerman, M. Kol, *Chem. Commun.* **1981**, *10*, 443.

[9] R. E. Banks, N. J. Lawrence, A. L. Popplewell, *J. Chem. Soc., Chem. Commun.* **1994**, 343.

[10] E. Differding, H. Ofner, *Synlett* **1991**, 187.

[11] J. H. Clark, *Chem. Rev.* **1980**, *80*, 429.

[12] A. J. Borodine, *Liebigs. Ann. Chem.* **1863**, *126*, 58.

[13] J. A. Wilkinson, *Chem. Rev.* **1992**, *92*, 505.

[14] H.-J. Bertram, S. Böhm, L. Born, *Synthesis*, 937.

[15] G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojma, I. Kerekes, J. A. Olah, *J. Org. Chem.* **1979**, *44*, 3872.

[16] T. Inagaki, T. Fukuhara, S. Hara, *Synthesis* **2003**, *8*, 1157.

[17] D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. Garcia-Fortanet, T. Kinzel, S. L. Buchwald, *Science* **2009**.

[18] E. Differding, R. W. Lang, *Tetrahedron Lett.* **1988**, *29*, 6087.

[19] F. A. Davis, P. Zhou, P. J. Carroll, *J. Org. Chem.* **1993**, *58*, 4890.

[20] F. A. Davis, P. Zhou, C. K. Murphy, G. Sundarababu, H. Y. Qi, W. Han, R. M. Przeslawski, B. C. Chen, P. J. Carroll, *J. Org. Chem.* **1998**, *63*, 2273.

[21] Y. Takeuchi, T. Suzuki, A. Satoh, T. Shirigami, N. Shibata, *J. Org. Chem.* **1999**, *64*, 5708.

[22] N. Shibata, Z. Liu, Y. Takeuchi, *Chem. Pharm. Bull.* **2000**, *48*, 1954.

[23] Z. Liu, N. Shibata, Y. Takeuchi, *J. Org. Chem.* **2000**, *65*, 7583.

[24] D. Cahard, C. Audouard, J. C. Plaquevent, N. Roques, *Org. Lett.* **2000**, *2*, 3699.

[25] N. Shibata, E. Suzuki, Y. Takeuchi, *J. Am. Chem. Soc.* **2000**, *122*, 10728.

[26] M. Abdul-Ghani, R. E. Banks, M. K. Besheesh, I. Shariff, R. G. Syvret, *J. Fluorine Chem.* **1995**, *73*, 255.

[27] N. Shibata, E. Suzuki, T. Asahi, M. Shiro, *J. Am. Chem. Soc.* **2001**, *123*, 7001.

[28] L. Hintermann, A. Togni, *Angew. Chem. Int. Ed.* **2000**, *39*, 4359.

[29] T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Tomita, *J. Am. Chem. Soc.* **1990**, *112*, 8563.

[30] D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem. Int. Ed.* **2001**, *40*, 93.

[31] Y. Hamashima, K. Yagi, H. Takano, L. Tamas, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 14530.

[32] Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240.

[33] J. A. Ma, D. Cahard, *Tetrahedron: Asymmetry* **2004**, *15*, 1007.

[34] N. Shibata, T. Ishimaru, T. Nagai, J. Kohno, T. Toru, *Synlett* **2004**, 1703.

[35] N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem. Int. Ed.* **2005**, *44*, 4204.

[36] S. Kanemasa, Y. Oderaotoshi, S. Sakaguchi, H. Yamamoto, J. Tanaka, E. Wada, D. P. Curran, *J. Am. Chem. Soc.* **1998**, *120*, 3074.

[37] G. L. Hann, P. Sampson, *J. Chem. Soc., Chem.Commun.* **1989**, 1650.

[38] A. J. Beaumont, C. Kiely, D. Rooney, *J. Fluorine Chem.* **2001**, *108*, 47.

[39] D. M. Hodgson, A. R. Gibbs, G. P. Lee, *Tetrahedron* **1996**, *52*, 14361.

[40] M. Mizuno, M. Kanai, A. Iida, K. Tomioka, *Tetrahedron: Asymmetry* **1996**, *7*, 2483.

[41] H. Yamashita, T. Mukaiyama, *Chem. Lett.* **1985**, 1643.

[42] T. Iida, N. Yamamoto, S. Matsunaga, H.-G. Woo, M. Shibasaki, *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2223.

[43] H. Yamashita, *Chem. Lett.* . **1987**, 525.

[44] K. B. Hansen, J. L. Leighton, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*.

[45] S. Bruns, G. Haufe, *Tetrahedron Asymmetry* **1999**, *10*, 1563.

[46] L. E. Martinez, J. L. Leighton, D. H. Carsten, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5897.

[47] K. B. Hansen, J. L. Leighton, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118* 10924.

[48] S. E. Schaus, J. F. Larrow, E. N. Jacobsen, *J. Org. Chem.* **1997**, *62*, 4197.

[49] S. Bruns, G. Haufe, *J. Fluorine Chem.* **2000**, *104*, 247.

[50] G. Haufe, S. Bruns, *Adv. Synth. Cat.* **2002**, *344*, 165.

[51] W. S. Johnson, M. S. Plummer, S. P. Reddy, W. R. Bartlett, *J. Am. Chem. Soc.* **1993**, *115*, 515.

[52] W. S. Johnson, R. A. Buchanan, W. R. Bartlett, F. S. Tham, R. K. Kullnig, *J. Am. Chem. Soc.* **1993**, *115*, 504.

[53] W. S. Johnson, V. R. Fletcher, B. Chenera, W. R. Bartlett, F. S. Tham, R. K. Kullnig, *J. Am. Chem. Soc.* **1993**, *115*, 497.

[54] W. S. Johnson, B. Chenera, F. S. Tham, R. K. Kullnig, *J. Am. Chem. Soc.* **1993**, *115*, 493.

[55] J. Murata, M. Tamura, A. Sekiya, *Green Chem.* **2002**, *4*, 60.

[56] T. Hanamoto, S. Harada, K. Shindo, M. Kondo, *Chem. Commun.* **1999**, 2397.

[57] G. D. Crouse, J. D. Webster, *J. Org. Chem.* **1992**, *57*, 6643.

[58] T. Hanamoto, K. Shindo, M. Matsuoka, Y. Kiguchi, M. Kondo, *J. Chem. Soc., Perkin Trans. 1* **2000**, 103.

[59] X. Yue, X. Zhang, F. L. Qing, *Org. Lett.* **2009**, *11*, 73.

[60] W. J. Middleton, *J. Org. Chem.* **1975**, *40*, 574.

[61] Y.-Y. Wu, X. Zhang, W. D. Meng, F. L. Qing, *Org. Lett.* **2004**, *6*, 3941.

[62] Z.-Y. Yang, D. J. Burton, *J. Fluorine Chem.* **1989**, *44*, 339.

[63] Z.-Y. Yang, D. J. Burton, *J. Org. Chem.* **1991**, *56*, 1037.

[64] D. Seyferth, R. M. Simon, D. J. Sepelak, H. A. Klein, *J. Org. Chem.* **1980**, *45*, 2273.

[65] D. Seyferth, R. M. Simon, D. J. Sepelak, H. A. Klein, *J. Am. Chem. Soc.* **1983**, *105*, 4634.

[66] D. Seyferth, K. R. Wursthorn, *J. Organomet. Chem.* **1979**, *182*, 455.

[67] N. Boyer, P. Gloanec, G. De Nanteuil, P. Jubault, J.-C. Quirion, *Eur. J. Org. Chem.* **2008**, 4277.

[68] E. Juaristi, D. Quintana, J. Escalante, *Aldrichim. Acta* **1994**, *27*, 3.

[69] T. C. Boge, G. I. Georg, *Enantioselective Synthesis of β-amino acids* Wiley-VCH, New York, **1996**.

[70] J. J. McAtee, R. F. Schinazi, D. C. Liotta, *J. Org. Chem.* **1998**, *63*, 2161.

[71] P. Lin, J. Jiang, *Tetrahedron* **2000**, *56*, 3635.

[72] N. Reineke, N. A. Zaidi, M. Mitra, D. O'Hagan, A. S. Batsanov, J. A. K. Howard, D. Y. Naumov, *J. Chem. Soc. Perkin Trans. 1* **1996**, 147.

[73] T. Saeki, Y. Takashima, K. Tamao, *Synlett* **2005**, 1771.

[74] K. Manabe, S. Ishikawa, *Synthesis* **2008**, 2645.

[75] D. W. Robertson, J. H. Krushinski, R. W. Fuller, J. D. Leander, *J. Med. Chem.* **1988**, *31*, 1418.

[76] J. Ichikawa, Y. Wada, M. Fujisawa, K. Sakoda, *Synthesis* **2002**, 1917.

[77] S. Yamada, T. Takahashi, T. Konno, T. Ishihara, *Chem. Commun.* **2007**, 3679.

[78] Y. Yamauchi, T. Fukuhara, S. Hara, H. Senboku, *Synlett* **2008**, 438.

[79] M. Schlosser, D. Michael, Z.-W. Guo, C. J. Sih, *Tetrahedron* **1996**, *52*, 8257.

[80] F. Bellezza, A. Cipiciani, G. Ricci, R. Ruzziconi, *Tetrahedron* **2005**, 8005.

[81] H. Fujisawa, T. Fujiwara, Y. Takeuchi, K. Omata, *Chem. Pharm. Bull.* **2005**, *53*, 524.

[82] T. Miura, Y. Ito, M. Murakami, *Chem. Lett.* **2008**, *37*, 1006.

[83] M. Hudlicky, *J. Fluorine Chem* **1989**, *44*, 345.

[84] T. Narumi, K. Tomita, E. Inokuchi, K. Kobayashi, S. Oishi, H. Ohno, N. Fujii, *Org. Lett.* **2007**, *9*, 3465.

[85] G. Dutheuil, S. Couve-Bonnaire, X. Pannecoucke, *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 1290.

[86] T. Narumi, A. Niida, K. Tomita, S. Oishi, A. Otaka, H. Ohno, N. Fujii, *Chem. Commun.* **2006**, 4720.

[87] Y. Nakamura, M. Okada, A. Sato, H. Horikawa, M. Koura, A. Saito, T. Taguchi, *Tetrahedron* **2005**, *61*, 5741.

[88] T. Allmendinger, E. Felder, E. Hungerbuhler, *Tetrahedron Lett.* **1990**, *31*, 7301.

[89] P. Bey, J. R. McCarthy, I. A. McDonald, *ACS Symp. Ser.* **1991**, *456*, 105.

[90] O. Yokokoji, T. Shimizu, S. Kumai, *Chem. Abstr.* **1996**, *124*, 316586.

CHAPTER TWO

2 Synthesis of Allylic Fluorides and Allylic Chlorides

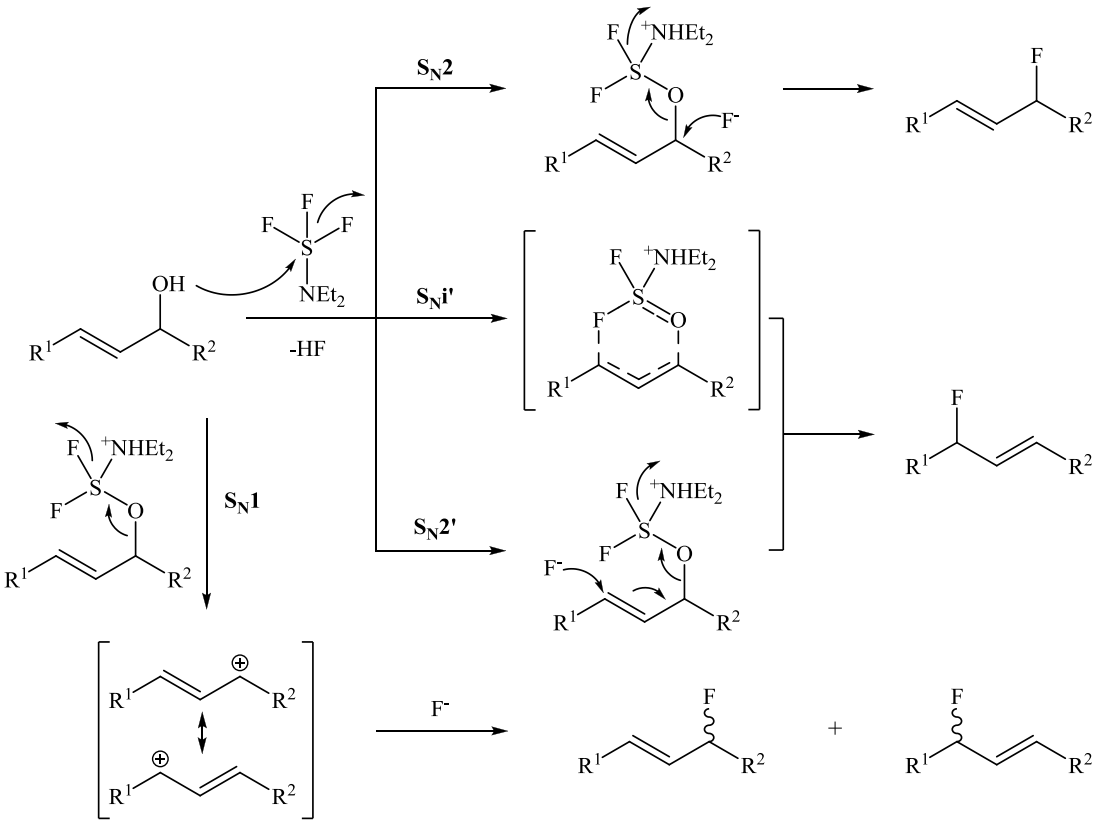
2.1 Introduction

This chapter will focus on the synthesis of allylic fluorides and allylic chlorides. Allylic fluorides can be synthesised by several routes, nucleophilically using reagents such as DAST, Ghosez's reagent and metal fluorides, or electrophilically using reagents such as Selectfluor and NFSI. Allylic chlorides are generally prepared from their preceding allylic alcohols with a number of reagents including $SOCl_2$, PCl_3 and *N*-chlorosuccinimide.

In this chapter a library of allylic fluorides will be synthesised, and their reactions with Pd(0) to form π-allyl complexes studied to determine the feasibility of allylic fluoride C-F activation. An analogous library of allylic chlorides will also be synthesised, as reactions of allylic chlorides with Pd(0) are well understood and as such will be used as model systems for the optimisation of reaction conditions for Pd π-allyl complexes. Once established these can be applied to the allylic fluorides and the reaction products examined in order to identify whether the same product can be generated. Both systems will then be reacted with sources of fluoride and a variety of nucleophiles.

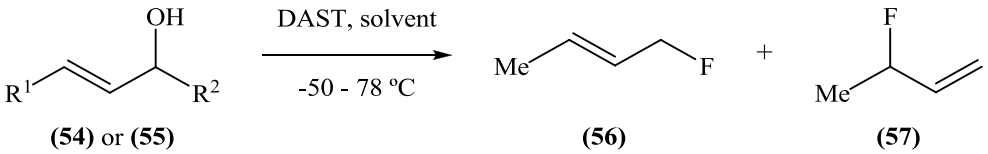
2.1.1 Synthesis of Allylic Fluorides *via* Nucleophilic Fluorination

DAST is the most widely used reagent for dehydroxyfluorination of allylic alcohols, however, it cannot always exert the desired control over regioselectivity and stereoselectivity, as there is the possibility of the fluorination step proceeding *via* an S_N2, S_N2', S_Ni' or S_N1 mechanism, depending on the structure of the starting substrate (Scheme 2.1).[1]



Scheme 2.1 *Mechanism of dehydroxyfluorination of allylic alcohols with DAST*

In 1975 Middleton reported the first dehydroxyfluorination using DAST.[2] The reaction was conducted by slow addition of the alcohol (crotyl alcohol **(54)** or 3-buten-2-ol **(55)**) to a solution of DAST in an inert solvent cooled to -50 to -78 ºC, resulting in a mixture of two fluorinated products 1-fluorobut-2-ene **(56)** and 3-fluorobut-1-ene **(57)** (Table 2.1) (Scheme 2.2). Diglyme was found to be a convenient solvent for the preparation of low boiling fluorides as it was possible for the product to be distilled out of the reaction mixture, whilst HF, which forms in the reaction, remained behind complexed to the diglyme. However, when the solvent was changed to isooctane, the amount of product formed due to transposition of the double bond was minimised.



(54) or **(55)** **(56)** **(57)**

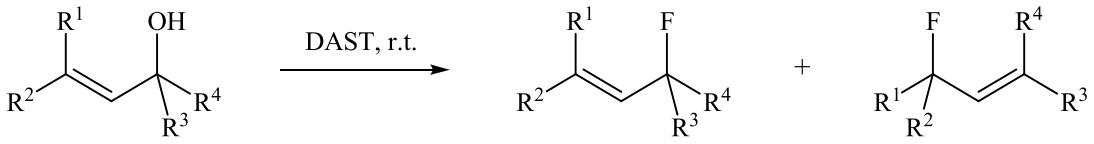
Scheme 2.2 *Synthesis of **(56)** and **(57)***

Alcohol	R^1	R^2	Solvent	(56) Yield (%)	(57) Yield (%)
(54)	Me	H	Diglyme	28	72
(54)	Me	H	Isooctane	36	64
(55)	H	Me	Diglyme	22	78
(55)	H	Me	Isooctane	9	91

Table 2.1 *Reaction of allylic alcohols with DAST*

In dehydroxyfluorinations undesired side products can be formed *via* carbonium ion type rearrangements and dehydration. The former, carbonium ion type rearrangements, are less likely to occur when DAST is used as a reagent in comparison to other sources of nucleophilic fluorine such as SeF_4.pyridine. This has been exemplified through the fluorination of isobutyl alcohol, when DAST was used the ratio of products was 2:1 of isobutyl fluoride to *tert*-butyl fluoride, whereas the same reaction with SeF_4.pyridine has reportedly only afforded the rearranged *tert*-butyl fluoride.[3] Dehydration is also less problematic with DAST as a fluorinating agent, with Middleton reporting that cyclooctanol reacts with DAST to yield a 70:30 ratio of cyclooctyl fluoride to cyclooctene, whereas the use of Et_2NCF_2CHClF afforded only cyclooctene.[2]

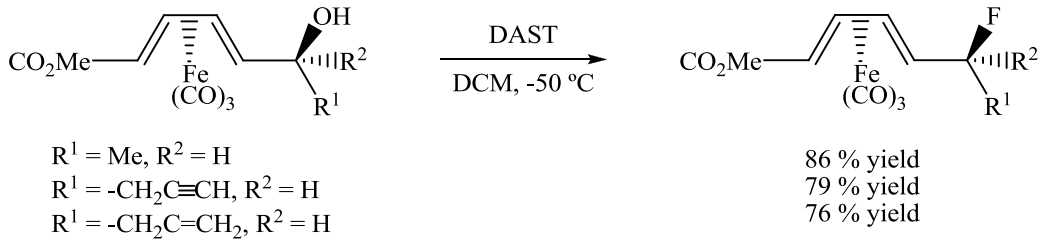
Many groups have studied at length the structural features of the starting allylic alcohol and their influence on regioselectivity in reactions with DAST.[4-8] In 1991 Mann reported that regioselectivity is poor when the allylic alcohol is substituted with alkyl groups, which was found to be a significant disadvantage in the fluorination of squalene derivatives, where a 3:7 mixture of primary and secondary allylic fluorides was obtained. When DAST was modified from trifluoride to difluoride, reaction with the allylic alcohol was wholly selective with the desired fluorinated squalene as the only product.[9] Conversely, Grée and co-workers found that when allylic alcohols were substituted with phenyl groups or strongly electron-withdrawing groups regioselectivity was high (Scheme 2.3).[4, 5]



$R^1 = R^3 = H$, $R^2 = Me$, $R^4 = Ph$	0	:	1	71 % yield
$R^1 = R^3 = H$, $R^2 = CO_2Me$, $R^4 = Me$	1	:	0	80 % yield
$R^1 = R^3 = H$, $R^2 = COPh$, $R^4 = Me$	1	:	0	70 % yield

Scheme 2.3 *Fluorination of allylic alcohols by Grée*

Further work by Grée *et al.* demonstrated how selectivity could be controlled by complexing the allylic alcohol to a metal prior to fluorination. With rhenium complexing to the substrate nucleophilic displacement of the hydroxyl group occurred with complete regiocontrol affording the allylic fluoride, in moderate to good yields (40-76 %), as a single diastereoisomer with retention of configuration.[10] It was also found that $Fe(CO)_3$ complexes of dienyl alcohols could be used to control diastereoselectivity (Scheme 2.4). Retention of configuration was achieved when secondary alcohols were used, affording the corresponding fluorinated products in good yields (76 – 86 %).[11]



Scheme 2.4 *Fluorination of Fe complexes of dienyl alcohols*

Although DAST is the most commonly used source of nucleophilic fluorine several others are occasionally used and will be discussed here. (Diethylamino)(dimethylamino) sulphur difluoride **(58)** (Figure 2.1) in particular is a viable alternative as less double bond transposition is observed. This is illustrated by Scheme 2.2, where the ratio of products when R^1 = Me and R^2 = H is 72:28 in diglyme, whereas when the reaction is conducted with **(58)** the ratio of products is 79:21. In isooctane DAST affords the products in a ratio of 64:36, whereas **(58)** yields them in the far more desirable ratio of 87:13.

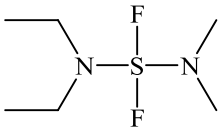
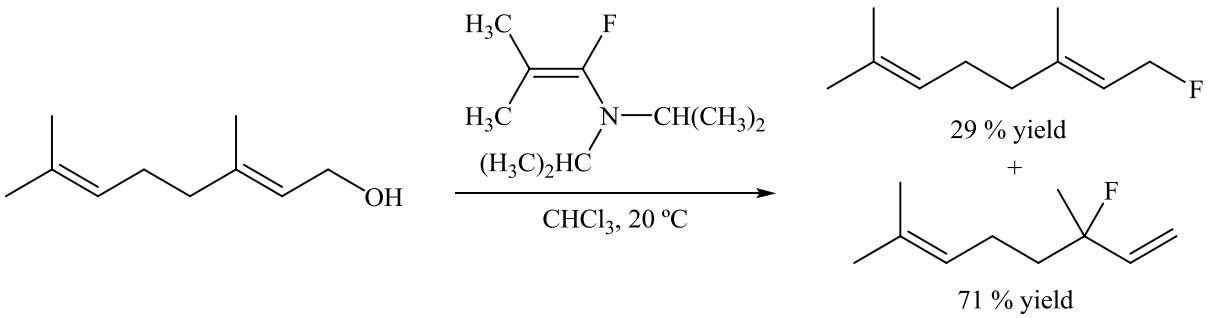


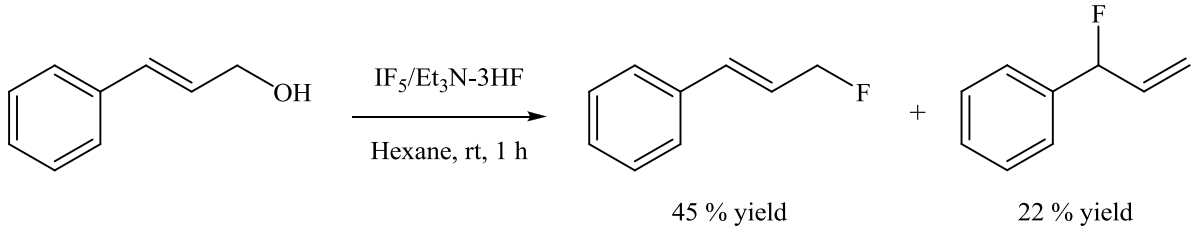
Figure 2.1 *(Diethylamino)(dimethylamino) sulphur difluoride* ***(58)***

Another nucleophilic fluorinating reagent is Ghosez's reagent (*N*,*N*-diisopropyl-1-fluoro-2-methylpropenamine), however, reaction with Ghosez's reagent generally leads to formation of the more substituted fluoride.[12] An example of this selectivity can be seen in Scheme 2.5.



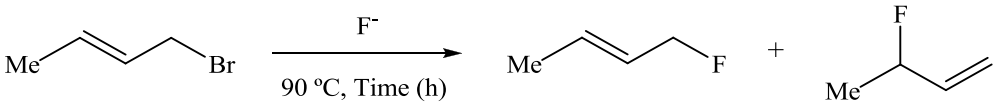
Scheme 2.5 *Fluorination using N,N-diisopropyl-1-fluoro-2-methylpropenamine*

In contrast to Ghosez's reagent, $IF_5/Et_3N.3HF$, a reagent that is non-hazardous, easy to handle, inexpensive, selective and can be used in mild conditions, leads preferentially to the primary allylic fluoride in moderate yield (Scheme 2.6). [13]



Scheme 2.6 *Fluorination with $IF_5/Et_3N.3HF$*

Finally, allylic fluorides can also be synthesised by substitution of another halide, for this type of reaction the most commonly employed reagents are tetraalkylammonium or metal fluorides. However, metal fluorides have low solubility and nucleophilicity in polar aprotic solvents, therefore high temperatures and long reactions times are necessary. The use of additives can also be advantageous, in order to improve reactivity. The results in Table 2.2, clearly illustrate that the use of KF affords the primary allylic fluoride, whereas PbF_2 leads to formation of the secondary allylic fluoride[14, 15]



Scheme 2.7 *Fluorination via inorganic fluoride sources*

Fluoride	Temp (ºC)	Time (h)	1º: 2º	Yield (%)
KF/CaF_2	90	38	98:2	83
KF/18-crown-6	90	48	97:3	86
PbF_2	90	24	32:68	37
$NaBr/PbF_2$	90	5	31:69	80

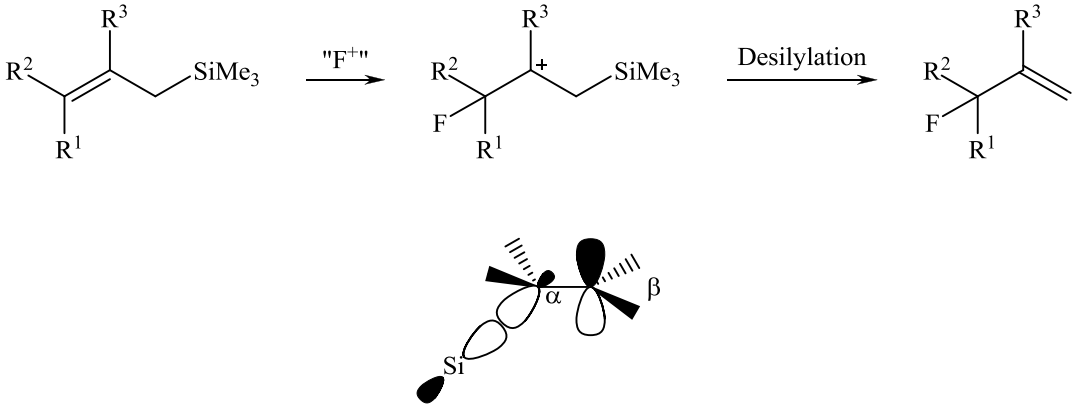
Table 2.2 *Fluorination via inorganic fluoride sources*

2.1.2 Synthesis of Allylic Fluorides *via* Electrophilic Fluorination

There are a variety of reagents that can be used for electrophilic fluorination, and the reader is directed to this review.[16] Here, the focus will be on the application of Selectfluor and, in particular, its fluorination of organosilane derivatives.

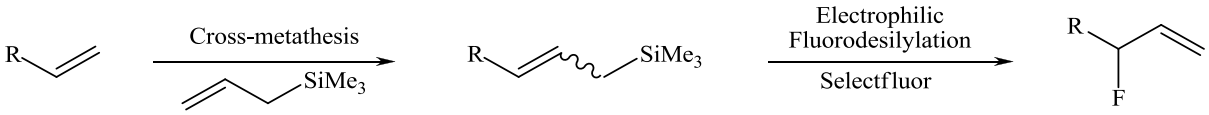
Organosilanes, with the silyl groups directly attached or adjacent to an aryl or alkenyl group, are useful synthetic intermediates and are able to react with electrophiles to give structurally diverse products. In these reactions, the reactivity of the π-nucleophile is enhanced by the silyl group and controls the sense of regiochemistry upon addition of the electrophile (Scheme 2.8). Reactions take advantage of the β-effect of a silicon centre and,

when using electrophilic sources of fluorine, structurally diverse fluorinated compounds are accessible.[17]



Scheme 2.8 *Regioselective fluorination via a silicon-stabilised carbocation*

Various allylic fluorides have been prepared by Gouverneur *et al.*[18] *via* a two-step process, involving a cross-metathesis of allyltrimethylsilane with different olefinic partners followed by a fluorodesilylation of the corresponding functionalized allylsilanes with Selectfluor (Scheme 2.9). The reaction takes place according to an S_E2' mechanism. The methodology has also been applied to the preparation of terminal secondary and tertiary allylic fluorides bearing different functionalities such as ethers, esters and acetals. The allylic fluorides have been obtained in good isolated yields, with no by-products being detected in the crude reaction mixtures. However, the reaction does not allow synthesis of α-fluorinated carbonyl derivatives, as the corresponding allylsilanes featuring electron-deficient enone functionalities are not sufficiently reactive towards Selectfluor.

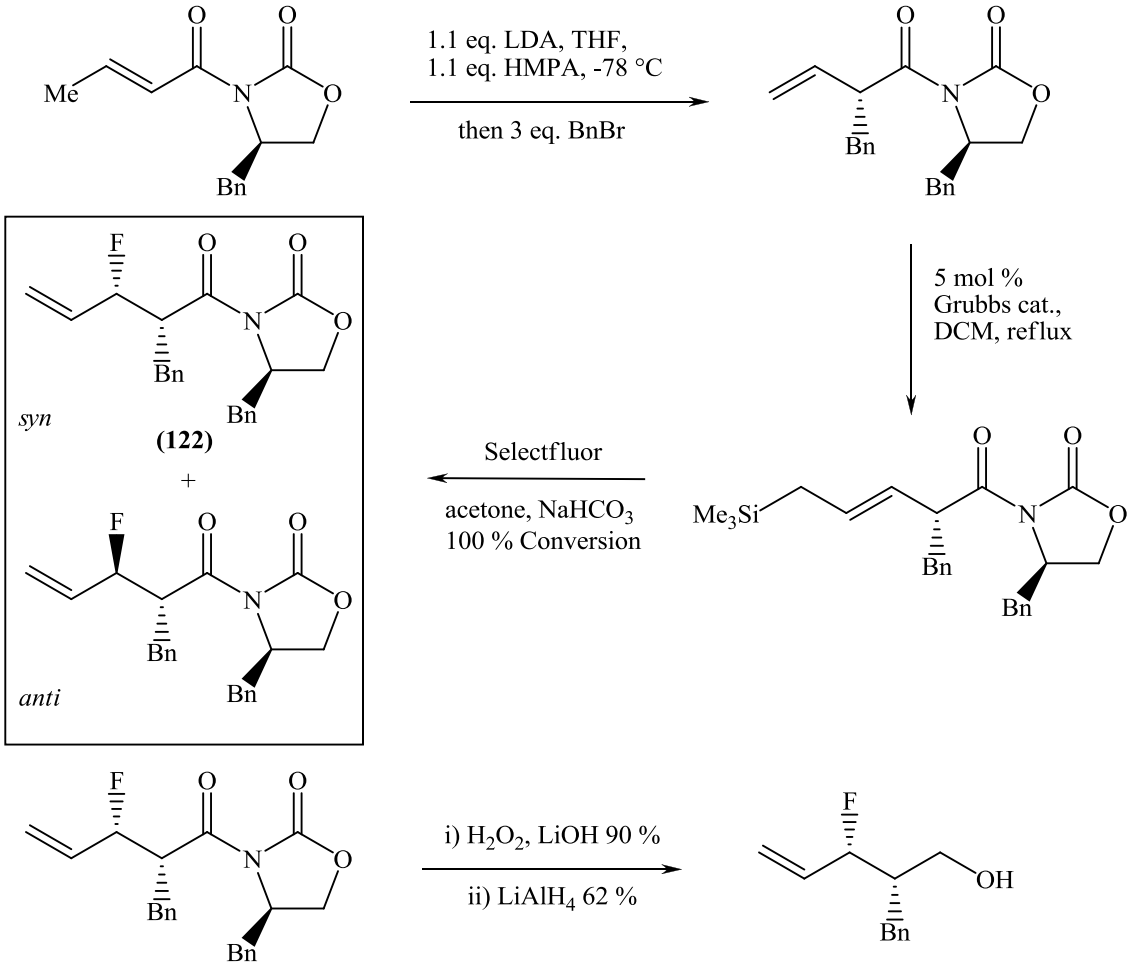


Scheme 2.9 *Sequential cross-metathesis/fluorodesilylation*

The same methodology has been applied to the synthesis of enantioenriched allylic fluorides using two complementary strategies. The first approach utilises non-racemic chiral organosilanes combined with achiral fluorinating reagents. The second approach entails treatment of prochiral allylsilanes with chiral fluorinating reagents.

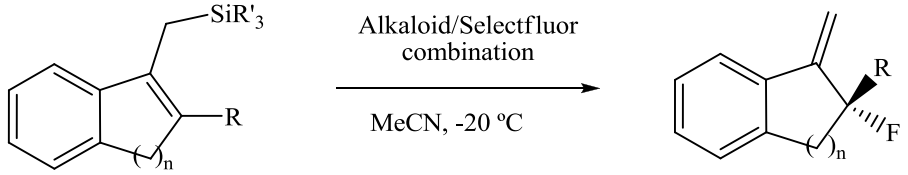
The first approach has been applied by Tredwell *et al.*[19] to chiral allylsilanes possessing a stereogenic centre on the allylic carbon not substituted by the silyl group. These precursors could be readily prepared as single *trans*-isomers by cross-metathesis of commercially available allyltrimethylsilane with olefinic partners. Treatment with Selectfluor afforded the

desired allylic fluorides as a mixture of diastereomers, which were separated by column chromatography. Hydrolytic cleavage of the chiral auxiliary afforded the β-fluorinated carboxylic acid as a single diastereoisomer, and the corresponding alcohol obtained by reduction of fluorinated acids with lithium aluminium hydride (Scheme 2.10).



Scheme 2.10 *Asymmetric synthesis of allylic fluorides*

Enantiopure N-F reagents have also been utilised in the synthesis of allylic fluorides.[20] Allylsilanes derived from indanone and tetralone were reacted in the presence of chiral *N*-fluorocinchona alkaloids, which were prepared *in situ* by mixing commercially available cinchona alkaloids with Selectfluor (Scheme 2.11).



Scheme 2.11 *Enantioselective fluorodesilylation of prochiral allylsilanes*

n	R	R'	Alkaloid	*ee* (%)
1	H	Me	$(DHQ)_2PYR$	60
1	CH_2Ph	Me	DHQB	85
1	CH_2Ph	Me	$(DHQ)_2PYR$	96
2	H	Me	DHQPE	30
1	H	Ph	$(DHQ)_2PYR$	87

Table 2.3 *Results of enantioselective fluorodesilylation of prochiral allylsilanes.*

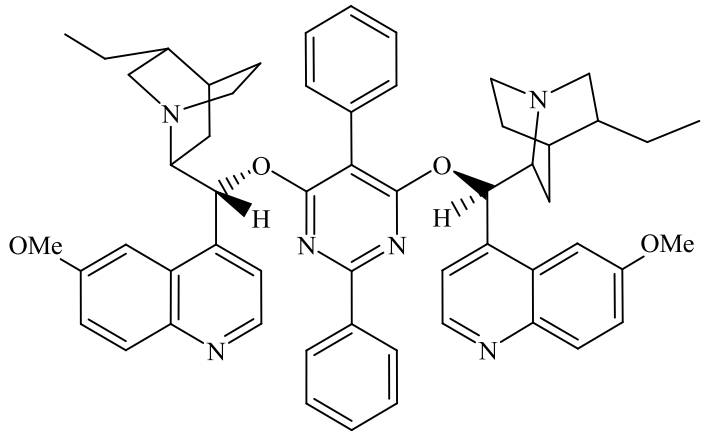


Figure 2.2 *$(DHQ)_2PYR$*

Though numerous alkaloids were screened, the reagent derived from hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether ($(DHQ)_2PYR$) (Figure 2.2) was the most successful, affording the fluorinated benzyl-substituted allylsilane derived from indanone with a 96 % *ee*. Enantioselectivities were also influenced by substrate and starting material, with greater enantiomeric excesses for substrates substituted by large groups (R= CH_2Ph, 85 % *ee* vs R= Me, 60 % *ee*). Increased enantiomeric excesses were achieved when indanones were used in comparison with tetralones. The results also showed that when the three methyl groups attached to the silicon are replaced by phenyl groups higher enantiomeric excesses (R'= Ph, 87 % *ee vs* R'= Me, 60 % *ee*) were achieved.

2.1.3 Allylic chlorides from Allylic Alcohols

Allylic chlorides are an important class of compounds which can undergo an array of transformations. They are also important in reactions such as metal-catalysed allylation reactions, with recent examples including nickel-catalysed Negishi reactions[21] and stereospecific zirconium-mediated S_N2' substitutions.[22] Over the years numerous methods have been developed to convert allylic alcohols into the corresponding chlorides, including;

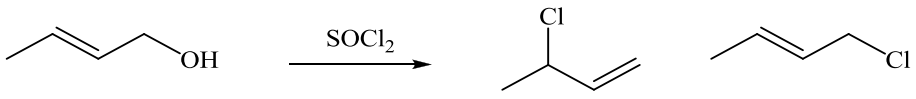
a) Reaction with conventional halide-producing reagents like $SOCl_2$[23-25] or PX_3[26-28]

b) Reaction with dimethyl sulphide and an *N*-halosuccinimide[29]

c) Formation of a sulphonate ester, or other reactive group followed by displacement with halide ion in an aprotic solvent[30, 31]

Many of these methods will be discussed further; however, the synthesis of allylic chlorides from olefins will not be reviewed in this work. [32-39]

In 1955 Young and co-workers utilised thionyl chloride for the conversion of alcohols to chlorides, and found that the use of solvent in the reaction was imperative,[23, 40] since, without solvent a mixture of isomeric chlorides was obtained. However, if thionyl chloride was used in dilute ether solution then the reaction mechanism was found to proceed *via* the more dominant reaction pathway – S_Ni'. As demonstrated in Scheme 2.12, when crotyl alcohol was reacted in thionyl chloride alone, it yielded a mixture of products, however, in a diethyl ether solution the desired α-methyl allyl chloride was obtained in a 99 % yield. This was also observed with α-methyl allyl alcohol; without solvent a mixture of products is obtained [33 % $CH_3CHClCH{=}CH_2$: 67 % $CH_3CH{=}CHCH_2Cl$], however, with solvent a 100 % yield of crotyl chloride is obtained.



No solvent	71 %	29 %
Diethyl ether	99 %	

Scheme 2.12 *Chlorination with $SOCl_2$*

Collington and Meyers[30] found that when the allylic alcohol 3-propylhex-2-en-1-ol was reacted with a mixture of CH_3SO_2Cl, LiCl and *s*-collidine (2,4,6-trimethylpyridine) in DMF at 0 ºC, the corresponding chloride was obtained in excellent yield, without any rearranged chloride. It was also noted that any non allylic alcohol (3-propylhex-3-en-1-ol) present in the starting material was not converted to allylic chloride instead this was converted to the corresponding mesylate. This is attributed to the fact that the mild conditions used to facilitate the reaction impede displacement of the saturated mesylate by the chloride ion, whilst allowing the more labile allylic mesylate to react. The ratio of homoallylic mesylate to allylic chloride products obtained was in accordance with the ratio of starting homoallylic alcohol to allylic alcohol (Table 2.4).

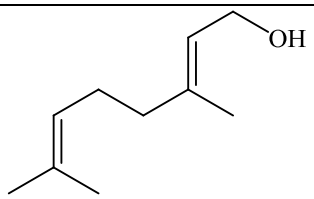
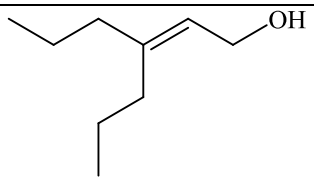
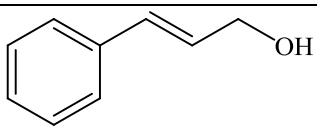
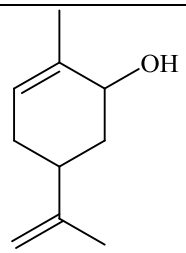
Alcohol	Chloride (%)	Homoallylic Isomer (%)[a]	Homoallylic Mesylate (%)[b]
	87	21	20 ± 2
	83	10	8 ± 2
	82	-	-
	50	10	9 ± 2

Table 2.4 *Yields of allylic chlorides obtained by Collington and Meyers*

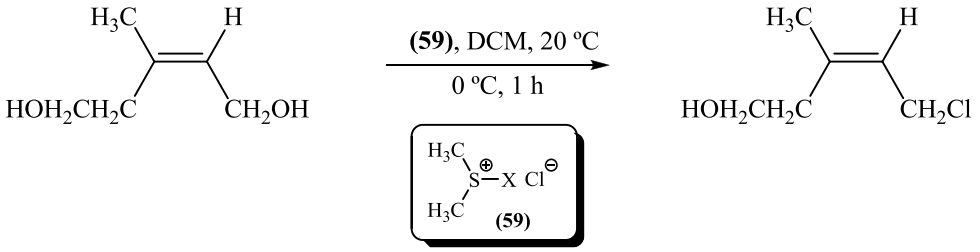
[a] isomer distribution determined by vpc
[b] determined by integration of the CH_3SO_2OR singlet in the NMR spectrum of allylic chloride

Following on from the work by Meyers, Snyder also reported that no allylic rearrangement was found when using the reagent triphenylphosphine–carbon tetrachloride (Scheme 2.13).[41] With primary alcohols the corresponding chloride was obtained in 100 % yields, whilst with the secondary alcohol, but-3-en-2-ol, the corresponding chloride was afforded in 89 % yield.

$$ROH + PPh_3 + CCl_4 \longrightarrow RCl + PPh_3PO + HCCl_3$$

Scheme 2.13 *Reaction of allylic alcohols with triphenylphosphine-carbon tetrachloride*

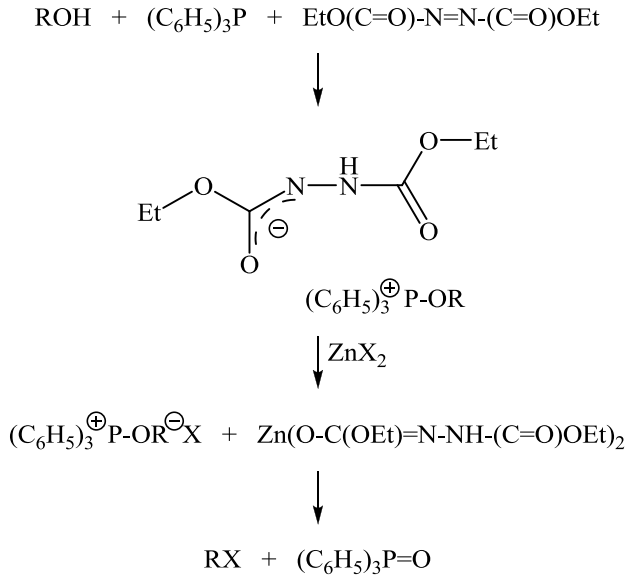
In 1972 Corey *et al*. found that the complex formed from the reaction of equimolar quantities of *N*-chlorosuccinimide and methyl sulphide, when reacted further in DCM with an equivalent of benzhydrol, afforded the benzhydryl chloride in >95 % yield, this was also the case with the alcohols 2-cyclohexen-1-ol and benzyl alcohol. These mild reactions were then applied with *cis*-3-methyl-2-penten-1,5-diol, which when reacted with complex **(59)** in DCM at – 20 ºC, followed by 0 ºC for 1 hour, afforded only the corresponding chloride, that was isolated in 87 % yield (Scheme 2.14).



Scheme 2.14 *Reaction of cis-3-methyl-2-penten-1,5-diol with* ***(59)***

Magid and co-workers demonstrated in 1977, that allylic alcohols could be converted into the corresponding chlorides by using hexachloroacetone/triphenylphosphine.[42] The allylic alcohol was reacted with hexachloroacetone and a slight excess of triphenylphosphine, with a very rapid reaction (< 20 minutes), affording the corresponding chloride in excellent high yields. Three allylic alcohols were tested; *(E)*-but-2-en-1-ol, *(Z)*-but-2-en-1-ol and but-3-en-2-ol, affording the desired allylic chlorides in 99 %, 98 % and 94 % yields respectively.

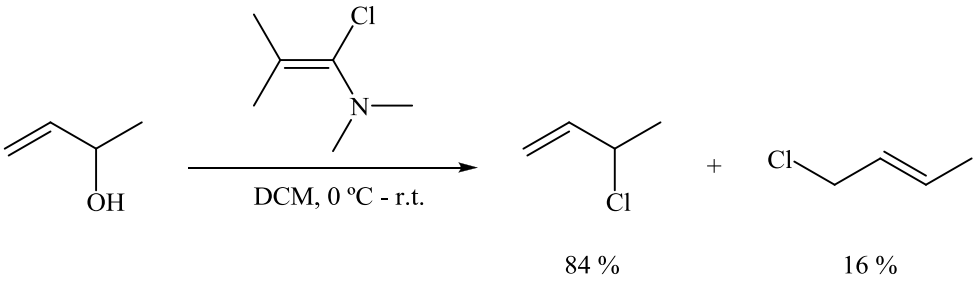
In 1984 Ho and Davies also reported a convenient method utilising triphenylphosphine, however, this time in conjunction with diethyl azodicarboxylate in THF in the presence of anhydrous zinc chloride.[43] It was found that the covalent bond character between zinc metal and oxygen led to the formation of a reactive alkoxyphosphonium halide (Scheme 2.15). Here the reaction proceeded *via* an S_N2 type displacement of the resulting alkoxyphosphonium species by the chloride anion. The reaction procedure converted primary, secondary and allylic alcohols in good yields (66-92 %) to the corresponding chlorides.



Scheme 2.15 *Reaction of allylic alcohols with PPh_3, diethyl azodicarboxylate and $ZnCl_2$*

Munyemana and co-workers[12] reported the synthesis of allylic and alkyl chlorides from the corresponding alcohols by employing an equimolar amount of the reagent tetramethyl-α-

chloroenamine at room temperature in DCM. Primary alcohols were converted in excellent yields (95-99 %), whilst the secondary allylic alcohol evaluated afforded the desired product in slightly lower yield (84 %), since there was also formation of the rearranged chloride (Scheme 2.16).



Scheme 2.16 *Chlorination of But-3-en-2-ol*

More recently Yadav and Babu[44] have reported a simple, inexpensive and high yielding procedure for the conversion of allylic acetates and alcohols into the corresponding chlorides using acetyl chloride and ethanol. The process consists of mixing 1 equivalent of allylic acetate/alcohol with 8 equivalents of ethanol and acetyl chloride and stirring at 23 ºC, until the reaction is complete by TLC, after which the solvent is removed *in vacuo* to afford the chlorinated product. Selected results are summarised in Table 2.5. All of the reactions conducted with allylic acetate were very high yielding and selective, with the exception of substrates **(61)** and **(63)**, where mixtures were obtained. The allylic alcohols were for the most part as reactive and selective as the corresponding allyl acetate, however, substrate **(61)** reacted very slowly, after 24 hours only traces of the allylic chlorides were formed, with additional equivalents of AcCl and EtOH failing to improve the product yield.

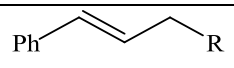
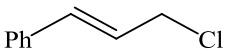
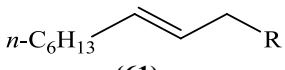
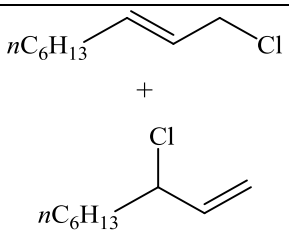
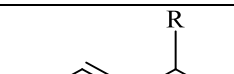
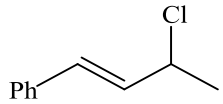
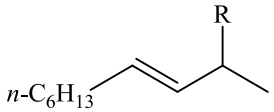
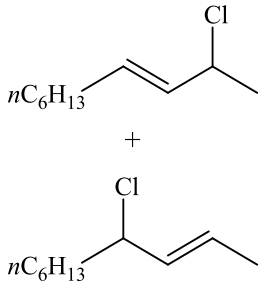
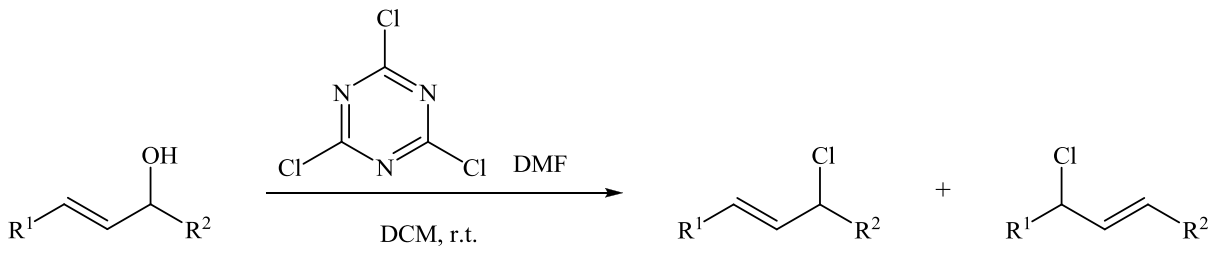
Substrate	R = OAc R= OH Time (min)		Product	R = OAc R= OH Yield (%)	
 **(60)**	30	30		96	91
 **(61)**	150	1440		94[a]	-
 **(62)**	30	30		95	93
 **(63)**	30	30		92[b]	94[b]

Table 2.5 *Reactions of allylic acetates and alcohols with acetyl chloride and ethanol*

[a] 6.7:1 mixture of *(E)*-1-chloro-2-nonene and 3-chloro-1-nonene
[b] 1:1 mixtures of isomeric chlorides

Roy and co-worker's, building on previous work conducted by De Luca *et al.* [30] in the synthesis of alkyl chlorides using cyanuric chloride (TCT), achieved the synthesis of unsymmetrical allylic chlorides using TCT with DMF (Scheme 2.17).[45, 46] The results showed that the product formed was dependent on the electronic and steric nature of the substituents (Table 2.6). In entries 1 and 3, chlorine addition occurs on the less hindered site, whereas in entry 4 complete *tele*-substitution occurs. However, in entry 2, elimination occurs affording the conjugated diene, whilst in entry 5 the presence of an electron withdrawing group, means that formation of the *ipso*-substituted product is favoured in contrast to the *tele*-substituted product.



Scheme 2.17 *Reaction of allylic alcohols with TCT and DMF*
(For a definition of R see Table 2.6)

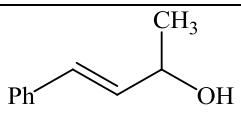
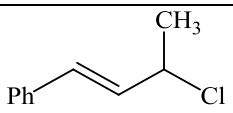
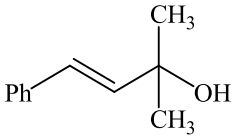
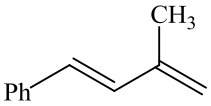
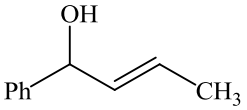
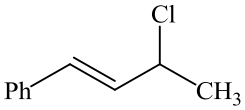
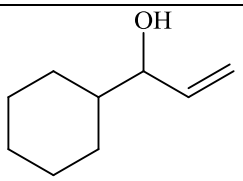
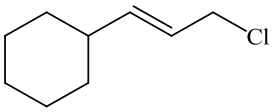
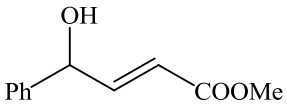
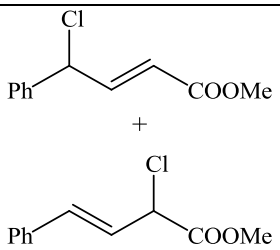
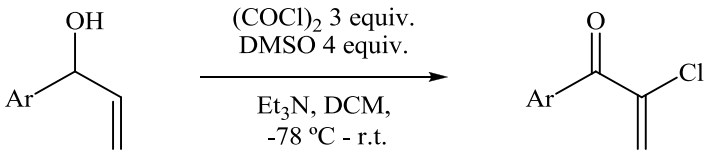
Entry	Substrate	Product	Time (min)	Yield (%)[a]
1			60	75
2			60	70
3			120	73
4			50	71
5			50	81 (83:17)

Table 2.6 *Reaction of cyanuric chloride with unsymmeytrical allylic alcohols*
[a]Ratio of products determined by ^{1}H NMR

More recently Chisholm and co workers[47] have reported that aryl allylic alcohols can be converted into halogenated unsaturated ketones or allylic halides using an excess of the Moffatt-Swern reagent (Scheme 2.18). It was found that electron-poor aromatic rings favoured formation of the halogenated ketone, whilst electron-donating substituents in the *para*- or *ortho*- positions on the aromatic ring favoured formation of the allylic halide as exemplified by selected results (Table 2.7). With the methoxy substituent in the *meta*-position, the halogenated ketone is formed in a moderate 65 % yield, however, when in *para*- and *ortho*- positions the corresponding allylic chlorides are formed in 73 and 83 % yields respectively.



Scheme 2.18 *Reactions of arly allylic alcohols with Moffatt-Swern reagent*

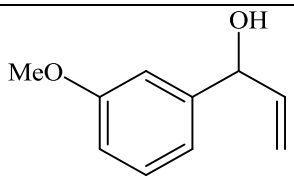
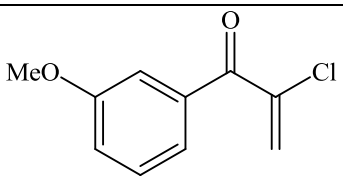
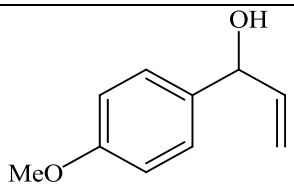
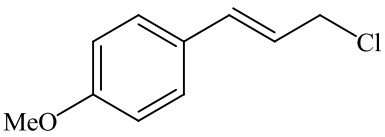
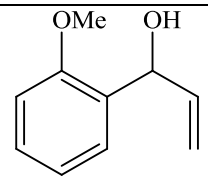
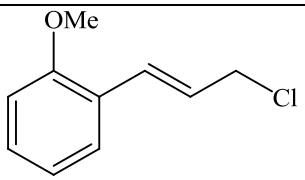
Alcohol	Product	Yield (%)
		65
		73
		83

Table 2.7 *Reactions of aryl allylic alcohols with Moffatt-Swern reagent*

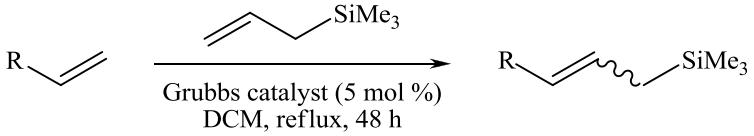
2.2 Results and Discussion

In this chapter analogous libraries of allylic fluorides and allylic chlorides were synthesised utilising literature protocols. These compounds were then utilised in Chapter Three in order to synthesise novel palladium allyl complexes. Previously, work conducted by Hintermann and Togni[48] has examined the reaction of 1,3-diphenylallylfluoride with Pd(0). However, this work will investigate the reaction in more detail, and determine whether substituents on the ring influence the reactivity of allylic halides with Pd(0) and the subsequent reactions with nucleophiles.

2.2.1 Synthesis of Allyl Fluorides

In contrast to literature reports, initial attempts to prepare allyl fluorides *via* nucleophilic substitution with fluoride in protic solvents, failed to afford the desired products. In view of the problems and product mixtures highlighted above, in this work, we have focussed on the electrophilic synthetic protocols.

The synthetic route undertaken by Gouverner[18] in preparing allylic fluorides was *via* a two-step process. Firstly, the cross-metathesis of allyltrimethylsilane with varying olefenic partners, followed by fluorodesilylation of the corresponding allylsilane with Selectfluor.



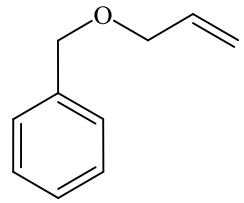
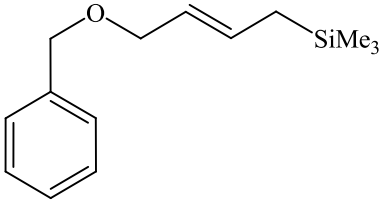
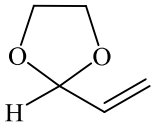
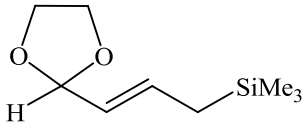
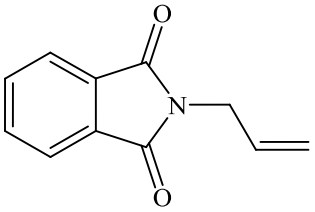
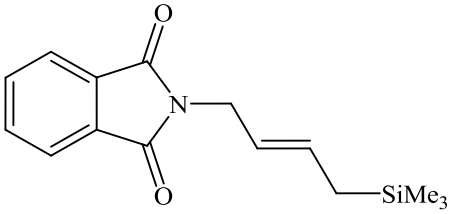
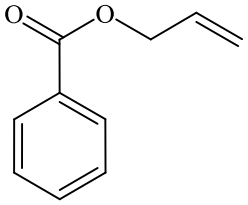
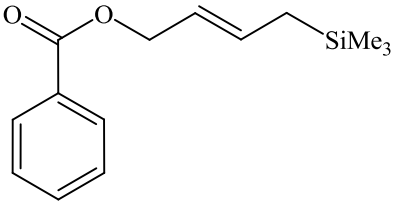
Starting Substrate	Product	Yield (%)
 **(64)**	 **(68)**	29
 **(65)**	 **(69)**	74
 **(66)**	 **(70)**	79
 **(67)**	 **(71)**	65

Table 2.8 *Yields obtained of products* ***(68) - (71)***

(4-(benzyloxy)but-2-enyl)trimethylsilane **(68)** was prepared by stirring allyl benzyl ether **(64)** with three equivalents of allyltrimethylsilane in DCM and heating to reflux under an atmosphere of argon for 48 hours. Over the 48 hour time period 5 mol % Grubbs 2nd generation catalyst was added in small portions. After which, purification by column chromatography [hexane: diethyl ether (97:3)] was meant to afford the desired product. However, the product obtained also contained starting material, due to the close proximity of the starting material and product Rf values. Alteration of the solvent mixture to hexane yielded a small amount of product, but an insufficient quantity to continue with the fluorination step. The reaction was repeated, and monitored closely throughout the reflux by ^{1}H NMR spectroscopy. After 48 hours the ^{1}H NMR spectrum still showed half of the reaction mixture to be starting material, therefore a longer reaction time was given, and a small amount of extra Grubbs catalyst added, in an attempt to drive the reaction to

completion. This enabled the reaction mixture to form a little more product but the reaction was not found to go to completion even after an extra 72 hours, and the addition of more catalyst. Therefore purification was conducted using column chromatography [hexane: diethyl ether (97:3)], affording the desired product as a cloudy oil, in a 29 % yield.

After the disappointing yields obtained in the synthesis of **(68)**, (3-[1,3]dioxalan-2-yl-allyl) trimethylsilane **(69)** was prepared with relative ease. The reaction was conducted as described by Gouverneur *et al*., yielding the pure product in 74 % yield as an oil.

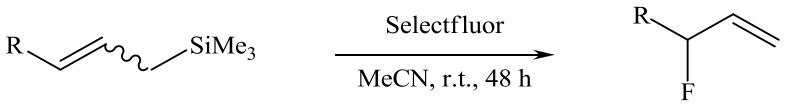
2-(4-trimethylsilanyl-but-2-enyl)isindole-1,3-dione **(70)** was synthesised after firstly preparing 2-allyl-isoindole-1,3-dione **(66),** following the protocol by Abulikemu *et al.,*[49] and was obtained as white crystals in a moderate 51 % yield. The subsequent reaction with allyltrimethylsilane afforded the desired product as a white solid in 79 % yield.

Benzoic acid 4-trimethylsilanyl-but-2-enyl ester **(71)** was synthesised by firstly forming the starting allyl benzoate **(67)**, which was prepared following the protocol by Yasui *et al*.[50] Allyl alcohol and benzoyl chloride were stirred in the presence of triethylamine, after workup, the desired product was afforded in 90 % yield. Therefore, allyl benzoate was reacted with 3 equivalents of allyl trimethylsilane in DCM with 5 mol % Grubbs catalyst. The reaction mixture was refluxed for 48 hours under an atmosphere of argon, after which column chromatography [hexane: diethyl ether (95:5)], afforded the product **(71)** as an oil in 65 % yield (Table 2.8).

The fluorination step for **(69)** proved problematic. The reaction was conducted as described in the literature, **(69)** was stirred with 1 equivalent of Selectfluor in MeCN, under an atmosphere of argon for 48 hours at room temperature. The crude reaction mixture was then purified *via* column chromatography [hexane: diethyl ether (96:4)] However, only a single fluorine peak at δ_F -150 ppm was observed in the $^{19}F\{^1H\}$ NMR spectrum, indicative of the Selectfluor BF_4^- counter ion. The reaction was repeated, using different solvent combinations for purification by column chromatography, however, the desired product **(72)** was not formed.

In contrast, both **(68)** and **(71)** showed excellent conversion to the corresponding allylic fluorides (**(73)** and **(75)**) and were isolated by column chromatography [hexane: diethyl ether (95:5)] as oils in 33 % and 55 % yield. The fluorination of **(70)** also proceeded smoothly and the desired allylic fluoride **(74)** was afforded as a white solid in 77 % yield

after purification *via* column chromatography [hexane: diethyl ether (85:15)]. All three products exhibited a characteristic signal at *ca.* – 185 ppm in their $^{19}F\{^{1}H\}$ NMR spectra (Table 2.9).



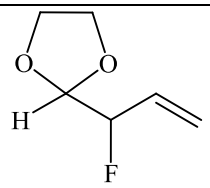
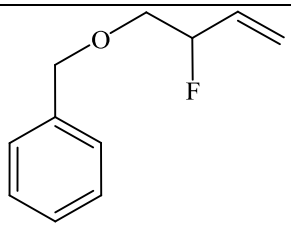
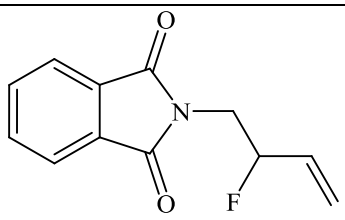
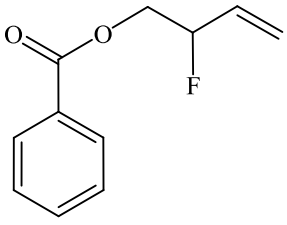
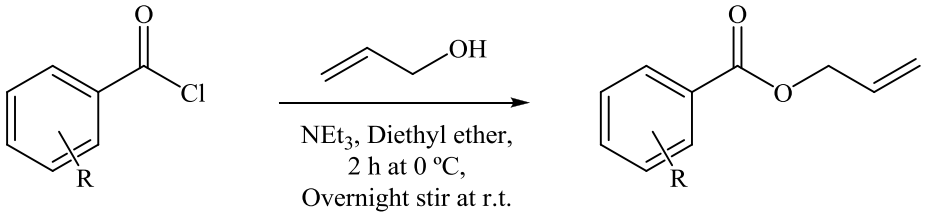
Starting Substrate	Product	Yield (%)
(69)	 **(72)**	0
(68)	 **(73)**	33
(70)	 **(74)**	77
(71)	 **(75)**	55

Table 2.9 *Yields obtained of fluorinated products* ***(72)-(75)***

2.2.1.2 Synthesis of Derivatised Allyl Benzoates

After synthesising several allylic fluorides as conducted by Gouverneur, it was found that there was the possibility of creating a new library of allylic fluoride compounds which were derivatised on the benzoate ring. It could then be observed whether functionalisation of the ring had an effect on the allylic portion of the substrate in reactions with palladium in

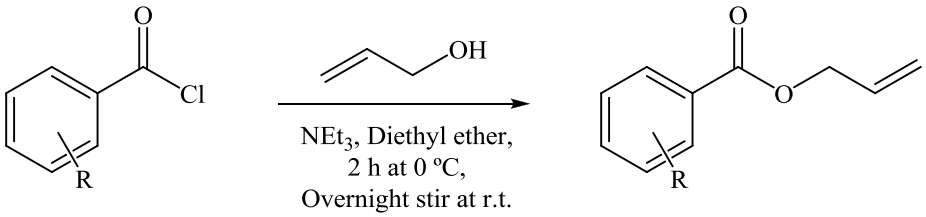
Chapter Three. Following the protocol outlined by Yasui, 1.1 equivalents of the derivatised benzoyl chloride was stirred in anhydrous diethyl ether, the reaction mixture cooled to 0 °C and then 1 equivalent of allyl alcohol was added in addition to 1.1 equivalents of triethylamine, the reaction mixture was then stirred at 0 °C for 2 hours, after which work up, drying over magnesium sulphate, and removal of solvent *in vacuo* afforded the derivatised allyl benzoate as an oil (Scheme 2.19).[50] The derivatised allyl benzoates were all obtained in good yields (Table 2.10).



Scheme 2.19 *General reaction scheme for synthesis of derivatised allyl benzoates (For a definition of R see Table 2.10)*

No further purification was required for allyl 2-fluorobenzoate **(83)**, allyl 4-(trifluoromethyl) benzoate **(84)** and the novel compound allyl 3-fluorobenzoate **(82)**. Previously allyl 2-fluoro benzoate **(83)** has been synthesised by Ebert *et al.*[51] in 95 % yield, in a 2 step copper mediated reaction, whilst allyl 4-(trifluoromethyl)benzoate **(84)** had been synthesised by Deming[52] by reacting equimolar amounts of 4-(trifluoromethyl)benzoyl chloride, allyl alcohol and pyridine in DCM for 2 hours then quenching the reaction with water affording the product as an oily white solid in a moderate 68 % yield. Both allyl 4-fluorobenzoate **(81)** and allyl 4-methylbenzoate **(85)** did not give 100 % conversion to product and therefore further purification by column chromatography was required. Allyl 4-fluorobenzoate **(81)** was purified by firstly eluting the column with hexane and then a mixture of hexane: diethyl ether (90:10), to yield the isolated product in 81 % yield. Previously Raj synthesised allyl 4-fluorobenzoate **(81)** in a moderate 62 % yield, by treating allyl alcohol and 4-fluorobenzaldehyde with acetone cyanohydrin and potassium hydroxide.[53] Allyl 4-methylbenzoate **(85)** was purified by column chromatography [hexane: diethyl ether (90:10)], affording the product in a 63 % isolated yield. This is not as high as the yield obtained by Bhattacharya[54] who synthesised the compound by stirring a mixture of potassium thiocyanate, methyl 4-methylbenzoate and dry Triton-x-405 (catalyst), at 185 ºC for 4 hours, and then cooling to 70 ºC and adding allyl bromide, followed by stirring for an additional 6 hours, workup, and then the product was obtained in an 85 % yield. However, though this is a higher yield than that isolated by using Yasui's method, the methodology doesn't seem as green as perpetuated by the authors especially with heating to

such high temperatures. All products were fully characterised by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy and mass spectrometry.



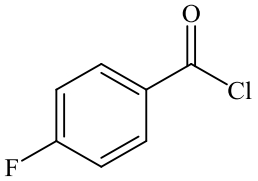
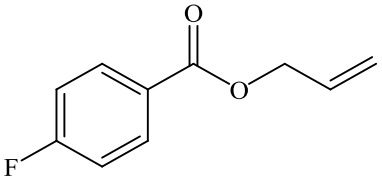
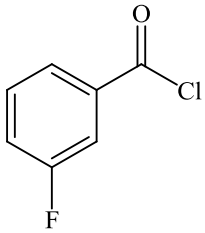
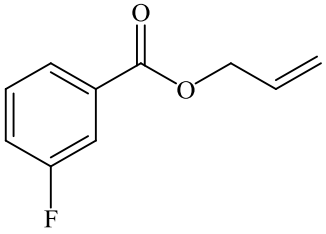
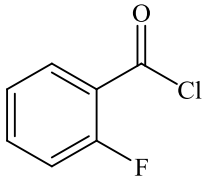
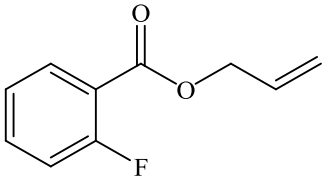
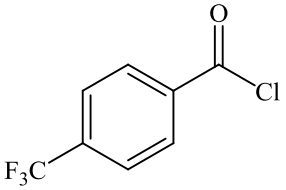
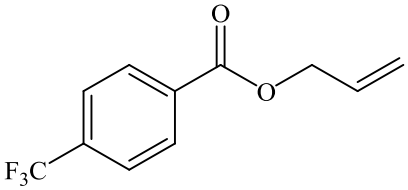
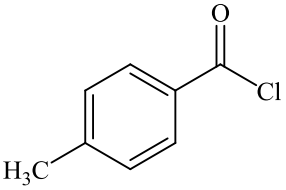
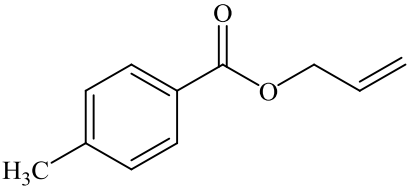
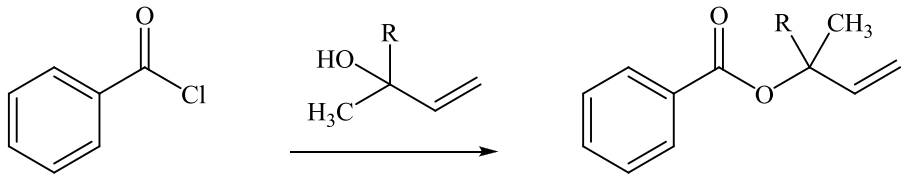
Benzoyl Chloride	Product	Literature Yield (%)	Yield (%)
 **(76)**	 **(81)**	62	81
 **(77)**	 **(82)**	-	97
 **(78)**	 **(83)**	95	98
 **(79)**	 **(84)**	68	95
 **(80)**	 **(85)**	85	63

Table 2.10 *Yields obtained of* ***(81)-(85)***

Two allyl alcohols were also synthesised with methyl substituents alpha to the benzoate (Table 2.11). Methylallyl benzoate **(87)** was synthesised following the method outlined by Nakamura *et al.*[55] 1 equivalent of 3-buten-2-ol was stirred in pyridine, the mixture cooled to 0 °C and 1 equivalent of benzoyl chloride added. The reaction mixture was then stirred at room temperature for 2 hours, after which aqueous workup, drying over magnesium sulphate and removal of solvent *in vacuo* yielded the product as a colourless oil in 71 % yield. Dimethylallyl benzoate **(86)** was synthesised following Yasui's protocol[50] whereby a flask was charged with 1.2 equivalents of sodium hydride, cooled to 0 ºC and 1 equivalent of dimethylallyl alcohol added. The mixture was stirred at 0 ºC for 10 minutes and then at room temperature for 15 minutes, after which the flask was cooled to 0 ºC, 1.2 equivalents of benzoyl chloride added and the resultant mixture stirred at 0 ºC for 2 hours followed by room temperature overnight. After work up, drying over magnesium sulphate, removal of solvent *in vacuo* and distillation under reduced pressure dimethylallyl benzoate **(86)** was formed as a colourless oil in a low 27 % isolated yield, attributable to losses incurred on the Kugelröhr apparatus.



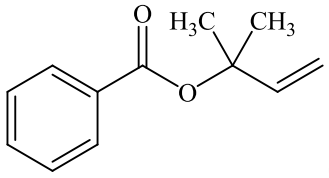
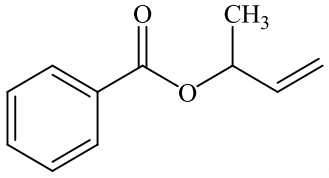
R	Conditions	Product	Yield (%)
CH_3	NaH, DMF, 2 h at 0 ºC, Overnight stir at r.t	 **(86)**	27
H	Pyridine, 0 ºC, 2 h at r.t	 **(87)**	71

Table 2.11 *Yields obtained of* ***(86)*** *and* ***(87)***

Once methylallyl benzoate **(87)** and dimethylallyl benzoate **(86)** were synthesised they were reacted with 3 equivalents of allyltrimethylsilane and 5 mol % 2nd generation Grubbs catalyst in DCM, as previously described. However, with methylallyl benzoate **(87)** it was found that after 48 hours the reaction had not gone to completion, but instead only 50 % conversion had occurred, therefore an additional portion of Grubbs catalyst was added to the reaction mixture and the reaction refluxed for a further 48 hours, an aliquot was taken from the reaction mixture and conversion had increased to 75 %. The reaction mixture was

purified using column chromatography [hexane: diethyl ether (95:5)], however, the product was obtained as a mixture with the starting material. Therefore, the reaction was repeated on a 2 mmol scale, after 48 hours the reaction had reached 65 % conversion. The reaction mixture was then purified *via* column chromatography [hexane: 100] followed by [hexane: diethyl ether (95:5)], however, no pure product could be isolated.

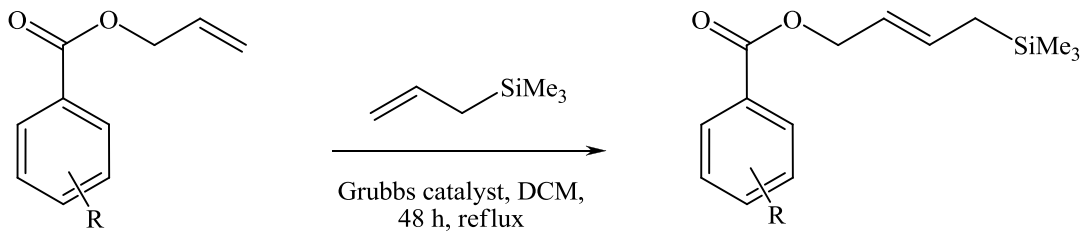
The reaction of dimethylallyl benzoate **(86)** with allyltrimethylsilane proceeded in a similar manner, after 48 hours there was only 33 % conversion, therefore the reaction mixture was refluxed for an additional 48 hours, however, there was no improvement of the conversion. Purification of the mixture was attempted by column chromatography [hexane: diethyl ether (97:3)], however, no desired product was recovered only unwanted starting material. Hence, the reactions of methyl and dimethylallyl benzoate proved unsuccessful in affording the corresponding silyl products. This could be attributable to the methyl substituents hindering the metathesis mechanism.

2.2.1.3 Synthesis of Silyl Derivatised Allyl Benzoates

Once all the derivatised allyl benzoates had been synthesised they were reacted with 3 equivalents of allyltrimethylsilane and 5 mol % 2nd generation Grubbs catalyst in DCM, as previously described (Scheme 2.20). The yields obtained range from low to very good (34-83 %) (Table 2.12). Both the 4-fluoro **(81)** and 3-fluoro benzoates **(82)** exhibited good conversion to **(88)** and **(89)** in the crude ^{1}H NMR spectra, 91 % and 77 % respectively, after 48 hours. Both reactions were then worked up by removing the solvent *in vacuo* and purifying by column chromatography [hexane (100)] followed by [hexane: diethyl ether (96:4)]. However, despite the fact that very small fractions were collected both the product and unreacted starting material came out together. The unreacted starting material does not affect the fluorination step, therefore most of the product: starting material mixture was used for the next synthetic step, whilst a small amount was retained so that it could be purified fully in order for full characterisation to be conducted.

After testing several solvent systems, it was found that chloroform: hexane (70:30) could be used to successfully separate the desired product from the starting material. This solvent system was then also used to separate **(89)** from starting material, affording the product in 71 % yield. Allyl 2-fluorobenzoate **(83)** was converted to the corresponding silyl product **(90)** in 77 % yield after 48 hours. The product mixture was purified in the same way affording the silyl product in a 56 % isolated yield.

The conversion of **(84)** and **(85)** to product was a little lower (53 and 66 %), and they were only isolated as oils following column chromatography [chloroform: hexane (70:30)] in 35 and 34 % yields respectively (**(91)** and **(92)**). All products were fully characterised by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy and mass spectrometry.



Scheme 2.20 *General reaction scheme for synthesis of silyl derivatised allyl benzoates*

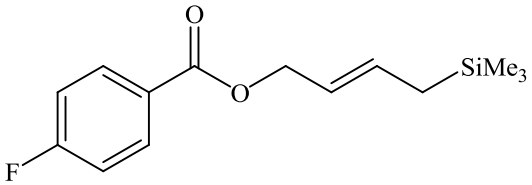
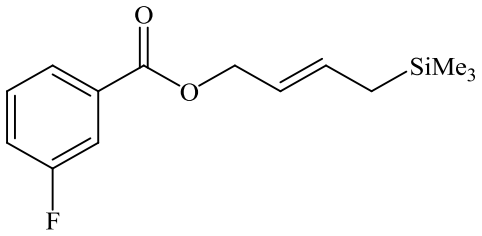
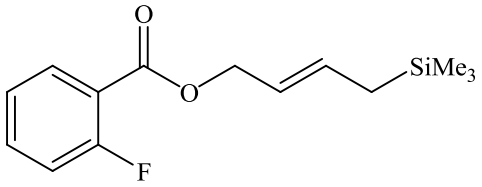
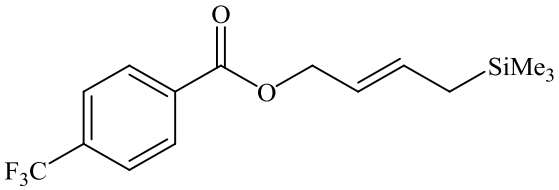
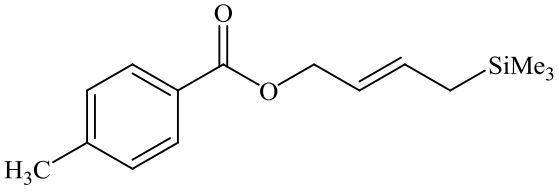
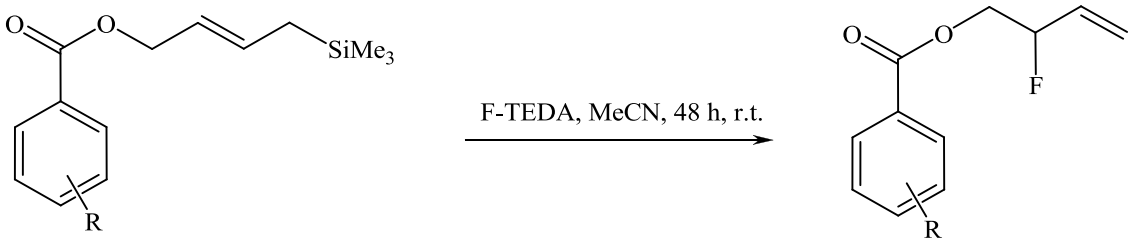
Starting substrate	Product	Yield (%)
(81)	 **(88)**	83
(82)	 **(89)**	71
(83)	 **(90)**	56
(84)	 **(91)**	35
(85)	 **(92)**	34

Table 2.12 *Yields of **(88)-(92)***

2.2.1.4 Synthesis of Fluorinated Derivatised Allyl Benzoates

After synthesising several silyl derivatised allyl benzoates, they were reacted further with 1-1.5 equivalents of Selectfluor in acetonitrile at room temperature for 48 hours. The isolated yields of products ranged from low to moderate (31-53 %), despite excellent conversions. A slight excess of Selectfluor was used in all reactions to ensure that complete conversion had occurred, as in many cases the starting reagent was a mixture of silyl allyl benzoate and allyl benzoate.



Scheme 2.21 *General scheme for synthesis of fluorinated derivatised allyl benzoates (For a definition of R see Table 2.13)*

As previously described it was often difficult to fully isolate the silyl allyl benzoate from the reaction mixture and therefore it was easier to remove the starting material during the purification of the fluorinated product. Firstly, 4-(trimethylsilyl)but-2-enyl 4-fluoro benzoate **(88)** was reacted with 1.15 equivalents of Selectfluor for 48 hours, after which an aliquot of the reaction mixture was taken and analysed by ^{1}H and ^{19}F NMR spectroscopy, both spectra showed that the reaction had gone to completion. The product was then isolated by column chromatography [hexane: diethyl ether (92:8)], and the product **(93)** was isolated pure as an oil in 37 % yield. Similarly 4-(trimethylsilyl)but-2-enyl 3-fluoro benzoate **(89)** was reacted with 1.2 equivalents of Selectfluor, and the crude ^{1}H and ^{19}F NMR spectra showed complete conversion to product after 48 hours. As the reaction was conducted in acetonitrile this solution was concentrated before loading onto the column as this solvent worked better than DCM in the previous purification of 2-fluorobut-3-enyl 4-fluorobenzoate. The column was then eluted with [hexane: diethyl ether (92:8)] and the product **(94)** successfully isolated in a 31 % yield as an oil. In the same way 4-(trimethylsilyl)but-2-enyl 2-fluorobenzoate **(90)**, 4-(trimethylsilyl)but-2-enyl 4-(trifluoro-methyl)benzoate **(91)** and 4-(trimethylsilyl)but-2-enyl 4-methylbenzoate **(92)** were also reacted with Selectfluor (1.45, 1.52 and 1 equivalent respectively), and after purification by column chromatography as outlined previously, the fluorinated products were isolated as oils in 31, 53 and 50 % yields respectively. All products were fully characterised by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy and mass spectrometry.

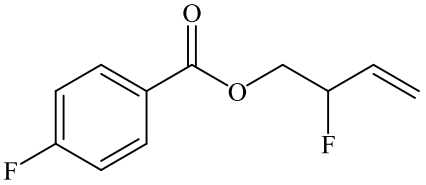
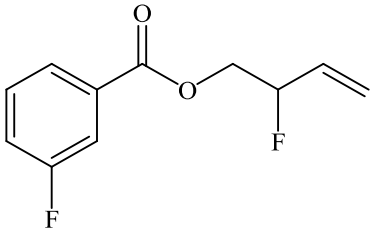
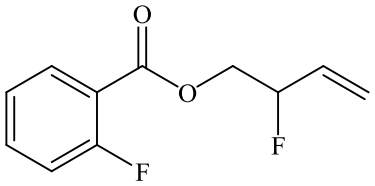
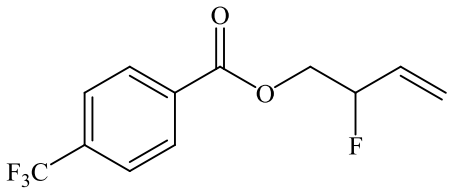
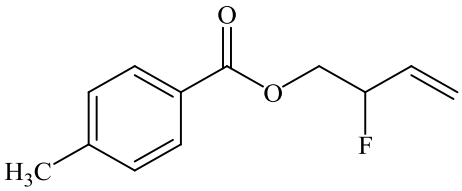
Starting substrate	Conditions	Product	Yield (%)
(88)	Selectfluor, (1.15 equiv)	 **(93)**	37
(89)	Selectfluor, (1.2 equiv)	 **(94)**	31
(90)	Selectfluor, (1.45 equiv)	 **(95)**	31
(91)	Selectfluor, (1.52 equiv)	 **(96)**	53
(92)	Selectfluor, (1 equiv)	 **(97)**	50

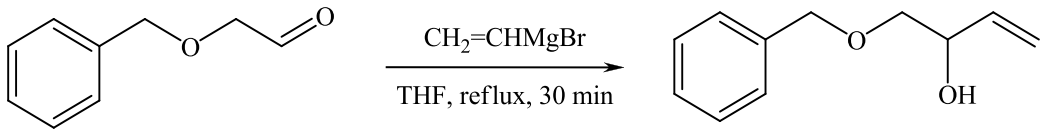
Table 2.13 *Yields of* ***(93)-(97)***

2.2.2 Synthesis of Allylic Chlorides

In this work allylic chloride analogues of the range of allylic fluorides described earlier were synthesised in a 2 step procedure, *via* formation of the respective allyl alcohol, followed by chlorination using tetramethyl-α-chloro-enamine.

2.2.2.1 Synthesis of Allylic Alcohols

2.2.2.1.1 Synthesis of 1-(Benzyloxy)but-3-en-2-ol (39)



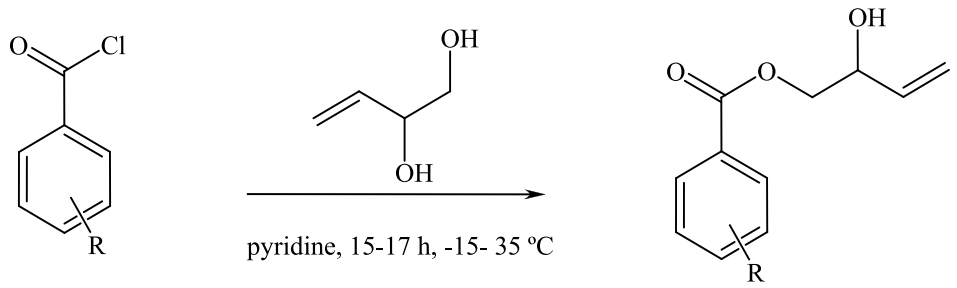
(98)

Scheme 2.22 *Synthesis of* ***(98)***

Allylic alcohol **(98)** was synthesised following Trost's[56] protocol; benzyloxyacetaldehyde was added dropwise to a solution of vinylmagnesium bromide (1.1 equivalents) in THF, causing the temperature to rise to 60 °C. The reaction mixture was refluxed for 30 minutes, after which, cooling, aqueous workup, drying over magnesium sulphate and removal of solvent *in vacuo* yielded the crude product. Analysis by ^{1}H NMR spectroscopy of the crude reaction mixture revealed conversion to product to be 91 %. Purification by column chromatography [hexane: ethyl acetate (80:20)] afforded the desired product in 81 % yield as a yellow oil.

2.2.2.1.2 Synthesis of 2-hydroxybut-3-enyl benzoate and related Allylic Alcohols

The protocol by Ziegler,[57] was utilised in the synthesis of the benzoyl-derivatised allylic alcohols by reaction of the appropriate benzoyl chloride with but-3-ene-1,2-diol. Products were obtained in moderate yields (40 - 66 %), either as oils or as white solids (Scheme 2.23) (Table 2.14).



Scheme 2.23 *General reaction scheme for synthesis of* ***(100-105)***
(For a definition of R see Table 2.14)

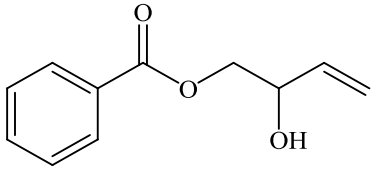
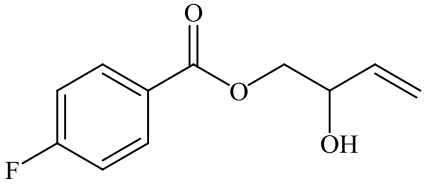
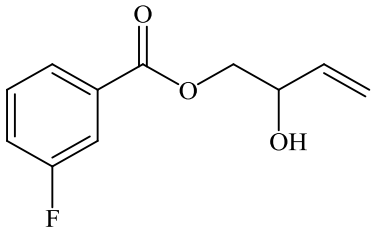
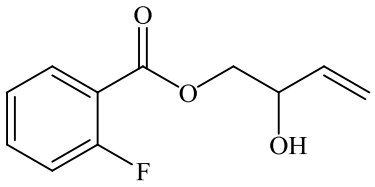
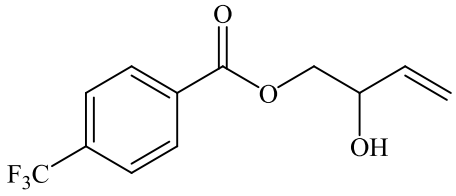
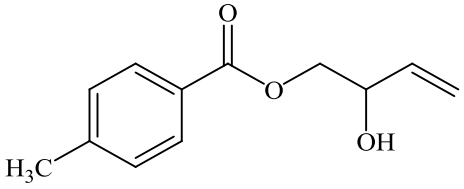
Starting substrate	Product	Yield (%)
(99)	 **(100)**	31
(76)	 **(101)**	59
(77)	 **(102)**	42
(78)	 **(103)**	42
(79)	 **(104)**	66
(80)	 **(105)**	40

Table 2.14 *Yields obtained of Allylic Alcohols*

The synthesis of 2-hydroxybut-3-enyl benzoate **(100)** was conducted following the method outlined by Ziegler;[57] a solution of benzoyl chloride **(99)** (1.2 equivalents) and pyridine was added dropwise to a mixture of (±)3-butene-1,2-diol and pyridine, at - 35 ºC, the mixture was left to stir at - 35 ºC for 17 hours, after which workup, drying over sodium

sulphate and removal of solvent *in vacuo* yielded the crude product. Purification by chromatography [chloroform: hexane (80:20)] afforded the product as an oil in 31 % yield, which although lower than that reported in the literature (57 %) could be attributed to difficulties in maintaining the reaction temperature at - 35 ºC for the whole reaction period. 4-methyl-2-hydroxybut-3-enyl benzoate **(105)** was formed, having previously been synthesised by Ziegler, using slightly different conditions to those described earlier for the synthesis of **(100)**; a solution of (±)3-butene-1,2-diol (1.1 equivalents) and pyridine were cooled to - 15 ºC, 4-methylbenzoyl chloride **(80)** (1 equivalent) was added and the mixture left to stir at - 15 ºC for 15 hours, after which workup, drying over sodium sulphate and removal of solvent *in vacuo* yielded the crude product. Purification by chromatography [chloroform: hexane (80:20)] afforded the product as a white solid in 40 % yield. The solid readily formed crystals which were analysed by single crystal X-ray crystallography (Figure 2.3). The synthesis of 2-hydroxybut-3-enyl 4-(trifluoromethyl)benzoate **(104)** was conducted similarly but by cooling to -35 ºC for 17 hours. The crude product was purified utilising the same solvent system, affording the product as a white crystalline product in 66 % yield (Figure 2.3).

Single crystals of **(101)**, **(104)** and **(105)** suitable for single crystal structure analysis were grown by dissolving the materials in a small amount of DCM and layering with hexane. Molecular structures are shown in Figure 2.3 and Figure 2.4, with selected bond lengths (Å) and bond angles (º) listed in Table 2.15 and Table 2.16.

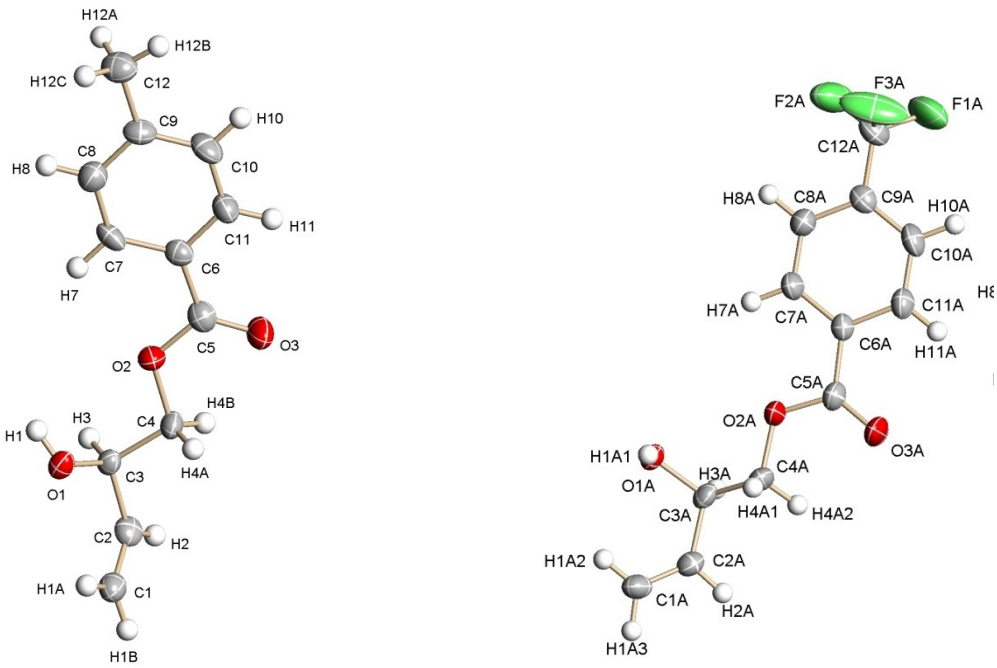


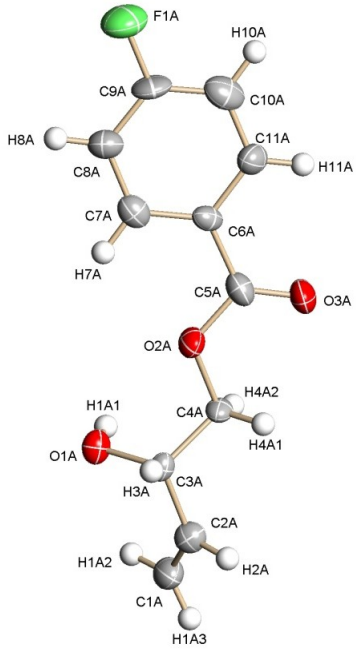
Figure 2.3 *Crystal structures of 2-hydroxybut-3-enyl 4-methylbenzoate* ***(105)*** *and 2-hydroxy but-3-enyl 4-(trifluoromethyl)benzoate* ***(104)***

Both **(105)** and **(104)** exhibit two unique molecules in the unit cell. The structural data confirm the formation of the desired products, but are unremarkable. There is only one noticeable difference observed between the two molecules in the bond angle between O(3)-C(5)-O(2), as in **(105)** it is 121.7(6) whilst in **(104)** it is 124.2(3), therefore suggesting that the substituents on the ring may be having an effect on the carbonyl portion of the compound but not extending to the allylic portion.

Bond Lengths (Å)	**(105)**		**(104)**	
C1-C2	1.322(7)	1.315(7)	1.305(4)	1.311(4)
O3-C5	1.211(6)	1.215(6)	1.195(3)	1.207(3)
O2-C5	1.346(7)	1.342(7)	1.333(3)	1.334(3)
O1-C3	1.430(6)	1.420(6)	1.428(3)	1.429(3)
Bond Angles (°)				
C(1)-C(2)-C(3)	125.5(6)	124.8(5)	125.5(3)	125.6(3)
O(3)-C(5)-O(2)	121.7(6)	122.2(6)	124.2(3)	123.4(3)

Table 2.15 *Selected bond lengths and bond angles for **(104)** and **(44)***

The allylic alcohols **(103)**, **(102)** and **(101)** were also synthesised in a facile manner using Ziegler's protocol, and the desired products afforded as white crystalline solids in 42, 42 and 59 % yields respectively. The structure of **(101)** was determined by X-ray crystallography (Figure 2.4).



Bond Lengths (Å)	**(101)**
C1-C2	1.318(8)
O3-C5	1.207(7)
O2-C5	1.338(8)
O1-C3	1.451(6)
Bond Angles (°)	
C(1)-C(2)-C(3)	126.7(6)
O(3)-C(5)-O(2)	120.3(7)

Table 2.16

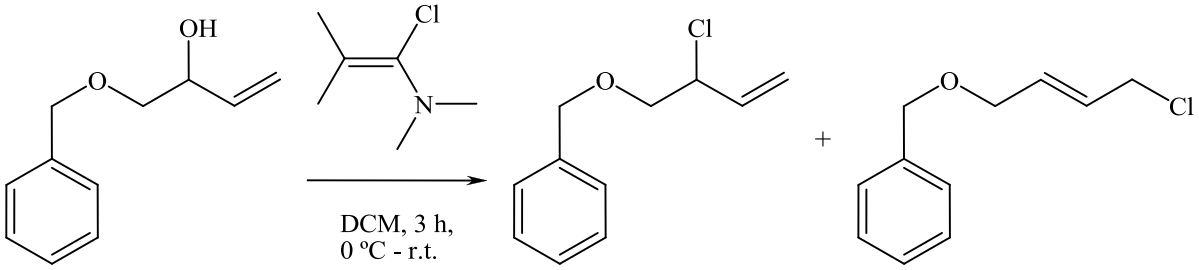
Figure 2.4 *Crystal Structure of **(101)** with selected bond lengths and bond angles*

The structural data confirmed the formation of the desired product but are unremarkable and are similar to those observed with **(105)** and **(104)**.

2.2.3 Synthesis of Allylic Chlorides

Once all the allylic alcohols had been prepared they could be converted to their corresponding chlorides with tetramethyl-α-chloroenamine using the method outlined by Munyemana.[12]

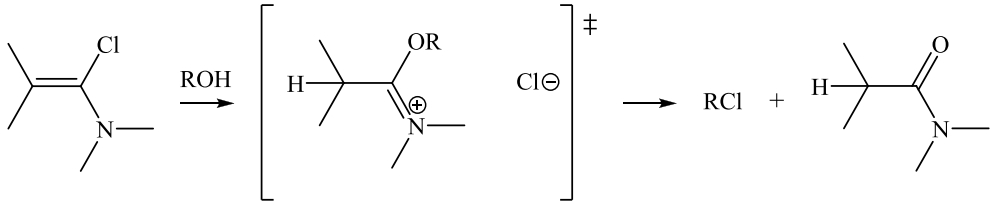
2.2.3.1 Synthesis of ((2-chlorobut-3-enyloxy)methyl)benzene (106)



(106) **(107)**

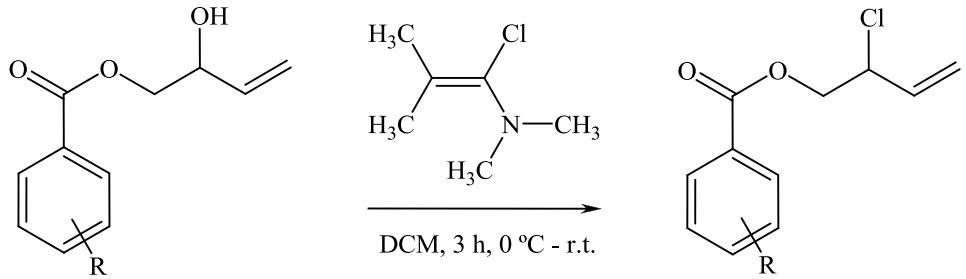
Scheme 2.24 *Synthesis of* ***(106)***

The novel allyl chloride **(106)** was synthesised, by reaction of 1-(benzyloxy)but-3-en-2-ol in DCM at 0 ºC, with one equivalent of tetramethyl-α-chloroenamine. The reaction mixture was stirred at room temperature for 3 hours. After which, purification by chromatography [DCM: cyclohexane (50:50)] afforded the product as an oil in 52 % yield. In addition, ((4-chlorobut-2-enyloxy)methyl)benzene **(107)** was also isolated in a 15 % yield from the purification column. Previously, **(107)** had been synthesised by Bandini and co workers[58] *via* the reaction of allyl chloride with (allyloxymethyl)benzene, catalysed by Hoveyda's catalyst. Both products were fully characterised. However, since **(107)** is an unwanted co-product no attempts were made when chlorinating the other allylic alcohols to isolate and characterise it. It was reported by Munyemana that the chlorination of secondary alcohols would give some rearranged chloride product, and that this was dependent on time, as the rearranged chloride was thought to form after the formation of the desired chloride.[12] Therefore, as all the allylic alcohols being converted to chlorides were secondary it was likely that this might impair product conversions. The most probable mechanistic pathway for the synthesis of the allyl chloride(s) is likely to involve the formation of an intermediate iminium salt, and attack of the chloride displacing the amide which is a good leaving group, affording the desired allylic chloride and *N,N*-dimethylisobutyramide as the co-product (Scheme 2.25).



Scheme 2.25 *Mechanistic pathway for synthesis of allylic chloride*

2.2.3.2 Synthesis of 2-chlorobut-3-enyl benzoate and related Allylic Chlorides



Scheme 2.26 *General reaction scheme for synthesis of allylic chlorides* ***(108)*** *–* ***(113)*** *(For a definition of R see Table 2.17)*

The same methodology was then extended to the chlorination of the derivatised benzoyl alcohols and the desired products were obtained in moderate yields (32-74 %) (Table 2.17). Both **(100)** and **(101)** proceeded in good conversion to product and were isolated by column chromatography [DCM: cyclohexane (50:50)] in 65 % and 74 % yields respectively. The main by-products were the rearranged chlorides 4-chlorobut-2-enyl benzoate and 4-chlorobut-2-enyl 4-fluorobenzoate, however, as these were not desired products, no attempts were made to isolate or characterise them.

The isolated yields of **(110)** – **(113)** were lower than expected. Here chromatography revealed both unreacted starting material and 1-chloroallyl product. Although the addition of aliquots of tetramethyl-α-enamine and longer reaction times were attempted, isolated yields of the products could not be improved substantially. All products were fully characterised by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy and mass spectrometry.

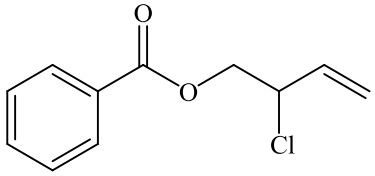
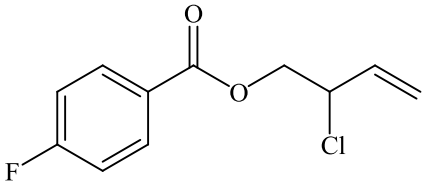
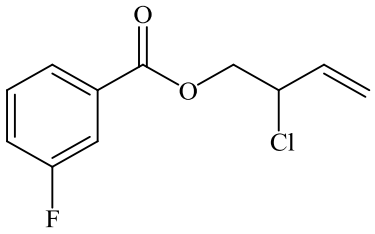
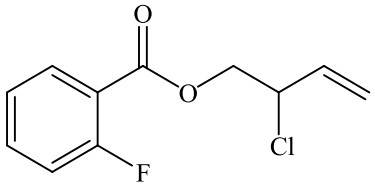
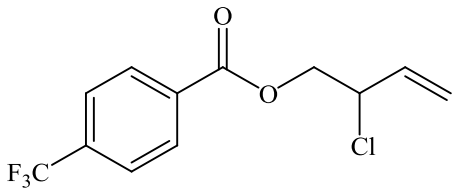
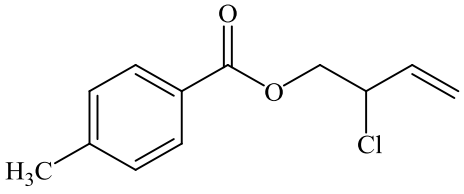
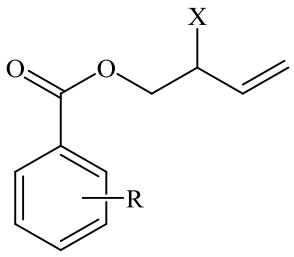
Starting substrate	Product	Yield (%)
(100)	 **(108)**	65
(101)	 **(109)**	74
(102)	 **(110)**	34
(103)	 **(111)**	47
(104)	 **(112)**	37
(105)	 **(113)**	32

Table 2.17 *Yields obtained of Allylic Chlorides* ***(108) – (113)***

2.3 Conclusions

The novel compounds, 2-fluorobut-3-enyl 2-fluorobenzoate **(95)**, 2-fluorobut-3-enyl 3-fluorobenzoate **(94)**, 2-fluorobut-3-enyl 4-fluorobenzoate **(93)**, 2-fluorobut-3-enyl 4-(trifluoromethyl) benzoate **(96)** and 2-fluorobut-3-enyl 4-methylbenzoate **(97)** (Figure 2.5), have been synthesised *via* a two-step process. Firstly, the cross-metathesis of allyltrimethylsilane with varying olefenic partners, followed by fluorodesilylation of the corresponding allylsilane with Selectfluor. Their structures were determined by NMR spectroscopy and mass spectrometry. The novel compounds 2-hydroxybut-3-enyl 4-fluoro benzoate **(101)**, 2-hydroxybut-3-enyl 3-fluorobenzoate **(102)**, 2-hydroxybut-3-enyl 2-fluorobenzoate **(103)**, 2-hydroxybut-3-enyl 4-(trifluoromethyl)benzoate **(104)** (Figure 2.5) have also been synthesised, structures determined by NMR spectroscopy, mass spectroscopy and X-ray crystallography. These compounds were then reacted further with tetramethyl-α-chloroenamine to afford the corresponding novel allylic chlorides, ((2-chloro but-3-enyloxy)methyl)benzene **(106)**, 2-chlorobut-3-enyl 4-fluorobenzoate **(109)**, 2-chlorobut-3-enyl 3-fluorobenzoate **(110)**, 2-chlorobut-3-enyl 2-fluorobenzoate **(111)**, 2-chlorobut-3-enyl 4-(trifluoromethyl)benzoate **(112)** and 2-chlorobut-3-enyl 4-methyl benzoate **(113)** (Figure 2.5), which have been successfully separated from their rearranged products by column chromatography and characterised fully by NMR spectrometry and mass spectroscopy. In Chapter Three the reaction of these allylic chlorides and allylic fluorides with sources of Pd(0) will be described.



(95) = R= 2-F, X= F
(94) = R= 3-F, X= F
(93) = R= 4-F, X= F
(96) = R= 4-CF_3, X= F
(97) = R= 4-CH_3, X= F
(103) = R= 2-F, X= OH
(102) = R= 3-F, X= OH
(101) = R= 4-F, X= OH
(104) = R= 4-CF_3, X= OH
(111) = R= 2-F, X= Cl
(110) = R= 3-F, X= Cl
(109) = R= 4-F, X= Cl
(112) = R= 4-CF_3, X= Cl
(113) = R= 4-CH_3, X= Cl

Figure 2.5 *Novel compounds synthesised in Chapter Two*

2.4 References

[1] R. Roig, J. M. Percy, in *Science of Synthesis*, Georg Thieme Verlag, Stuttgart, New York, **2005**, pp. 319.

[2] W. J. Middleton, *J. Org. Chem.* **1975**, *40*, 574.

[3] G. A. Olah, M. Nojma, I. Kerekes, *J. Am. Chem. Soc.* **1974**, *96*, 925.

[4] A. Boukerb, D. Grée, M. Laabassi, R. Grée, *J. Fluorine Chem* **1998**, *88*, 23.

[5] D. Grée, L. Vallerie, R. Grée, L. Toupet, I. Washington, J.-P. Pelicier, M. Villacampa, J. M. Pérez, K. N. Houk, *J. Org. Chem.* **2001**, *66*, 2374.

[6] G. M. Blackburn, D. E. Kent, *J. Chem. Soc. Chem. Commun.* **1981**, 511.

[7] G. M. Blackburn, D. E. Kent, *J. Chem. Soc., Perkin Trans 1* **1986**, 913.

[8] G. B. Hammond, D. J. deMendonca, *J. Fluorine Chem* **2000**, *102*, 189.

[9] J. Mann, G. P. Smith, *J. Chem. Soc. Perkin Trans. 1* **1991**, 2884.

[10] S. Legoupy, C. Crévisy, J.-C. Guillemin, R. Grée, *J. Fluorine Chem* **1999**, *93*, 171.

[11] D. M. Grée, C. J. M. Kermarrec, J. T. Martelli, R. L. Grée, J.-P. Lellouche, L. J. Toupet, *J. Org. Chem.* **1996**, *61*, 1918.

[12] F. Munyemana, A.-M. Frisque-Hesbain, A. Devos, L. Ghosez, *Tetrahedron Lett.* **1989**, *30*, 3077.

[13] N. Yoneda, T. Fukuhara, *Chem. Lett.* **2001**, 222.

[14] J. Ichihara, T. Matsuo, T. Hanafusa, T. Ando, *J. Chem. Soc. Chem. Commun.* **1986**, 793.

[15] J. Ichihara, Y. Takai, K. Tomioka, *J. Fluorine Chem* **1995**, *71*, 131.

[16] M. C. Pacheco, S. Purser, V. Gouverneur, *Chem. Rev.* **2008**, *108*, 1943.

[17] V. Gouverneur, B. Greedy, *Chem. Eur. J.* **2002**, *8*, 767.

[18] S. Thibaudeau, V. Gouverneur, *Org. Lett.* **2003**, *5*, 4891.

[19] M. Tredwell, K. Tenza, M. C. Pacheco, V. Gouverneur, *Org. Lett.* **2005**, *7*, 4495.

[20] B. Greedy, J. M. Paris, T. Vidal, V. Gouverneur, *Angew. Chem. Int. Ed.* **2003**, *42*, 3291.

[21] S. Sunghee, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 2756.

[22] R. J. Fox, G. Lalic, R. G. Bergmann, *J. Am. Chem. Soc.* **2007**, *129*, 14144.

[23] W. G. Young, F. F. Caserio, D. D. Brandon, *J. Am. Chem. Soc.* **1960**, *82*, 6163.

[24] W. S. Johnson, T. Li, C. A. Harbert, W. R. Bartlett, T. R. Herrin, B. Staskun, D. H. Rich, *J. Am. Chem. Soc.* **1970**, *92*, 4461.

[25] E. Meléndez, M. Pardo, *Bull. Soc. Chim. Fr.* **1974**, 632.

[26] E. J. Corey, D. E. Cane, L. Libit, *J. Am. Chem. Soc.* **1971**, *93*, 7016.

[27] B. M. Trost, D. F. Taber, J. B. Alper, *Tetrahedron Lett.* **1976**, 3857.

[28] D. F. Taber, *J. Am. Chem. Soc.* **1977**, *99*, 3513.

[29] E. J. Corey, C. U. Kim, M. Takeda, *Tetrahedron Lett.* **1972**, 4339.

[30] E. W. Collington, A. I. Meyers, *J. Org. Chem.* **1971**, *36*, 3044.

[31] A. I. Meyers, E. W. Collington, *Tetrahedron* **1971**, *27*, 5979.

[32] S. G. Hegde, M. K. Vogel, J. Saddler, T. Hrinyo, N. Rockwell, R. Haynes, M. Oliver, J. Wolinky, *Tetrahedron Lett.* **1980**, *21*, 441.

[33] M. P. VanBrunt, R. O. Ambenge, S. M. Weinreb, *J. Org. Chem.* **2003**, *68*, 3323.

[34] J. A. Tunge, S. R. Mellegard, *Org. Lett.* **2004**, *6*, 1205.

[35] M. Yamanaka, M. Arisawa, A. Nishida, M. Nakawaga, *Tetrahedron Lett.* **2002**, *43*, 2403.

[36] F. J. Moreno-Dorado, F. M. Guerra, F. L. Manzano, F. J. Aladro, Z. D. Jorge, G. M. Massanet, *Tetrahedron Lett.* **2003**, *44*, 6691.

[37] C. Walling, W. Thaler, *J. Am. Chem. Soc.* **1961**, *83*, 3877.

[38] T. Hori, K. B. Sharpless, *J. Org. Chem.* **1979**, *44*, 4204.

[39] T. Hori, K. B. Sharpless, *J. Org. Chem.* **1979**, *44*, 4208.

[40] F. F. Caserio, G. E. Denis, R. H. DeWolfe, W. G. Young, *J. Am. Chem. Soc.* **1955**, *77*, 4182.

[41] E. I. Snyder, *J. Org. Chem.* **1972**, *37*, 1466.

[42] R. M. Magid, O. S. Fruchey, W. L. Johnson, *Tetrahedron Lett.* **1977**, 2999.

[43] P.-T. Ho, N. Davies, *J. Org. Chem.* **1984**, *49*, 3027.

[44] V. K. Yadav, K. G. Babu, *Tetrahedron* **2003**, *59*, 9111.

[45] S. Roy, T. Das, M. Saha, S. K. Chaudhuri, S. Bhar, *Synth. Commun.* **2007**, *37*, 4367.

[46] L. De Luca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2002**, *4*, 553.

[47] J. Yin, C. E. Gallis, J. D. Chisholm, *J. Org. Chem.* **2007**, *72*, 7054.

[48] L. Hintermann, F. Lang, P. Maire, A. Togni, *Eur. J. Inorg. Chem.* **2006**, 1397.

[49] A. Abulikemu, G. Halasz, A. Csampai, A. Gomory, J. Rabai, *J. Fluorine Chem* **2004**, *125*, 1143.

[50] K. Yasui, K. Fugami, S. Tanaka, Y. Tamaru, *J. Org. Chem.* **1995**, *60*, 1365.

[51] G. W. Ebert, W. L. Juda, R. H. Kosakowski, B. Ma, L. Dong, K. E. Cummings, M. V. B. Phelps, A. E. Mostafa, J. Luo, *J. Org. Chem.* **2005**, *70*, 4314

[52] T. J. Deming, B. M. Novak, *J. Am. Chem. Soc.* **1993**, *115*, 9101.

[53] I. Victor Paul Raj, A. Sudalai, *Tetrahedron Lett.* **2005**, *46*, 8303

[54] A. Bhattacharya, N. C. Patel, T. Vasques, R. Tichkule, G. Parmar, J. Wu, *Tetrahedron Lett.* **2006**, *47*, 565.

[55] K. Nakamura, K. Takenaka, *Tetrahedron: Asymmetry* **2002**, *13*, 415.

[56] B. M. Trost, C. Nübling, *Carbohydr. Res.* **1990**, *202*, 1.

[57] T. Ziegler, F. Bien, C. Jurisch, *Tetrahedron: Asymmetry* **1998**, *9*, 765.

[58] M. Bandini, P. G. Cozzi, S. Licciulli, A. Umani-Ronchi, *Synthesis* **2004**, *3*, 409.

CHAPTER THREE

3 Activation of Allylic Fluorides and Chlorides by Palladium

3.1 Introduction

This chapter will focus on the activation of the C-Cl and C-F bond by reaction with Pd(0), in order to examine whether identical reaction conditions can be employed and if the same products can be generated.

3.1.1 Reactions of Allyl Chlorides with Palladium

In 1964 Dent, Long and Wilkinson synthesised π-allylic palladium chloride complexes (yields > 80 %) by passing carbon monoxide through a mixture of the allylic chloride and sodium chloropalladate dissolved in methanol.[1] Prior to this method π-allylic palladium chloride complexes had been synthesised by reacting palladium chloride with an allylic alcohol[2, 3] or chloride,[4, 5] however, the yields rarely exceeded 50 %.

Following on from this work, Ito and co-workers found that with $Pd_2(dba)_3$ oxidative addition reactions occurred with allylic chlorides and that the substituents on the allylic chloride affected the rate of reaction, with allyl chloride being more reactive than methallyl chloride, crotyl chloride and cinnamyl chloride (Figure 3.1).[6]

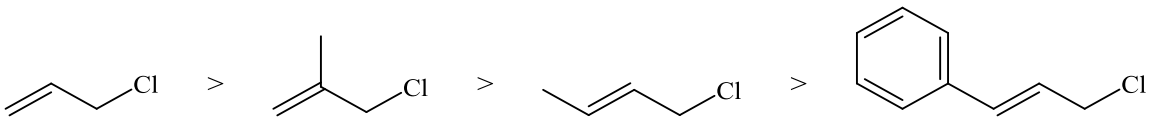
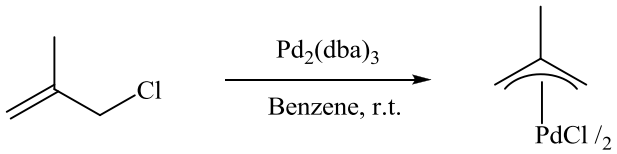


Figure 3.1 *Order of reactivity of allylic chlorides with $Pd_2(dba)_3$*

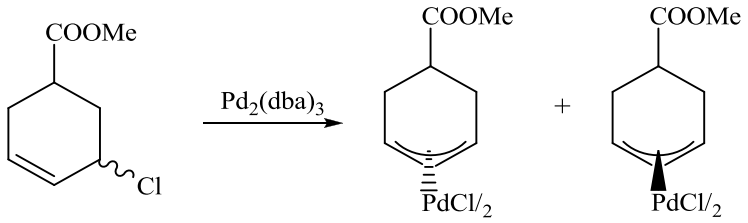
The reaction was conducted by mixing an excess of the allylic chloride in a benzene solution of $Pd_2(dba)_3$ at room temperature under nitrogen. The reaction mixture changes colour from purple to a yellow-green. Washing with hexane removed the dba and recrystallisation from methanol afforded the product as a yellow solid.



Scheme 3.1 *Reaction of methallyl chloride with $Pd_2(dba)_3$*

The majority of reported oxidative addition reactions of allylic compounds proceed *via* anti addition,[7-11] with very few examples of syn addition.[12-16] In 1990 Kurosawa reported the first syn oxidative addition of allylic chlorides to palladium,[17] followed very closely by Vitagliano.[18]

Kurosawa reacted a mixture of allylic chlorides **(114)** and **(115)** with $Pd_2(dba)_3$ at room temperature for several hours obtaining a mixture of *trans* and *cis* isomers (Scheme 3.2). The product ratio was found to be dependent on the solvent used however, there was no observation of *trans* to *cis* isomerisation or interconversion between *trans* and *cis* products under the reaction conditions employed.



(114) - cis
(115) - trans

Scheme 3.2 *Reaction of* ***(114)*** *and* ***(115)*** *with* $Pd_2(dba)_3$

The structure of the allyl product obtained was determined by conversion to the known compounds methyl 5-phenylcyclohex-3-enecarboxylate, *via* attack of phenyl anion (with retention of stereochemistry)[19] and dimethyl 2-(5-(methoxycarbonyl) cyclohex-2-enyl) malonate, *via* attack of dimethyl malonate (with inversion of stereochemistry).[19] The *cis* and *trans* configurations of these derivatives have previously been established.[8, 11]

Allylic Chloride	Pd(0)	Solvent	Syn (%)	Anti (%)
(114)	Pd(COD)(MA)*	Benzene	75	25
		DCM	53	47
		THF	50	50
		MeCN	0	100
(115)	$Pd_2(dba)_3$	Benzene	100	0
		DCM	94	6
		THF	95	5
		Acetone	75	25
		DMF	29	71
		MeCN	5	95
		DMSO	3	97
	Pd(COD)(MA)	Benzene	100	0
		DCM	91	9
		THF	93	7
		MeCN	4	96

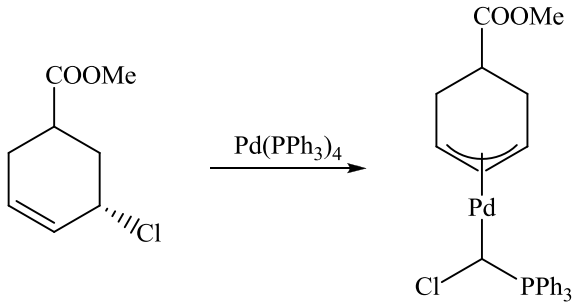
Table 3.1 *Reaction of* ***(114)*** *and* ***(115)*** *with* $Pd_2(dba)_3$

* Isomer ratio determined by ^1H NMR
* (MA) = maleic anhydride, (COD) = 1,5-cyclooctadiene

In the reaction of **(115)** in solvents such as benzene, DCM and THF, syn addition occurred almost exclusively (Table 3.1). In contrast, when MeCN and DMSO were used as the solvents anti addition was observed. This was the case for both $Pd_2(dba)_3$ and Pd(COD)(MA) starting materials. This may be due to the fact these solvents can prevent Pd-Cl bond formation inherent in syn addition through coordination to Pd, or by stabilising the anti addition transition state in which charge separation takes place to a greater extent than in syn addition. Whereas syn addition which leads to the *trans* isomer may be proceeding *via* an S_N2' mechanism.

With **(114)** both DCM and THF afforded equimolar amounts of the syn and anti addition products. Whilst MeCN exclusively yielded the product of anti addition and benzene afforded predominantly the syn addition product.

Interestingly, when **(115)** was reacted with $Pd(PPh_3)_4$ (Scheme 3.3), anti addition occurred when both benzene and DCM were used affording the *cis* isomer exclusively.



Scheme 3.3 *Reaction of* ***(115)*** *with* $Pd(PPh_3)_4$

Further work by Kurosawa *et al.* examined the influence of the ligand bound to Pd(0), that was also found to affect the stereochemistry of the oxidative addition.[20] The results in Table 3.2 reveal that the reactions of Pd(COD)(MA) and $Pd(NBE)_2$(MA), in the absence of additives proceed with the preferential formation of the syn addition product. Upon the addition of additives, the percentage of anti product obtained increases. This may be due to the replacement of the maleic anhydride ligand by the additive, forming anti addition directive complexes such as $Pd(COD)_2$ or $Pd(NBE)_3$. However, little if any, evidence of free maleic anhydride was observed when ^{1}H NMR spectroscopy was conducted on the mixtures of Pd(COD)(MA) with COD or that of $Pd(NBE)_2$(MA) with NBE [each in a (1:10 ratio)]. This suggests that the Pd(0) complexes possessing the more electron-donating olefin ligands, $Pd(COD)_2$ or $Pd(NBE)_3$, undergo anti oxidative addition much faster than Pd(COD)(MA) and $Pd(NBE)_2$(MA), undergo syn addition. In contrast, $Pd(NBE)_3$ formed almost exclusively the anti product. However, addition of electron-withdrawing additives caused the selectivity to decrease forming more syn product.

These results demonstrate that the stereochemistry of the oxidative addition of allylic chlorides to Pd(0) is sensitive to both the reaction solvent and the metal bound ligand group.

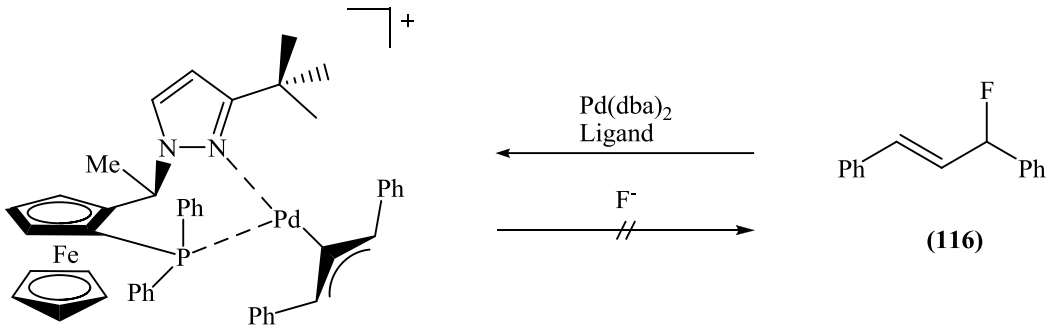
Pd(0)	Additive (equiv.)	Syn (%)	Anti (%)
Pd(COD)(MA)	None	91	9
	Styrene (10)	62	38
	COD (10)	58	42
	NBE (10)	58	42
	NBE (100)	38	62
$Pd(NBE)_2(MA)$	None	92	8
	NBE (10)	34	66
$Pd(NBE)_3$	None	7	93
	AN (5)	20	80
	DMF (5)	87	13
	FMN(5)	93	7

Table 3.2 *Stereoselectivity in oxidative addition of* ***(115)*** *with olefin-Pd(0) complexes in DCM*

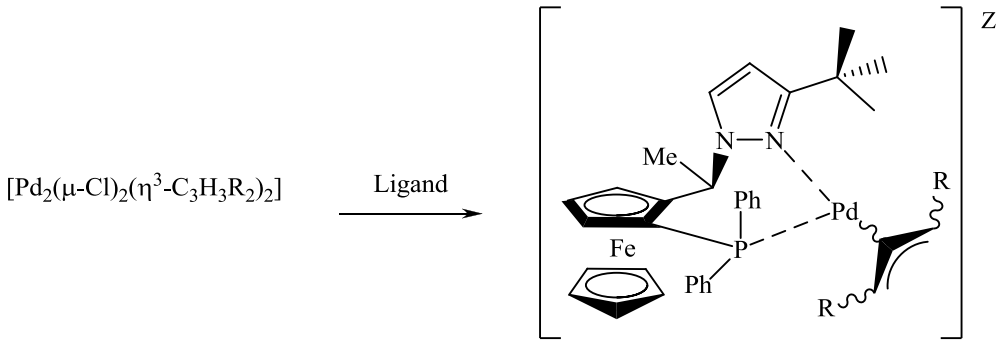
* COD = 1,5-cyclooctadiene, NBE = norbornene, AN = acrylonitrile, DMF = dimethyl fumarate, FMN = fumaronitrile

3.1.2 Reactions of Allyl Fluorides with Palladium

Togni examined whether fluoride could attack cationic π-allyl palladium(II) complexes as a nucleophile, thus leading to allylic fluorination (Scheme 3.4).[21] The catalyst was generated *in situ* from $Pd(dba)_2$ and phosphanyl-ferrocenyl pyrazole. The sources of nucleophilic fluoride tested were TBAT ($NBu_4[SiF_2Ph_3]$)[22] and Me_4NF.[23] Both are soluble in aprotic organic solvents, thus preventing the reduction of the nucleophilicity of fluoride, which is reduced by solvation in protic media or in the presence of trace amounts of water[24] However, nucleophilic attack of fluoride on the allyl component and the liberation of an allyl fluoride was never observed. Indeed, it was instead demonstrated that the allyl fluoride **(116)** could oxidatively add to palladium(0) precursors (Scheme 3.4). It was, therefore, inferred that catalytic allylic substitution with fluoride is a kinetically strongly disfavoured process, if at all possible.[25]



Scheme 3.4 *Attempt toward Pd-mediated allylic fluorination*

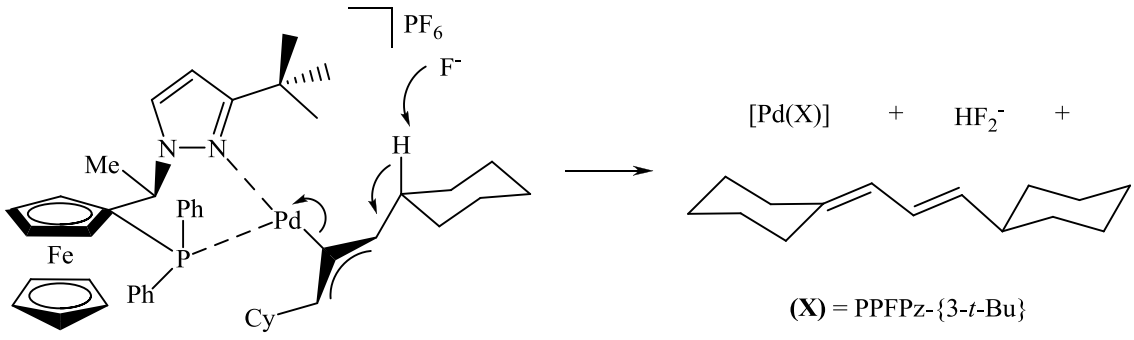


(117) R= Ph
(118) R= Cyclohexyl
(119) R_2= 1,2-C_6H_4

(120) R= Ph, Z= PF_6
(121) R= Cyclohexyl, Z= PF_6
(122) R_2= 1,2-C_6H_4, Z= SbF_6

Scheme 3.5 *Scheme showing synthesis of allyl complexes*

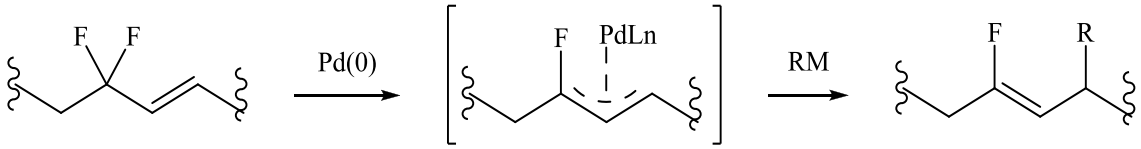
A stoichiometric variant of the reaction with attack of fluoride ion on isolated cationic η^3-palladium (II) and platinum (II) complexes has also been studied. In the first series of experiments allyl complexes, **(120)–(122)** (Scheme 3.5 for synthesis) were reacted with one of the fluoride sources, TBAT, Me_4NF or Schwesinger's phosphazenium fluoride P_2F, then mixed in a deuterated solvent for ease of sample monitoring. ^1H, ^{19}F and ^{31}P NMR spectroscopy were used to monitor the reactions. When no change was observed at room temperature samples were warmed to 50 ºC. The only specific reaction pattern was observed with complex **(121)** and the fluoride sources Me_4NF and P_2F, where the diene **(123)** was formed in an elimination reaction (Scheme 3.6).



(121) **(123)**

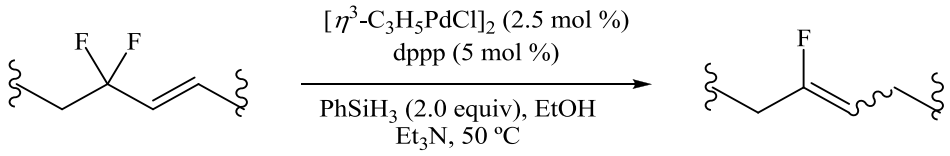
Scheme 3.6 *Fluorination mediated elimination of diene* ***(121)*** *from* ***(123)***

More recently, work by Narumi has shown that selective mono-defluorination of allylic difluorides can be achieved *via* catalysis with Pd(0). Inspired by the research of Hudlicky,[26] where hydrogenolysis of allyl fluorides in the presence of Pd/C was found to be a convenient route for the replacement of a fluorine atom by hydrogen, Narumi and co-workers [27] reacted *gem*-difluorides with a Pd catalyst and additives that have an affinity for fluorine in order to promote the elimination of fluorine. This reaction led to the generation of a fluorinated π-allyl Pd intermediate that on reaction with a nucleophile afforded a (*Z*)-fluoroalkene (Scheme 3.7). These products are an important class of compounds that can be utilised as peptide isosteres,[28-31] enzyme inhibitors[32] and in liquid crystalline materials.[33]



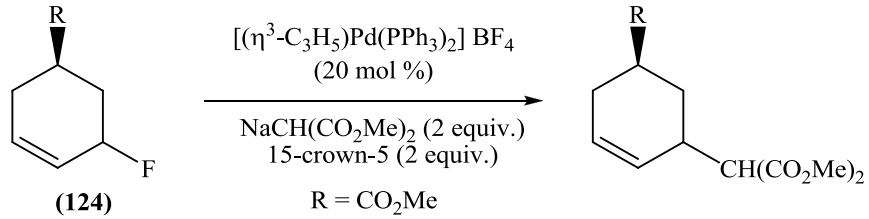
Scheme 3.7 *Synthesis of fluoroalkene via Pd catalysis*

The reaction was conducted using readily available allylic difluorides. Initially, in order to optimise and hone reaction conditions, γ,γ-difluoro-α−β-enoate was used and reacted with dimethyl sodiomalonate in the presence of Pd catalyst and dppe. Several additives were screened including TMSCl, Et_4Si, $(EtO)_4Si$ and Me_3Al, however, none promoted the desired defluorination reaction. However, $PhSiH_3$ was found to promote the formation of the desired product. After optimisation of solvent and temperature, it was found that $PhSiH_3$ with NEt_3 in EtOH at 50 ºC yielded the desired product in 96 % yield (Scheme 3.8). These conditions were then used in reactions with different allylic difluorides, all of which were found to be chemoselective with good to excellent yields being obtained of the desired product (64 – 99 %). In addition it was noted that *N*-Boc amides, esters and substituents such as alkyl and siloxy groups at the δ carbon did not affect the reaction and that amides, peptides, (Z)-enoates and lactams could all be used to give the desired fluoroalkene. A mechanistic study demonstrated that the reactive species was formed *via* the Et_3N promoted dehydrogenative coupling of $PhSiH_3$ with EtOH.



Scheme 3.8 *Pd and Et_3N catalysed reductive defluorination*

During the course of the research in this thesis, work has been published by Gouverneur *et. al*.[34] which examines the oxidative addition of Pd(0) to allylic fluorides and more specifically the role of allylic fluorides in catalytic allylic alkylation reactions. Three different isomeric mixtures of **(124)** were reacted with $[(\eta^3\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$, dimethyl sodiomalonate and 15-crown-5. It was observed that varying the reaction solvent had little effect, however, substituting PPh_3 by biphep as the ligand profoundly altered the stereoselectivity of the reaction with a change in the syn/anti ratio from 76:24 to 37:63 (Table 3.3).



(124)

Syn/anti ratio of (124)	Solvent	Time (h)	Syn/anti ratio in product
40:60	DCM	0.25	76:24
10:90	DCM	0.25	72:28
87:13	DCM	0.25	73:27
40:60	MeCN	18	73:27
40:60	THF	24	72:28[b]
40:60	DCM	0.25	37:63[a]
40:60	THF	24	32:68[a, b]

Table 3.3 *Allylic alkylation of allyl fluoride with malonate ion*

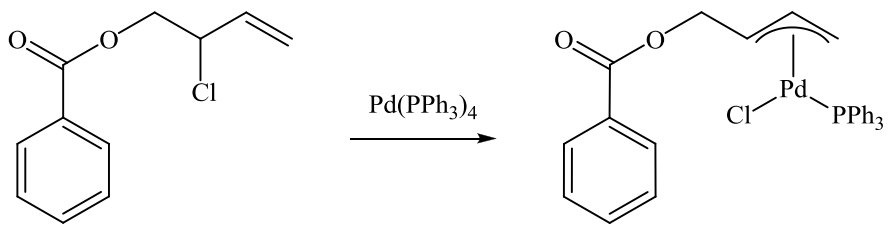
[a] Catalyst used was $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$, biphep

[b] 10 mol % catalyst used without 15-crown-5

In order to quantify the reactivity of fluoride as a leaving group, allylic alkylations were conducted using **(124)**, where R = Ac, Bz and CO_2Me. It was found that the leaving group susceptibility was OCO_2Me > OBz » F » OAc. It was also noted that the stereochemical course of displacement of fluoride is not governed by the normal double-inversion retention mechanism.

3.2 Results and Discussion

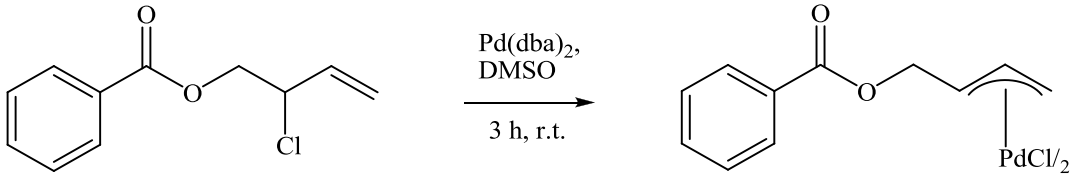
3.2.1 Reactions of Allyl Chlorides with Palladium



(108)

Scheme 3.9 *Reaction of 2-chlorobut-3-enyl benzoate with $Pd(PPh_3)_4$*

The synthesis of palladium allyl complexes from allylic chlorides was first attempted using the method outlined by Kurosawa. Here an excess of 2-chlorobut-3-enyl benzoate **(108)** was reacted with $Pd(PPh_3)_4$ in anhydrous DCM at room temperature. However, ^{1}H NMR spectroscopy revealed that although the desired product was formed, considerable quantities of allylic chloride starting material and triphenylphosphine were also present. Therefore an alternative synthetic route was considered. Following Bäckvall's protocol,[35] equimolar amounts of 2-chlorobut-3-enyl benzoate **(108)** and $Pd(dba)_2$ were mixed in DMSO and the reaction mixture was stirred at room temperature for 3 hours. The product was extracted with chloroform, washed with water, dried over magnesium sulphate, followed by removal of solvent and drying *in vacuo* to afford the crude product as a yellow solid. ^{1}H NMR spectroscopy showed that only dba and product were present. The crude product was then purified by column chromatography [DCM:hexane (70:30)] to afford the product, Bis[μ-chloro-bis(butenyl-(1,2,3-η)-benzoate]dipalladium **(125)** as a bright yellow solid in 71 % yield.



(108) **(125)**

Scheme 3.10 *Synthesis of **(125)***

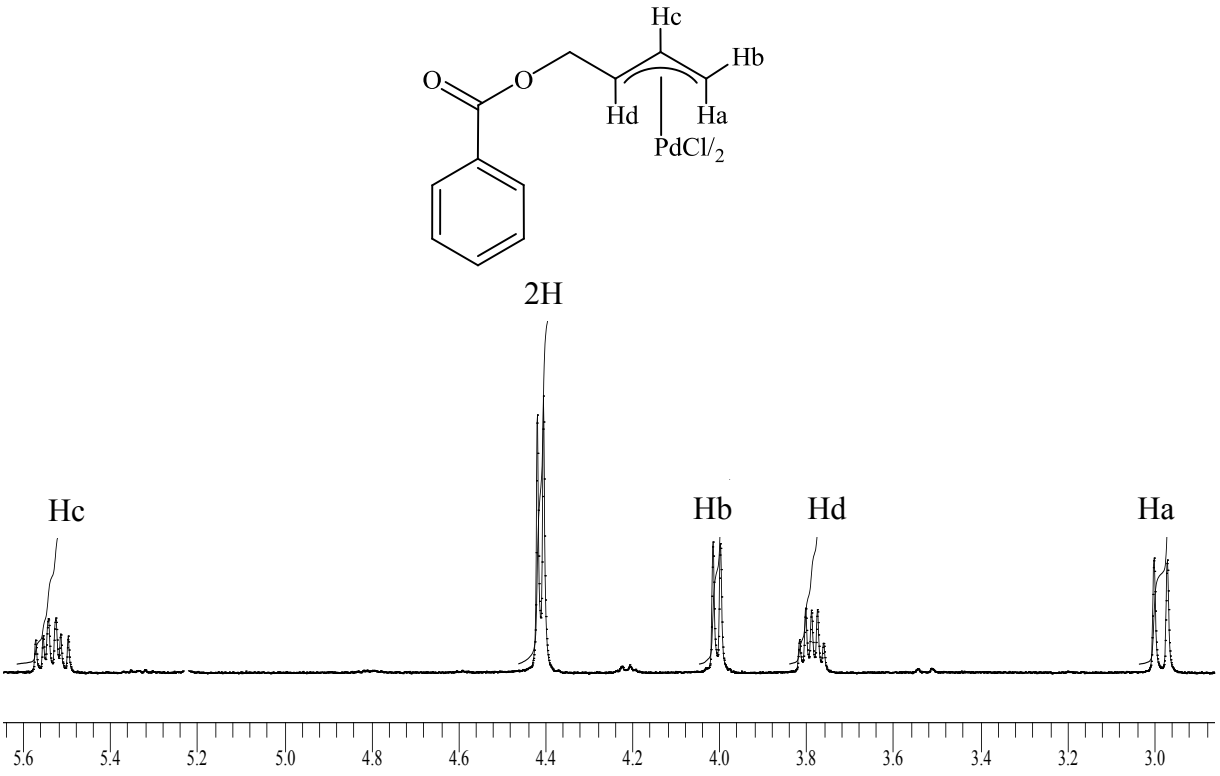
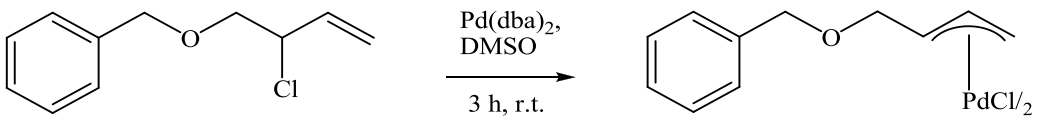


Figure 3.2 *^{1}H NMR spectrum of* ***(125)***

COSY ^{1}H-^{1}H NMR spectroscopy enabled full analysis of the peaks so that correct assignments could be made (Figure 3.2). Interestingly, the two protons α to the oxygen, though inequivalent appear almost as a doublet in the ^{1}H NMR spectrum, representing the central lines of a highly second-order AB multiplet.

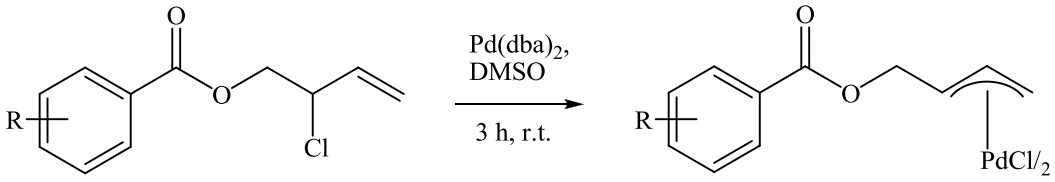


(106) **(126)**

Scheme 3.11 *Synthesis of* ***(126)***

The synthesis of **(126)** was conducted as described previously, the ^{1}H NMR spectrum of the crude reaction mixture exhibited only dba and desired product, whilst purification by column chromatography [DCM:hexane (70:30)] afforded the desired product in 63 % yield as a yellow solid.

This reaction protocol was extended to the derivatised allylic chlorides **(109)** – **(113)**, which were reacted with $Pd(dba)_2$ in exactly the same manner to afford the analogous Pd(II) chloride-bridged dimers in 39-73 % yields (Table 3.4).



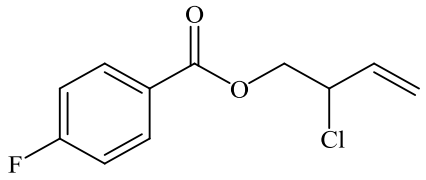
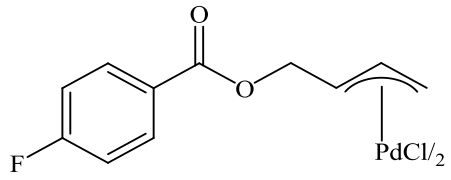
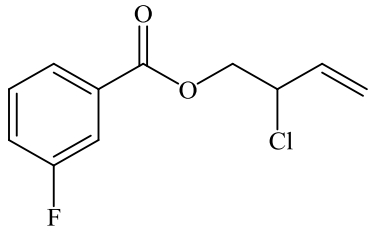
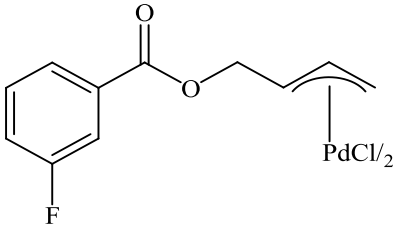
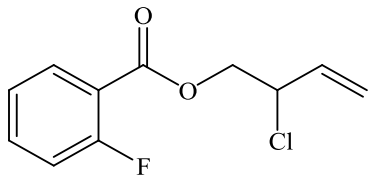
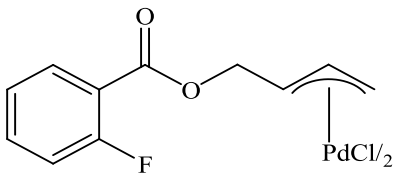
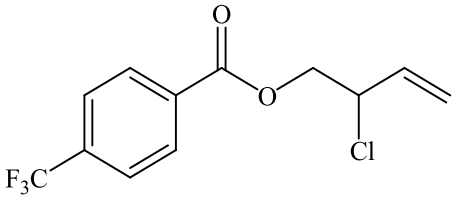
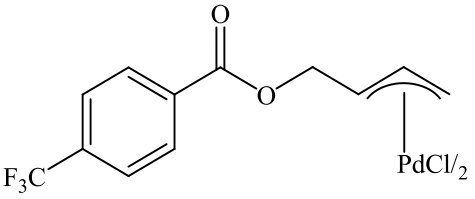
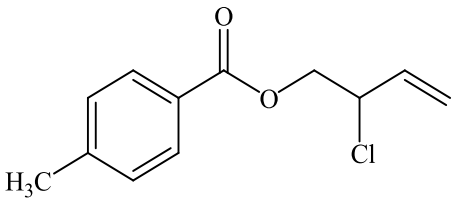
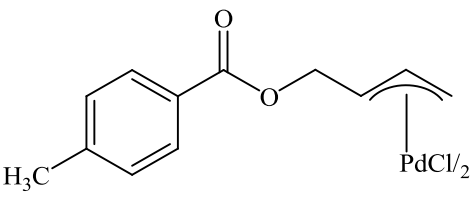
Starting substrate	Product	Yield (%)
 **(109)**	 **(127)**	73
 **(110)**	 **(128)**	60
 **(111)**	 **(129)**	71
 **(112)**	 **(130)**	53
 **(113)**	 **(131)**	39

Table 3.4 *Yields of* ***(127) - (131)***

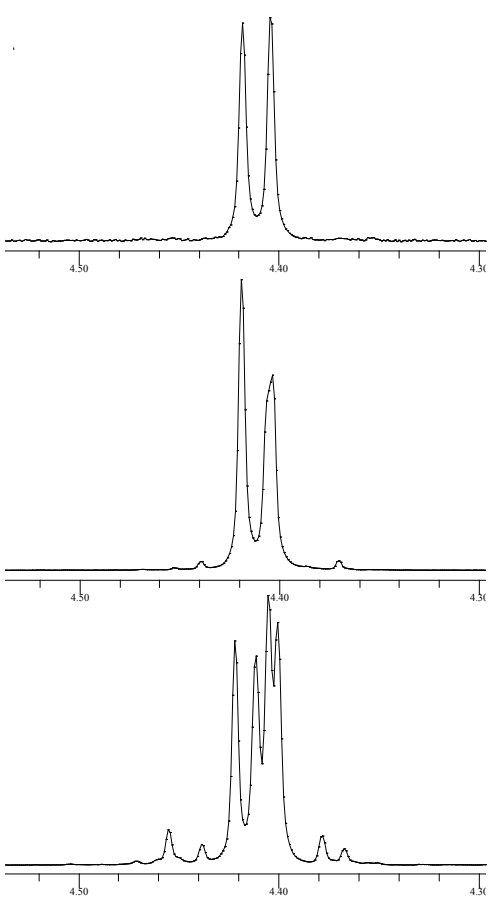


Figure 3.3 *^{1}H NMR spectra of inequivalent protons α to oxygen atom in **(125)**, **(128)** and **(129)**.*

Though all of the chloro-bridged palladium complexes synthesised have two hydrogen atoms α to the oxygen atom which are inequivalent, only in the ^{1}H NMR spectra of compounds **(126)**, **(128)** and **(129)** is this observed, with **(128)** an AB multiplet is evident. Whilst with **(129)** the two protons appear as second order AB multiplets which are clearly diastereotopic. However, in the ^{1}H NMR spectra of **(125)**, **(127)**, **(130)** and **(131)** an apparent doublet is seen (Figure 3.3).

The reaction of **(109)** with $Pd(dba)_2$ proceeded with the product being isolated in 73 % yield and after the pure product was left in deuterated chloroform overnight, crystals were readily formed confirming the structure as a chloro-bridged palladium complex (Figure 3.4). After reacting **(110)** with $Pd(dba)_2$, though the ^{1}H NMR spectrum of the crude product showed complete conversion, the isolated yield obtained after column chromatography [DCM:hexane (70:30)] was only 60 %. Despite excellent separation by TLC and facile removal of dba as the first spot, the product was difficult to remove from the column, even with a polar solvent such as DCM. However, once isolated and analysed like **(127)**, it also became crystalline overnight (Figure 3.5).

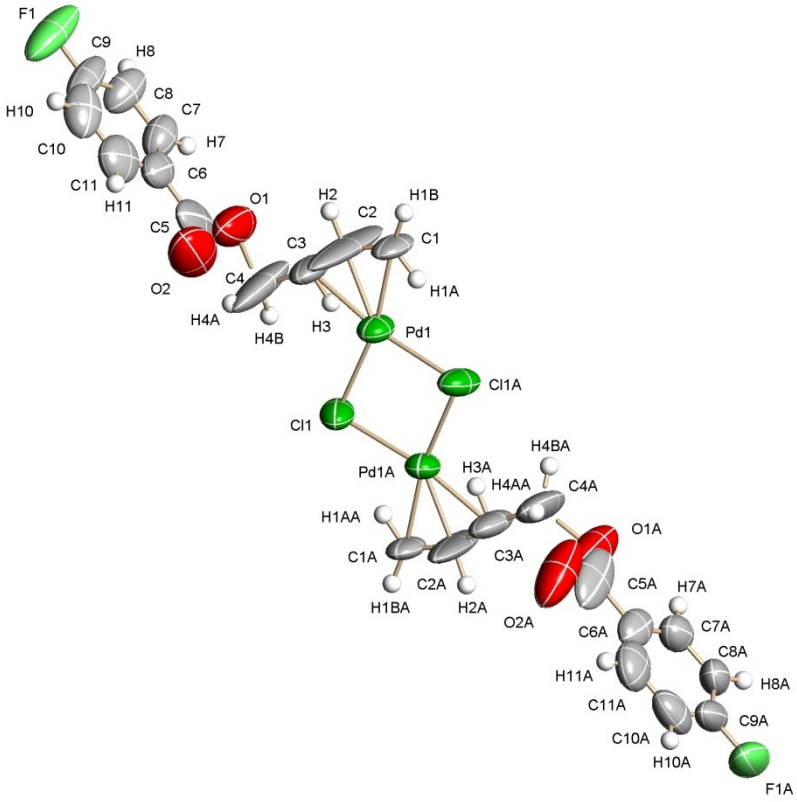


Figure 3.4 *Crystal structure of* ***(127)*** *figure shows 50 % displacement ellipsoids.*

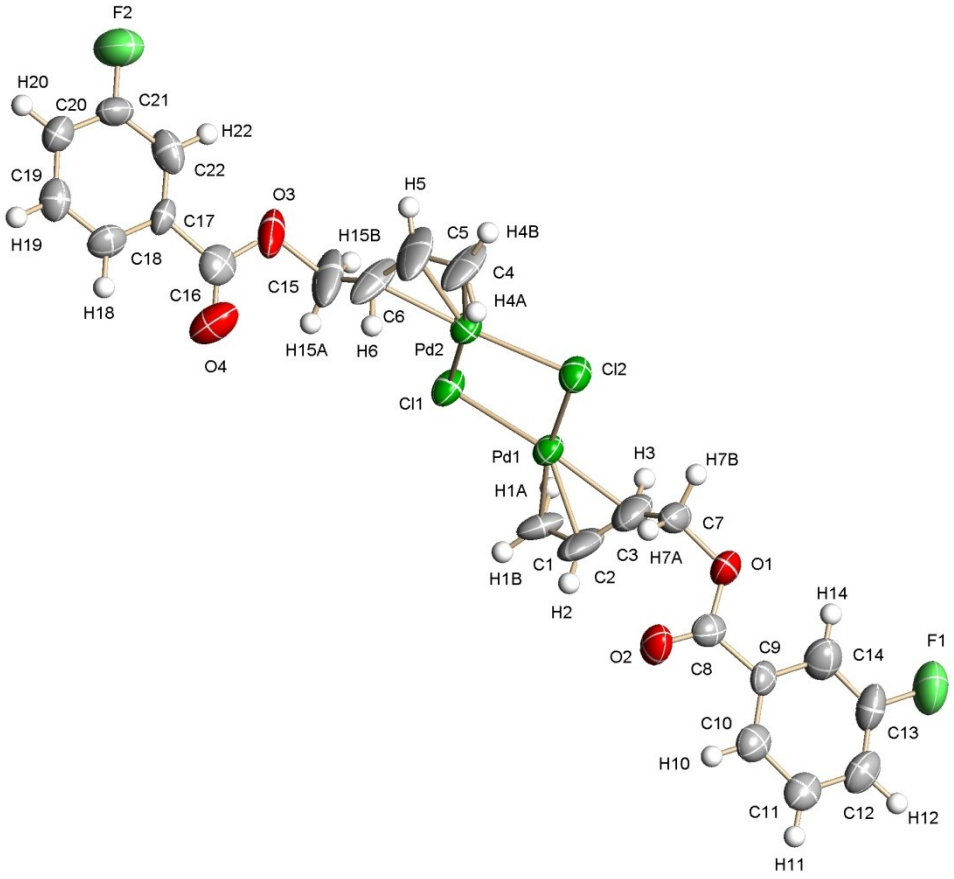


Figure 3.5 *Crystal structure of* ***(128)*** *figure shows 50 % displacement ellipsoids.*

A comparison of the bond lengths and angles of **(127)** and **(128)**, shows that the influence of the fluorine atom on the allylic portion of the complex is minimal as the bond lengths for Pd(1)-C(3)/C(1) and Pd(1)-Cl(1)/Cl(2) are virtually the same for both, even though in **(128)** the fluorine atom is *meta* to the ester functionality. The bond lengths are also similar to those found in other palladium chloro-bridged dimers.[36]

Bond Length (Å)	**(127)**	**(128)**
Pd(1)-Cl(1)	2.403(2)	2.408(3)
Pd(1)-Cl(2)/Cl(1A)	2.396(3)	2.409(3)
Pd(1)-C(3)	2.112(9)	2.109(12)
Pd(1)-C(1)	2.108(10)	2.112(10)
Pd(1)-C(2)	2.019(12)	2.049(12)
C(13)/C(9)-F(1)	1.350(13)	1.365(12)
Bond Angles (º)		
C(3)-Pd(1)-Cl(1)	67.2(5)	68.4(5)
C(3)-Pd(1)-C-(1)/(2)	101.2(3)	101.1(4)
C(1)-Pd-(1)Cl-(1)/(2)	168.2(3)	169.4(3)
F(1)-C(13)-C(14)		117.7(12)
F(1)-C(9)-C(8)	117.5(15)	

Table 3.5 *Selected Bond lengths and bond angles for **(127)** and **(128)***

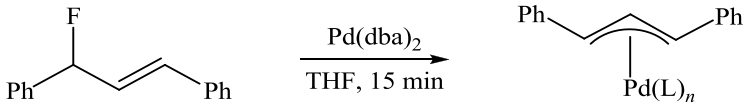
3.2.2 Reactions of Allyl Fluorides with Palladium

3.2.2.1 Initial Studies – Activation of Allylic Fluorides with Pd(0)

As described previously, the reaction of fluoride with cationic allyl complexes, fails to yield the corresponding allylic substitution products, thereby demonstrating that the reaction may be thermodynamically unfavourable. However, when Togni[37] and co-workers conducted the reverse reaction, oxidative addition of allylic fluorides to Pd(0), the reaction afforded the corresponding η^3-allylpalladium (II) compound (Scheme 3.12). A solution of 1,3-diphenyl allylfluoride in hexane was stirred with $Pd(dba)_2$ in THF and after 15 minutes the colour of the reaction mixture changed from violet to yellow. The yellow precipitate was isolated by filtration and dried *in vacuo* before being characterised by ^1H and ^{19}F NMR spectroscopy. However, it was stated by Togni, that;

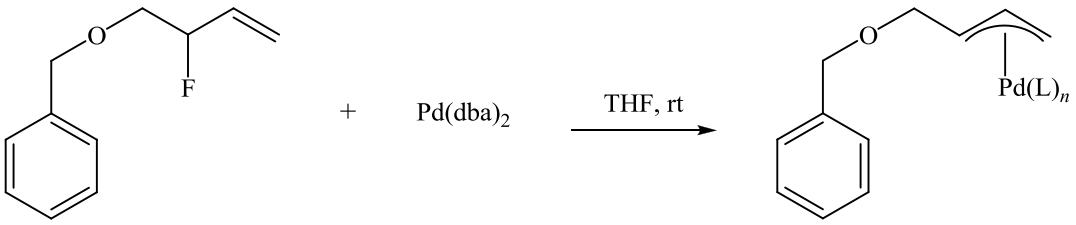
"The product could not be further purified and was only analyzed spectroscopically for the presence of the (1,3-diphenylallyl)palladium (II) fragment."

Therefore, as the product was only analysed for the allyl fragment, it is not known whether a palladium fluoro-bridged complex is being formed in the reaction or whether the palladium is also coordinating to the dba.



Scheme 3.12 *Oxidative addition of 1,3-diphenyallyl fluoride to Pd(0)*

In order to achieve similar oxidative addition of an allylic fluoride to palladium, the reaction of ((2-fluorobut-3-enyloxy) methyl)benzene **(73)** was conducted in the same manner as Hintermann.[37] **(73)** was stirred with $Pd(dba)_2$ in THF at room temperature (Scheme 3.13) (entry 1, Table 3.6). After stirring for an hour no colour change was observed, therefore, the reaction mixture was allowed to stir for a further 12 hours. After which a precipitate had formed though there was no colour change as reported in the literature. The reaction solvent was removed *via* cannula, the product dried *in vacuo* and ^{1}H and ^{19}F NMR spectroscopy was conducted using deuterated benzene as solvent. The ^{1}H and ^{19}F NMR spectra both revealed that the starting material **(73)** was no longer present. Hence, the allyl fluoride had been activated. However, due to the dominance of dba and C_6D_6 in the ^{1}H NMR spectra it was difficult to definitively establish that a π-allyl complex had formed, as claimed by Togni.[37]



(73)

Scheme 3.13 *Reaction of ((2-fluorobut-3-enyloxy)methyl)benzene with $Pd(dba)_2$*

In an attempt to establish the nature of the activated product, a series of scoping experiments varying the substrate, substrate: Pd ratio, solvent, Pd starting material and temperature were undertaken with mixed results. A selection of which are detailed in Table 3.6, though full reaction details are described in the Appendix.

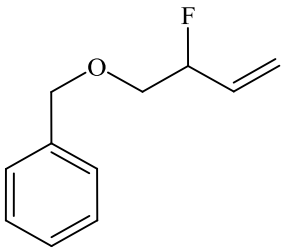
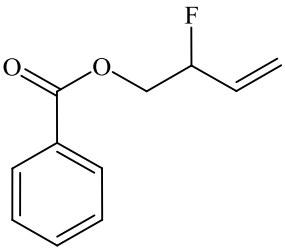
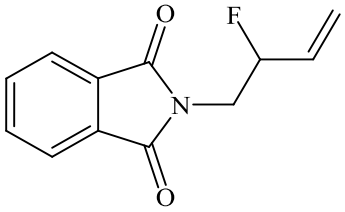
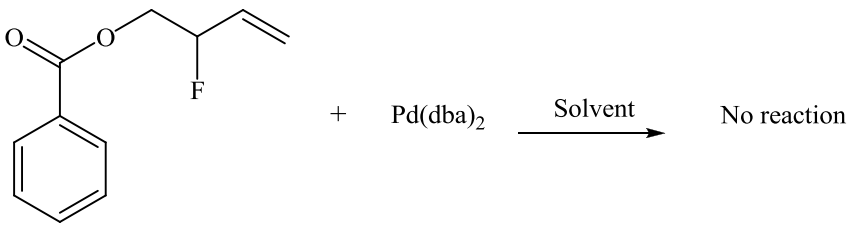
Allyl fluoride	No.	Pd(0)	Solvent	Temp (°C)	^{19}F NMR
 **(73)**	1	$Pd(dba)_2$ (17 mol %)	THF	r.t.	No peak at -185 ppm (s.m peak)
 **(75)**	2	$Pd(dba)_2$ (17 mol %)	DCM	r.t.	No reaction
	3	$Pd(dba)_2$ (17 mol %)	Toluene	r.t.	No reaction
	4	$Pd(dba)_2$ (17 mol %)	Toluene	-78 – r.t.	No reaction
	5	$Pd(dba)_2$ (17 mol %)	THF	-78 – r.t.	No reaction
	6	$Pd(dba)_2$ (100 mol %)	Toluene	30 – 70	No reaction
	7	$Pd(dba)_2$ (100 mol %)	Toluene	r.t.	No reaction
	8	$Pd(PPh_3)_4$ (17 mol %)	Toluene	-78	Broad peak at -171 ppm**
 **(74)**	9	$Pd(dba)_2$ (100 mol %)	DMSO	r.t.	No peak at -184 ppm (s.m peak)
	10	$Pd(PPh_3)_4$ (17 mol %)	Toluene	-78	Broad peak at -168 ppm*
	11	$Pd(PPh_3)_4$ (100 mol %)	Toluene	-78	Broad peak at -168 ppm*

Table 3.6 *Reaction Conditions used in oxidative addition of Pd(0) to* ***(73)****,* ***(75)*** *and* ***(74)***
*NMR conducted in d-acetone
**NMR conducted in MeOD



(75)

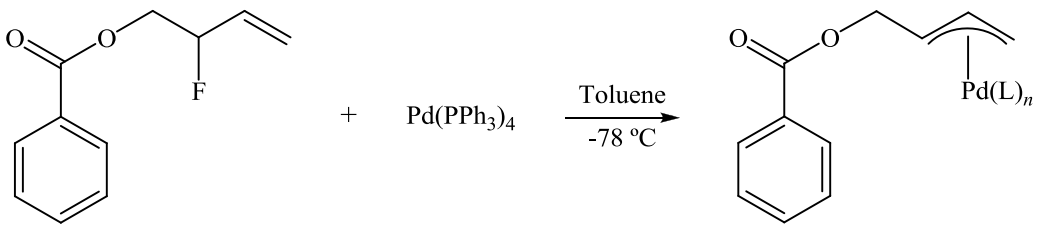
Scheme 3.14 *Reaction of 2-fluorobut-3-enyl benzoate* ***(75)*** *with* $Pd(dba)_2$

Entries 2 and 3 demonstrated that conducting the reaction of 2-fluorobut-3-enyl benzoate **(75)** with $Pd(dba)_2$ (17 mol %) at room temperature in DCM and toluene afforded only starting material, as observed in both the ^{1}H and ^{19}F NMR spectra. This was also the case

when the reaction was conducted in THF and toluene at – 78 ºC for 1 hour and then warmed over 24 hours to room temperature (entries 4 and 5).

Conducting the reaction using equimolar amounts of allylic fluoride and $Pd(dba)_2$ in toluene at room temperature and with heating also resulted in starting material (entries 6 and 7).

However, it was found that when $Pd(PPh_3)_4$ was used and the reaction mixture was stirred at – 78 ºC for 1 hour, a precipitate clearly formed (entry 8). Analysis by ^1H and ^{19}F NMR spectroscopy in MeOD revealed that the starting allylic fluoride was no longer present and there were peaks that could be attributed to the formation of a π-allyl palladium species. Further analysis by 2-D ^1H-^1H COSY NMR exhibited that the allylic peaks were coupling to each other as seen in the π-allyl palladium complexes synthesised from allylic chlorides. In the ^{19}F NMR spectrum a very broad peak was observed at -171.5 ppm, the identity of which is unclear, although it was postulated that fluoride may have reacted with the glass of the NMR tube. The reaction solvent, which was removed from the precipitate, was also analysed by ^1H and ^{19}F NMR spectroscopy and was found to contain unreacted starting material and triphenylphosphine. The mixture also readily formed crystals and X-ray crystallography determined triphenylphosphine oxide also to be present.



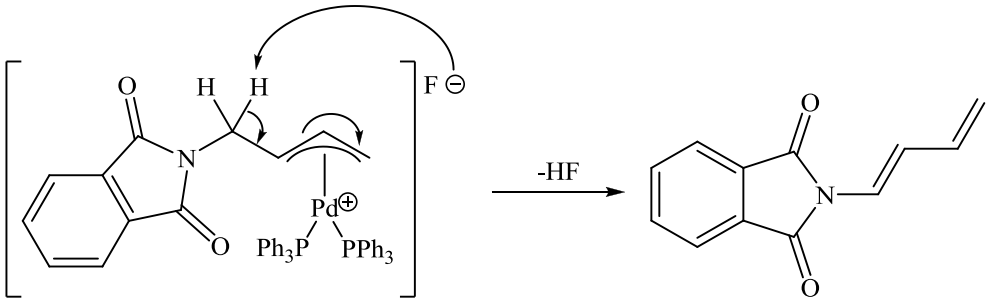
(75)

Scheme 3.15 *Reaction of 2-fluorobut-3-enyl benzoate with $Pd(PPh_3)_4$*

The same reaction conditions were used with 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione **(74)** (entry 10). After removal of the reaction solvent and drying of the precipitate *in vacuo*, ^1H and ^{19}F NMR spectroscopy showed that the starting material was no longer present, however, the peaks were very broad, hence there was difficulty in confirming if the desired π-allyl complex had formed. A broad signal was seen at -168.1 ppm in the ^{19}F NMR spectrum synonymous to that observed in the reaction described previously. However, the reaction solvent that had been removed was analysed by ^1H NMR spectroscopy and found not to contain starting material as in the previous reaction, rather, a new product 2-(buta-1,3-dienyl)isoindoline-1,3-dione (**133**)[38] could be readily identified. Figure 3.6 highlights the most reasonable route to this species, formed by the fluoride acting as a base to yield the

elimination product. This is strong evidence that the π-allyl species had formed, as there would be no other pathway for this elimination product to be formed.

.



(132) **(133)**

Figure 3.6 *Formation of* ***(133)***

Due to the broad ^{1}H NMR spectrum obtained the reaction was repeated, with equimolar amounts of **(74)** and $Pd(PPh_3)_4$ and stirred at – 78 ºC for 8 hours (entry 11). A yellow precipitate was formed, the reaction solvent removed and the product dried *in vacuo*. Analysis of the precipitate, by ^{1}H and ^{19}F NMR spectroscopy, confirmed that the starting material was no longer present. However, due to the intensity of the triphenylphosphine groups in the spectra, it was difficult to fully assign the product peaks. Although, it was clearly evident that the elimination product **(133)** had formed once again. The reaction solvent was also analysed and exhibited a very broad peak at -168.4 ppm in the ^{19}F NMR spectrum.

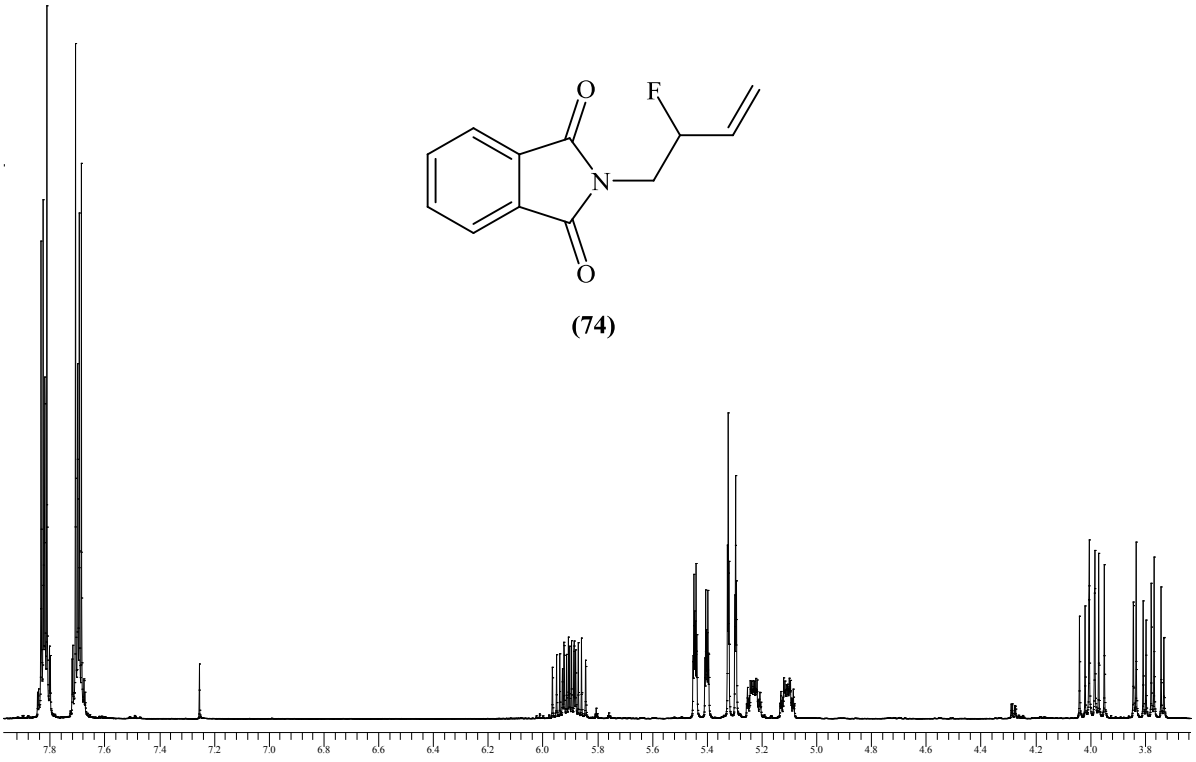
Due to the difficulties in isolating the π-allyl species, which were clearly forming, the same reaction conditions which had been employed to synthesise the chloro-bridged palladium allyl complexes were used with 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione **(74)** (entry 9). After stirring equimolar quantities of **(74)** and $Pd(dba)_2$ in DMSO at room temperature for 4 hours, the mixture was worked up as described previously and dried over magnesium sulphate, filtered and the solvent removed *in vacuo*. The yellowish product was analysed by ^{1}H and ^{19}F NMR spectroscopy and once more no direct evidence of the desired π-allyl complex was observed. Rather, the presence of 2-(buta-1,3-dienyl)isoindoline-1,3-dione **(133)** was confirmed. Therefore, it can be inferred that although the π-allyl complex must have formed, due to the presence of fluoride the elimination product was obtained. It also means that if a fluoro-bridged palladium complex is forming it is not sufficiently stable to be isolated and characterised in the same manner as the chloro-bridged palladium complexes described earlier.

Therefore, from the range of different reaction conditions tested it is evident that in the reactions conducted in toluene at -78 ºC with $Pd(PPh_3)_4$, the substrate clearly undergoes oxidative addition to Pd(0), as demonstrated by the formation of the elimination product in entries 13 and 14. Whilst those reactions conducted with $Pd(dba)_2$ (both at low and elevated temperatures) were unsuccessful, affording only the starting allylic fluoride.

3.2.2.2 Activation of Allylic Fluoride with Pd(0) in the presence of a nucleophile- Trapping the Allyl Pd Intermediate

During this time, work was published by Gouverneur *et. al.* which also examined the oxidative addition of Pd(0) to allylic fluorides.[34] Whereas the work in this thesis focussed on isolation of the π-allyl palladium species, Gouverneur *et al.* concentrated on the formation of the π-allyl species *in situ* and its subsequent reaction with a nucleophile such as dimethyl malonate, in order to quantify the reactivity of fluoride as a leaving group in comparison with OAc, OBz and OCO_2Me. It was reported that NMR experiments were conducted in order to monitor the reaction and observe the changes occurring.

In light of the scoping experiments discussed previously, this methodology was utilised in the reaction of **(74)** with 20 mol % $Pd(dba)_2$ and 2 equivalents of PPh_3 in anhydrous $CDCl_3$. The reaction mixture was stirred for 1 minute under nitrogen before transferring a small aliquot to a Young's NMR tube. The progress of the reaction was then monitored by ^1H, $^{19}F\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectroscopy (see Tables 6.1 and 6.2 in Chapter 6). Initially only the allylic fluoride **(74)**, PPh_3 and dba were evident in the ^1H NMR spectrum, though a new small broad peak was observed at – 157.9 ppm in the ^{19}F NMR spectrum. Over time, **(74)** (see Figure 3.7 for initial spectra) began to disappear from both the ^1H and ^{19}F NMR spectra and peaks became apparent that were attributable to the desired π-allyl species **(132)** (3.0, 3.8, 4.1 and 4.5 ppm) and the elimination product **(133)** (5.1, 5.3, 6.3 and 6.8 ppm) (see Figure 3.8). The initially small peak at -157.9 ppm in the ^{19}F NMR spectrum grew becoming a very large broad peak and the allylic fluoride peak at -184.7 ppm was barely visible (see Figure 3.9). Electrospray mass spectrometry of the reaction mixture confirmed formation of the allylpalladium cationic complex **(132)** with a strong signal for the cation at *m/z* 830.



(74)

Figure 3.7 *Starting material* ***(74)*** *in* $CDCl_3$

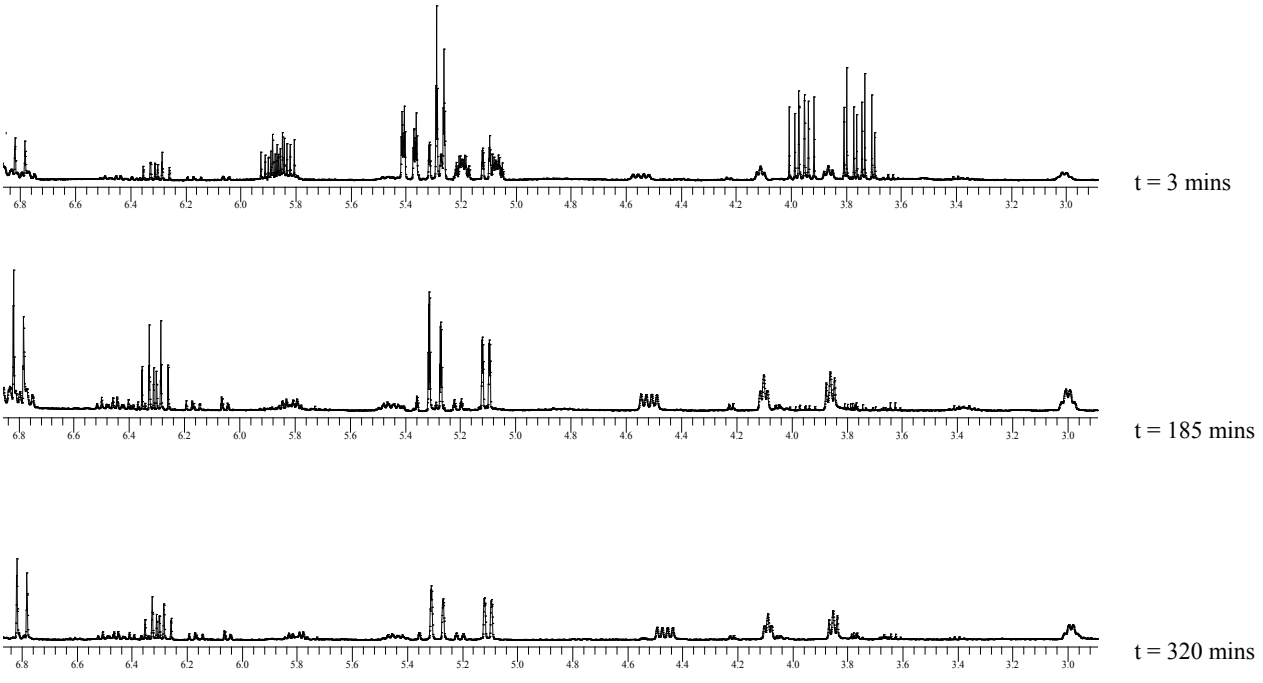


Figure 3.8 *Formation of cationic species* ***(132)*** *and elimination product* ***(133)*** *by monitoring* ^{1}H *NMR over time*

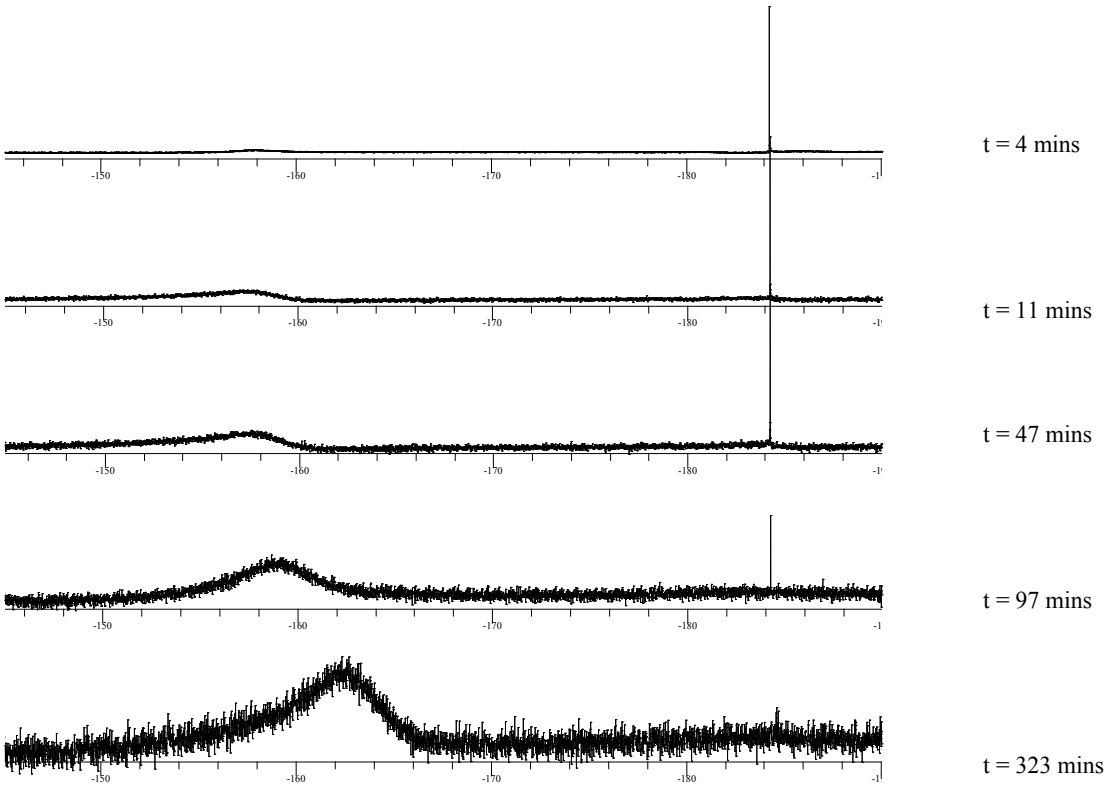
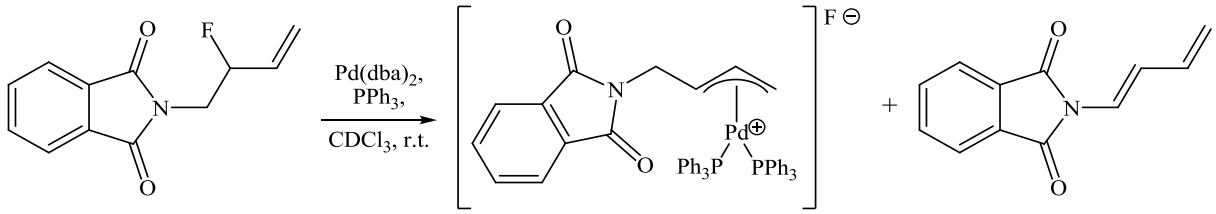


Figure 3.9 *Monitoring formation of cationic species* ***(132)*** *by* ^{19}F *NMR Spectroscopy*



(74) **(132)** **(133)**

Scheme 3.16 *Reaction of 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione with* $Pd(dba)_2$ *and* PPh_3

It is postulated that the elimination product **(133)** is forming in addition to the desired π-allyl species, due to the fluoride acting as a base and thereby removing the proton alpha to the nitrogen group. This is aided by the electron withdrawing effect of the phthalimido group (Figure 3.10).

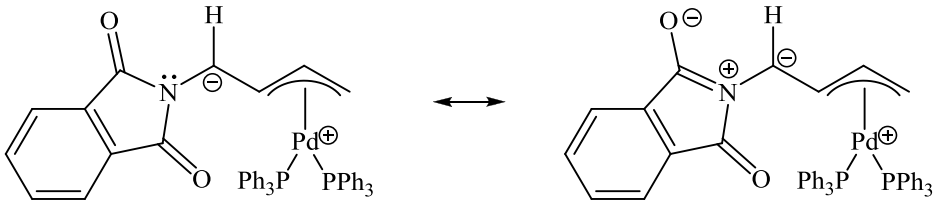
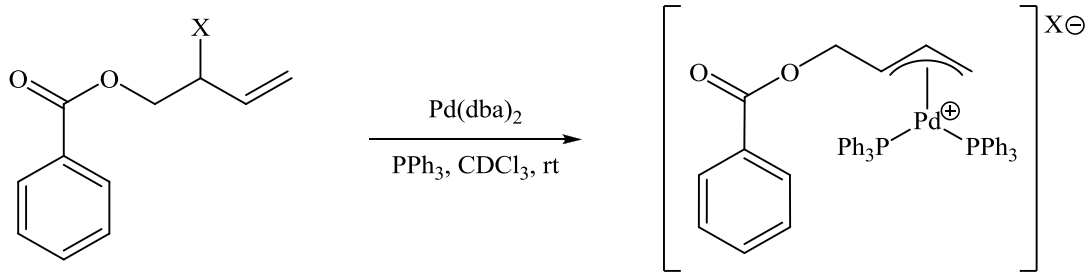


Figure 3.10 *Resonance stabilisation of* ***(133)***

Though the reaction was conducted on a small scale, this experiment clearly shows that a π-allyl complex is formed (peaks at 3.0, 3.8, 4.1 and 4.5 ppm in Figure 3.8) and subsequently reacts to form the elimination product **(133)** (peaks at 5.1, 5.3, 6.3 and 6.8 ppm in Figure 3.8). Although the cationic Pd(II) species proved difficult to separate from **(133)**, dba and any excess PPh_3, 2-(buta-1,3-dienyl) isoindoline-1,3-dione **(133)** was obtained as a yellow solid in 50 % yield.

Following on from the NMR experiment undertaken with **(74)**, the same experiments were conducted with 2-chlorobut-3-enyl benzoate **(108)** and 2-fluorobut-3-enyl benzoate **(75)** in order to compare whether an allylic chloride and fluoride would form the same π-allyl palladium complex. Both **(75)** and **(108)** were reacted with 0.5 equivalents of $Pd(dba)_2$ and 1 equivalent of PPh_3, and small aliquots of the reaction mixture transferred into an NMR tube. The progress of the reactions were then monitored by ^1H, $^{19}F\{^1H\}$, $^{31}P\{^1H\}$ NMR and electrospray mass spectrometry. Unfortunately, due to the excess of PPh_3 in the reaction mixtures the ^1H NMR spectra were largely uninterpretable.



X= Cl **(108)**
X= F **(75)**

X= Cl **(135)**
X= F **(134)**

Scheme 3.17 *Synthesis of **(134)** and **(135)***

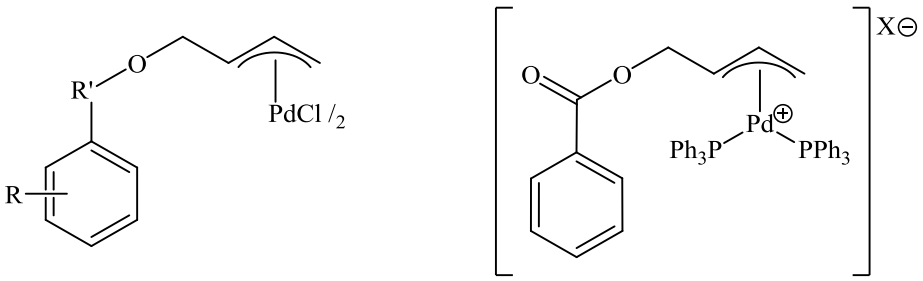
Therefore, with 2-fluorobut-3-enyl benzoate **(75)**, the reaction was predominantly monitored by ^{19}F NMR spectroscopy. Over 80 minutes the allyl fluoride peak at – 187.5 ppm was observed and seen to decrease in height and broaden before finally disappearing, whilst simultaneously a new signal at – 170.8 ppm developed from a small peak to a large broad peak. After 80 minutes it was apparent that **(75)** had disappeared and this was confirmed by the electrospray mass spectrum, where a signal was seen at *m/z* 805 attributable to product **(134)**.

With the reaction of 2-chlorobut-3-enyl benzoate **(108)** as only ^1H and $^{31}P\{^1H\}$ NMR spectroscopy could be used to monitor the reaction, they were closely observed. However, the ^1H NMR spectra were dominated by triphenylphosphine and the $^{31}P\{^1H\}$ NMR spectra contained several peaks which were difficult to assign. Therefore the reaction was

monitored for 80 minutes and the mixture subjected to electrospray mass spectrometry. Here a signal in the spectrum at *m/z* 805 synonymous with the desired cationic palladium species **(135)** was observed. No isolation was attempted of the two products due to the difficulty with **(74)**. Though the ^{1}H NMR spectra for both cationic complexes was largely uninterpretable, it was evident that no elimination product was present, confirming that the formation of **(133)** is aided by the phthalimido group withdrawing electrons. Clearly, as there are no nitrogen groups in **(134)** and **(135)** the analogous elimination reactions do not occur. Therefore, these reactions have demonstrated that in order to achieve C-F bond activation ligands such as PPh_3 are required in order to stabilise the intermediate, it has also revealed that if a fluoro-bridged dimer is forming it is not sufficiently stable to be isolated or observe *via* ^{1}H NMR spectroscopy or mass spectrometry.

3.3 Conclusions

The novel Pd(II) chloride-bridged dimers **(125)**, **(126)**, **(127)**, **(128)**, **(129)**, **(130)** and **(131)** have been synthesised from their corresponding allylic chlorides and purified by column chromatography. Their structures were determined by NMR spectroscopy, mass spectrometry and X-ray crystallography. The novel cationic complexes **(132)**, **(134)** and **(135)** have also been synthesised but not isolated in the reactions of **(74)**, **(75)** and **(108)** with $Pd(dba)_2$ and PPh_3 in $CDCl_3$. Their structures were determined by NMR spectroscopy and mass spectrometry. It was observed that the allylic chloride **(108)** and allylic fluoride **(75)** both oxidatively add to Pd(0) in the same manner. However, with **(74)** though the cationic species was formed, due to the electron-withdrawing property of the phthalimido group, the protons alpha to nitrogen are susceptible to elimination by fluoride which acts as a base to form 2-(buta-1,3-dienyl)isoindoline-1,3-dione **(133)**. In the next chapter only the cationic species **(135)** synthesised from **(108)** will be reacted further with nucleophiles, though both **(108)** and **(75)** form the same product, it is easier to synthesise the allylic chloride precursor rather than the allylic fluoride.



(125) R= H R'= C=O
(126) R= H R'= CH_2
(127) R= 4-F R'= C=O
(128) R= 3-F R'= C=O
(129) R= 2-F R'= C=O
(130) R= CF_3 R'= C=O
(131) R= CH_3 R'= C=O

(134) X= F
(135) X= Cl

Figure 3.11 *Novel compounds synthesised **(125) – (135)***

3.4 References

[1] W. T. Dent, R. Long, A. J. Wilkinson, *J. Chem. Soc.* 1964, 1585.

[2] J. Smidt, W. Hafner, *Angew. Chem.* 1959, *71*, 284.

[3] I. I. Moiseev, E. A. Fedorovskaya, Y. K. Syrkin, *J. Inorg. Chem. U.S.S.R.* 1959, *4*, 2461.

[4] R. Hüttel, J. Kratzer, *Angew. Chem.* 1959, *71*, 456.

[5] R. Hüttel, J. Kratzer, M. Bechter, *Chem. Ber.* 1961, *94*, 766.

[6] T. Ito, S. Hasegawa, Y. Takahashi, Y. Ishii, *J. Organomet. Chem.* 1974, *73*, 401.

[7] C. C. Tseng, S. J. Yen, H. L. Goering, *J. Org. Chem.* 1986, *51*, 2892.

[8] F. K. Sheffy, J. P. Godschalx, J. K. Stille, *J. Am. Chem. Soc.* 1984, *106*, 4833.

[9] E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* 1984, *25*, 3063.

[10] T. Hayashi, T. Hagihara, M. Konishi, M. Kumada, *J. Am. Chem. Soc.* 1983, *105*, 7767.

[11] B. M. Trost, T. R. Verhoeven, *J. Am. Chem. Soc.* 1980, *102*, 4730.

[12] S. Valverde, M. Bernabe, S. Garcia-Ochoa, A. M. Gomez, *J. Org. Chem.* 1990, *55*, 2294.

[13] I. Stary, P. Kocovsky, *J. Am. Chem. Soc.* 1989, *111*, 4981.

[14] J. W. Faller, D. Linebarrier, *Organomet.* 1988, *7*, 1670.

[15] H. L. Goering, S. S. Kantner, C. C. Tseng, *J. Org. Chem.* 1983, *48*, 715.

[16] C. Gallina, P. G. Ciattini, *J. Am. Chem. Soc.* 1979, *101*, 1036.

[17] H. Kurosawa, S. Ogoshi, Y. Kawasaki, S. Maurai, M. Miyoshi, I. Ikeda, *J. Am. Chem. Soc.* 1990, *112*, 2813.

[18] A. Vitagliano, B. Akermark, S. Hansson, *Organomet.* 1991, *10*, 2592.

[19] T. Hayashi, M. Konishi, M. Kumada, *J. Chem. Soc. Chem. Commun.* 1984, 107.

[20] H. Kurosawa, H. Kajimaru, S. Ogoshi, H. Yoneda, K. Miki, N. Kasai, S. Murai, I. Ikeda, *J. Am. Chem. Soc.* 1992, *114*, 8417.

[21] A. Togni, A. Mezzetti, P. Barthazy, C. Becker, I. Devillers, R. Frantz, L. Hintermann, M. Perseghini, M. Sanna, *Chimia* 2001, *55*, 801.

[22] A. S. Pilcher, H. L. Ammon, P. Deshong, *J. Am. Chem. Soc.* 1995, *117*, 5166.

[23] K. O. Christe, W. W. Wilson, R. D. Wilson, R. Bau, J. A. Feng, *J. Am. Chem. Soc.* 1990, *112*, 7619.

[24] D. Landini, A. Maia, A. Rampoldi, *J. Am. Chem. Soc.* 1989, *54*, 328.

[25] L. Hintermann, PhD thesis, ETH-Zurich 2000.

[26] M. Hudlicky, *J. Fluorine Chem* 1989, *44*, 345.

[27] T. Narumi, K. Tomita, E. Inokuchi, K. Kobayashi, S. Oishi, H. Ohno, N. Fujii, *Org. Lett.* 2007, *9*, 3465.

[28] G. Dutheuil, S. Couve-Bonnaire, X. Pannecoucke, *Angew. Chem., Int. Ed. Engl.* 2007, *46*, 1290.

[29] T. Narumi, A. Niida, K. Tomita, S. Oishi, A. Otaka, H. Ohno, N. Fujii, *Chem. Commun.* 2006, 4720.

[30] Y. Nakamura, M. Okada, A. Sato, H. Horikawa, M. Koura, A. Saito, T. Taguchi, *Tetrahedron* 2005, *61*, 5741.

[31] T. Allmendinger, E. Felder, E. Hungerbuhler, *Tetrahedron Lett.* 1990, *31*, 7301.

[32] P. Bey, J. R. McCarthy, I. A. McDonald, *ACS Symp. Ser.* 1991, *456*, 105.

[33] O. Yokokoji, T. Shimizu, S. Kumai, *Chem. Abstr.* 1996, *124*, 316586.

[34] A. Hazari, V. Gouverneur, J. Brown, *Angew. Chem. Int. Ed.* 2009, *48*, 1296.

[35] K. L. Granberg, J.-E. Bäckvall, *J. Am. Chem. Soc.* 1992, *114*, 6858.

[36] J. Kjellgren, M. Kritikos, K. J. Szabo, *J. Organomet. Chem.* 2006, *691*, 3640.

[37] L. Hintermann, F. Lang, P. Maire, A. Togni, *Eur. J. Inorg. Chem.* 2006, 1397.

[38] A. Terada, *Nippon Kagaku Zasshi* 1960, *81*, 1773.

CHAPTER FOUR

4 Reactions of Palladium Allyl Complexes with Nucleophiles

4.1 Introduction

Isolated π-allyl palladium complexes are utilised in a number of synthetic procedures, however, many synthetic applications utilize the fact that π-allyl palladium complexes can be generated *in situ* from palladium catalysts and organic substrates, in order to yield the desired product. Hence, in this chapter reactions of both the isolated π-allyl palladium (II) chloride dimers and *in situ* π-allyl palladium complexes derived from allylic fluorides and chlorides formed will be investigated with a variety of nucleophiles, in particular fluoride ion.

4.1.1 Reactions of π-allyl complexes with nucleophiles

In 1965 Tsuji *et al.* reported the reaction of π-allyl palladium chloride with malonate and acetoacetate, demonstrating that π-allyl complexes are electrophilic.[1] Since then a vast quantity of literature has been written which discusses the reactions of π-allyl palladium (II) complexes with nucleophiles, as this can occur *via* two different pathways leading to either inversion[2-6] or retention[7-9] of configuration, depending on the nature of the nucleophile (Figure 4.1). Soft nucleophiles (pKa < 20) such as stabilised carbanions, amines, and alcohols react with overall retention, whilst hard nucleophiles (pKa > 20) such as hydrides and organometallics lead to net inversion by attack at palladium.

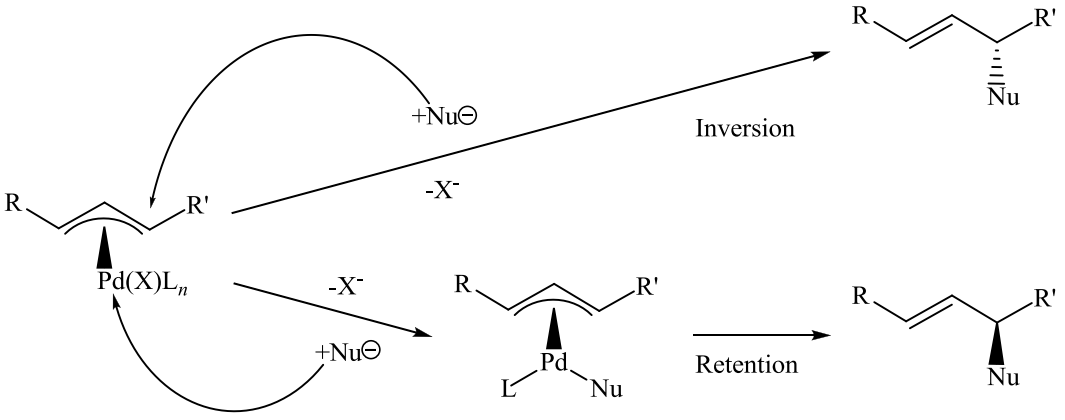
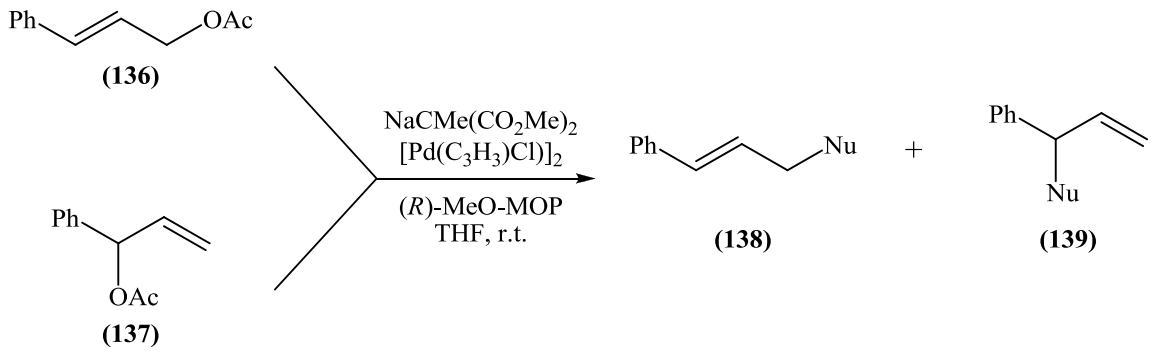


Figure 4.1 *Stereochemistry of Pd-catalysed allylation of nucleophiles*

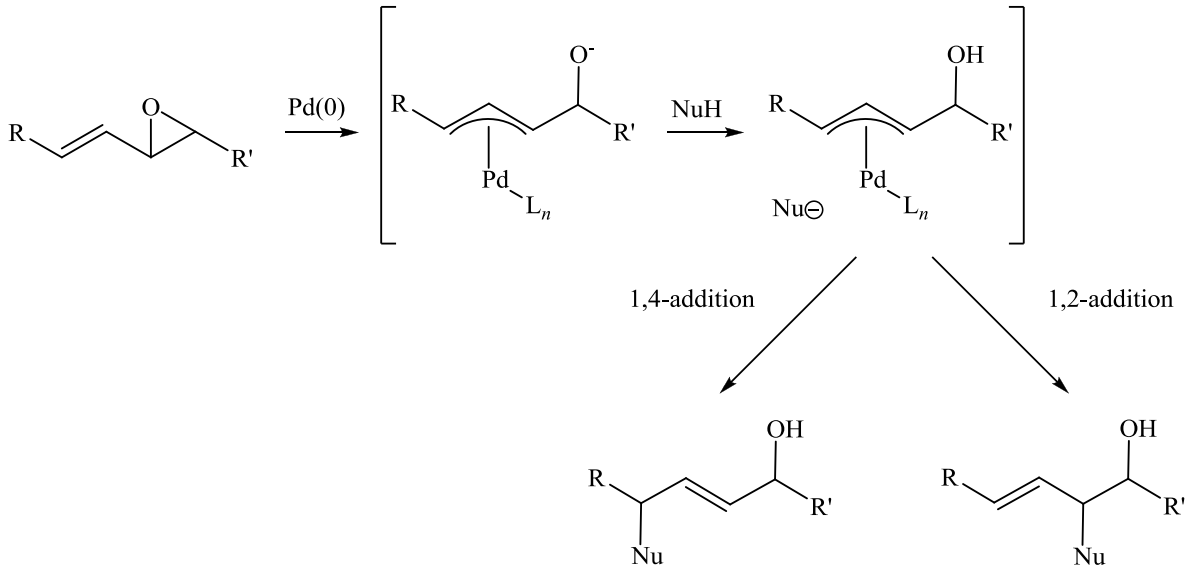
In π-allyl palladium complexes, nucleophilic attack usually occurs at the least hindered carbon atom. However, it was reported by Hayashi[10] that the regiochemistry in the allylation of $NaCMe(CO_2Me)_2$ with allylic acetates was partially retained in the final products when the palladium catalyst was used in conjunction with bulky ligands such as (*R*)-MeO-MOP. In the reaction of **(136)**, nucleophilic attack occurred at the least substituted carbon affording predominantly **(138)** [**(138)**:**(139)**, (79:21)]. However,

nucleophilic substitution of **(137)**, occurred at the more sterically hindered carbon, affording **(139)** as the major product [**(138)**:**(139)**, (23:77)] (Scheme 4.1). This is known as the memory effect and has also been observed by Acemoglu and Williams in the reactions of allylic acetates with $NaCH(CO_2t\text{-}Bu)_2$, using bulky aliphatic phosphine ligands.[11]



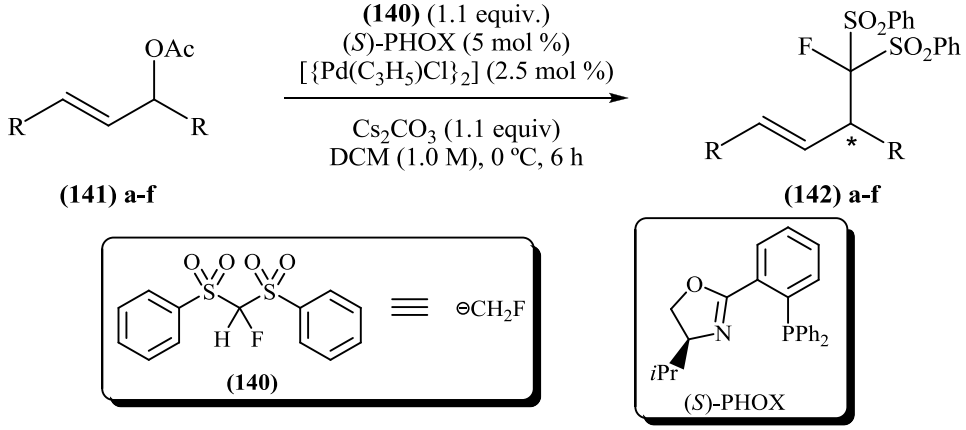
Scheme 4.1 *Synthesis of* ***(138)*** *and* ***(139)***

Often nucleophilic attack can also be directed by nearby atoms, as demonstrated in Scheme 4.2 where formation of the 1,4 adduct is preferred due to the electronic effect of the epoxide oxygen. Palladium catalyses the ring opening of the epoxide leading to formation of the π-allyl palladium complex with generation of an alkoxide anion. This can then abstract a proton from the nucleophile, affording α-hydroxy-π-allylpalladium. Subsequent reductive elimination can afford either the 1,4 or 1,2 products.[12, 13]



Scheme 4.2 *1,2-addition and 1,4-addition products from α-hydroxy-π-allyl palladium*

In many cases reactions of allylic compounds with nucleophiles are conducted in one step, rather than forming and isolating the π-allyl palladium complex first. This method has been utilised by Shibata's group, where a series of allylic acetates were reacted with the novel monofluoromethylating reagent 1-fluorobis(phenylsulfonyl)methane **(140)**.[14] Initially, in order to hone reaction conditions, they tried palladium catalysed fluoro*bis* (phenylsulfonyl)methylation with (2*E*)-1,3-bis(4-iso-butylphenyl)-2-propenyl acetate **(141a)** with catalytic quantities of [{Pd(C_3H_5)Cl}$_2$] and ligand (*S*)-1-(1'-diphenylphosphino) (ferrocenyl-1'-naphthyl sulfoxide ((*S*)-PHFS)[15] or (4*S*)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline ((*S*)-PHOX) at 0 ºC.[16-18] It was found that the reaction proceeded best when using (*S*)-PHOX as a ligand and cesium carbonate as a base in DCM at 0 ºC with stirring for 6 hours, affording the desired product **(142a)** in a good 83 % yield and excellent 94 % *ee*. Therefore, this protocol was extended to a variety of allylic acetates bearing different functional groups (Table 4.1). The desired products were all obtained in good to excellent yields (69-92 %) and high enantioselectivities (91-96 % *ee*).



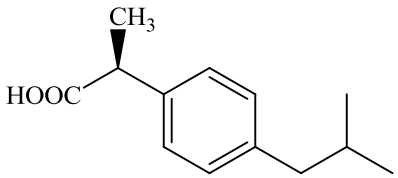
Scheme 4.3 *Palladium-catalysed enantioselective allylic fluorobis(phenylsulfonyl) methylation of allylic acetates **(141)a-f.***

(141)	R	(142)	Yield (%)	*ee* (%)[a]
a	*i*BuC$_6$H$_4$	a	89	91 (*S*)
b	Ph	b	92	96 (*R*)
c	4-MeOC$_6$H$_4$	c	74	91
d[b]	4-BrC$_6$H$_4$	d	69	94 (*R*)
e	2-naphthyl	e	89	92
f[c]	2-(6-methoxynaphthyl)	f	72	91

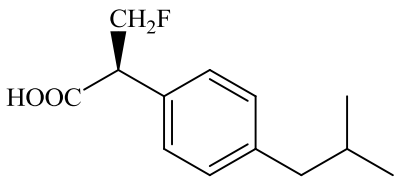
Table 4.1 *Palladium-catalysed enantioselective allylic fluorobis(phenylsulfonyl) methylation of allylic acetates **(141)a-f.***

[a] Determined by HPLC analysis using CHIRALPAK AD-H or OD-H. [b] Reaction conditions: **(140)** (1.0 equiv), **(141)** (2.0 equiv.), Cs_2CO_3 (2.0 equiv), [{Pd(C_3H_5)Cl}$_2$] (2.5 mol %) and (S)-PHOX (5 mol %) at r.t. for 6 h.
[c] (*R*)-PHOX (5 mol %) was used instead of (*S*)-PHOX.

Further reactions were conducted with **(142a)** in order to synthesise the methylfluorinated (*R*) and (*S*) analogues of ibuprofen (Figure 4.2). Currently racemic ibuprofen is sold worldwide, as it converts from the (*R*) to the (*S*) isomer after ingestion. The (*S*) isomer is called dexibuprofen and has very different pharmacological properties to the racemic version. Therefore several groups have synthesised chiral derivatives in order to gain further insight into this system.[19-23] Here, **(142a)** was converted to (*S*)- methyl fluorinated ibuprofen **(143)** in a similar method to the conventional synthesis of ibuprofen.[24] Firstly, ozonolysis of **(142a)** (*R* and *S*) was conducted in a methanol/DCM (3:1) mixture at – 78 ºC for just over 3 hours. Subsequently, reduction with $NaBH_4$ afforded the monofluoromethylated alcohols in excellent yields and enantioselectivities ((*R*) = 85 %, 91 % ee, (*S*) = 87 %, 91 % ee). The sulfonyl group was removed next by reaction with activated magnesium in methanol at 0 ºC for 2 hours, followed by oxidation with Jones reagent in acetone at room temperature for 1 hour, to afford the desired product **(143)** in good yields with high enantioselectivity, ((*R*) = 73 %, 91 % ee, (*S*) = 79 %, 91 % ee).



(*S*)- ibuprofen

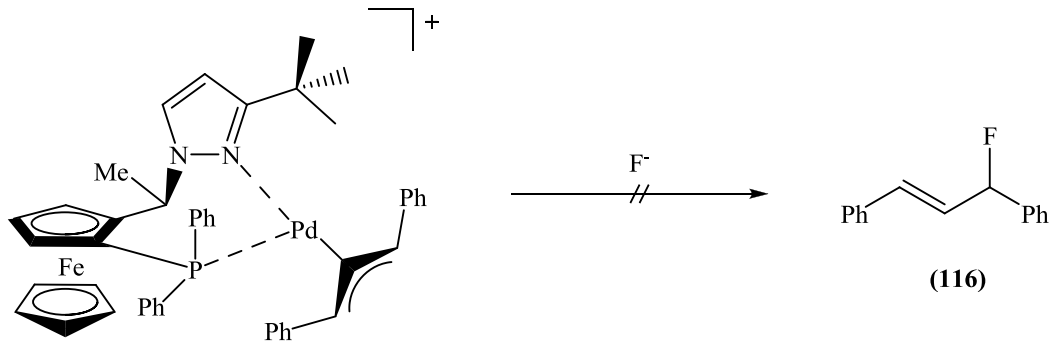


(*S*)- methyl fluorinated ibuprofen **(143)**

Figure 4.2 *(S)-ibuprofen and (S)-methyl fluorinated ibuprofen*

4.2 Results and Discussion

One of the key objectives of this work was to prepare allylic fluorides by reaction of Pd-allyl species with fluoride ion. Previously, there has only been one, unsuccessful report of an attempt to achieve this transformation by Togni *et al.*[25] whereby, initially catalytic fluorination was attempted with 1,3-diphenylallyl ethyl carbonate, and the catalyst was generated *in situ* from $Pd(dba)_2$ and phosphanyl-ferrocenyl pyrazole (Scheme 4.4). The sources of nucleophilic fluoride tested were TBAT ($NBu_4[SiF_2Ph_3]$)[26] and Me_4NF.[27] Both are soluble in aprotic organic solvents, thus minimizing any reduction in the nucleophilicity of fluoride, which can occur by solvation in protic media or in the presence of trace amounts of water.[28] However, nucleophilic attack of fluoride on the allyl component and the liberation of an allyl fluoride was never observed. Attempting the reaction with a stoichiometric amount of palladium was also unsuccessful.



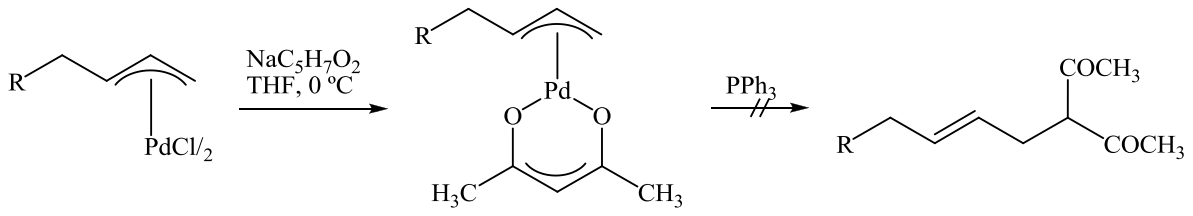
Scheme 4.4 *Attempted fluorination of 1,3-diphenylallyl ethyl carbonate*

However, the limited scope of this previous report did not, necessarily, indicate that such a transformation was not achievable.

Prior to the fluoride ion reaction chemistry, some of the Pd-allyl species prepared in Chapter Three were reacted with conventional carbon based nucleophiles to demonstrate that they followed established reaction trends.

4.2.1 Reactions of palladium chloro-bridged complexes with nucleophiles

Initially the palladium (II) chloro-bridged dimers **(125)** and **(126)** were reacted with sodium acetylacetonate, following the protocol outlined by Hayashi and co-workers.[29] The Pd dimer was stirred in THF and cooled to 0 ºC, followed by addition of sodium acetyl acetonate to the reaction flask and the mixture was then stirred at 0 ºC for 1 hour. After which, the reaction mixture was quenched with water, extracted with diethyl ether, the organic layer dried over magnesium sulphate and the solvent removed *in vacuo* to afford the products **(145)** and **(146)** in 66 % yield (Scheme 4.6) (Table 4.2).

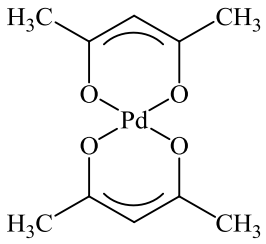


(125) R = OBz
(126) R = OBn

(145) R = OBz
(146) R = OBn

Scheme 4.5 *Synthesis of **(145)** and **(146)***

However, the reactions did not go to completion as the co-product palladium acetylacetonate **(144)** was also formed which was identified by single crystal X-ray crystallography (Figure 4.3). Although attempts were made by column chromatography and recrystallisation, it was difficult to separate the desired product fully from **(144)**.



(144)

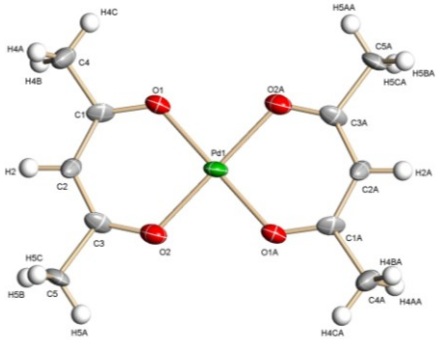


Figure 4.3 *Structure of co-product* ***(144)***

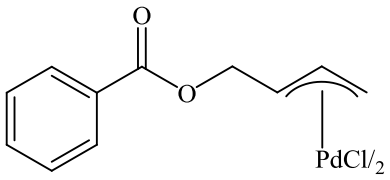
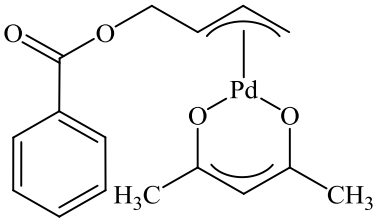
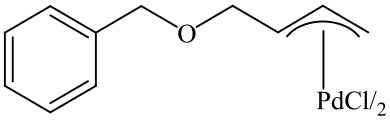
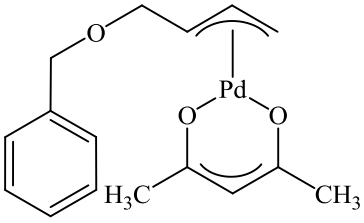
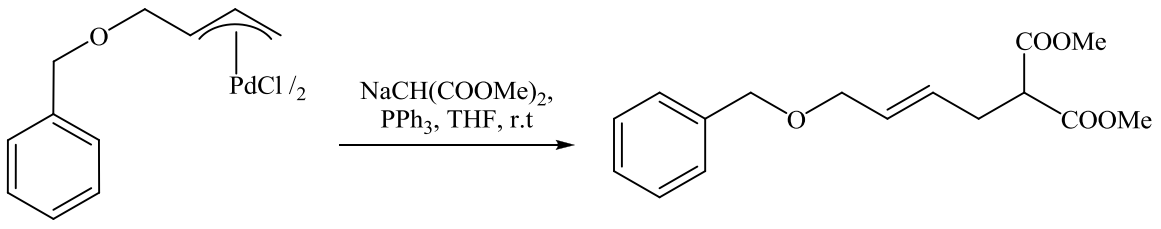
Starting Substrate	Product	Yield (%)*
 **(125)**	 **(145)**	66
 **(126)**	 **(146)**	66

Table 4.2 Yields obtained *of* ***(145)*** *and* ***(146)***

* Yield based on conversion in ^{1}H NMR spectrum

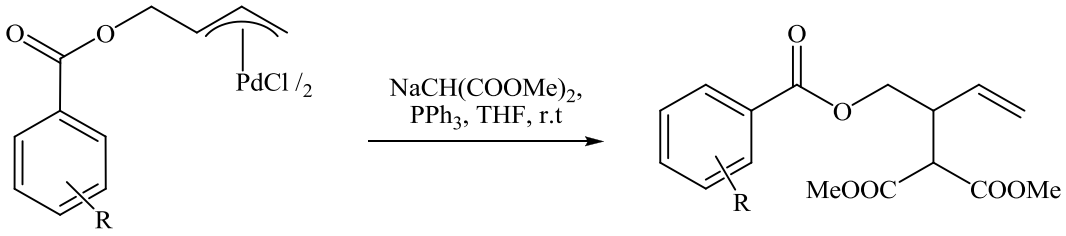
Therefore, as the Pd(II) intermediates could not be isolated pure, they were not reacted further with triphenylphosphine in order to obtain the desired substituted products (Scheme 4.5). Similarly, pure products could not be isolated using the method described by Bäckvall.[30] Subsequently, an alternative method by Hayashi *et al.*[31] was employed, where **(126)** was stirred in THF, followed by the addition of 4 equivalents of triphenylphosphine and sodium dimethylmalonate (Scheme 4.6). The reaction mixture was stirred overnight. After which the formed precipitate was filtered off and solvent removed *in vacuo* to give the crude product which was purified by column chromatography [hexane: ethyl acetate (70:30)], affording the novel desired product as a colourless oil in 44 % yield, which was characterised by ^{1}H NMR spectroscopy and mass spectrometry.



(126) **(147)**

Scheme 4.6 *Synthesis of* ***(147)***

This procedure was then utilised in reactions with **(125)**, **(127)** and **(130)**. The corresponding novel products **(148, 149, 150)** were isolated only in moderate yields, due to difficulties associated with separating the desired product from the excess triphenylphosphine and dimethyl malonate.



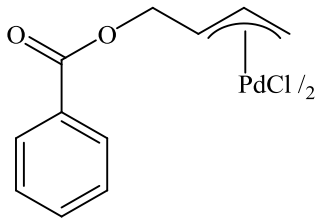
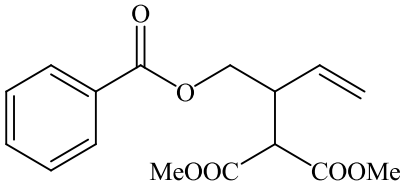
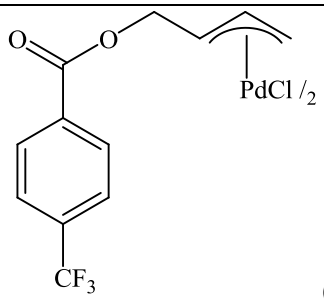
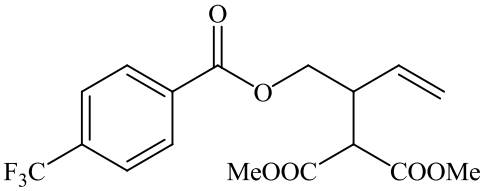
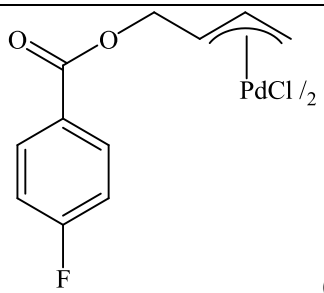
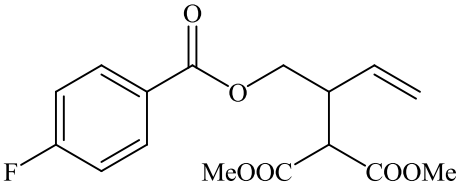
Starting substrate	Product	Yield (%)
 **(125)**	 **(148)**	37
 **(130)**	 **(149)**	21
 **(127)**	 **(150)**	21

Table 4.3 *Products obtained in reaction with sodium dimethyl malonate*

Interestingly, even though the same reaction conditions were used with **(126)** as with **(125)-(130)**, the products obtained are different. For **(126)**, nucleophilic attack occurs at carbon 1, whilst it occurs at carbon 3 in **(125)-(130)** (Figure 4.4). The only difference between the substrates is that **(126)** possesses an ether functionality, whilst **(125)-(130)** have an ester.

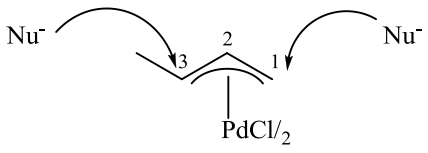
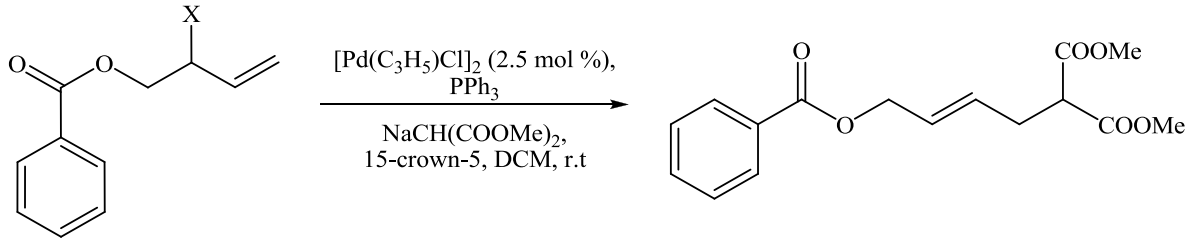


Figure 4.4 *Nucleophilic attack at Pd allyl*

4.2.2 Reactions of palladium cationic complexes with dimethyl malonate anion

Having reacted the Pd (II) chloro-bridged dimers with both pentane-2,4-dione and dimethyl malonate, it was decided to react the palladium cationic complexes synthesised in Chapter Three with dimethyl malonate anion. This would enable a one pot reaction to be conducted as opposed to forming and isolating the Pd π-allyl complex prior to nucleophilic attack. It would also enable a comparison of the reactivity to be made between neutral Pd π-allyl compounds and cationic palladium allyl complexes.

However, first it was necessary to investigate whether the palladium cationic complexes synthesised from 2-chlorobut-3-enyl benzoate **(108)** and 2-fluorobut-3-enyl benzoate **(75)** would afford the same product or different products when reacted with sodium dimethyl malonate.



(108) X= Cl
(75) X = F

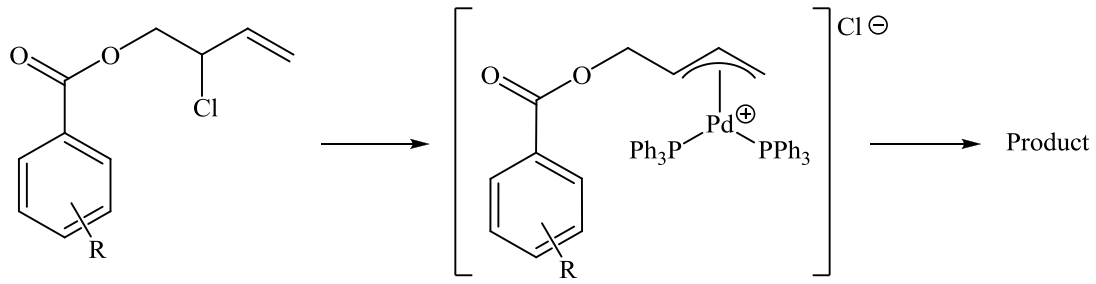
(151)

Scheme 4.7 *Synthesis of **(151)** from **(108)** and **(75)***

Therefore, **(75)** and **(108)** were both reacted with sodium dimethyl malonate following the method outlined by Gouverneur *et al.*[32] Firstly, the catalyst was prepared by stirring $[Pd(C_3H_5)Cl]_2$ with PPh_3 in anhydrous DCM. After which **(75)/(108),** sodium dimethyl malonate and 15-crown-5 were added. The reaction mixture was left to stir overnight, after which the reaction mixture was quenched with water, the aqueous phase extracted with diethyl ether, the organic phases dried over $MgSO_4$ and concentrated *in vacuo*. Analysis by ^1H NMR spectroscopy of the crude products, showed that both **(75)** and **(108)** had formed the same product, which was purified by column chromatography [hexane: ethyl acetate (70:30)], affording the same isolated product **(151)** in moderate yields (46 and 40 %), which was characterised by ^1H and ^{13}C NMR spectroscopy and mass spectrometry.

Consequently, as the same product was formed *via* the palladium cationic complex synthesised from 2-fluorobut-3-enyl benzoate **(75)** and 2-chlorobut-3-enyl benzoate **(108)**. Subsequent nucleophilic reactions were conducted with palladium cationic complexes synthesised from **(108)** since the chlorinated allyl substrates can be synthesised more readily. In order to investigate whether substituents on the benzene ring influence the

palladium allyl fragment and nucleophilic attack, sodium dimethyl malonate was reacted with **(110)** and **(112)** (Table 4.4).



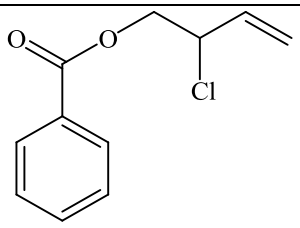
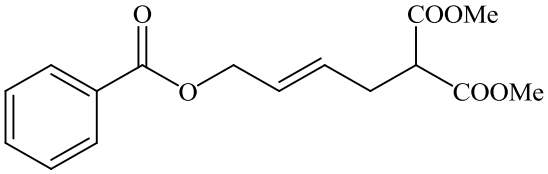
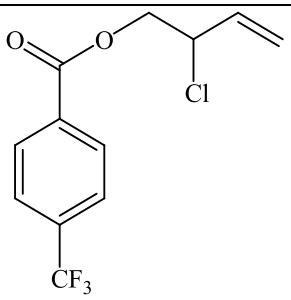
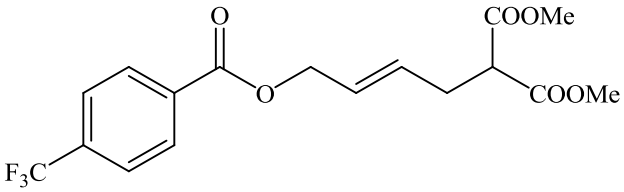
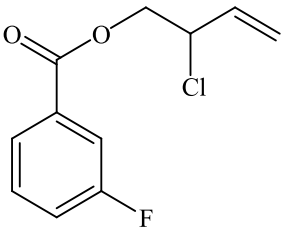
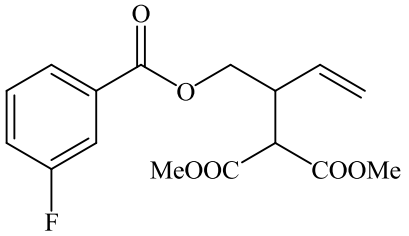
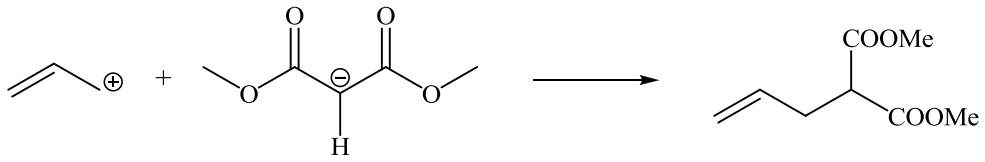
Starting substrate	Product	Yield (%)
 **(108)**	 **(151)**	40
 **(112)**	 **(152)**	29
 **(110)**	 **(153)**	24

Table 4.4 *Yields obtained of* ***(151)-(153)***

The novel compounds **(152)** and **(153)** were fully characterised by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy. Here, in comparison to the reaction of Pd chloro-bridged dimer **(130)** with sodium dimethyl malonate, where nucleophilic attack occurred at the more hindered carbon atom, in the one pot reaction of **(112)** with Pd(0) and sodium dimethyl malonate; attack occurred at the less hindered carbon atom. This was also the case in the reaction of **(108)**. However, when R = *m*-F **(110)**, nucleophilic attack occurred at the more hindered carbon. Therefore, it can be inferred that both the nature of the Pd(II)-allyl intermediate and the

substituents on the benzene ring do have an impact on the site of nucleophilic attack. Consequently in order to fully understand why nucleophilic attack has occurred at the more hindered carbon in **(110)** further synthetic work and possibly, modelling studies would need to be conducted.

In the reaction of **(112)** with sodium dimethyl malonate the co-product dimethyl 2-allyl malonate **(154)** was also isolated. This is formed as a result of excess sodium dimethyl malonate reacting with the allyl from the [{Pd(C_3H_5)Cl}$_2$] starting material (Scheme 4.8).



(154)

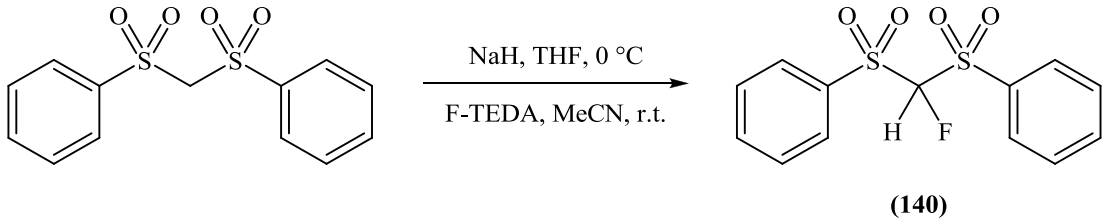
Scheme 4.8 *Synthesis of* ***(154)***

Having reacted a variety of the derivatised allylic chlorides in a palladium catalysed reaction with sodium dimethyl malonate, efforts were concentrated on reacting *in situ* formed palladium cationic complexes with other carbon-based nucleophiles and sources of fluoride ion.

4.2.3 Reactions of Pd cationic complexes with other carbon based nucleophiles

Having established the regioselectivity attained when **(108)** and **(112)** underwent nucleophilic attack *via* their palladium cationic complexes, reactions were conducted with other carbon-based nucleophiles in order to observe whether the same regioselectivity was retained. The Shibata reagent; 1-fluoro *bis*(phenylsulfonyl)methane **(140)**, is a novel reagent for introducing the CH_2F moiety into organic substrates.[14] Therefore this reagent was utilised in reactions with **(112)** and **(108)**, as once the corresponding product has formed, the sulphonyl groups can be cleaved in order to yield the potentially valuable fluoromethylated compounds.

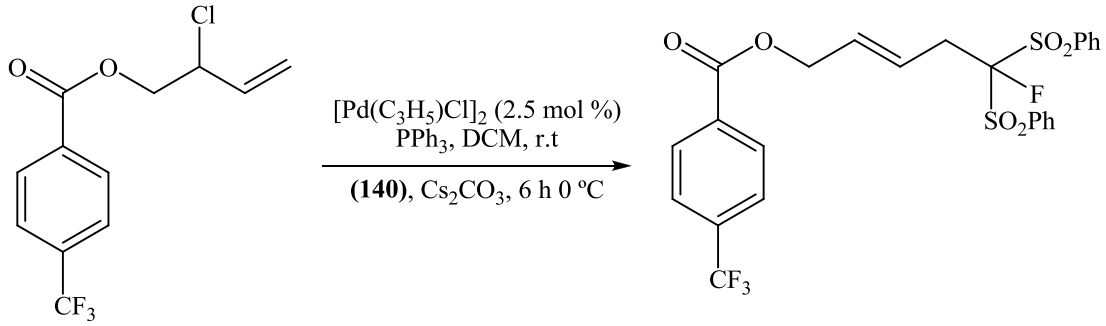
The Shibata reagent, 1-fluoro *bis*(phenylsulfonyl)methane **(140)**, was synthesised following the literature protocol. A mixture of NaH and anhydrous THF was cooled to 0 °C and then charged with *bis*(phenylsulfonyl)methane. A solution of Selectfluor in dry MeCN was added dropwise and the reaction mixture was stirred for 3 hours at room temperature. Work up of the crude product followed by purification *via* column chromatography [hexane: DCM (20:80)] afforded the product **(140)** as a white solid in a moderate 58 % yield (Scheme 4.9).



(140)

Scheme 4.9 *Synthesis of* ***(140)***

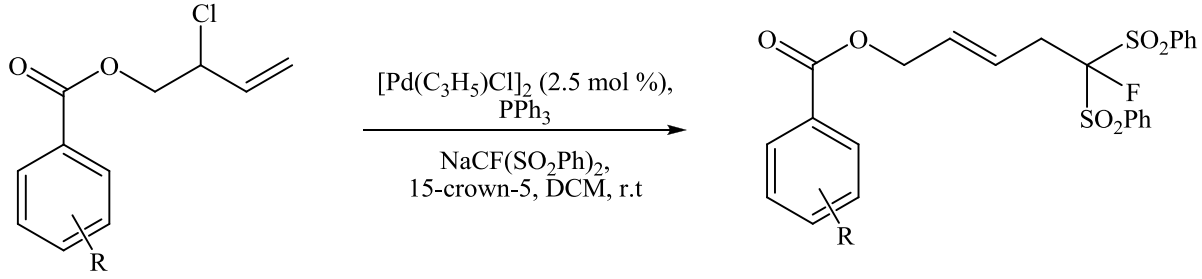
Having synthesised **(140)**, it was utilised in a reaction with **(112)**, following the protocol described by Shibata (Scheme 4.10). The crude reaction mixture showed that the reaction had not gone to completion as the starting allylic chloride **(112)** was present in addition to the CH_2F reactant **(140)**. However, column chromatography [hexane: ethyl acetate (70:30)] of the crude product mixture did afford a small amount of novel product **(155)** (15 % yield), as an oil which was characterised by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy. A characteristic triplet was observed in the ^{19}F NMR spectrum at -142 ppm.



(112) **(155)**

Scheme 4.10 *Synthesis of* ***(155)***

In view of the low yield, the reaction with 2-chlorobut-3-enyl 4-(trifluoromethyl)benzoate **(112)** was repeated using the same conditions as those used in the sodium dimethyl malonate reactions (Scheme 4.11) having isolated pre-formed sodium 1-fluoro bis(phenylsulfonyl) methane. The reaction of 2-chlorobut-3-enyl benzoate **(108**) was also attempted.

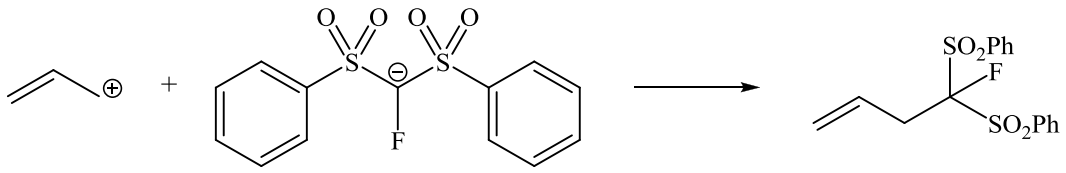


(108) R= H
(112) R = *p*-CF_3

(155) R = *p*-CF_3

Scheme 4.11 *Synthesis of* ***(155)***

The desired product was afforded with the trifluoromethyl-substituted ester **(112)** but not with the unsubstituted **(108)**. Instead, purification of the crude reaction mixture from **(108)** afforded only starting materials and co-product allyl 1-fluoro-*bis* (phenylsulfonyl)methane **(156)**. Whilst the desired product obtained from **(112)** was also difficult to isolate *via* column chromatography due to the formation of the co-product **(156)**, Scheme 4.12. In both instances the co-product **(156)** was forming as a result of excess sodium 1-fluoro-*bis*(phenylsulfonyl)-methane reacting with the allyl fragment from the $[\{Pd(C_3H_5)Cl\}_2]$ starting material, as observed previously with sodium dimethyl malonate.



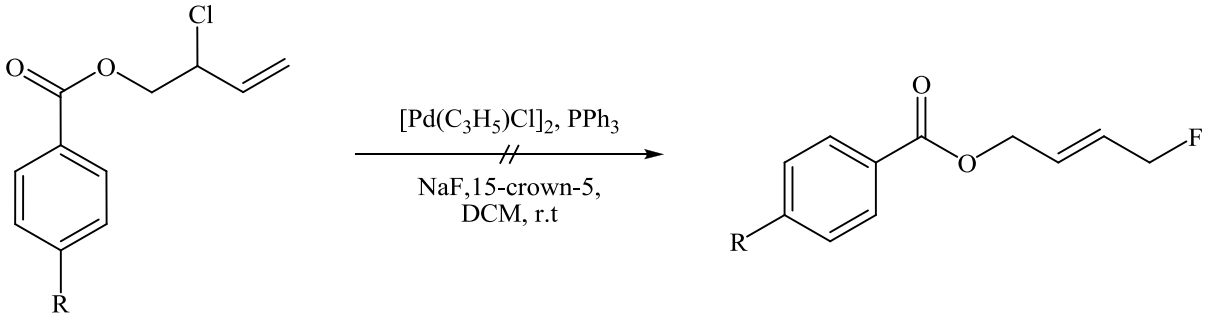
(140) **(156)**

Scheme 4.12 *Synthesis of* ***(156)***

4.2.4 Reactions of Pd Cationic Complexes with Fluoride

The palladium cationic complexes were utilised in reactions with a variety of sources of fluoride ion. They were used in preference to the Pd chloro-bridged dimers in these reactions as there was no need to isolate the Pd π-allyl complex prior to reaction with the fluoride ion, and therefore the reaction could proceed in fewer steps. The successful reaction of fluoride with a Pd π-allyl complex would provide an alternative route to allylic fluorides, with the possibility of determining regioselectivity by varying substituents on the ring, as demonstrated by the reaction of **(112)** and **(110)** with sodium dimethyl malonate.

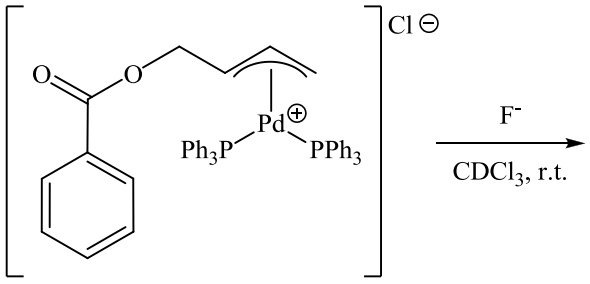
Initially, NaF was utilised in reactions with **(112)** and **(108)**, and the same reaction conditions were employed as done so previously with sodium dimethyl malonate. It was thought that the 15-crown-5 would capture the sodium ion enabling the fluoride to attack the π-allyl complex. However, after the reaction mixture had been stirred overnight at room temperature, work up, followed by analysis of the crude reaction mixtures by ^{1}H NMR spectroscopy exhibited only starting material to be present in both cases. With no allylic fluoride peaks observed in the ^{19}F NMR spectrum (Scheme 4.13).



(108) R= H
(112) R= CF_3

Scheme 4.13 *Attempted synthesis of allylic fluoride with NaF*

Therefore, subsequent reactions were conducted by firstly forming the palladium cationic complex, as described in Chapter Three, by stirring 2-chlorobut-3-enyl benzoate **(108)**, PPh_3 and $Pd(dba)_2$ in $CDCl_3$. After 2 hours an excess of the fluoride source was injected and the reaction monitored by ^1H and ^{19}F NMR spectroscopy and mass spectrometry (Table 4.5) (Scheme 4.14).



(135)

Scheme 4.14 *Reaction of* ***(135)*** *with fluoride*

Fluoride source	**^{19}F NMR after 1 h (ppm)**	**^{19}F NMR after 24 h (ppm)**	**^{19}F NMR after work up (ppm)**
TBAF	-128.9	-128.9	-
HF.pyridine	-128.7 (broad peak) and -151.0 (singlet)	-128.7 (broad peak) and -151.0	-151.9
TREAT HF	-129.2 (broad peak), -151.9 (small peak) and -165.3	-129.6 (s), -146.5 (m), -152.5 (d) and -159.6 (broad peak)	-152.5
TASF	-157.6 and -158.1	157.2 (s) and -159.6 (broad peak)	-152.1

Table 4.5 *Spectral data obtained from reactions of* ***(135)*** *with fluoride*

The reaction of **(135)** with TBAF (tetrabutylammonium fluoride), was monitored for 24 hours, after 1 hour the ^{1}H NMR spectrum was dominated by peaks from the butyl groups and the ^{19}F NMR spectrum exhibited a peak at -128.9 ppm indicative of the TBAF signal. Analysis by mass spectrometry, showed that **(135)** was still present with a signal at 805 Daltons, however, the strongest signal was attributable to the tetrabutyl ammonium cation at 242 Daltons. No change was observed in either the ^{1}H or ^{19}F NMR spectra after 24 hours. Therefore, after stirring the reaction mixture for an additional 48 hours at room temperature, work up, followed by analysis of the crude reaction mixtures by ^{1}H NMR spectroscopy, revealed that none of the desired allylic fluoride product had been formed. Instead only PPh_3, dibenzylideneacetone (dba) and butyl peaks were present. There was also no peak observed in the ^{19}F NMR spectrum, and mass spectrometry only exhibited a strong signal at *m/z* 242 (tetrabutylammonium cation).

The reaction of **(135)** with HF. pyridine gave a similar result. After 1 hour, the ^{1}H NMR spectrum exhibited peaks from PPh_3, dibenzylideneacetone (dba) and **(135)**, whilst 2 signals were observed in the ^{19}F NMR spectrum, -128 ppm (HF.pyridine) and -151.9 ppm (BF_4, from HF attacking the glass). Mass spectrometry confirmed the presence of **(135)** in the reaction solution with a signal at 805 Daltons. The ^{1}H and ^{19}F NMR spectra were unchanged after 24 hours, as was the mass spectrum. Analysis of the product after work up, revealed no desired product to be present only **(135)** starting material.

The reaction of **(135)** with TASF (*tris*(dimethylamino)sulfonium difluorotrimethylsilicate) proceeded in a similar manner to that observed with TBAF, with the ^{1}H NMR spectrum dominated by peaks from the *tris*(dimethylamino) sulfonium cation (Figure 4.5). The ^{19}F NMR exhibited a broad peak at -158 ppm, indicative of TASF. Whilst the mass spectrum revealed that **(135)** (*m/z* 805), was still present though the most intense signal was from the *tris*(dimethylamino) sulfonium cation at *m/z* 164. Little change was observed after 24 hours. Therefore the reaction mixture was quenched and analysis of the crude product by ^{19}F NMR spectroscopy revealed a peak at -152 ppm, but not in the allylic fluoride region, therefore confirming that the allylic product had not formed. Whilst, ^{1}H NMR spectroscopy revealed PPh_3, dibenzylideneacetone (dba) and some peaks which were not associated with starting material or desired product, hence, were uninterpretable.

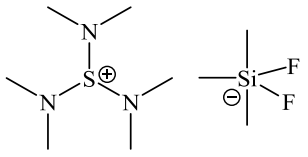


Figure 4.5 *Structure of TASF*

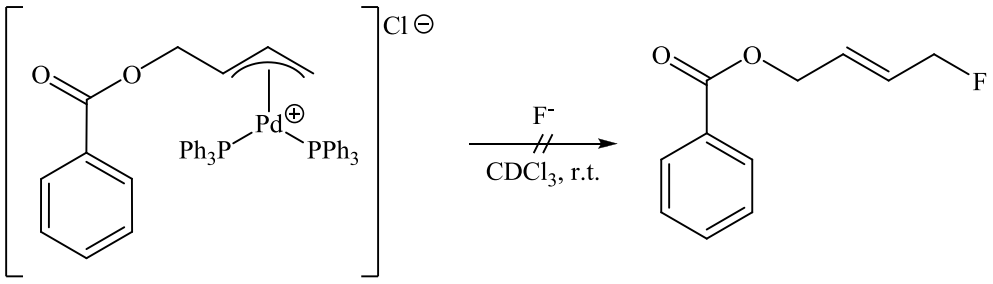
The reaction of TREAT HF was conducted in the same way, and after 1 hour, the ^{1}H NMR spectrum revealed peaks attributable to PPh_3, dba, triethylamine and **(135)**. Whilst the ^{19}F NMR exhibited peaks at -129.2, -165.3 and -151.9 ppm, which are all observed when a ^{19}F NMR spectrum of TREAT HF is conducted on its own in $CDCl_3$. Mass spectrometry also confirmed the presence of **(135)** with a signal at *m/z* 805. After 24 hours the peaks in both ^{1}H and ^{19}F NMR spectra were relatively unchanged, as was the mass spectrum. Therefore, work up followed by a final analysis of the spectroscopic data revealed that none of the desired allylic fluoride product was present. The only new peaks were in the ^{1}H NMR spectrum, and were the same as previously observed with TASF and HF.pyridine, which were not associated with starting material or desired product and therefore difficult to interpret.

Though several different sources of fluoride were reacted with **(135)**, none formed the corresponding allylic fluoride successfully. All reactions were conducted at room temperature, and therefore the disappointing results concur with the single report of Togni.[25] The fact that the reaction was unsuccessful could be attributed to several factors, firstly that the reaction equilibrium favoured the formation of Pd allyl as this was thermodynamically more favourable than the corresponding allylic fluoride and therefore, even if the desired product was forming, due to the reaction equilibrium it was short lived and swiftly formed the Pd allyl starting material again. It could also be that the reaction mixture needed to be heated in order to initiate the desired reaction to occur, or that the reaction needed colder reaction temperatures in order for the product to form. These are all factors that could be further investigated in order to fully explore and understand the reaction mechanism occurring.

4.3 Conclusions

The palladium (II) chloro-bridged dimers **(125)** and **(126)** were reacted with sodium acetyl-acetonate to form the desired product, however, their isolation from the co-product **(144)**, which had been identified by X-ray crystallography, proved problematic. Therefore, alternative routes were investigated which afforded the desired products in reaction with dimethyl malonate. It was observed that reaction of sodium dimethyl malonate with bis[μ-chloro-bis(butenyl-(1,2,3-η)-oxy) methyl) benzene]dipalladium **(126)** occurred at the less hindered carbon, whilst reaction with bis[μ-chloro-bis(butenyl-(1,2,3-η)-benzoate] dipalladium **(125)** afforded the product, where nucleophilic attack had occurred at the more hindered carbon. Pd cationic complexes derived from allylic fluorides and allylic chlorides

were both reacted with sodium dimethyl malonate affording the same product, therefore, the Pd π-allyl complexes were subsequently synthesised from the allylic chloride. It was observed that in reaction with sodium dimethyl malonate the substituent on the benzene had an effect on the outcome of nucleophilic attack, when R = *para*-CF_3, the less hindered carbon was attacked, however, when R = *meta*-F, attack occurred at the more hindered carbon atom. Pd cationic complexes were also reacted with sodium 1-fluoro bis(phenylsulfonyl)methane **(140)**, affording the desired novel product **(155)** in addition to the novel co-product allyl 1-fluoro bis(phenylsulfonyl)methane **(156)**, forming as a result of excess sodium 1-fluoro-bis (phenylsulfonyl)methane reacting with the allyl fragment from the $[\{Pd(C_3H_5)Cl\}_2]$ starting material. Finally, the reaction of **(135)** with TBAF, TASF, HF.pyridine, TREAT HF and NaF was investigated (Scheme 4.15). The reactions were monitored by ^1H and ^{19}F NMR spectroscopy, however, formation of the desired allylic fluoride was not observed, under the reaction conditions employed. Therefore, further work is still required to fully examine this reaction. In chapter five, a novel library of analogous allylic difluorides will be synthesised and their reactions with Pd(0) investigated.



(135)

Scheme 4.15 *Attempted synthesis of allylic fluorides*

4.4 References

[1] J. Tsuji, H. Takahashi, M. Morikawa, *Tetrahedron Lett.* **1965**, 4387.

[2] B. M. Trost, T. R. Verhoeven, *J. Am. Chem. Soc.* **1978**, *100*, 3435.

[3] B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton, T. J. Dietsche, *J. Am. Chem. Soc.* **1978**, *100*, 3416.

[4] D. J. Collins, W. R. Jackson, R. N. Timms, *Aust. J. Chem.* **1977**, *30*, 2167.

[5] B. Akermark, A. Jutand, *J. Organomet. Chem.* **1981**, *217*, C41.

[6] B. Akermark, J.-E. Bäckvall, A. Löwenborg, K. Zetterberg, *J. Organomet. Chem.* **1979**, *166*, C33.

[7] J. S. Temple, M. Riedliker, J. Schwartz, *J. Am. Chem. Soc.* **1982**, *104*, 1310.

[8] Y. Castanet, F. Petit, *Tetrahedron Lett.* **1979**, 3221.

[9] D. N. Jones, S. D. Knox, *J Chem. Soc., Chem. Commun.*, 165.

[10] T. Hayashi, M. Kawatsura, Y. Uozumi, *J. Am. Chem. Soc.* **1998**, *120*, 1681.

[11] L. Acemoglu, J. M. J. Williams, *Adv. Synth. Cat.* **2001**, *343*, 75.

[12] J. Tsuji, H. Kataoka, Y. Kobayashi, *Tetrahedron Lett.* **1981**, *22*, 2575.

[13] B. M. Trost, G. A. Molander, *J. Am. Chem. Soc.* **1981**, *103*, 5969.

[14] T. Fukuzumi, N. Shibata, M. Sugiura, H. Yasui, S. Nakamura, T. Toru, *Angew. Chem. Int. Ed.* **2006**, *45*, 4973.

[15] S. Nakamura, T. Fukuzumi, T. Toru, *Chirality* **2004**, *16*, 10.

[16] P. V. Matt, A. Pfaltz, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*.

[17] J. Sprinz, G. Helmchen, *Tetrahedron Lett.* **1993**, *34*, 1769.

[18] G. J. Dawson, C. G. Frost, J. M. J. Williams, S. J. Coote, *Tetrahedron Lett.* **1993**, *34*, 3149.

[19] O. Goj, S. Kotila, G. Haufe, *Tetrahedron* **1996**, *52*, 12761.

[20] W. J. Middleton, E. M. Bingham, *J. Fluorine Chem.* **1983**, *22*, 561.

[21] Y. Yamazaki, S. Yusa, Y. Kageyama, H. Tsue, K. Hirao, H. Okuno, *J. Fluorine Chem.* **1996**, *79*, 167.

[22] M. Schlosser, D. Michael, Z.-W. Guo, C. J. Sih, *Tetrahedron* **1996**, *52*, 8257.

[23] Y. Takeuchi, H. Fujisawa, T. Fujiwara, M. Matsuura, H. Komatsu, S. Uneo, T. Matsuzaki, *Chem. Pharm. Bull.* **2005**, *53*, 1062.

[24] L. Acemoglu, J. M. J. Williams, *J. Mol. Catal. A.* **2003**, *196*, 3.

[25] L. Hintermann, F. Lang, P. Maire, A. Togni, *Eur. J. Inorg. Chem.* **2006**, 1397.

[26] A. S. Pilcher, H. L. Ammon, P. Deshong, *J. Am. Chem. Soc.* **1995**, *117*, 5166.

[27] K. O. Christe, W. W. Wilson, R. D. Wilson, R. Bau, J. A. Feng, *J. Am. Chem. Soc.* **1990**, *112*, 7619.

[28] D. Landini, A. Maia, A. Rampoldi, *J. Org. Chem.* **1989**, *54*, 328.

[29] T. Hayashi, A. Yamamoto, Y. Ito, *J. Organomet. Chem.* **1988**, *338*, 261.

[30] J.-E. Bäckvall, R. E. Nordberg, D. Wilhelm, *J. Am. Chem. Soc.* **1985**, *107*, 6892.

[31] T. Hayashi, M. Konishi, M. Kumada, *J. Chem. Soc. Chem. Commun.* **1984**, 107.

[32] A. Hazari, V. Gouverneur, J. Brown, *Angew. Chem. Int. Ed.* **2009**, *48*, 1296.

CHAPTER FIVE

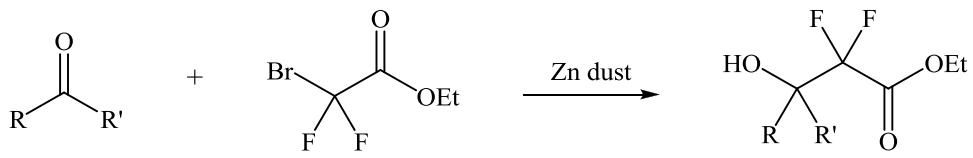
5 Synthesis and Reactions of Difluoroallylic Compounds

5.1 Introduction

The CF_2 group is a key structural unit in many fluorinated compounds of biological and pharmaceutical significance.[1] The synthesis of *gem*-difluorinated compounds can be conducted in two ways either by direct fluorination, which can occur by the use of nucleophilic[2-6] or electrophilic[7-9] fluorinating agents, or by utilising a difluoro building block.[10, 11] This chapter will focus on the latter approach in order to synthesise an analogous library of allylic difluorides to the allylic fluorides and chlorides synthesised in Chapter Two. Once synthesised the allylic difluorides will be utilised in reactions with Pd(0), as although allylic fluorides can be activated with Pd, in doing so they lose fluorine and react with nucleophiles to afford non-fluorinated products. However, activation of allylic difluorides followed by reaction with nucleophiles would yield fluoroalkenes. These products are an important class of compounds that can be utilised as peptide isosteres,[12-15] enzyme inhibitors[16] and in liquid crystalline materials.[17]

5.1.1 Difluoromethylene Synthons

The most common CF_2 synthon approach is the Reformatsky reaction of halodifluoroacetates and halodifluoroketones. Fried reported the preparation of 2,2-difluoro-3-hydroxy esters by the Reformatsky reaction of ethyl bromodifluoroacetate with aldehydes and ketones in 1984 (Scheme 5.1).[10] Upon comparison of both the one pot and 2-step procedure, Fried found that addition of the aldehyde after the zinc had reacted with ethyl bromodifluoroacetate for a few minutes led to higher yields of product and was, therefore, preferred. It could also be used for the synthesis of more sensitive substrates as it required lower reaction temperatures.

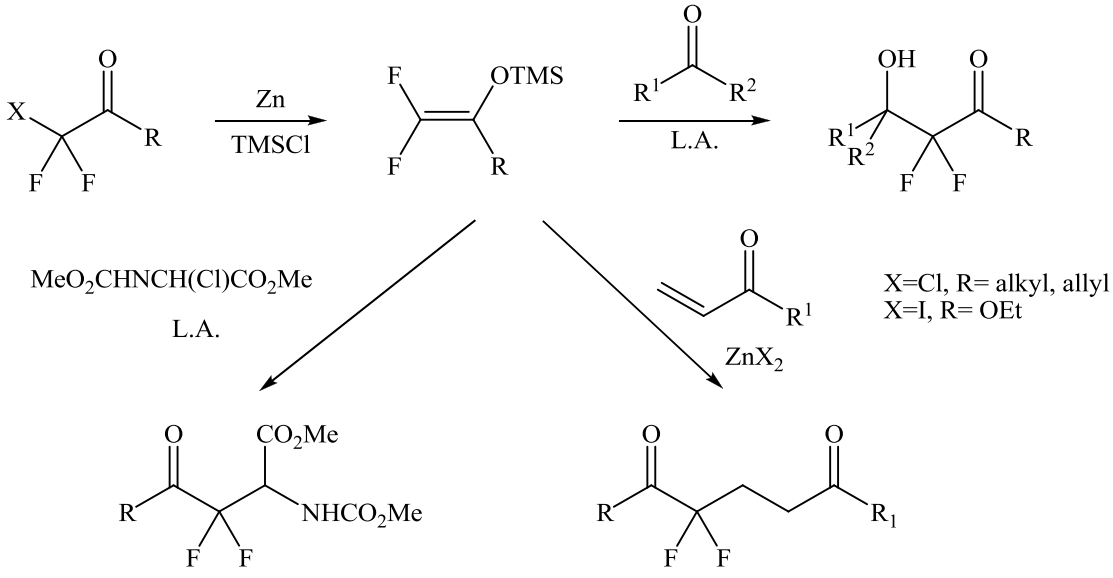


Scheme 5.1 *General reaction scheme for the synthesis of 2,2-difluoro-3-hydroxyesters*

Simultaneously, Ishihara reported the zinc-mediated reaction of chlorodifluoromethyl ketones with aldehydes and ketones affording 2,2-difluoro-3-hydroxy ketones in moderate to good yields (38-95 %). It was found that a catalytic quantity of titanium tetrachloride was integral to the reaction, as with zinc alone only starting material was afforded. Therefore, the reactive species in the reaction was the bivalent titanium compound which,

on attack of the chlorine atom of the chlorodifluoromethyl ketone, yielded the corresponding enolate.[11] Following on from this work, Ishihara and Kuroboshi found that the use of copper chloride[18, 19] or silver acetate as catalysts also improved the reaction of chlorodifluoromethyl ketones with carbonyl compounds to yield the corresponding α,α-difluoro-β-hydroxy ketones in high yields (60-100 %). Further studies by Lang demonstrated that inexpensive chlorodifluoroacetic acid was a viable replacement for bromodifluoroacetic acid, with higher yields afforded when the reaction was conducted in DMF.[20] Whilst milder conditions could be employed by using a catalytic amount of $CeCl_3$[21] or Et_2AlCl with AgOAc.[22] Altenburger reported how the use of ultrasonication at room temperature under inert conditions enabled the generation of the organozinc reagent prior to the addition of the aldehyde. This is especially essential when using nitro aldehydes, where a two-step process is required, as the traditional one-pot reflux procedure results in 0 % yield, in contrast to 80 % yield of product when ultrasonication was employed.[23]

Yamana[24] reported the first synthesis of 2,2-difluoro enol silyl ethers from chloro difluoromethyl ketones by reaction with zinc dust and chlorotrimethylsilane in anhydrous acetonitrile at 60 ºC. Yields obtained varied from moderate to good (35-74 %). However, Kitagawa found that though silyl enolates generated from halodifluoroketones could be isolated, those generated from halodifluoroesters[25] were found to be unstable and subsequently were reacted *in situ* with the zinc dihalide acting as a Lewis acid. The use of silylenol ethers as intermediates was found to improve the stereoselectivity of the reaction. Generally, Reformatsky reactions preferentially yield the syn product with α-alkyloximes and α-aminoaldehydes and the anti product with α-hydroxyaldehydes (Scheme 5.2).



Scheme 5.2 *General reactions of silyl enolates*

The first enantioselective Reformatsky reaction was reported in 1995 by Braun. Benzaldehyde was reacted with methyl bromodifluoroacetate in the presence of chiral-β-amino alcohols, affording the desired product in 61 % yield and 84 % *ee*.[26]

The versatility of Reformatsky reactions has enabled its use to form general synthons for further functionalisation,[27, 28] in addition to the preparation of difluoromethylene analogues of amino acids for the incorporation into peptides.[29] Two significant examples being potent HIV protease inhibitors[30] and renin inhibitors[31] both prepared under standard unactivated conditions.

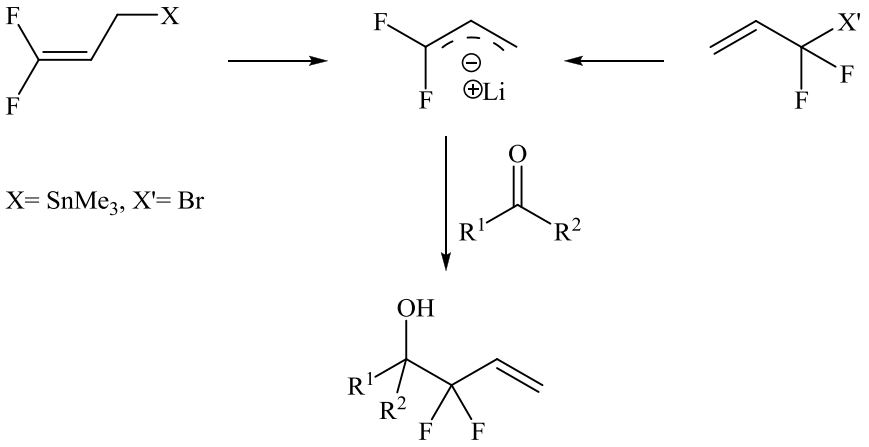
5.1.2 Difluoroallyl anions

Difluoroallyl anions are versatile synthons for the synthesis of *gem*-difluorinated molecules. In 1979 Seyferth[32] reported the synthesis of difluoroallyllithium by transmetallation of *gem*-difluoroallyl stannane with *n*-butyl lithium. However, it was found to be unstable in solution even at -95 ºC (Scheme 5.3).

$$Me_3SnCH_2CH{=}CF_2 \quad + \quad n\text{-BuLi} \xrightarrow[-95\ ^oC]{THF} Li[CF_2CHCH_2] \quad + \quad n\text{-}C_4H_9SnMe_3$$

Scheme 5.3 *Synthesis of difluoroallyllithium*

Therefore, 3-bromo-3,3-difluoropropene was utilised as an alternate precursor of *gem* (difluoroallyl) lithium. It was postulated that the $CH_2{=}CHCF_2Br$/*n*-BuLi reaction would proceed at a rate comparable to or even faster than the addition of *n*-BuLi to the carbonyl substrate when an *in situ* procedure is used. The $CH_2{=}CHCF_2Br$/*n*-BuLi reaction was conducted in a 5:1:1 mixture of THF/Et_2O/pentane at -95 ºC under a nitrogen atmosphere in the presence of an excess of triorganosilane with good yields of the desired $R_3SiCF_2CH{=}CH_2$ obtained (27-74 %). Whereas previously with $Me_3SnCH_2CH{=}CF_2$/*n*-BuLi, the difluoroallyl lithium was generated by reaction at the CH_2 terminus, in $CH_2{=}CHCF_2Br$/*n*-BuLi difluoroallyl lithium is generated by reaction at the CF_2 terminus (Scheme 5.4). However, in both cases the same intermediate is formed.



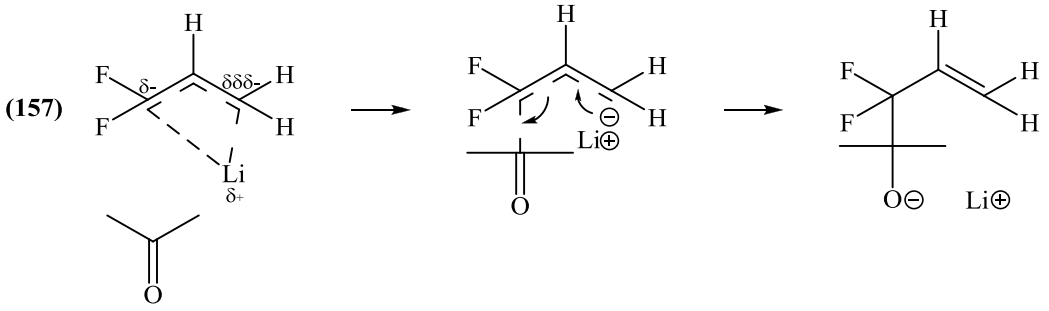
Scheme 5.4 *Formation and reaction of difluoroallyllithium*

The *in situ* Li-halogen exchange route to *gem*-(difluoroallyl) lithium, allowed the difluoroallylation of aldehydes, ketones, diallylketones and an alkyl aryl ketone (Table 5.1). It was, however, noted that when substrates with more reactive carbonyls were used such as acrolein and benzaldehyde, competing *n*-BuLi addition became more of an issue. Allylation of esters was also conducted successfully affording difluoroallyl ketones in good yields.

Reactant	Product	Yield (%)
Me_3SiCl	$Me_3SiCF_2CH=CH_2$	27
Et_3SiCl	$Et_3SiCF_2CH=CH_2$	51
n-Pr_3SiCl	*n*-$Pr_3SiCF_2CH=CH_2$	50
$PhMe_2SiCl$	$PhMe_2SiCF_2CH=CH_2$	71
Me_2SiCl_2	$Me_2Si(CF_2CH=CH_2)_2$	74
n-$C_4H_9CH=O$	*n*-$C_4H_9CH(OH)CF_2CH=CH_2$	87
$(CH_3)_3CCH=O$	$(CH_3)_3CCH(OH)CF_2CH=CH_2$	95
$CH_2=CH-CH=O$	$CH_2=CHCH(OH)CF_2CH=CH_2$ ($CH_2=CHCH(OH)C_4H_9$-*n*)	20 (51)
PhCH=O	$PhCH(OH)CF_2CH=CH_2$ ($PhCH(OH)(CH_2)_3CH_3$)	15 (78)
$(CH_3)_2C=O$	$(CH_3)_2C(OH)CF_2CH=CH_2$	42
$(C_2H_5)C=O$	$(C_2H_5)C(OH)CF_2CH=CH_2$	70
$C_5H_{10}C=O$	$(C_5H_{10})C(OH)CF_2CH=CH_2$	59
$PhC(O)CH_3$	$PhC(CH_3)(OH)CF_2CH=CH_2$	73
$ClCH_2CO_2Me$	$ClCH_2C(O)CF_2CH=CH_2$	95
$(CH_3)_2CHCO_2Me$	$(CH_3)_2CHC(O)CF_2CH=CH_2$	62
$(CH_3)_3CCO_2Me$	$(CH_3)_3CC(O)CF_2CH=CH_2$	49

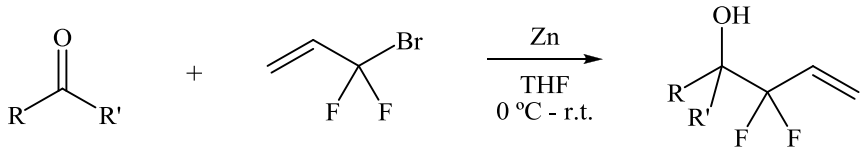
Table 5.1 *Reactions of in situ generated gem-(difluoroallyl) lithium*

Gem(difluoroallyl) lithium in solution is best described by **(157)**. The inductive effect of the fluorine substituents is expected to stabilise the carbanion centre, however, this effect is cancelled by destabilising repulsion between the lone pair of electrons on fluorine substituents and electrons in the carbanion orbital. Therefore, a possible mechanistic pathway for the reaction of *gem*-(difluoroallyl) lithium with a carbonyl is illustrated in Scheme 5.5. Allylic lithium reagents exist in ether solvents in tight ion pairs. Where there is a considerable covalent bonding contribution lithium is expected to coordinate at the site of greatest negative charge thereby blocking the CH_2 terminus from attack by electrophiles.



Scheme 5.5 *Mechanistic pathway for the reaction of gem-(difluoroallyl) lithium with a carbonyl*

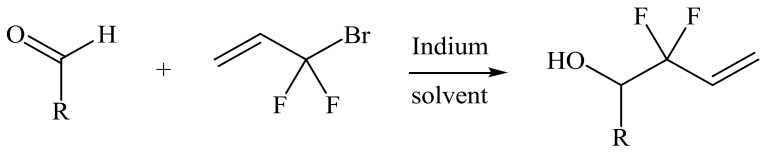
Following on from Seyferth's work, Burton[33, 34] developed a route to the direct allylation of aldehydes and ketones *via* the *in situ* reaction of 3-bromo-3,3-difluoropropene with acid washed zinc powder and carbonyl substrates. This method circumvented issues such as the use of thermally unstable intermediates as well as competitive reactions of the carbonyl substrates with *n*-butyllithium. Products were obtained in moderate to good yields (45-73 %) (Table 5.2).



R	R'	Product	Yield (%)
C_6H_5	H	$C_6H_5CH(OH)CF_2CH{=}CH_2$	67
n-C_6H_{13}	H	*n*-$C_6H_{13}CH(OH)CF_2CH{=}CH_2$	53
n-C_5H_{11}	H	*n*-$C_5H_{11}CH(OH)CF_2CH{=}CH_2$	47
C_6H_5CHMe	H	$C_6H_5CHMeCH(OH)CF_2CH{=}CH_2$	47
i-Bu	Me	*i*-$BuC(OH)(Me)CF_2CH{=}CH_2$	55
C_6H_5	Me	$C_6H_5C(OH)(Me)CF_2CH{=}CH_2$	45
C_6H_5	CF_3	$C_6H_5C(OH)(CF_3)CF_2CH{=}CH_2$	73
p-MeC_6H_4	CF_3	*p*-$MeC_6H_4C(OH)\ (CF_3)CF_2CH{=}CH_2$	69

Table 5.2 *Reactions of aldehydes and ketones with Zn activated 3-bromo-3,3-difluoropropene*

Subsequently, Kirihara found that *gem*-difluoroallylindium generated from 3-bromo-3,3-difluoropropene and indium reacted with aldehydes affording *gem*-difluorohomoallyl alcohols in excellent yields under mild conditions (Table 5.3).[35]



Scheme 5.6 *Reaction of aldehydes with 3-bromo-3,3-difluoropropene and indium*

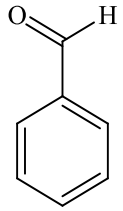
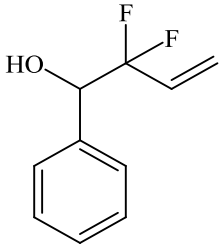
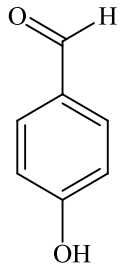
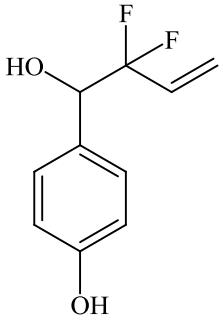
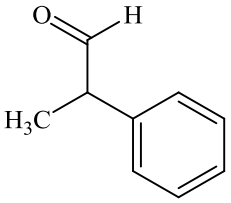
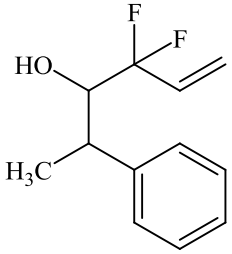
Aldehyde	Product	Solvent	Yield (%)
		H_2O DMF THF	100 99 33
		DMF	97
		DMF	87

Table 5.3 *Yields obtained by Kirihara*

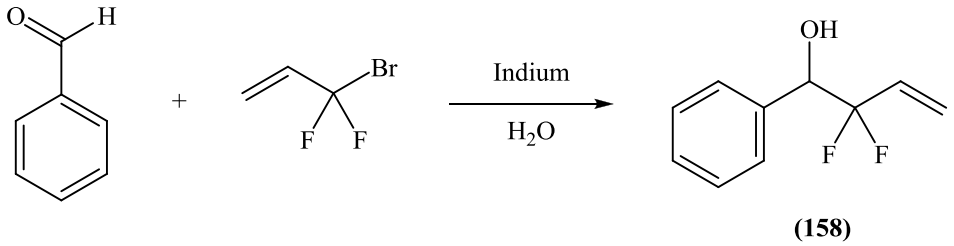
More recently, Percy[36] has also reacted 3-bromo-3,3-difluoropropene with various aldehydes in the presence of indium powder. However, when similar reaction conditions were applied to those of Kirihara, the method failed to work with stirring alone. Percy subsequently showed that when the reaction mixture was sonicated the desired products could be obtained although not in the high yields claimed by Kirihara.[35]

5.2 Results and Discussion

5.2.1 Synthesis of 2,2-difluoro-1-phenylbut-3-en-1-ol (158)

The synthesis of 2,2-difluoro-1-phenylbut-3-en-1-ol **(158)** was initially conducted following the method outlined by Percy but with the solvent used by Kirihara. A mixture of

benzaldehyde, 3-bromo-3,3-difluoropropene, indium and water were sonicated at room temperature for 3 hours, after which work up of the mixture and analysis of the crude reaction mixture by ^{1}H and ^{19}F NMR spectroscopy confirmed that the desired product had formed. In particular, ^{19}F NMR spectroscopy revealed a diagnostic AB pattern characteristic of diastereotopic fluorine atoms in the product. However, the presence of benzoic acid was also observed. The crude mixture was purified by column chromatography [diethyl ether: petroleum ether (15:85)] and the product isolated in a moderate 54 % yield, in keeping with the yield obtained by Percy. In a series of experiments, the reaction conditions were varied in an attempt to reproduce the excellent yields claimed by Kirihara. Using the molar ratio of reagents, indium: 3-bromo-3,3-difluoropropene: benzaldehyde [(2):(2):(1)], the desired product was afforded in an excellent 99 % yield after purification by column chromatography using the solvent system [diethyl ether: petroleum ether (15:85)].



Scheme 5.7 *Synthesis of* ***(158)***

Kirihara postulated that there may be two possible mechanistic pathways by which the reaction was proceeding. Firstly through a sesqui(difluoroallyl) indium (III) sesqui bromide species, or secondly by formation of difluoroallyl indium (I). In the former, nucleophilic addition of 3-bromo-3,3-difluoropropene occurs across the indium, whilst in the latter case a transmetallation reaction occurs to afford the desired product.

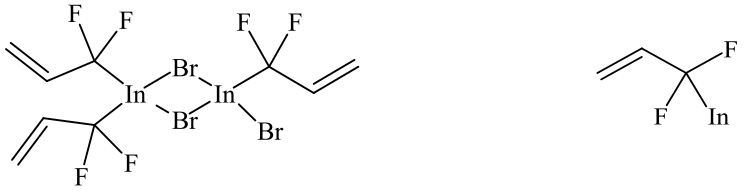
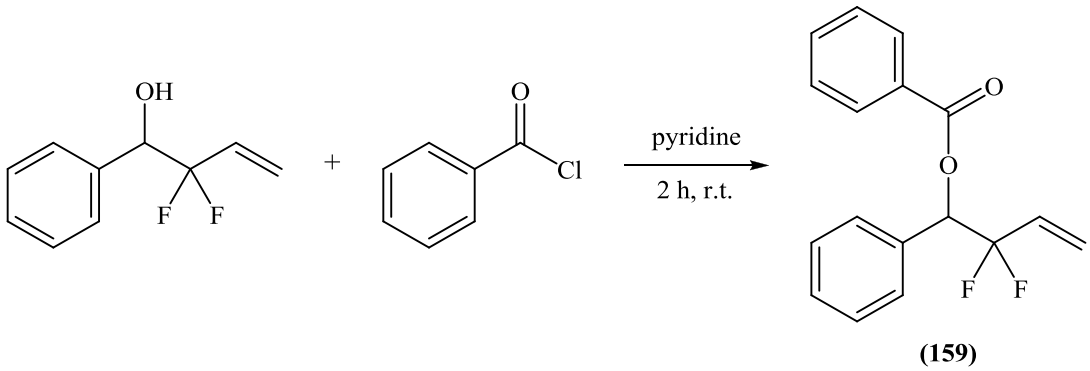


Figure 5.1 *Sesqui(difluoroallyl)indium(III) sesquibromide and Difluoroallylindium (I)*

5.2.2 Synthesis of difluoroallylic esters

Once the reaction conditions for the synthesis of **(158)** had been optimised and a substantial amount of **(158)** had been formed it was reacted further to form difluoroallylic esters using the method outlined by Nakamura.[37] The product **(159)** was synthesised by charging a reaction flask with **(158)** and pyridine and cooling to 0 ºC, after which benzoyl chloride was added and the reaction mixture warmed to room temperature and stirred for 2 hours.

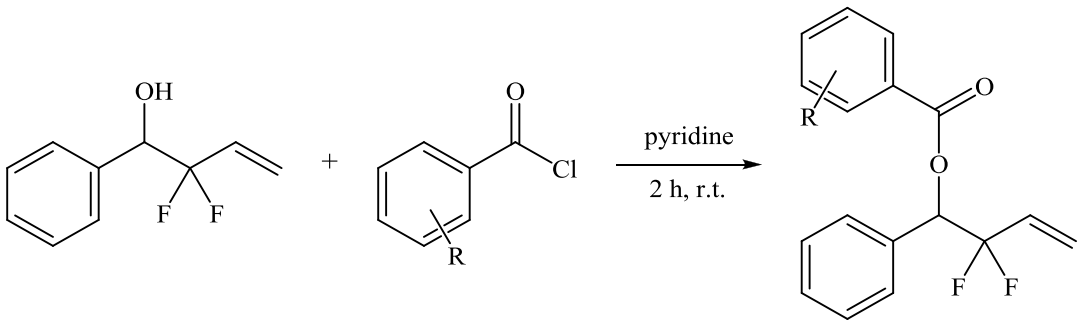
Workup of the reaction followed by drying over magnesium sulphate and removal of the solvent *in vacuo* afforded the crude product, which was purified by column chromatography. Initially [ethyl acetate: hexane (50:50)] was used as the solvent system but was unsuccessful in separating the product from benzoyl chloride which was used in excess. Therefore, [chloroform: hexane (50:50)] was used and the desired product isolated in 27 % yield.



(159)

Scheme 5.8 *Synthesis of 2,2-difluoro-1-phenylbut-3-enyl benzoate **(159)***

The same procedure was employed in the synthesis of **(160)**, where 4-fluorobenzoyl chloride was used, the reaction was conducted in the same manner and the product was isolated in a moderate 43 % yield. Further reactions were conducted in order to synthesise more difluoroallylic esters which were derivatised on the benzyl ring with isolated yields of the desired products ranging from 22 – 55 %. However, whereas in the synthesis of **(159)** and **(160)** the reaction mixture was warmed to room temperature after the addition of the benzoyl chloride, in the subsequent syntheses of **(161)** and **(162)**, the reaction mixture was maintained at 0 ºC for 4 hours. After which the crude reaction mixture underwent workup and purification by column chromatography. **(163)** and **(164)** were formed in the same way as **(160)**, however, the reaction mixture was stirred at room temperature for 4 hours instead of 2 hours to ensure that the product formed in good conversion. Column chromatography was carried out on the crude reaction mixture using [chloroform: hexane (30:70)], affording the desired products in 34 % and 20 % isolated yields respectively.



Scheme 5.9 *General reaction scheme for the synthesis of difluoroallyl esters (For a definition of R see Table 5.4)*

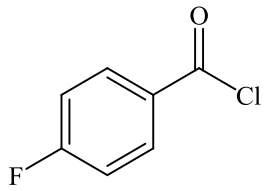
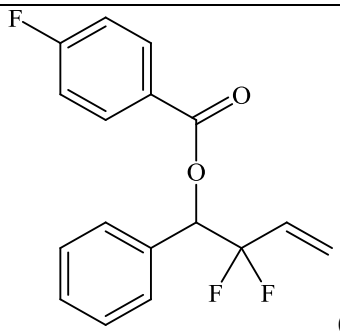
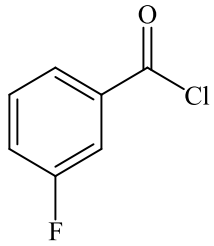
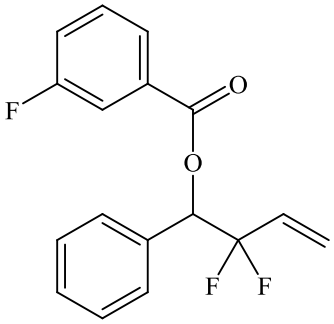
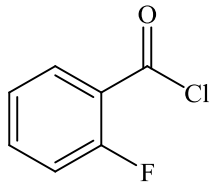
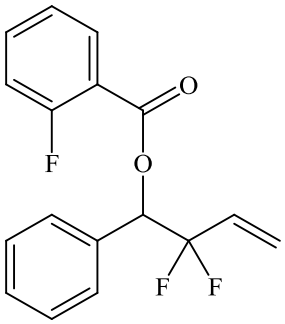
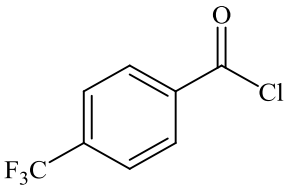
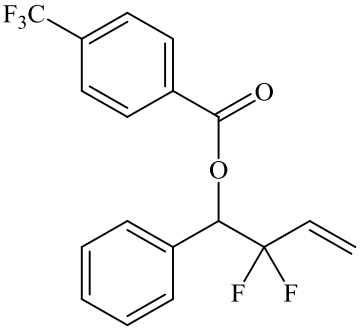
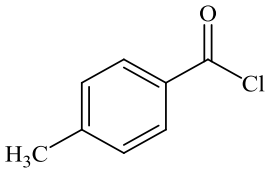
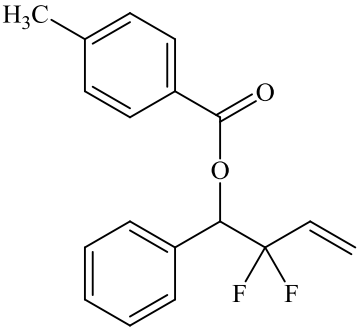
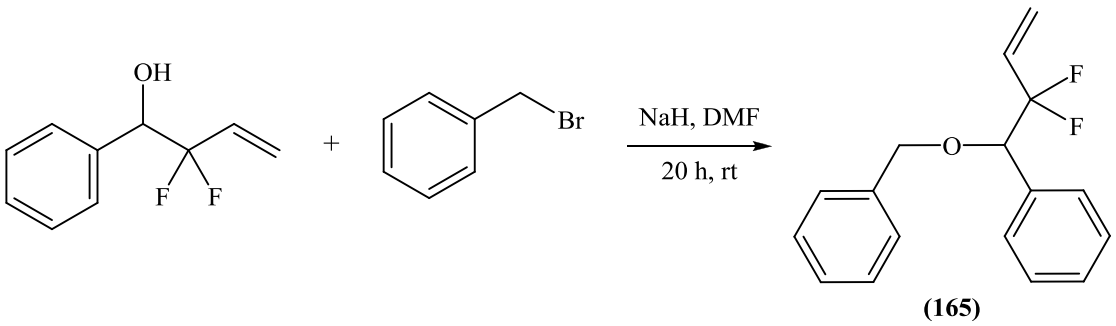
Starting Substrate	Reaction Conditions	Product	Yield (%)
 **(76)**	Stir for 2 h r.t	 **(160)**	43
 **(77)**	Stir for 4 h 0 ºC	 **(161)**	37
 **(78)**	Stir for 4 h 0 ºC	 **(162)**	55
 **(79)**	Stir for 4 h r.t	 **(163)**	34
 **(80)**	Stir for 4 h r.t	 **(164)**	20

Table 5.4 *Yields obtained of* ***(160) – (164)***



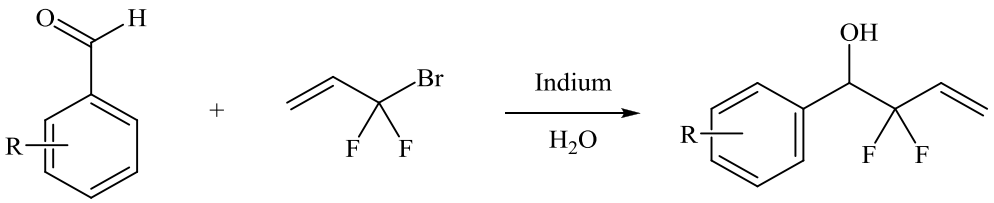
(165)

Scheme 5.10 *Synthesis of* ***(165)***

2,2-difluoro-1-phenylbut-3-en-1-ol **(158)** was also employed in the synthesis of the corresponding ether. Initially the method outlined by Elshani[38] was used, however, analysis of the crude reaction mixture by ^{1}H and ^{19}F NMR spectroscopy showed no desired product had formed therefore the protocol by Wu[39] was adopted. A suspension of NaH in anhydrous DMF was stirred at 0 ºC, and a solution of 2,2-difluoro-1-phenylbut-3-en-1-ol in DMF was added to the reaction mixture dropwise. The mixture was stirred at room temperature for 1 hour, after which benzyl bromide was added and the reaction mixture stirred for a further 20 hours. After workup, drying over magnesium sulphate and removal of the solvent *in vacuo* the crude product was purified by column chromatography [hexane: chloroform (50:50)], affording the desired product **(165)** in a low 15 % yield. However, once again the use of DMF as a solvent meant that its subsequent removal at the end of the reaction was difficult and, therefore, may have attributed to the low yield of product obtained.

5.2.3 Synthesis of Derivatised Difluoro phenyl alcohols

Kirihara's protocol was also extended to the synthesis of difluorophenyl alcohols which were derivatised on the ring. This was accomplished by reacting substituted benzaldehydes with 3-bromo-3,3-difluoropropene and indium in water. All compounds were successfully synthesised and purified by column chromatography both **(166)** and **(167)** were purified using the solvent system [hexane: ethyl acetate (80:20)] affording the desired product in moderate yields (Table 5.5). Whilst **(168)** was purified using [hexane: ethyl acetate (90:10)], and **(169)** needed no further purification as the starting material 2,3,4,5,6-penta fluorobenzaldehyde was fully converted to the corresponding product **(167)**, which was obtained as a white solid in excellent yield.



Scheme 5.11 *Reaction scheme for the synthesis of derivatised difluorophenyl alcohols (For a definition of R see Table 122)*

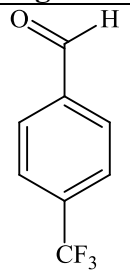
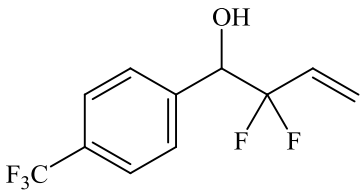
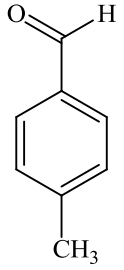
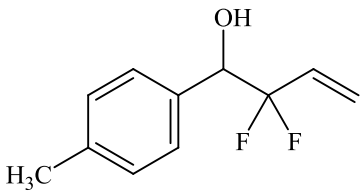
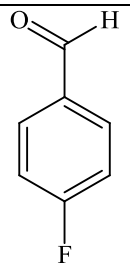
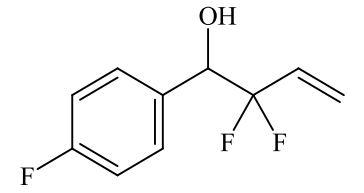
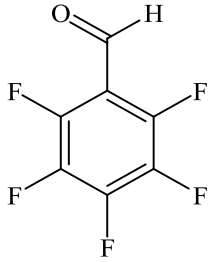
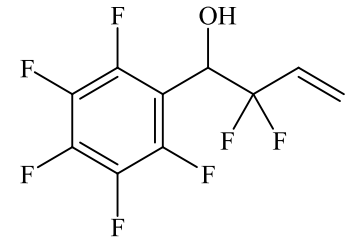
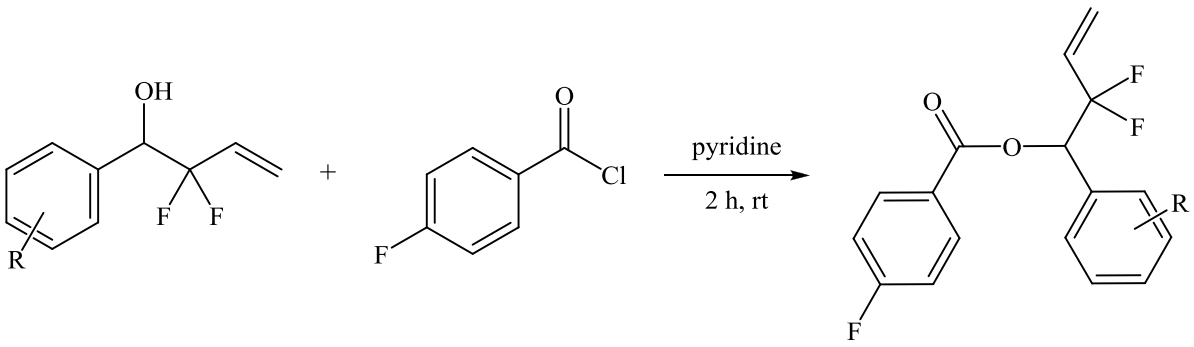
Starting Substrate	Product	Yield (%)
	 **(166)**	30
	 **(167)**	18
	 **(168)**	41
	 **(169)**	95

Table 5.5 *Summary of yields obtained in synthesis of derivatised difluorophenyl alcohols*

The novel derivatised difluoro phenyl alcohols **(166)** - **(169)** were then reacted further utilising the protocol by Nakamura.[37] 2,2-difluoro-1-*p*-tolylbut-3-en-1-ol **(167)** was stirred with pyridine and cooled to 0 ºC, followed by the addition of 4-fluorobenzoyl chloride, the reaction mixture was then warmed to room temperature and stirred for 2 hours. After work up the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the desired product in 18 % yield. The reactions of **(166)**, **(168)** and **(169)** were conducted in the same way affording substantially better yields of the desired benzoyl protected alcohols (see Table 5.6).



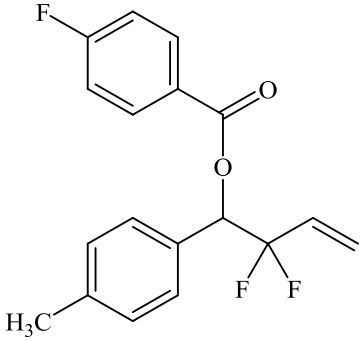
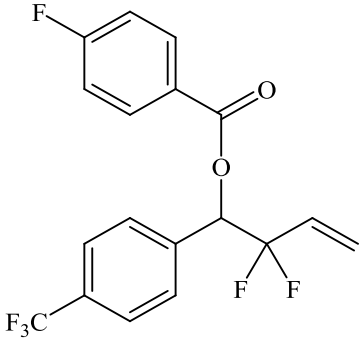
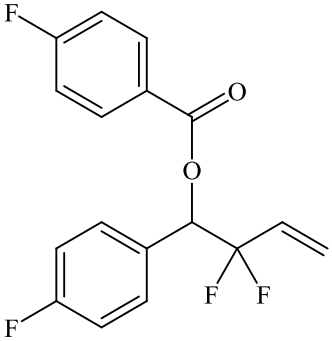
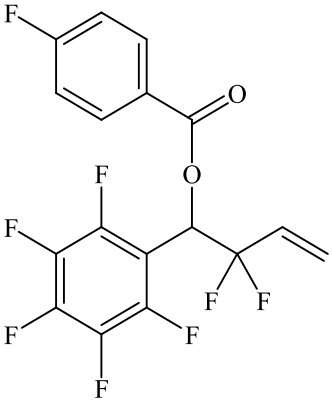
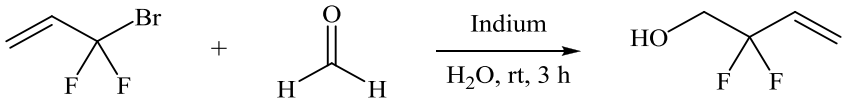
Starting Substrate	Product	Yield (%)
(167)	 **(170)**	18
(166)	 **(171)**	63
(168)	 **(172)**	60
(169)	 **(173)**	95

Table 5.6 *Yields obtained of* ***(170) – (173)***

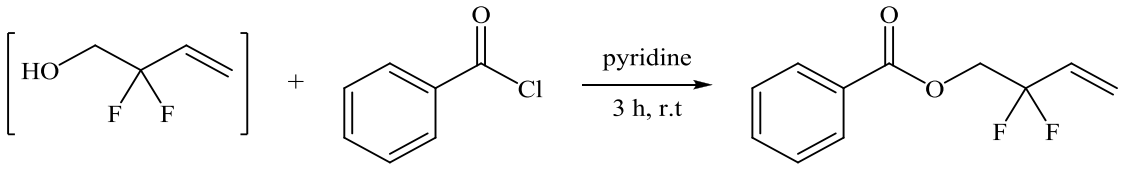
5.2.4 Synthesis of Allylic Difluorides

In order to form the direct difluoro analogues of the allylic fluorides synthesised in Chapter Two, 3-bromo-3,3-difluorpropene was added to a mixture of formaldehyde and indium in water and sonicated for 3 hours, work up of the reaction mixture, followed by drying over magnesium sulphate and removal of the solvent *in vacuo* afforded the crude reaction mixture which was analysed by ^{1}H and ^{19}F NMR spectroscopy. However, both exhibited clearly that no product **(174)** was present. Therefore, it was postulated that due to the low molecular weight of the product forming, as with the starting material 3-bromo-3,3-difluoropropene which is extremely volatile, the desired product may have been lost during the removal of solvent *in vacuo* if it had indeed been formed.



Scheme 5.12 *Attempted synthesis of* ***(174)***

Hence, to circumvent this problem the reaction was repeated, however, after the work up and drying over magnesium sulphate the DCM solution with product was reacted further with benzoyl chloride and pyridine in order to form **(175)**. In the reaction pyridine is acting as a base and no solvent is required therefore, the presence of DCM was unlikely to hinder the reaction. After the reaction mixture of benzoyl chloride, pyridine and DCM product had stirred at room temperature for 3 hours, work up, drying over magnesium sulphate and removal of solvent *in vacuo* afforded the crude product, which when analysed by ^{1}H and ^{19}F NMR spectroscopy revealing the desired product to be present. Purification by column chromatography [chloroform: hexane (50:50] afforded the product in an excellent 86 % isolated yield.

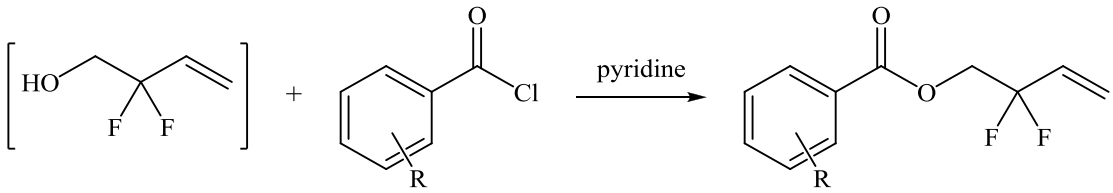


(175)

Scheme 5.13 *Synthesis of* ***(175)***

The same methodology was then extended to the reactions of derivatised benzoyl chlorides with the DCM solution of 2,2-difluorobut-3-en-1-ol. The desired products were obtained in moderate yields (11-36 %). With the exception of 4-(trifluoromethyl)benzoyl chloride which did not undergo any reaction, this could be attributable to the CF_3 group being too

electron withdrawing in comparison to the presence of a single fluorine atom on the ring. These novel allylic difluoride compounds contained equivalent fluorine atoms, and therefore a single peak was present in the ^{19}F NMR spectrum at *ca.* -105.7 ppm.



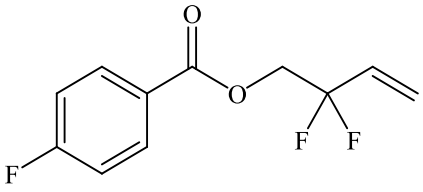
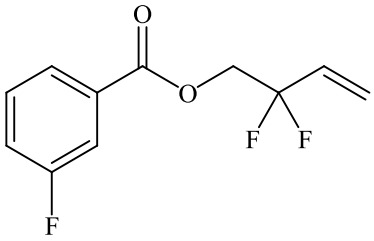
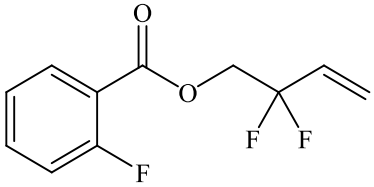
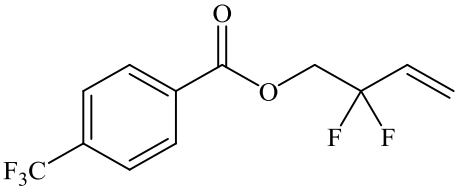
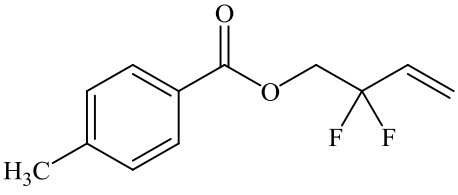
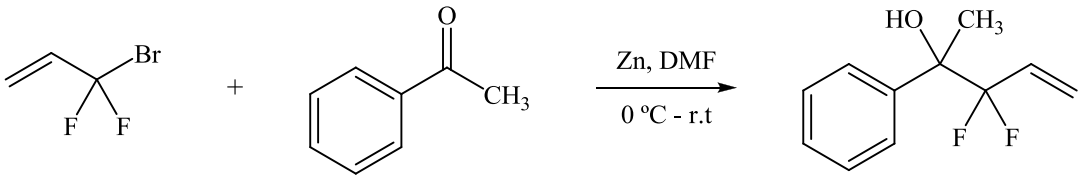
Starting Substrate	Reaction Conditions	Product	Yield (%)
(76)	Stir for 3 h 0 ºC	 **(176)**	28
(77)	Stir for 3 h 0 ºC	 **(177)**	36
(78)	Stir for 3 h 0 ºC	 **(178)**	25
(79)	Stir for 3 h r.t	 **(179)**	0
(80)	Stir for 3 h r.t	 **(180)**	11

Table 5.7 *Yields obtained of* ***(176) – (180)***

5.2.5 Metal-mediated synthesis of 3,3-difluoro-2-phenylpent-4-en-2-ol (181)

After the successful synthesis of several novel difluoro compounds derived from aldehydes, the reaction of acetophenone with 3-bromo-3,3-difluoropropene was examined. Previously acetophenone has been successfully reacted with 3-bromo-3,3-difluoropropene in zinc mediated reactions, however, there were no reports in the literature where indium has successfully been used to catalyse the reaction. Therefore, a flask was charged with acetophenone, 3-bromo-3,3-difluoropropene, indium and water and the reaction mixture was sonicated for 24 hours, however, work up and analysis of the crude reaction mixture by ^{1}H and ^{19}F NMR spectroscopy showed that no product was present. This agreed with the report of Kirihara where it had been stated that when catalysed by indium no reaction occurred and that if a compound had both aldehyde and ketone functionalities, the reaction would occur at the carbonyl of the aldehyde preferentially. Hence, the reaction was repeated using the method outlined by Burton, acid washed zinc powder, acetophenone and DMF were cooled to 0 ºC, whilst a solution of 3-bromo-3,3-difluoropropene in THF was added dropwise, the reaction mixture was then warmed to room temperature and stirred overnight, after which workup, drying over magnesium sulphate and removal of solvent *in vacuo* afforded the crude product. However, ^{1}H and ^{19}F NMR spectroscopy demonstrated that only 4 % conversion to product had occurred, analysis by TLC also showed that the product and starting material had very similar R_f values and, therefore, would be difficult to separate even after trying several different solvent systems.



(181)

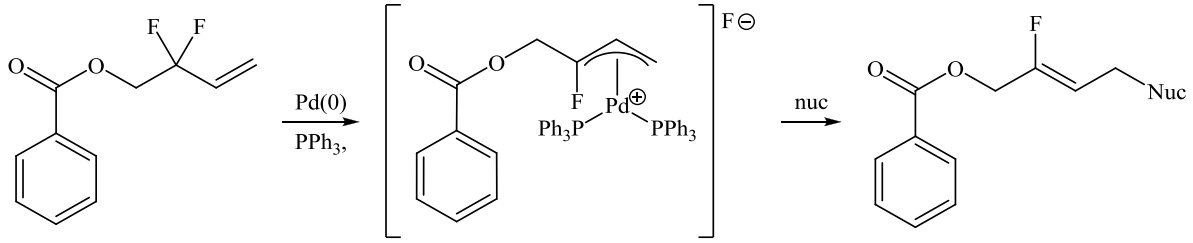
Scheme 5.14 *Synthesis of* ***(181)***

The reaction was then repeated however, THF was used as the solvent. After stirring the reaction mixture overnight a small aliquot was analysed by ^{1}H and ^{19}F NMR spectroscopy which exhibited that once again only a small amount of product had formed, therefore, the reaction mixture was heated to 45 ºC for 24 h. After which another aliquot was removed from the reaction mixture and analysed exhibiting that 10 % conversion to product had occurred. Therefore, in order to further encourage the formation of desired product the reaction mixture was sonicated for 60 h, after which workup, drying over magnesium sulphate and removal of solvent *in vacuo* afforded the crude product. ^{1}H and ^{19}F NMR spectroscopy of the crude product exhibited 20 % conversion to desired product, which is lower than the 45 % reported by Burton.

5.2.6 Reactions of Difluoroallylic Products with Palladium (0)

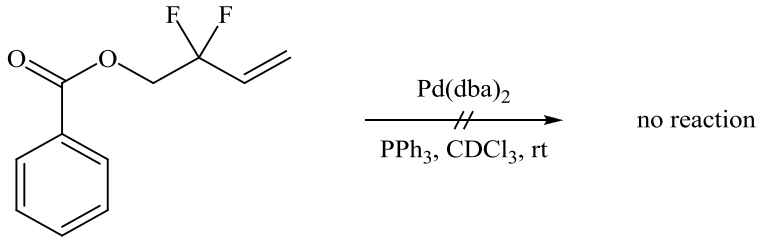
Having synthesised a small library of allylic difluorides, analogous to the allylic fluorides synthesised in Chapter Two, further reactions were conducted in order to establish whether these allylic difluorides and the starting material, 3-bromo-3,3-difluoropropene could oxidatively add to Pd(0) complexes.

In Chapter Three, C-F activation of allylic fluorides was observed with Pd(0) in the presence of PPh_3, these Pd cationic complexes were successfully reacted with nucleophiles in Chapter Four giving rise to a non-fluorinated product. Therefore, activation of an allylic difluoride by Pd(0), followed by subsequent reaction with a nucleophile could lead to fluoroalkenes (Scheme 5.15).



Scheme 5.15 *Proposed reaction scheme*

Therefore, the oxidative addition of the allylic difluorides with Pd(0) was conducted by reacting 2,2-difluorobut-3-enyl benzoate with $Pd(dba)_2$ and PPh_3 in $CDCl_3$, the reaction was monitored by ^1H and ^{19}F NMR spectroscopy, however, no reaction was observed. Therefore, the reaction mixture was heated to reflux overnight in order to initiate a reaction, but with no success.

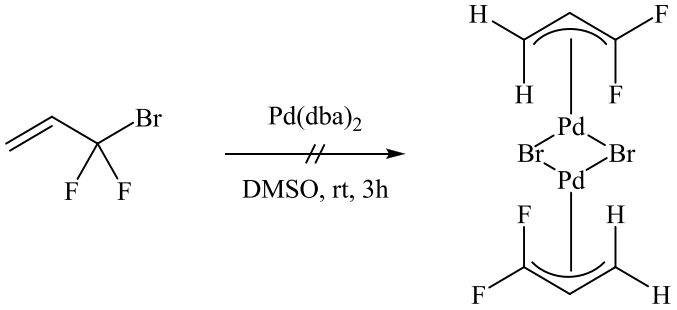


Scheme 5.16 *Reaction of 2,2-difluorobut-3-enyl benzoate with $Pd(dba)_2$*

The reaction was repeated but this time with $Pd(PPh_3)_4$ as the source of Pd(0), however, this also only exhibited 2,2-difluorobut-3-enyl benzoate **(175)** starting material, when analysed by ^1H and ^{19}F NMR spectroscopy. Conducting the reaction with $Pd(PPh_3)_4$ and the nucleophile sodium dimethyl malonante also failed to activate the C-F bond and form the corresponding fluoroalkene. Therefore, these experiments indicate that in Narumi's Pd catalysed activation of allylic difluorides, the Ph_3SiH is a key component in the activation

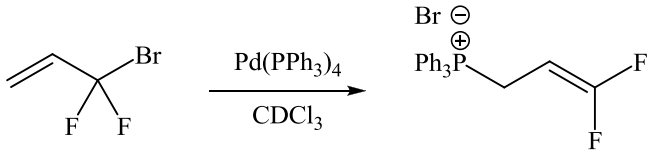
process.[40] Unfortunately, time did not allow to employ the reaction conditions reported by Narumi in the activation of the allylic difluorides synthesised in this thesis.

During the course of this work efforts were also concentrated on the oxidative addition of 3-bromo-3,3-difluoropropene with $Pd(dba)_2$ in DMSO, using the same conditions employed for the successful synthesis of the palladium chloride dimers (Scheme 5.17). However, in this reaction no product was obtained.



Scheme 5.17 *Reaction of 3-bromo-3,3-difluoropropene) with $Pd(dba)_2$*

In contrast, 3-bromo-3,3-difluoropropene did react with $Pd(PPh_3)_4$ in deuterated chloroform and the reaction was monitored by ^1H and ^{19}F NMR spectroscopy.



Scheme 5.18 *Synthesis of 3,3-difluoroallyltriphenylphosphonium bromide **(182)***

An instantaneous reaction to form 3,3-difluoroallyltriphenylphosphonium bromide **(182)** was observed. Burton had previously reported the synthesis of **(182)** by heating 3-bromo-3,3-difluoropropene with PPh_3 in benzene at 70 ºC in a sealed tube for 3 hours.[41] Therefore, the instantaneous reaction observed in this case is a result of the $Pd(PPh_3)_4$ catalysing the reaction. Indeed, 3-bromo-3,3-difluoropropene does not react with PPh_3 in the absence of $Pd(PPh_3)_4$ unless the mixture is heated to high temperatures in agreement with Burton's observations. The progress of the reaction was monitored by mass spectrometry in an attempt to demonstrate the intermediacy of a Pd(II) species. The cationic intermediate was observed at 707 $[M]^+$ a characteristic Pd isotope pattern was seen in the spectra which concurred with the predicted simulation (Figure 5.3). Therefore the final product is likely to be formed *via* attack of PPh_3, a reagent not known for its high nucleophilicity, at this Pd-activated intermediate.

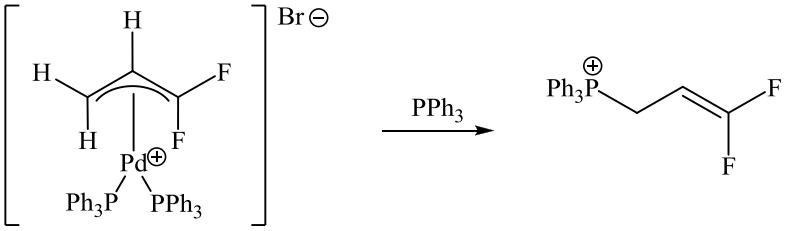


Figure 5.2 *Cationic intermediate species formed*

When the reaction was repeated with 50 mol % $Pd(dba)_2$ and PPh_3 (1 equivalent), the expected product, 3,3-difluoroallyltriphenylphosphonium bromide **(182)** was formed, however, the staring material was not fully consumed.

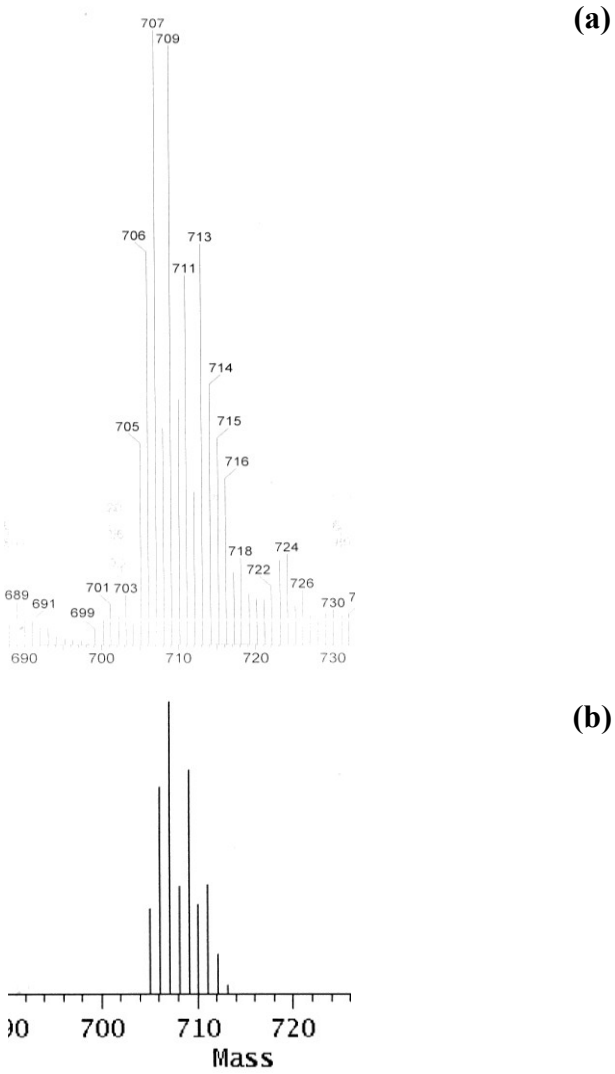
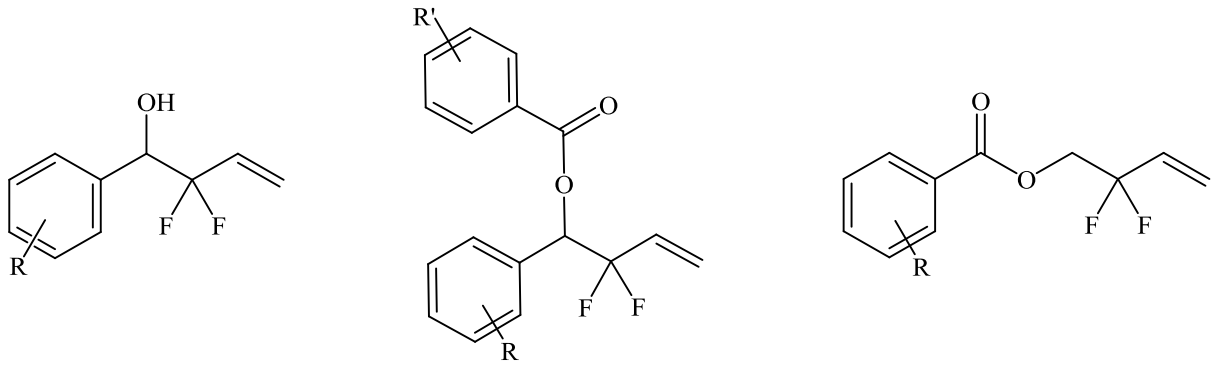


Figure 5.3 *Mass Spectra of cationic intermediate, observed* ***(a)*** *and predicted* ***(b)***

5.3 Conclusions

Following Kirihara's protocol 2,2-difluoro-1-phenylbut-3-en-1-ol **(158)** was successfully synthesised in 99 % yield, it was then utilised by reacting with derivatised benzoyl chlorides to synthesise a series of novel difluoroesters **(159)**, **(160)**, **(161)**, **(162)**, **(163)** and **(164)**. All

compounds were purified successfully by column chromatography. Their structures were determined by NMR spectroscopy and mass spectrometry. A series of novel derivatised difluoro phenyl alcohols **(166)**, **(167)**, **(168)** and **(169)**, were synthesised by reacting derivatised benzaldehydes with 3-bromo-3,3-difluoropropene in the presence of indium. These were then reacted further with 4-fluorobenzoyl chloride to form the corresponding difluoroesters **(170)**, **(171)**, **(173)** and **(173)**. The novel allylic difluorides **(175)**, **(176)**, **(177)**, **(178)** and **(180)** were synthesised by reaction of 2,2-difluorobut-3-en-1-ol in DCM solution with derivatised benzoyl chlorides. Attempts to activate these difluoroallyls with Pd(0) were unsuccessful, whilst the intermediate formed by the reaction of 3-bromo-3,3-difluoropropene with $Pd(PPh_3)_4$ was so reactive, almost instantaneous decomposition to a known phosphonium salt occurred.



(168) R= 4-F	**(159)** R= H	R'= H	**(175)** R= H
(166) R= CF_3	**(160)** R= H	R'= 4-F	**(176)** R= 4-F
(167) R= CH_3	**(161)** R= H	R'= 3-F	**(177)** R= 3-F
(169) R= (2,3,4,5,6)-F	**(162)** R= H	R'= 2-F	**(178)** R= 2-F
	(163) R= H	R'= CF_3	**(180)** R= CH_3
	(164) R= H	R'= CH_3	
	(170) R= CH_3	R'= 4-F	
	(172) R= 4-F	R'= 4-F	
	(171) R= CF_3	R'= 4-F	
	(173) R= (2,3,4,5,6)-F	R'= 4-F	

Figure 5.4 *Novel compounds synthesised in Chapter Five*

5.4 References

[1] M. J. Tozer, T. F. Herpin, *Tetrahedron* **1996**, *52*, 8619.

[2] S.-H. An, M. Bobek, *Tetrahedron Lett.* **1986**, *27*, 3219.

[3] W. J. Middleton, E. M. Bingham, *J. Org. Chem.* **1980**, *45*, 2883.

[4] S. Stavber, Z. Koren, M. Zupan, *Synlett* **1994**, 265.

[5] A. J. Bloodworth, K. J. Bowyer, J. C. Mitchell, *Tetrahedron Lett.* **1987**, *28*, 5347.

[6] J. P. Praly, G. Descotes, *Tetrahedron Lett.* **1987**, *28*, 1405.

[7] R. E. Banks, N. J. Lawrence, A. L. Popplewell, *J. Chem. Soc., Chem. Commun.* **1994**, 343.

[8] G. Resnati, D. D. DesMarteau, *J. Org. Chem.* **1992**, *57*, 4281.

[9] W. Ying, D. D. DesMarteau, Y. Gotoh, *Tetrahedron* **1996**, *52*, 15.

[10] J. Fried, E. A. Hallman, *Tetrahedron Lett.* **1984**, *25*, 2301.

[11] T. Ishihara, M. Yamanaka, T. Ando, *Chem. Lett.* **1984**, 1165.

[12] G. Dutheuil, S. Couve-Bonnaire, X. Pannecoucke, *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 1290.

[13] T. Narumi, A. Niida, K. Tomita, S. Oishi, A. Otaka, H. Ohno, N. Fujii, *Chem. Commun.* **2006**.

[14] Y. Nakamura, M. Okada, A. Sato, H. Horikawa, M. Koura, A. Saito, T. Taguchi, *Tetrahedron* **2005**, *61*, 5741.

[15] T. Allmendinger, E. Felder, E. Hungerbuhler, *Tetrahedron Lett.* **1990**, *31*, 7301.

[16] P. Bey, J. R. McCarthy, I. A. McDonald, *ACS Symp. Ser.* **1991**, *456*, 105.

[17] O. Yokokoji, T. Shimizu, S. Kumai, *Chem. Abstr.* **1996**, *124*, 316586.

[18] M. Kuroboshi, T. Ishihara, *Tetrahedron Lett.* **1987**, *28*, 6481.

[19] M. Kuroboshi, T. Ishihara, *Bull. Chem. Soc. Jap.* **1990**, *63*, 428.

[20] R. W. Lang, B. Schaub, *Tetrahedron Lett.* **1988**, *29*, 2943.

[21] Y. Shen, M. Qi, *J. Fluorine Chem.* **1994**, *67*, 229.

[22] T. T. Curran, *J. Org. Chem.* **1993**, *58*, 229.

[23] J. M. Altenburger, D. Schirlin, *Tetrahedron Lett.* **1991**, *32*, 7255.

[24] Y. Yamana, T. Ishihara, T. Ando, *Tetrahedron Lett.* **1983**, *24*, 507.

[25] O. Kitagawa, T. Taguchi, Y. Kobayashi, *Tetrahedron Lett.* **1988**, *29*, 1803.

[26] M. Braun, A. Vonderhagen, D. Waldmuller, *Liebigs. Ann.* **1995**, 1447.

[27] T. Tsukamoto, T. Kitazume, *J. Chem. Soc., Chem. Commun.* **1992**, 540.

[28] T. Tsukamoto, T. Kitazume, *J. Chem. Soc., Perkin Trans 1* **1993**, 1177.

[29] V. P. Kukhar, V. A. Soloshonok, *Fluorine-containing Amino Acids*, Chichester, **1995**.

[30] H. L. Sham, N. E. Wideburg, S. G. Spanton, W. E. Kohlbrenner, D. A. Betebenner, D. J. Kempf, D. W. Norbeck, J. J. Plattner, J. W. Erickson, *J. Chem. Soc., Chem.Commun.* **1991**, 110.

[31] H. L. Sham, C. A. Rempel, H. Stein, J. Cohen, *J. Chem. Soc., Chem. Commun.* **1990**, 904.

[32] D. Seyferth, K. R. Wursthorn, *J. Organomet. Chem.* **1979**, *182*, 455.

[33] Z.-Y. Yang, D. J. Burton, *J. Fluorine Chem.* **1989**, *44*, 339.

[34] Z.-Y. Yang, D. J. Burton, *J. Org. Chem.* **1991**, *56*, 1037.

[35] M. Kirihara, T. Takuwa, S. Takizawa, T. Momose, H. Nemoto, *Tetrahedron* **2000**, *56*, 8275.

[36] C. Audouard, J. Fawcett, G. Griffiths, J. Percy, S. Pintat, C. Smith, *Org. Biomol. Chem.* **2004**, *2*, 528.

[37] K. Nakamura, K. Takenaka, *Tetrahedron: Asymmetry* **2002**, *13*, 415.

[38] S. Elshani, E. Kobzar, R. A. Bartsch, *Tetrahedron* **2000**, *56*, 3291.

[39] Y. Wu, J. Gao, *Org. Lett.* **2008**, *10*, 1533.

[40] T. Narumi, K. Tomita, E. Inokuchi, K. Kobayashi, S. Oishi, H. Ohno, N. Fujii, *Org. Lett.* **2007**, *9*, 3465.

[41] W. Qiu, D. J. Burton, *J. Fluorine Chem.* **1993**, *65*, 143.

CHAPTER SIX

6 Experimental Details

6.1 General Experimental Procedures

6.1.1 Nuclear Magnetic Resonance Spectroscopy

The ^{1}H, $^{19}F\{^{1}H\}$, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded on a Bruker AM 300 spectrometer, a Bruker DRX 400 spectrometer or a Bruker AV 500 spectrometer at the ambient temperature of the probe unless otherwise stated. ^{1}H and ^{13}C NMR spectra were referenced internally using the residual *protio* solvent resonance relative to $SiMe_4$ (δ = 0 ppm), whilst ^{19}F NMR were referenced to external $CFCl_3$ (δ = 0 ppm) and ^{31}P NMR spectra were referenced externally to 85 % H_3PO_4 (δ = 0 ppm). All chemical shifts are quoted in δ (ppm) and coupling constants in Hertz (Hz), using the high-frequency positive convention. Abbreviations have the usual meaning: s – singlet; d – doublet; t – triplet; q – quartet; qt – quintet; ap - apparent. The following spectrometer frequencies were used:

Bruker AM 300 Spectrometer:	^{1}H NMR spectra, 300.03 MHz,
	^{13}C NMR spectra, 75.4426 MHz,
	^{19}F NMR spectra, 282.3103 MHz,
	^{31}P NMR spectra, 121.99 MHz.
Bruker DRX 400 Spectrometer:	^{1}H NMR spectra, 400.13 MHz,
	^{13}C NMR spectra, 100.6128 MHz,
	^{19}F NMR spectra, 376.4984 MHz,
	^{31}P NMR spectra, 161.98 MHz.
Bruker AV 500 Spectrometer:	^{1}H NMR spectra, 500.13 MHz,
	^{13}C NMR spectra, 125.758 MHz.

The solvent most frequently used was deuterated chloroform ($CDCl_3$) and data are reported for samples dissolved in this solvent unless otherwise stated in the experimental data below. However, if this was not possible due to solubility issues an alternative *deutero* solvent was employed, and failing that a common laboratory solvent was used with a sealed, deuterated benzene (C_6D_6), capillary insert tube. Spectra of air-/moisture-sensitive compounds were obtained by preparing the samples under an inert atmosphere in a flush-box using dried deuterated solvents. The solutions were then loaded into either a Young's NMR tube or a Teflon-sealed screw-cap NMR tube.

6.1.2 Mass Spectrometry

Electron impact (EI) and fast atom bombardment (FAB) mass spectra were recorded on a Kratos concept 1H, double focussing forward geometry mass spectrometer. 3-Nitrobenzyl alcohol was used as the matrix for the FAB spectra. Electrospray mass spectra were obtained on a Micromass Quatro LC.

6.1.3 Infrared Analysis

Infra red spectra were recorded on a Perkin Elmer FT-IR spectrometer at 4 cm^{-1} resolution (16 scans) with a Universal ATR sampling accessory.

6.1.4 Elemental Analysis

All elemental analyses were performed by the Elemental Analysis Service at the London Metropolitan University.

6.1.5 X-ray crystallography

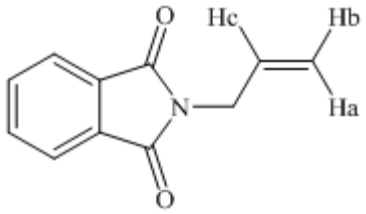
X-ray crystallography data were collected on a Bruker Apex SMART 2000 diffractometer. Crystal data and structure refinement can be found in the Appendix.

6.1.6 Starting Materials

Starting materials were used as received from Sigma Aldrich, Lancaster, Apollo, Fluorochem, ABCR, Alfa Aesar, Acros organics or Strem. Where dried solvents were necessary, dichloromethane, hexane, diethyl ether, tetrahydrofuran, and acetonitrile were distilled using an Innovative Technology Pure Solv automated still. All dried solvents were stored in sealed ampoules under an atmosphere of dry nitrogen over 4Å molecular sieves. Pyridine was refluxed over calcium hydride and distilled into a dried ampoule under nitrogen.

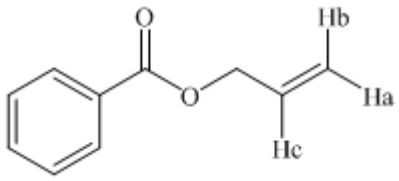
6.2 Experimental Details for Chapter 2

6.2.1 Preparation of 2-Allyl-isoindole-1,3-dione (66)[1]



The title compound was prepared following the method outlined by Abulikemu *et al.* without modification.[1] A 100 cm^3, round-bottomed flask equipped with a magnetic stirrer and condenser was charged with a solution of allyl amine (0.57 g, 10 mmol) in acetic acid (5 cm^3) and stirred. Phthalic anhydride (1.48 g, 10 mmol) was added, and the mixture was heated to reflux for 2 h. On addition of water (40 cm^3) a precipitate formed, that was filtered and dried *in vacuo* over potassium hydroxide pellets. Recrystallisation from hexane afforded the product as white needles (0.94 g, 51 %). δ_H 4.21 (2H, ap.dt, $^3J_{HH}$ = 5.6 Hz, $^4J_{HH}$ = 1.4 Hz, N-CH_2), 5.13 (1H, dd, $^3J_{HH}$ = 10.3 Hz, $^2J_{HH}$ =1.2 Hz, *Hb*), 5.18 (1H, dd, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ =1.2 Hz, *Ha*), 5.81 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 5.6 Hz, *Hc*), 7.65 (2H, dd, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 3.1 Hz, *ArH-4*) 7.79 (2H, dd, $^3J_{HH}$ = 5.4 Hz, $^4J_{HH}$ = 3.1 Hz, *ArH-5*); δ_C 39.0 (N*C*H_2), 116.6 (CH*C*H_2), 122.2 (*ArCH-4*), 130.5 (*C*HCH_2), 131.0 (*ArC-3*), 133.0 (*ArCH-5*), 166.8 (C=O).

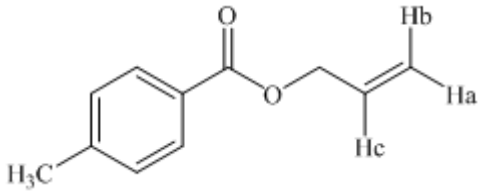
6.2.2 Preparation of Allyl Benzoate (67)[2]



The title compound was prepared following the method outlined by Yasui *et al.* without modification.[2] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with benzoyl chloride (7.73 g, 6.38 cm^3, 55 mmol) and anhydrous diethyl ether (50 cm^3). The reaction mixture was cooled to 0 °C using an ice bath. Allyl alcohol (2.90 g, 3.40 cm^3, 50 mmol) and triethylamine (5.56 g, 7.67 cm^3, 55 mmol) were added and the reaction mixture then stirred at 0 ºC for 2 h, after which it was warmed to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate (70 cm^3) and the organic layer extracted and washed successively with 2M HCl (2 x 10 cm^3), saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and solvent removed *in vacuo* to yield the product as a colourless oil (7.29 g, 90 %). δ_H 4.75 (2H, ap.dt, $^3J_{HH}$ = 5.6 Hz, $^4J_{HH}$ = 1.4 Hz, -*OCH*$_2$), 5.21 (1H, ddt, $^3J_{HH}$ = 10.4 Hz, $^2J_{HH}$ = 1.8 Hz, $^4J_{HH}$ = 1.5 Hz, *Ha*), 5.34 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = 1.8 Hz, $^4J_{HH}$ = 1.5 Hz, *Hb*), 5.97 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 5.6 Hz, *Hc*), 7.36 (2H, tm, $^3J_{HH}$ = 7.5 Hz, *ArH-3*), 7.49 (1H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-4*), 7.99 (2H, dm, $^3J_{HH}$ = 7.1 Hz, *ArH-2)*; δ_C

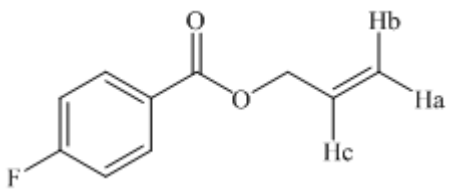
65.5 (O*CH*$_2$), 118.2 (CH*CH*$_2$), 128.4 (*ArCH-3*), 129.5 (*ArCH-2*), 130.1 (*ArC-1*), 132.2 (*ArCH-4*), 133.0 (*CH*CH$_2$), 166.2 (C=O).

6.2.3 Preparation of allyl 4-methylbenzoate (85)[3]



The title compound was prepared following the method outlined by Yasui *et al.* without modification.[2] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with *p*-toluoyl chloride (1 g, 0.86 cm^3, 6.47 mmol) and anhydrous diethyl ether (7 cm^3). The reaction mixture was cooled to 0 °C using an ice bath. Allyl alcohol (0.34 g, 0.40 cm^3, 5.89 mmol) and triethylamine (0.66 g, 0.9 cm^3, 6.47 mmol) were added and the reaction mixture then stirred at 0 ºC for 2 h, after which it was warmed to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate (10 cm^3) and the organic layer extracted and washed successively with 2M HCl (2 x 2 cm^3), saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and solvent removed *in vacuo* to provide the crude product, which was purified by column chromatography [hexane: diethyl ether (90:10)], to yield the product as a colourless oil (0.65 g, 63 %). δ_H 2.44 (3H, s, CH_3), 4.84 (2H, ap.dt, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 1.6 Hz, O-C*H*$_2$), 5.31 (1H, ddt, $^3J_{HH}$ = 10.6 Hz, $^2J_{HH}$ = 1.6 Hz, $^4J_{HH}$ = 1.2 Hz, *Ha*), 5.43 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = 1.6 Hz, $^4J_{HH}$ = 1.6 Hz, *Hb*), 6.06 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.5 Hz, *Hc*), 7.26 (2H, dm, $^3J_{HH}$ = 8.6 Hz, *ArH-3*), 7.98 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-2)*; δ_C 21.7 (CH_3), 65.4 (O*CH*$_2$), 118.1 (CH*CH*$_2$), 127.5 (*ArC-1*), 129.1 (*ArCH-3*), 129.8 (*ArCH-2*), 132.4 (*CH*CH$_2$), 143.7 (*ArC-4*), 166.3 (C=O). m/z (EI$^+$) 176 ([M]$^+$, 13 %), 119 ([M-OCH$_2$CH=CH$_2$]$^+$, 100 %). HRMS (EI) 176.08349 ($C_{11}H_{12}O_2$ requires 176.08343).

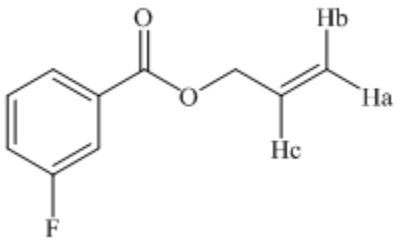
6.2.4 Preparation of allyl 4-fluorobenzoate (81)[4]



The title compound was prepared following the method outlined by Yasui *et al.* without modification.[2] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 4-fluorobenzoyl chloride

(1 g, 0.75 cm^3, 6.31 mmol) and anhydrous diethyl ether (7 cm^3). The reaction mixture was cooled to 0 °C using an ice bath. Allyl alcohol (0.33 g, 0.39 cm^3, 5.73 mmol) and triethylamine (0.64 g, 0.88 cm^3, 6.31 mmol) were added and the reaction mixture then stirred at 0 ºC 2 h, after which it was warmed to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate and the organic layer extracted and washed successively with 2M HCl (2 x 2 cm^3), saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and solvent removed *in vacuo* to provide the crude product, which was purified by column chromatography [hexane: diethyl ether (90:10)], to yield the product as a colourless oil (0.83 g, 81 %). δ_H 4.75 (2H, ap.dt, $^3J_{HH}$ = 5.8 Hz, $^4J_{HH}$ = 1.5 Hz, OC*H*$_2$), 5.23 (1H, ddt, $^3J_{HH}$ = 10.5 Hz, $^2J_{HH}$ = 1.5 Hz, $^4J_{HH}$ = 1.2 Hz, *Ha*), 5.34 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = 1.5 Hz, $^4J_{HH}$ = 1.5 Hz, *Hb*), 5.96 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 5.6 Hz, *Hc*), 7.04 (2H, ap.t $^3J_{HH}$ = $^3J_{HF}$ = 8.5 Hz, *ArH-3*), 8.01 (2H, dd, $^3J_{HH}$ = 9.1 Hz, $^4J_{HF}$ = 5.6, *ArH-2)*; δ_C 65.6 (O*CH*$_2$), 114.4 (d, $^2J_{CF}$ = 21.9 Hz, *ArCH-3*), 117.2 (CH*CH*$_2$), 125.5 (*ArC-1*), 131.1 (d, $^3J_{CF}$ = 9.8 Hz, *ArCH-2*), 131.2 (*CH*CH_2), 164.0 (C=O), 164.7 (d, $^1J_{CF}$ = 254.2 Hz, *ArCF*); δ_F -105.6 (1F, s, CF). m/z (EI^+) 180 ($[M]^+$, 10 %), 123 ($[M-OCH_2CH{=}CH_2]^+$, 100 %). HRMS (EI) 180.05847 ($C_{10}H_9O_2F$ requires 180.05843).

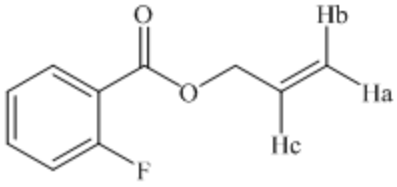
6.2.5 Preparation of allyl 3-fluorobenzoate (82)



The novel compound was prepared following the method outlined by Yasui *et al.* without modification.[2] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 3-fluorobenzoyl chloride (1 g, 0.77 cm^3, 6.31 mmol) and anhydrous diethyl ether (7 cm^3). The reaction mixture was cooled to 0 °C using an ice bath. Allyl alcohol (0.33 g, 0.39 cm^3, 5.73 mmol) and triethylamine (0.64 g, 0.88 cm^3, 6.31 mmol) were added and the reaction mixture then stirred at 0 ºC for 2 h, after which it was warmed to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate and the organic layer extracted and washed successively with 2M HCl (2 x 2 cm^3), saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and solvent removed *in vacuo* to yield the product as a colourless oil (1.00 g, 97 %). δ_H 4.75 (2H, ap.dt, $^3J_{HH}$ = 5.9 Hz, $^4J_{HH}$ = 1.6 Hz, OC*H*$_2$), 5.22 (1H, ddt, $^3J_{HH}$ = 10.6 Hz, $^2J_{HH}$ = 1.2 Hz, $^4J_{HH}$ = 1.2 Hz, *Ha*), 5.34 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = 1.2 Hz, $^4J_{HH}$ = 1.6 Hz, *Hb*), 5.95 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.9 Hz, *Hc*), 7.19 (1H, ap.tdd, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, $^4J_{HH}$ = 2.7 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-4*), 7.35

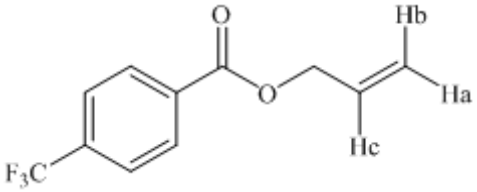
(1H, td, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HF}$ = 5.9 Hz, *ArH-5*), 7.67 (1H, ddd, $^{3}J_{HF}$ = 9.4 Hz, $^{4}J_{HH}$ = 2.7 Hz, $^{4}J_{HH}$ = 1.6 Hz, *ArH-2*), 7.79 (1H, dt, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.6 Hz, *ArH-6*); δ_C 64.9 (O*CH*$_2$), 115.5 (d, $^{2}J_{CF}$ = 23.1 Hz, *ArCH-2*), 117.5 (CH*CH*$_2$), 119.0 (d, $^{2}J_{CF}$ = 21.1 Hz, *ArCH-4*), 124.4 (*ArCH-6*), 129.0 (d, $^{3}J_{CF}$ = 8.0 Hz, *ArCH-5*), 130.9 (*CH*CH$_2$), 131.4 (d, $^{3}J_{CF}$ = 7.0 Hz, *ArC-1*), 161.6 (d, $^{1}J_{CF}$ = 247.5 Hz, *ArCF*), 164.1 (d, $^{4}J_{CF}$ = 3.0 Hz, C=O); δ_F -112.4 (1F, s, CF). m/z (EI$^+$) 180 ([M]$^+$, 70 %), 123 ([M-OCH$_2$CH=CH$_2$]$^+$, 100 %). HRMS (EI) 180.05842 ($C_{10}H_9O_2F$ requires 180.05843).

6.2.6 Preparation of allyl 2-fluorobenzoate (83)[5]



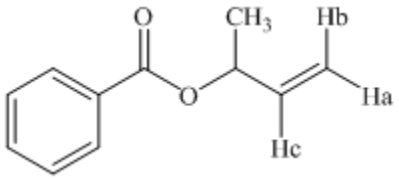
The title compound was prepared following the method outlined by Yasui *et al.* without modification.[2] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 2-fluorobenzoyl chloride (1 g, 0.75 cm^3, 6.31 mmol) and anhydrous diethyl ether (7 cm^3). The reaction mixture was cooled to 0 °C using an ice bath. Allyl alcohol (0.33 g, 0.39 cm^3, 5.73 mmol) and triethylamine (0.64 g, 0.88 cm^3, 6.31 mmol) were added and the reaction mixture then stirred at 0 ºC for 2 h, after which it was warmed to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate and the organic layer extracted and washed successively with 2M HCl (2 x 2 cm^3), saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and solvent removed *in vacuo* to yield the product as a colourless oil (1.01 g, 98 %). δ_H 4.78 (2H, ap.dt, $^{3}J_{HH}$ = 5.5 Hz, $^{4}J_{HH}$ = 1.6 Hz, OC*H*$_2$), 5.23 (1H, ddt, $^{3}J_{HH}$ = 10.6 Hz, $^{2}J_{HH}$ = 1.2 Hz, $^{4}J_{HH}$ = 1.6 Hz, *Ha*), 5.37 (1H, ddt, $^{3}J_{HH}$ = 17.2 Hz, $^{2}J_{HH}$ = 1.6 Hz, $^{4}J_{HH}$ = 1.6 Hz, *Hb*), 5.97 (1H, ddt, $^{3}J_{HH}$ = 17.2 Hz, $^{3}J_{HH}$ = 10.6 Hz, $^{3}J_{HH}$ = 5.5 Hz, *Hc*), 7.07 (1H, ddd, $^{3}J_{HF}$ = 11.0 Hz, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HH}$ = 1.2 Hz, *ArH-3*), 7.14 (1H, td, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.2 Hz, *ArH-5)*, 7.45 (1H, dddd, $^{3}J_{HH}$ = 8.2 Hz, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HF}$ = 4.7 Hz, $^{4}J_{HH}$ = 2.0 Hz, *ArH-4*), 7.89 (1H, td, $^{3}J_{HH}$ = $^{4}J_{HF}$ = 7.4 Hz, $^{4}J_{HH}$ = 2.0 Hz, *ArH-6*); δ_C 65.8 (O*CH*$_2$), 117.0 (d, $^{2}J_{CF}$ = 22.1 Hz, *ArCH-3*), 118.4 (CH*CH*$_2$), 118.7 (d, $^{2}J_{CF}$ = 10.1 Hz, *ArC-1*), 123.9 (d, $^{4}J_{CF}$ = 6.0 Hz, *ArCH-5*), 131.9 (*ArCH-6*), 132.1 (*CH*CH$_2$), 134.5 (d, $^{3}J_{CF}$ = 9.1 Hz, *ArCH-4*), 162.0 (d, $^{1}J_{CF}$ = 260.6 Hz, *ArCF*), 164.1 (d, $^{3}J_{CF}$ = 3.0 Hz, C=O); δ_F -109.8 (1F, s, CF). m/z (EI$^+$) 180 ([M]$^+$, 55 %), 123 ([M-OCH$_2$CH=CH$_2$]$^+$, 100 %). HRMS (EI) 180.05838 ($C_{10}H_9O_2F$ requires 180.05843).

6.2.7 Preparation of allyl 4-(trifluoromethyl)benzoate (84)[6]



The title compound was prepared following the method outlined by Yasui *et al.* without modification.[2] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 4-(trifluoromethyl)benzoyl chloride (1 g, 0.71 cm^3, 4.79 mmol) and anhydrous diethyl ether (7 cm^3). The reaction mixture was cooled to 0 °C using an ice bath. Allyl alcohol (0.25 g, 0.3 cm^3, 4.35 mmol) and triethylamine (0.49 g, 0.69 cm^3, 4.79 mmol) were added and the reaction mixture then stirred at 0 ºC for 2 h, after which it was warmed to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate and the organic layer extracted and washed successively with 2M HCl (2 x 2 cm^3), saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and solvent removed *in vacuo* to yield the product as a colourless oil (1.05 g, 95 %). δ_H 4.78 (2H, ap.dt, $^3J_{HH}$ = 5.9 Hz, $^4J_{HH}$ = 1.6 Hz, OC*H*$_2$), 5.25 (1H, ddt, $^3J_{HH}$ = 10.6 Hz, $^2J_{HH}$ = 1.2 Hz, $^4J_{HH}$ = 1.2 Hz, *Ha*), 5.35 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = 1.2 Hz, $^4J_{HH}$ = 1.6 Hz, *Hb*), 5.97 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.9 Hz, *Hc*), 7.64 (2H, d, $^3J_{HH}$ = 8.2 Hz, *ArH-3*), 8.11 (2H, d, $^3J_{HH}$ = 7.8 Hz, *ArH-2)*; δ_C 66.1 (O*C*H$_2$), 118.7 (CH*C*H$_2$), 123.6 (q, $^1J_{CF}$ = 272.7 Hz, *ArCF*$_3$), 125.4 (*ArCH-3*), 130.0 (*ArCH-2*) 131.8 (*C*HCH$_2$), 133.4 (*ArC-1*), 134.5 (q, $^2J_{CF}$ = 33.2 Hz, *ArC-4*), 165.0 (C=O); δ_F -62.8 (3F, s, CF_3). m/z (EI$^+$) 230 ([M]$^+$, 40 %), 173 ([M-OCH$_2$CH=CH$_2$]$^+$, 100 %). HRMS (EI) 230.05534 ($C_{10}H_9O_2F$ requires 230.05524).

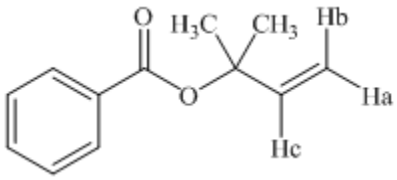
6.2.8 Preparation of But-3-en-2-yl benzoate (87)[7]



The title compound was prepared following the method outlined by Nakamura *et al.* without modification.[7] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 3-buten-2-ol (1.01 g, 1.21 cm^3, 14 mmol) and pyridine (5 cm^3) and the mixture was cooled to 0 °C using an ice bath. Benzoyl chloride (2.00 g, 1.65 cm^3, 14 mmol) was added and the reaction mixture then stirred at room temperature for 2 h. Brine and diethyl ether were then added to the mixture and the organic layer extracted and washed successively with 5 % HCl solution, saturated $NaHCO_3$, and

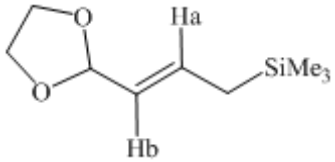
brine. The organic layer was dried over $MgSO_4$ and solvent removed *in vacuo* to yield the product as a colourless oil (1.74 g, 71 %). δ_H 1.37 (3H, d, $^3J_{HH}$ = 6.7 Hz, C*H*$_3$), 5.11 (1H, ap.dt, $^3J_{HH}$ = 10.6 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.6 Hz, *Ha*), 5.26 (1H, ap.dt, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.6 Hz, *Hb*), 5.49-5.56 (1H, m, C*H*CH$_3$), 5.89 (1H, ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.5 Hz, *Hc*), 7.36 (2H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-3*), 7.47 (1H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-4*) 7.99 (2H, d, $^3J_{HH}$ = 8.6 Hz, *ArH-2)*; δ_C 20.1 (CH$_3$), 71.5 (O*CH*), 115.8 (CH*CH*$_2$), 128.3 (*ArCH-3*), 129.6 (*ArCH-2*) 130.6 (*ArC-1*), 132.8 (*ArCH-4*), 137.8 (*CH*CH$_2$), 165.8 (C=O). m/z (EI$^+$) 176 ([M]$^+$, 38 %), 105 ([M-OCH(CH$_3$)CH=CH$_2$]$^+$, 100 %). HRMS (EI) 176.08340 ($C_{11}H_{12}O_2$ requires 176.08343).

6.2.9 Preparation of 2-methylbut-3-en-2-yl benzoate (86)[2]



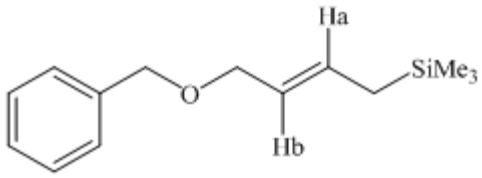
The title compound was prepared following the method outlined by Yasui *et al.* without modification.[2] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with NaH (0.58 g, 24 mmol); which had first been washed with anhydrous diethyl ether in the flush box, and DMF (20 cm^3). The reaction flask was cooled to 0 ºC and dimethylallyl alcohol (1.72 g, 2.09 cm^3, 20 mmol) was added. The mixture was stirred at 0 ºC for 10 min and then at room temperature for 15 min. The flask was then cooled to 0 ºC, and benzoyl chloride (3.37 g, 2.78 cm^3, 24 mmol) added, the resultant mixture was stirred at the same temperature for 2 h and then at room temperature overnight. After dilution with hexane (75 cm^3), the mixture was successively washed with cold, dilute aqueous ammonia (5 x 20 cm^3). Drying over $MgSO_4$, removal of the solvents, and distillation under reduced pressure (82 ºC/0.01 mmHg) provided dimethylallyl benzoate as a colourless oil (1.01 g, 27 %). δ_H 1.57 (6H, s, C*H*$_3$), 5.04 (1H, dd, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.18 (1H, dd, $^3J_{HH}$ = 17.6 Hz, $^2J_{HH}$ = 0.8 Hz, *Hb*), 6.10 (1H, dd, $^3J_{HH}$ = 17.6 Hz, $^3J_{HH}$ = 11.0 Hz, *Hc*), 7.31 (2H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-3*), 7.42 (1H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-4*) 7.92 (2H, dm, $^3J_{HH}$ = 8.6 Hz, *ArH-2*); δ_C 24.4 (CH$_3$), 79.0 (O*C*(CH$_3$)$_2$), 110.6 (CH*CH*$_2$), 126.0 (*ArCH-3*), 127.2 (*ArCH-2*) 129.4 (*ArC-1*), 130.3 (*ArCH-4*), 140.4 (*CH*CH$_2$), 163.1 (C=O).

6.2.10 Preparation of (3-[1,3]Dioxalan-2-yl-allyl)trimethylsilane (69)[8]



The title compound was prepared following the method outlined by Gouverneur *et al.*[8] without modification. A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and condenser and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with argon. The flask was charged with 2-vinyl-[1,3]dioxalane (0.1 cm^3, 1 mmol), allyltrimethylsilane (0.48 cm^3, 3 mmol) and anhydrous DCM (3 cm^3). The reaction mixture was heated to reflux. Second generation Grubbs catalyst (5 % mol, 84 mg, 0.10 mmol) was weighed into a V-shaped dropping tube in a dry box and then transferred to the reaction flask, addition was in three portions over 48 h. The reaction was left to reflux for 48 h. Purification by column chromatography [diethyl ether: hexane (4:96)] afforded the product as an oil (137 mg, 74 %), (E > 90 %). δ_H 0.00 (9H, s, *Me*$_3$Si), 1.52 (2H, dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.2 Hz, *CH*$_2$Si), 3.86 and 3.96 (4H, 2m, -O*CH*$_2$*CH*$_2$O-), 5.15 (1H, d, $^3J_{HH}$ = 6.7 Hz, -OC*H*RO-), 5.30 (1H, ddt, $^3J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 6.7 Hz, $^4J_{HH}$ = 1.2 Hz, *Ha*), 5.89 (1H, dt, $^3J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 8.5 Hz, *Hb*); δ_C 0.00 (CH_3), 25.0 (*CH*$_2$Si), 66.8 (2 x *CH*$_2$), 106.6 (*CH*CH_2), 126.6 (O_2CH*CH*), 136.7 (O_2*CH*).

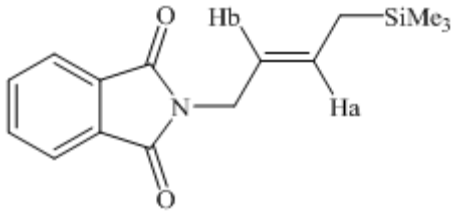
6.2.11 Preparation of (4-Benzyloxy-but-2-enyl)-trimethylsilane (68)[8]



The title compound was prepared following the method outlined by Gouverneur *et al.*[8] without modification. A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and condenser and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with argon. The flask was charged with allyl benzyl ether (312 mg, cm^3, 2.10 mmol), allyltrimethylsilane (1 cm^3, 6.30 mmol) and anhydrous DCM (6 cm^3). The reaction mixture was heated to reflux. Second generation Grubbs catalyst (5 % mol, 84 mg, 0.10 mmol) was weighed into a V-shaped dropping tube in a dry box and then transferred to the reaction flask, addition was in three portions over 48h. The reaction was left to reflux for 48 h. Purification by column chromatography [diethyl ether: hexane (3:97)] and concentration *in vacuo* afforded the product as an oil (141 mg , 29 %), (E/Z ratio 4:1). δ_H 0.02 and 0.03 (9H, 2 x s, *Me*$_3$Si), 1.51 (2H, d, $^3J_{HH}$ = 8.5 Hz, *CH*$_2$Si), 3.96 (1.6H, d, $^3J_{HH}$ = 6.4 Hz, $^4J_{HH}$ = 0.9 Hz, O*CH*$_{2\text{-}trans}$), 4.01 (0.4H, d, $^3J_{HH}$ = 5.9 Hz, O*CH*$_{2\text{-}cis}$), 4.47 and 4.50 (2H, 2 x s, -O*CH*$_2$Ph), 5.46 (1H, m, *Ha*), 5.68 (1H, m, *Hb*), 7.23-7.33 (5H, m, Ar*H*); δ_C -0.21 (CH_3), 24.9 (*CH*$_2$Si), 73.1 (O*CH*$_2$), 73.3 (*CH*$_2$Ar), 125.6 (*CH*$_{cis}$CH$_2$Si), 126.7

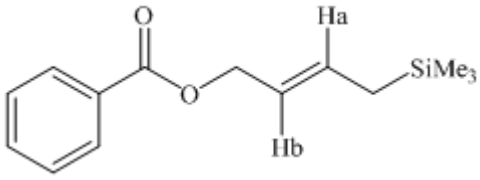
($CH_{trans}CH_2Si$), 129.4 (*ArCH-4*), 129.5 (*ArCH-3*), 129.7 (*ArCH-2*), 133.8 (OCH_2CH_{cis}), 134.1 (OCH_2CH_{trans}), 140.6 (*ArC-1*).

6.2.12 Preparation of 2-(4-trimethylsilanyl-but-2-enyl)isindole-1,3-dione (70)[8]



The title compound was prepared following the method outlined by Gouverneur *et al.*[8] without modification. A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and condenser and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with argon. The flask was charged with 2-allyl-isoindole-1,3-dione (0.56 g, 3.0 mmol), allyltrimethylsilane (1.44 cm^3, 9.0 mmol) and anhydrous DCM (10 cm^3). The reaction mixture was heated to reflux. Second generation Grubbs catalyst (15 % mol, 126 mg, 0.15 mmol) was weighed into a V-shaped dropping tube in a dry box and then transferred to the reaction flask, addition was in three portions over 48 h. The reaction was left to reflux for 48 h. Purification by flash column chromatography [diethyl ether: hexane (15:85)] and concentration *in vacuo* afforded the product as a white solid (0.64 g, 78 %), (E/Z 3:1 ratio). δ_H 0.00 and 0.08 (9H, 2 x s, Me_3Si), 1.47 (1.5H, d, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.2 Hz, $SiCH_{2\text{-}trans}$), 1.76 (0.5H, d, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ =1.5 Hz, $SiCH_{2\text{-}cis}$), 4.25 (1.5H, d, $^3J_{HH}$ = 6.7 Hz, $^4J_{HH}$ =1.2 Hz, $NCH_{2\text{-}trans}$), 4.30 (0.5H, d, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.5 Hz, $NCH_{2\text{-}cis}$) 5.33-5.45 (1H, m, *Ha*), 5.67 (0.25H, m, Hb_{cis}), 5.81 (0.75H, dtt, $^3J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz, Hb_{trans}), 7.73 (2H, dd, $^3J_{HH}$ = 5.3 Hz, $^4J_{HH}$ = 2.9 Hz, *ArH-4*) 7.87 (2H, dd, $^3J_{HH}$ = 5.6 Hz, $^4J_{HH}$= 2.9 Hz, *ArH-5*); δ_C 0.00 ($CH_{3\text{-}trans}$), 0.21 (CH_{3cis}), 21.0 ($SiCH_{2\text{-}cis}$), 24.8 ($SiCH_{2\text{-}trans}$), 36.7 ($NCH_{2\text{-}cis}$), 41.9 ($NCH_{2\text{-}trans}$), 122.6 ($CH_{cis}CH_2Si$), 123.4 ($CH_{trans}CH_2Si$), 125.2 (*ArCH-4*), 132.8 (NCH_2CH_{cis}), 134.3 (*ArC-3*), 134.4 (NCH_2CH_{trans}), 135.8 (*ArCH-5*), 170 (C=O).

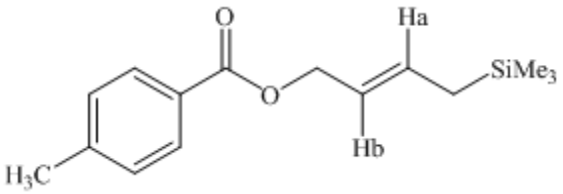
6.2.13 Preparation of Benzoic acid 4-trimethylsilanyl-but-2-enyl ester (71)[8]



The title compound was prepared following the method outlined by Gouverneur *et al.*[8] without modification. A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and condenser and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with argon. The flask was charged with allyl benzoate (324 mg, 2 mmol), allyltrimethylsilane (0.96 cm^3, 6 mmol) and anhydrous DCM (6 cm^3). The

reaction mixture was heated to reflux. Second generation Grubbs catalyst (5 % mol, 84 mg, 0.10 mmol) was weighed into a V-shaped dropping tube in a dry box and then transferred to the reaction flask, addition was in three portions over 48 h. The reaction was left to reflux for 48 h. Purification by flash column chromatography [diethyl ether: hexane (15:85)] and concentration *in vacuo* afforded the product as an oil (325 mg, 65 %), (E/Z ratio 4/1). δ_H 0.00 and 0.02 (9H, 2 x s, *Me*$_3$Si), 1.52 (1.6H, d, $^3J_{HH}$ = 8.2 Hz, Si*CH*$_{2\text{-}trans}$), 1.63 (0.4H, d, $^3J_{HH}$ = 9.1 Hz, Si*CH*$_{2\text{-}cis}$), 4.73 (1.6H, d, $^3J_{HH}$ = 6.7 Hz, $^4J_{HH}$ = 0.9 Hz, O*CH*$_{2\text{-}trans}$), 4.82 (0.4H, d, $^3J_{HH}$ = 7.31 Hz, O*CH*$_{2\text{-}cis}$), 5.47-5.60 (1H, m, *Ha*), 5.74 (0.2H, m, *Hb*$_{cis}$), 5.84 (0.8H, dtt, $^3J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz, *Hb*$_{trans}$), 7.41 (2H, tm, $^3J_{HH}$ = 7.0 Hz, *ArH-3*), 7.53 (1H, tm, $^3J_{HH}$ = 7.31 Hz, *ArH-4*), 8.02 (2H, dm, $^3J_{HH}$ = 8.5 Hz, *ArH-2*); δ_C 0.0 (CH_3), 21.4 (*CH*$_{2cis}$Si), 25.1 (*CH*$_{2\text{-}trans}$Si), 62.8 (O*CH*$_{2\text{-}cis}$), 68.1 (O*CH*$_{2\text{-}trans}$), 122.8 (*CH*$_{cis}$CH$_2$Si), 124.1 (*CH*$_{trans}$CH$_2$Si), 130.3 (*ArCH-3*), 132.6 (*ArCH-2*), 132.6 (*ArC-1*), 134.2 (OCH$_2$*CH*$_{cis}$), 134.7 (*ArCH-4*), 136.1 (OCH$_2$*CH*$_{trans}$), 168.5 (C=O).

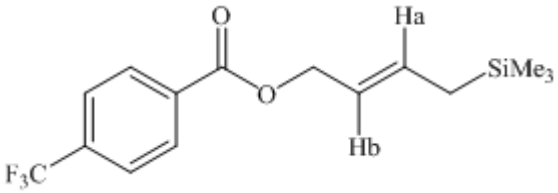
6.2.14 Preparation of 4-(trimethylsilyl)but-2-enyl 4-methylbenzoate (92)



The novel compound was prepared following the method outlined by Gouverneur *et al.*[8] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and condenser and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with argon. The flask was charged with allyl 4-methylbenzoate (430 mg, 2.44 mmol), allyltrimethylsilane (1.16 cm^3, 7.33 mmol) and anhydrous DCM (8 cm^3). The reaction mixture was heated to reflux. Second generation Grubbs catalyst (5 % mol, 110 mg, 0.10 mmol) was weighed into a V-shaped dropping tube in a dry box and then transferred to the reaction flask, addition was in three portions over 48 h. The reaction was left to reflux for 48 h. Purification by flash column chromatography [diethyl ether:hexane (15:85)] and concentration *in vacuo* afforded the product as an oil (216 mg, 34 %), (E/Z ratio 4/1); δ_H 0.00 and 0.02 (9H, 2 x s, *Me*$_3$Si), 1.52 (1.6H, d, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 1.2 Hz, *SiCH*$_{2\text{-}trans}$), 1.62 (0.4H, d, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ =1.6 Hz, *SiCH*$_{2\text{-}cis}$), 2.39 (3H, s, CH_3), 4.71 (1.6H, d, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ =1.2 Hz, O*CH*$_{2\text{-}trans}$), 4.80 (0.4H, d, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.2 Hz, O*CH*$_{2\text{-}cis}$) 5.48-5.60 (1H, m, *Ha*), 5.73 (0.2H, m, *Hb*$_{cis}$), 5.84 (0.8H, dtt, $^3J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz, *Hb*$_{trans}$), 7.21 (2H, d, $^3J_{HH}$ = 8.6 Hz, *ArH-3*) 7.91 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-2*); δ_C 0.0 (CH_3), 21.4 (Si*CH*$_{2\text{-}cis}$), 23.6 (CH_3), 24.9 (Si*CH*$_{2\text{-}trans}$), 62.6 (O*CH*$_{2\text{-}cis}$), 67.9 (O*CH*$_{2\text{-}trans}$), 122.9 (*CH*$_{cis}$CH$_2$Si), 124.3 (*CH*$_{trans}$CH$_2$Si), 129.9 (*ArC-1*), 130.0 (*ArCH-3*), 131.6 (*ArCH-2*), 134.0 (OCH$_2$*CH*$_{cis}$), 135.9 (OCH$_2$*CH*$_{trans}$), 145.4 (*ArC-4*),

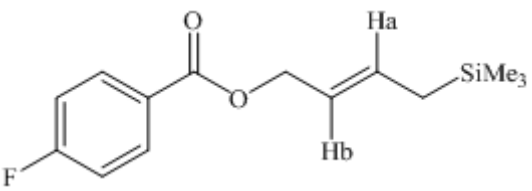
168.7 (C=O). m/z (EI$^+$) 262 ([M]$^+$, 75 %). HRMS (EI) 262.13846 ($C_{15}H_{22}O_2Si$ requires 262.13836).

6.2.15 Preparation of 4-(trimethylsilyl)but-2-enyl 4-(trifluoromethyl)benzoate (91)



The novel compound was prepared following the method outlined by Gouverneur *et al.*[8] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and condenser and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with argon. The flask was charged with allyl 4-(trifluoromethyl) benzoate (230 mg, 1 mmol), allyltrimethylsilane (0.48 cm^3, 3 mmol) and anhydrous DCM (3 cm^3). The reaction mixture was heated to reflux. Second generation Grubbs catalyst (5 % mol, 43 mg, 0.05 mmol) was weighed into a V-shaped dropping tube in a dry box and then transferred to the reaction flask, addition was in three portions over 48 h. The reaction was left to reflux for 48 h. Purification by flash column chromatography [diethyl ether/hexane (15:85)] and concentration *in vacuo* afforded the product as an oil (110 mg, 35 %), (E/Z ratio 4/1). δ_H 0.00 and 0.02 (9H, 2 x s, *Me*$_3$Si), 1.53 (1.6H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.2 Hz, Si*CH*$_{2\text{-}trans}$), 1.63 (0.4H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ =1.6 Hz, Si*CH*$_{2\text{-}cis}$), 4.75 (1.6H, d, $^3J_{HH}$ = 6.7 Hz, $^4J_{HH}$ = 1.2 Hz, O*CH*$_{2\text{-}trans}$), 4.85 (0.4H, d, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.2 Hz, O*CH*$_{2\text{-}cis}$) 5.48-5.60 (1H, m, *Ha*), 5.73-5.81 (0.2H, m, *Hb*$_{cis}$), 5.87 (0.8H, dtt, $^3J_{HH}$ = 14.9 Hz, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz, *Hb*$_{trans}$), 7.68 (2H, d, $^3J_{HH}$ = 8.2 Hz, *ArH-3*), 8.13 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-2*); δ_C -1.80 (*CH*$_{3\text{-trans}}$), -1.90 (*CH*$_{3\text{-cis}}$) 19.4 (Si*CH*$_{2\text{-}cis}$) 23.2 (Si*CH*$_{2\text{-}trans}$), 61.3 (O*CH*$_{2\text{-}cis}$), 66.7 (O*CH*$_{2\text{-}trans}$), 120.2 (*CH*$_{cis}$CH$_2$Si), 121.6 (*CH*$_{trans}$CH$_2$Si), 123.7 (q, $^1J_{CF}$ = 272.9 Hz, *ArCF*$_3$), 125.6 (*ArCH-3*), 130.0 (*ArCH-2*), 132.8 (OCH$_2$*CH*$_{cis}$), 133.8 (*ArC-1*), 134.3 (q, $^2J_{CF}$ = 32.7 Hz, *ArC-4*), 134.9 (OCH$_2$*CH*$_{trans}$), 165.3 (C=O); δ_F -63.8 (3F, s, CF$_3$). m/z (EI$^+$) 316 ([M]$^+$, 25 %). HRMS (EI) 316.11013 ($C_{15}H_{19}O_2F_3Si$ requires 316.11017).

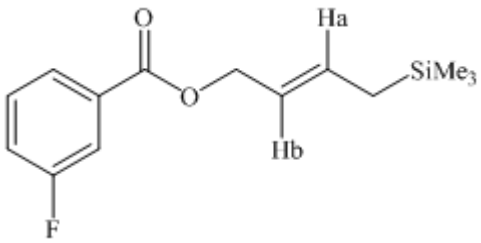
6.2.16 Preparation of 4-(trimethylsilyl)but-2-enyl 4-fluorobenzoate (88)



The novel compound was prepared following the method outlined by Gouverneur *et al.*[8] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and condenser and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with argon. The flask was charged with allyl 4-fluorobenzoate (198

mg, 1.1 mmol), allyltrimethylsilane (0.52 cm^3, 3.3 mmol) and anhydrous DCM (3 cm^3). The reaction mixture was heated to reflux. Second generation Grubbs catalyst (5 % mol, 50 mg, 0.06 mmol) was weighed into a V-shaped dropping tube in a dry box and then transferred to the reaction flask, addition was in three portions over 48 h. The reaction was left to reflux for 48 h. Purification by flash column chromatography [diethyl ether: hexane (4:96)] and concentration *in vacuo* afforded the product as an oil (0.24 g, 83 %), (E/Z ratio 3/1). δ_H 0.00 and 0.02 (9H, 2 x s, Me_3Si), 1.52 (1.5H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.2 Hz, Si$CH_{2\text{-}trans}$), 1.63 (0.5H, dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ =1.6 Hz, Si$CH_{2\text{-}cis}$), 4.72 (1.5H, dd, $^3J_{HH}$ = 6.7 Hz, $^4J_{HH}$ = 1.2 Hz, O$CH_{2\text{-}trans}$), 4.81 (0.5H, dd, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.6 Hz, O$CH_{2\text{-}cis}$) 5.47-5.59 (1H, m, *Ha*), 5.71-5.79 (0.3H, m, Hb_{cis}), 5.86 (0.7H, dtt, $^3J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz, Hb_{trans}), 7.08 (2H, ap.t, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, *ArH-3*), 8.04 (2H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HF}$ = 5.5 Hz, *ArH-2*); δ_C -1.91 ($CH_{3\text{-}trans}$), -2.01 ($CH_{3\text{-}cis}$) 19.4 (Si$CH_{2\text{-}cis}$) 23.1 (Si$CH_{2\text{-}trans}$), 60.9 (O$CH_{2\text{-}cis}$), 66.3 (O$CH_{2\text{-}trans}$), 115.4 (d, $^2J_{CF}$ = 28.9 Hz, *ArCH-3*), 120.5 ($CH_{cis}CH_2Si$), 121.9 ($CH_{trans}CH_2Si$), 126.8 (d, $^4J_{CF}$ = 2.5 Hz, *ArC-1*), 132.1 (d, $^3J_{CF}$ = 10.1 Hz, *ArCH-2*), 132.4 (OCH_2CH_{cis}), 134.4 (OCH_2CH_{trans}), 165.6 (C=O), 165.7 (d, $^1J_{CF}$ = 254.0 Hz, *ArCF*); δ_F -106.1 (1F, s, CF). m/z (EI^+) 266 ($[M]^+$, 100 %). HRMS (EI) 266.11344 ($C_{14}H_{19}O_2FSi$ requires 262.11336).

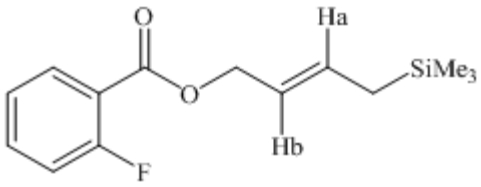
6.2.17 Preparation of 4-(trimethylsilyl)but-2-enyl 3-fluorobenzoate (89)



The novel compound was prepared following the method outlined by Gouverneur *et al.*[8] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and condenser and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with argon. The flask was charged with allyl 3-fluorobenzoate (176 mg, 1.0 mmol), allyltrimethylsilane (0.48 cm^3, 3 mmol) and anhydrous DCM (3 cm^3). The reaction mixture was heated to reflux. Second generation Grubbs catalyst (5 % mol, 43 mg, 0.05 mmol) was weighed into a V-shaped dropping tube in a dry box and then transferred to the reaction flask, addition was in three portions over 48 h. The reaction was left to reflux for 48 h. Purification by flash column chromatography [diethyl ether: hexane (4:96)] and concentration *in vacuo* afforded the product as an oil (0.19 g, 71 %), (E/Z ratio 4/1). δ_H 0.00 and 0.02 (9H, 2 x s, Me_3Si), 1.53 (1.6H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 0.8 Hz, Si$CH_{2\text{-}trans}$), 1.63 (0.4H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ =1.6 Hz, Si$CH_{2\text{-}cis}$), 4.73 (1.6H, dd, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 0.8 Hz, O$CH_{2\text{-}trans}$), 4.82 (0.4H, dd, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.2 Hz, O$CH_{2\text{-}cis}$) 5.47-5.59 (1H, m, *Ha*), 5.72-5.79 (0.2H, m, Hb_{cis}), 5.86 (0.8H, dtt, $^3J_{HH}$ = 14.9 Hz,

$^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz, *Hb$_{trans}$*), 7.20 (1H, ap.tdd, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, $^4J_{HH}$ = 2.7 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-4*), 7.39 (1H, td, $^3J_{HH}$ = 8.2 Hz, $^4J_{HF}$ = 5.5 Hz, *ArH-5*), 7.70 (1H, ddd, $^3J_{HF}$ = 9.4 Hz, $^4J_{HH}$ = 2.7 Hz, $^4J_{HH}$ = 1.6 Hz, *ArH-2*), 7.81 (1H, dt, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-6*); δ_C 0.00 (*CH$_{3\text{-}trans}$*), 0.11 (*CH$_{3\text{-}cis}$*), 21.4 (Si*CH$_{2\text{-}cis}$*) 25.2 (Si*CH$_{2\text{-}trans}$*), 63.1 (O*CH$_{2\text{-}cis}$*), 68.5 (O*CH$_{2\text{-}trans}$*), 118.5 (d, $^2J_{CF}$ = 23.4 Hz, *ArCH-2*), 121.8 (d, $^2J_{CF}$ = 21.1 Hz, *ArCH-4*), 122.4 (*CH$_{cis}$*CH$_2$Si), 123.3 (*CH$_{trans}$*CH$_2$Si), 127.3 (d, $^4J_{CF}$ = 3.0 Hz, *ArCH-6*), 132.0 (d, $^3J_{CF}$ = 8.3 Hz, *ArCH-5*), 134.6 (OCH$_2$*CH$_{cis}$*), 134.8 (d, $^3J_{CF}$ = 7.5 Hz, *ArC-1*), 136.6 (OCH$_2$*CH$_{trans}$*), 164.5 (d, $^1J_{CF}$ = 246.7 Hz, *ArCF*), 167.3 (C=O); δ_F -112.5 (1F, s, CF). m/z (EI$^+$) 266 ([M]$^+$, 100 %). HRMS (EI) 266.11325 ($C_{14}H_{19}O_2FSi$ requires 262.11336).

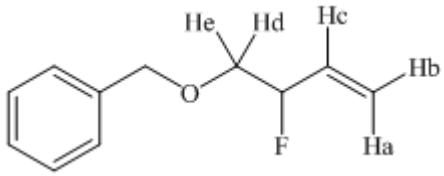
6.2.18 Preparation of 4-(trimethylsilyl)but-2-enyl 2-fluorobenzoate (90)



The novel compound was prepared following the method outlined by Gouverneur *et al.*[8] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and condenser and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with argon. The flask was charged with allyl 2-fluorobenzoate (360 mg, 2.0 mmol), allyltrimethylsilane (0.96 cm^3, 6.0 mmol) and anhydrous DCM (6 cm^3). The reaction mixture was heated to reflux. Second generation Grubbs catalyst (10 % mol, 86 mg, 0.10 mmol) was weighed into a V-shaped dropping tube in a dry box and then transferred to the reaction flask, addition was in three portions over 48 h. The reaction was left to reflux for 48 h. Purification by flash column chromatography [chloroform: hexane (70:30)] and concentration *in vacuo* afforded the product as an oil (0.30 g, 56 %), (E/Z ratio 3/1). δ_H 0.00 and 0.02 (9H, 2 x s, *Me$_3$*Si), 1.52 (1.5H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.2 Hz, Si*CH$_{2\text{-}trans}$*), 1.63 (0.5H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ =1.2 Hz, Si*CH$_{2\text{-}cis}$*), 4.74 (1.5H, dd, $^3J_{HH}$ = 6.7 Hz, $^4J_{HH}$ = 0.8 Hz, O*CH$_{2\text{-}trans}$*), 4.83 (0.5H, dd, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.2 Hz, O*CH$_{2\text{-}cis}$*) 5.48-5.60 (1H, m, *Ha*), 5.71-5.78 (0.3H, m, *Hb$_{cis}$*), 5.87 (0.7H, dtt, $^3J_{HH}$ = 14.9 Hz, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz, *Hb$_{trans}$*), 7.10 (1H, ddd, $^3J_{HF}$ = 11.0 Hz, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-3*), 7.17 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-5),* 7.49 (1H, dddd, $^3J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 7.4 Hz, $^4J_{HF}$ = 4.7 Hz, $^4J_{HH}$ = 2.0 Hz,, *ArH-4*), 7.91 (1H, td, $^3J_{HH}$ = $^4J_{HF}$ = 7.4 Hz, $^4J_{HH}$ = 2.0 Hz, *ArH-6*); δ_C 0.00 (*CH$_{3\text{-}trans}$*), 0.11 (*CH$_{3\text{-}cis}$*) 21.4 (Si*CH$_{2\text{-}cis}$*) 25.2 (Si*CH$_{2\text{-}trans}$*), 63.1 (O*CH$_{2\text{-}cis}$*), 68.4 (O*CH$_{2\text{-}trans}$*), 119.0 (d, $^2J_{CF}$ = 22.6 Hz, *ArCH-3*), 121.2 (d, $^2J_{CF}$ = 10.1 Hz, *ArC-1*), 122.5 (*CH$_{cis}$*CH$_2$Si), 123.8 (*CH$_{trans}$*CH$_2$Si), 125.9 (d, $^4J_{CF}$ = 3.8 Hz, *ArCH-5*), 134.1 (*ArCH-6*), 134.4 (OCH$_2$*CH$_{cis}$*), 136.3 (d, $^3J_{CF}$ = 8.8 Hz, *ArCH-4*), 136.4 (OCH$_2$*CH$_{trans}$*), 164.0 (d, $^1J_{CF}$ =

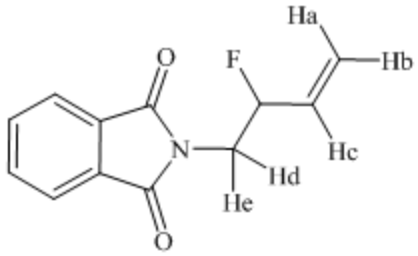
260.3 Hz, *ArCF*), 166.3 (C=O); δ_F -109.5 (1F, s, CF). m/z (EI^+) 266 ($[M]^+$, 8 %). HRMS (EI) 266.11345 ($C_{14}H_{19}O_2FSi$ requires 262.11336).

6.2.19 Preparation of (2-Fluoro-but-3-enyloxymethyl)-benzene (73)[8]



The title compound was prepared following the method outlined by Gouverneur *et al.*[8] without modification. A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with (4-Benzyloxy-but-2-enyl)-trimethylsilane (76 mg, 0.31 mmol), anhydrous MeCN (5 cm^3) and Selectfluor (115 mg, 0.31 mmol). The reaction mixture was stirred at room temperature under argon for 48 h. After which purification by flash chromatography [diethyl ether: hexane (5:95)] afforded the product as an oil (18 mg, 33 % yield). δ_H 3.49-3.52 (1H, m, *Hd*), 3.58 (1H, m, *He*), 4.53 (2H, AB, $^2J_{AB}$ = 12.0 Hz, CH_AH_BAr), 5.03 (1H, dm, $^2J_{HF}$ = 48.3 Hz, *CH*F), 5.23 (1H, ap.dt, $^3J_{HH}$ = 10.8 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.4 Hz, *Hb*), 5.35 (1H, ap.ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 2.9 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.4 Hz, *Ha*),), 5.83 (1H, dddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 15.2 Hz, $^3J_{HH}$ =10.8 Hz, $^3J_{HH}$ = 5.6 Hz, *Hc*), 7.20-7.38 (5H, m, *ArH*); δ_F -185.0 (1F, s, CHF).

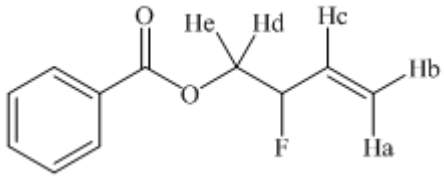
6.2.20 Preparation of 2-(2-Fluoro-but-3-enyl)-isoindole-1,3-dione (74)[8]



The title compound was prepared following the method outlined by Gouverneur *et al.*[8] without modification. A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 2-(4-trimethylsilanyl-but-2-enyl)-isindole-1,3-dione (0.85 g, 3.11 mmol), anhydrous MeCN (12 cm^3) and Selectfluor (1.10 g, 3.11 mmol). The reaction mixture was stirred at room temperature under argon for 48 h. After which purification by flash chromatography [diethyl ether: hexane (30: 70)] afforded the product as a white solid (0.68 g, 77 %). δ_H 3.76 (1H, ddd, $^3J_{HF}$ = 26.2 Hz, $^2J_{HH}$ = 14.5 Hz, $^3J_{HH}$ = 4.1 Hz, *Hd*), 3.97 (1H, ddd, $^3J_{HF}$ = 14.5 Hz, $^2J_{HH}$ = 14.5 Hz, $^3J_{HH}$ = 8.2 Hz, *He*), 5.02-5.25 (1H, dm, $^2J_{HF}$ = 48.9 Hz, *CH*F) 5.28 (1H, ap.dt, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.2 Hz, *Hb*), 5.39 (1H, ap.ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 3.1 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.2 Hz, *Ha*), 5.87 (1H, dddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 14.8 Hz, $^3J_{HH}$ = 11.0

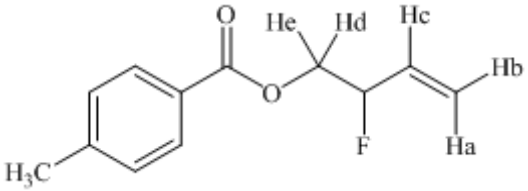
Hz, $^{3}J_{HH}$ = 5.9 Hz, *Hc*), 7.67 (2H, dd, $^{3}J_{HH}$ = 5.5 Hz, $^{4}J_{HH}$ = 3.1 Hz, *ArH-4*), 7.80 (2H, dd, $^{3}J_{HH}$ = 5.5 Hz, $^{4}J_{HH}$ = 3.1 Hz, *ArH-5*); δ_C 42.9 (d, $^{2}J_{CF}$ = 26.2 Hz, N*CH*$_2$), 91.5 (d, $^{1}J_{CF}$ = 174.1 Hz, *CH*F), 121.0 (d, $^{3}J_{CF}$ = 11.1 Hz, CH*CH*$_2$), 124.8 (*ArCH-4*), 133.3 (*ArC-3*), 134.5 (d, $^{2}J_{CF}$ = 19.1 Hz, *CH*CH$_2$), 135.5 (*ArCH-5*), 169.3 (C=O); δ_F -184.0 (1F, s, CHF). m/z (EI$^+$) 219 ([M]$^+$, 10 %) 160 ([M-CHFCH=CH$_2$]$^+$, 100 %). HRMS (EI) 219.06925 ($C_{12}H_{10}NO_2F$ requires 219.06931).

6.2.21 Preparation of 2-fluorobut-3-enyl benzoate (75)[8]



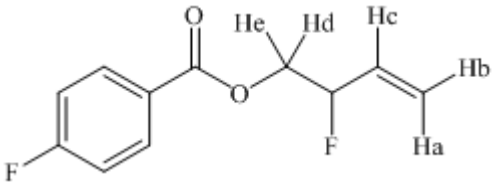
The title compound was prepared following the method outlined by Gouverneur *et al.*[8] without modification. A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with Benzoic acid 4-trimethylsilanyl-but-2-enyl ester (0.48 g, 1.95 mmol), anhydrous MeCN (10 cm^3) and Selectfluor (0.76 g, 2.15 mmol). The reaction mixture was stirred at room temperature under argon for 48 h. After which, purification by column chromatography [diethyl ether: hexane (3:97)] afforded the product as an oil (0.21 g, 55 %). δ_H 4.30 (1H, ddd, $^{3}J_{HF}$ = 20.3 Hz, $^{2}J_{HH}$ = 12.5 Hz, $^{3}J_{HH}$ = 7.0 Hz, *Hd*), 4.40 (1H, ddd, $^{3}J_{HF}$ = 26.6 Hz, $^{2}J_{HH}$ = 12.5 Hz, $^{3}J_{HH}$ = 3.1 Hz, *He*), 5.04-5.21 (1H, dm, $^{2}J_{HF}$ = 48.9 Hz, *CH*F), 5.28 (1H, ap.dt, $^{3}J_{HH}$ = 10.6 Hz, $^{2}J_{HH}$ = $^{4}J_{HH}$ = 1.2 Hz, *Hb*), 5.41 (1H, ap.ddt, $^{3}J_{HH}$ = 17.2 Hz, $^{4}J_{HH}$ = 3.1 Hz, $^{2}J_{HH}$ = $^{4}J_{HH}$ = 1.2 Hz, *Ha*), 5.80 (1H, dddd, $^{3}J_{HH}$ = 17.2 Hz, $^{3}J_{HF}$ = 14.9 Hz, $^{3}J_{HH}$ = 11.0 Hz, $^{3}J_{HH}$ = 5.9 Hz, *Hc*), 7.33 (2H, tm, $^{3}J_{HH}$ = 7.8 Hz, *ArH-3*), 7.46 (1H, tm, $^{3}J_{HH}$ = 7.4 Hz, *ArH-4*), 7.96 (2H, dm, $^{3}J_{HH}$ = 8.2 Hz, *ArH-2*); δ_C 65.8 (d, $^{2}J_{CF}$ = 23.2 Hz, O*CH*$_2$), 90.6 (d, $^{1}J_{CF}$ = 173.3 Hz, *CH*F), 119.4 (d, $^{3}J_{CF}$ = 11.4 Hz, CH*CH*$_2$), 128.1 (*ArCH-3*), 129.6 (*ArC-1*), 129.8 (*ArCH-2*), 132.0 (d, $^{2}J_{CF}$ = 19.2 Hz, *CH*CH$_2$), 133.2 (*ArCH-4*), 166.2 (C=O); δ_F -186.0 (1F, s, CHF). m/z (EI$^+$) 194 ([M]$^+$, 11 %) 105 ([M-O-CH$_2$CHFCH=CH$_2$]$^+$, 100 %). HRMS (EI) 194.07395 ($C_{11}H_{11}O_2F$ requires 194.07403).

6.2.22 Preparation of 2-fluorobut-3-enyl 4-methylbenzoate (97)



The novel compound was prepared following the method outlined by Gouverneur *et al.*[8] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 4-(trimethylsilyl)but-2-enyl 4-methylbenzoate (0.17 g, 0.64 mmol), anhydrous MeCN (10 cm^3) and Selectfluor (0.23 g, 0.64 mmol). The reaction mixture was stirred at room temperature under argon for 48 h. After which purification by column chromatography [diethyl ether: hexane (2: 98)] afforded the product as an oil (66 mg, 50 %). δ_H 2.25 (3H, s, C*H*$_3$), 4.23 (1H, ddd, $^3J_{HF}$ = 20.3 Hz, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 6.7 Hz, *Hd*), 4.33 (1H, ddd, $^3J_{HF}$ = 26.2 Hz, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 3.1 Hz, *He*), 4.98-5.15 (1H, dm, $^2J_{HF}$ = 48.9 Hz, *CH*F) 5.22 (1H, ap.dt, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.4 Hz, *Hb*), 5.35 (1H, ap.ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 3.1 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.4 Hz, *Ha*), 5.80 (1H, dddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 14.3 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.9 Hz, *Hc*), 7.08 (2H, dm, $^3J_{HH}$ = 7.8 Hz, *ArH-3*), 7.80 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-2*); δ_C 21.7 (*CH*$_3$), 65.7 (d, $^2J_{CF}$ = 24.1 Hz, O*CH*$_2$), 90.7 (d, $^1J_{CF}$ = 173.1 Hz, *CH*F), 119.3 (d, $^3J_{CF}$ = 12.1 Hz, CH*CH*$_2$), 127.0 (*ArC-1*), 129.1 (*ArCH-3*), 129.8 (*ArCH-2*), 132.1 (d, $^2J_{CF}$ = 19.1 Hz, *CH*CH$_2$), 144.0 (*ArC-4*), 166.3 (C=O); δ_F -185.6 (1F, s, CHF). m/z (EI$^+$) 208 ([M]$^+$, 47 %) 119 ([M-O-$CH_2CHFCH{=}CH_2$]$^+$, 100 %). HRMS (EI) 208.08958 ($C_{12}H_{13}O_2F$ requires 208.08963).

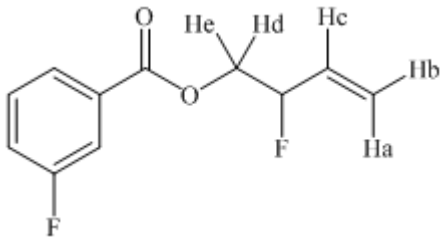
6.2.23 Preparation of 2-fluorobut-3-enyl 4-fluorobenzoate (93)



The novel compound was prepared following the method outlined by Gouverneur *et al.*[8] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 4-(trimethylsilyl)but-2-enyl 4-fluorobenzoate (0.231 g, 0.87 mmol), anhydrous MeCN (10 cm^3) and Selectfluor (0.37 g, 1.0 mmol). The reaction mixture was stirred at room temperature under argon for 48 h. After which purification by column chromatography [diethyl ether: hexane (8:92)] afforded the product as an oil (69 mg, 37 %). δ_H 4.30 (1H, ddd, $^3J_{HF}$ = 20.7 Hz, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 7.0 Hz, *Hd*), 4.40 (1H, ddd, $^3J_{HF}$ = 26.6 Hz, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 3.1 Hz, *He*), 5.05-5.22

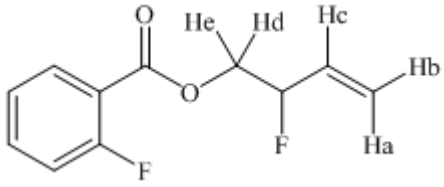
(1H, dm, $^2J_{HF}$ = 48.9 Hz, *CH*F), 5.30 (1H, ap.dt, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.2 Hz, *Hb*), 5.42 (1H, ap.ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HH}$ = 3.1 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.2 Hz, *Ha*) 5.86 (1H, dddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 14.9 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.5 Hz, *Hc*), 7.05 (2H, ap.t, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, *ArH-3*), 8.01 (2H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HF}$ = 5.5 Hz, *ArH-2*); δ_C 65.9 (d, $^2J_{CF}$ = 23.4 Hz, O*CH*$_2$), 90.6 (d, $^1J_{CF}$ = 173.4 Hz, *CH*F), 115.6 (d, $^2J_{CF}$ = 21.9 Hz, *ArCH-3*), 119.4 (d, $^3J_{CF}$ = 11.3 Hz, CH*CH*$_2$), 125.9 (d, $^4J_{CF}$ = 3.0 Hz, *ArC-1*), 131.9 (d, $^2J_{CF}$ = 18.9 Hz, *CH*CH$_2$), 132.3 (d, $^3J_{CF}$ = 16.6 Hz, *ArCH-2*), 165.2 (C=O), 165.9 (d, $^1J_{CF}$ = 254.4 Hz, *ArCF*). δ_F -105.1 (1F, s, CF), -186.8 (1F, s, CHF). m/z (EI$^+$) 212 ([M]$^+$, 3 %) 123 ([M-O-CH$_2$CHFCH=CH$_2$]$^+$, 100 %). HRMS (EI) 212.06472 ($C_{11}H_{10}O_2F_2$ requires 212.06464).

6.2.24 Preparation of 2-fluorobut-3-enyl 3-fluorobenzoate (94)



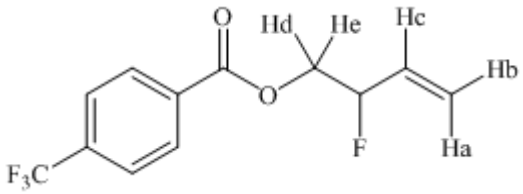
The novel compound was prepared following the method outlined by Gouverneur *et al.*[8] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 4-(trimethylsilyl)but-2-enyl 3-fluorobenzoate (0.25 mg, 0.95 mmol), anhydrous MeCN (10 cm^3) and Selectfluor (0.40 mg, 1.14 mmol). The reaction mixture was stirred at room temperature under argon for 48 h. After which purification by column chromatography [diethyl ether: hexane (8:92)] afforded the product as an oil (63 mg, 31 %). δ_H 4.35 (1H, ddd, $^2J_{HH}$ = 27.4 Hz, $^3J_{HF}$ = 20.3 Hz, $^3J_{HH}$ = 7.0 Hz, *Hd*), 4.44 (1H, ddd, $^2J_{HH}$ = 26.6 Hz, $^3J_{HF}$ = 12.1 Hz, $^3J_{HH}$ = 3.1 Hz, *He*), 5.08-5.25 (1H, dm, $^2J_{HF}$ = 48.5 Hz, *CH*F) 5.34 (1H, ap.dt, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.2 Hz, *Hb*), 5.46 (1H, ap.ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 2.7 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.2Hz, *Ha*) 5.88 (1H, dddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 14.9 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.9 Hz, *Hc*), 7.21 (1H, ap.tdd, $^3J_{HH}$ = $^3J_{HF}$ = 8.2 Hz, $^4J_{HH}$ = 2.7 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-4*), 7.35 (1H, td, $^3J_{HH}$ = 8.2 Hz, $^4J_{HF}$ = 5.5 Hz, *ArH-5*), 7.67 (1H, ddd, $^3J_{HF}$ = 9.4 Hz, $^4J_{HH}$ = 2.7 Hz, $^4J_{HH}$ = 1.6 Hz, *ArH-2*), 7.79 (1H, dt, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-6*); δ_C 66.1 (d, $^2J_{CF}$ = 23.1 Hz, *CH*$_2$), 90.5 (d, $^1J_{CF}$ = 174.1 Hz, *CH*F), 116.6 (d, $^2J_{CF}$ = 22.1 Hz, *ArCH-2*), 119.5 (d, $^3J_{CF}$ = 11.1 Hz, *CH*$_2$), 120.3 (d, $^2J_{CF}$ = 21.1 Hz, *ArCH-4*), 125.5 (*ArCH-6*), 130.1 (d, $^3J_{CF}$ = 7.0 Hz, *ArC-1*), 131.8 (C), 131.9 (d, $^2J_{CF}$ = 19.1 Hz, *CH*CH$_2$), 162.5 (d, $^1J_{CF}$ = 246.5 Hz, *ArCF*), 165.1 (d, $^4J_{CF}$ = 3.0 Hz, C=O); δ_F -112.2 (1F, s, CF), -186.1 (1F, s, CHF). m/z (EI$^+$) 212 ([M]$^+$, 43 %) 123 ([M-O-CH$_2$CHFCH=CH$_2$]$^+$, 100 %). HRMS (EI) 212.06456 ($C_{11}H_{10}O_2F_2$ requires 212.06464).

6.2.25 Preparation of 2-fluorobut-3-enyl 2-fluorobenzoate (95)



The novel compound was prepared following the method outlined by Gouverneur *et al.* [8] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 4-(trimethylsilyl)but-2-enyl 2-fluoro benzoate (0.29 g, 1.1 mmol), anhydrous MeCN (5 cm^3) and Selectfluor (0.57 g, 1.6 mmol). The reaction mixture was stirred at room temperature under argon for 48 h. After which purification by column chromatography [diethyl ether: hexane (8:92)] afforded the product as an oil (68 mg, 31 %). δ_H 4.32 (1H, ddd, $^2J_{HH}$ = 27.4 Hz, $^3J_{HF}$ = 20.3 Hz, $^3J_{HH}$ = 6.7 Hz, *Hd*), 4.41 (1H, ddd, $^2J_{HH}$ = 25.8 Hz, $^3J_{HF}$ = 12.5 Hz, $^3J_{HH}$ = 3.1 Hz, *He*), 5.04-5.21 (1H, dm, $^2J_{HF}$ = 48.5 Hz, *CH*F) 5.29 (1H, ap.dt, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.2 Hz, *Hb*), 5.41 (1H, ap.ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 3.1 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.2Hz, *Ha*), 5.86 (1H, dddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 14.9 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.9 Hz, *Hc*), 7.04 (1H, ddd, $^3J_{HF}$ = 11.0 Hz, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-3*), 7.10 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-5),* 7.43 (1H, dddd, $^3J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 7.4 Hz, $^4J_{HF}$ = 4.7 Hz, $^4J_{HH}$ = 2.0 Hz, *ArH-4*), 7.85 (1H, td, $^3J_{HH}$ = $^4J_{HF}$ = 7.4 Hz, $^4J_{HH}$ = 2.0 Hz, *ArH-6*); δ_C 65.0 (d, $^2J_{CF}$ = 24.1 Hz, O*CH*$_2$), 89.5 (d, $^1J_{CF}$ = 174.1 Hz, *CH*F), 116.0 (d, $^2J_{CF}$ = 23.1 Hz, *ArCH-3*), 117.2 (d, $^2J_{CF}$ = 10.1 Hz, *ArC-1*), 118.5 (d, $^3J_{CF}$ = 11.1 Hz, CH*CH*$_2$), 123.0 (d, $^4J_{CF}$ = 4.0 Hz, *ArCH-5*), 131.0 (d, $^2J_{CF}$ = 19.1 Hz, *CH*CH$_2$), 131.2 (*ArCH-6*), 133.8 (d, $^3J_{CF}$ = 10.1 Hz, *ArCH-4*), 161.1 (d, $^1J_{CF}$ = 260.1 Hz, *ArCF*), 162.9 (d, $^3J_{CF}$ = 3.0 Hz, C=O); δ_F -109.0 (1F, s, CF), -185.8 (1F, s, CHF). m/z (EI$^+$) 212 ([M]$^+$, 18 %) 123 ([M-O-CH$_2$ CHFCH=CH$_2$]$^+$, 100 %). HRMS (EI) 212.06462 ($C_{11}H_{10}O_2F_2$ requires 212.06464).

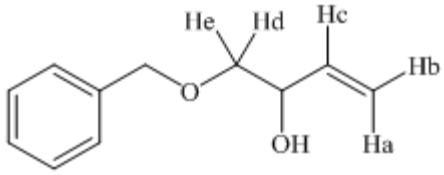
6.2.26 Preparation of 2-fluorobut-3-enyl 4-(trifluoromethyl)benzoate (96)



The novel compound was prepared following the method outlined by Gouverneur *et al.*[8] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 4-(trimethylsilyl)but-2-enyl 4-(trifluoromethyl)benzoate (0.08 g, 0.25 mmol), anhydrous MeCN (5 cm^3) and Selectfluor (0.13 g, 0.38 mmol). The reaction mixture was stirred at room temperature under argon for

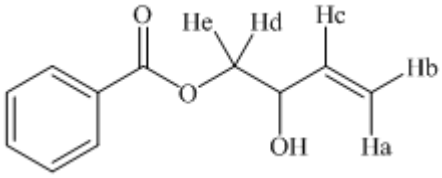
48 h. After which purification by column chromatography [diethyl ether: hexane (8:92)] afforded the product as an oil (35 mg, 53%). δ_H 4.39 (1H, ddd, $^2J_{HH}$ = 27.4 Hz, $^3J_{HF}$ = 20.3 Hz, $^3J_{HH}$ = 7.0 Hz, *Hd*), 4.43 (1H, ddd, $^2J_{HH}$ = 26.2 Hz, $^3J_{HF}$ = 14.1 Hz, $^3J_{HH}$ = 3.1 Hz, *He*), 5.10-5.27 (1H, dm, $^2J_{HF}$ = 48.9 Hz, *CH*F) 5.34 (1H, ap.dt, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.2 Hz, *Hb*), 5.46 (1H, ap.ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 2.7 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.2Hz, *Ha*) 5.88 (1H, dddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 14.3 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.9 Hz, *Hc*), 7.65 (2H, d, $^3J_{HH}$ = 8.2 Hz, *ArH-3*), 8.12 (2H, d, $^3J_{HH}$ = 7.8 Hz, *ArH-2*); δ_C 66.2 (d, $^2J_{CF}$ = 20.1 Hz, O*CH*$_2$), 90.4 (d, $^1J_{CF}$ = 174.1 Hz, *CH*F), 119.6 (d, $^3J_{CF}$ = 11.1 Hz, CH*CH*$_2$), 123.6 (q, $^1J_{CF}$ = 271.7 Hz, *ArCF*$_3$), 125.5 (*ArCH-3*), 130.2 (*ArCH-2*), 131.8 (d, $^2J_{CF}$ = 19.1 Hz, *CH*CH$_2$), 132.9 (*ArC-1*), 134.8 (q, $^2J_{CF}$ = 32.2 Hz, *ArC-4*), 165.0 (C=O); δ_F -63.0 (3F, s, CF_3), -186.2 (1F, s, CHF). m/z (EI$^+$) 262 ([M]$^+$, 7%) 173 ([M-O-CH_2CHFCH=CH_2]$^+$, 100%). HRMS (EI) 262.06152 ($C_{11}H_{10}O_2F_2$ requires 262.06144).

6.2.27 Preparation of 1-(Benzyloxy)but-3-en-2-ol (98)[9]



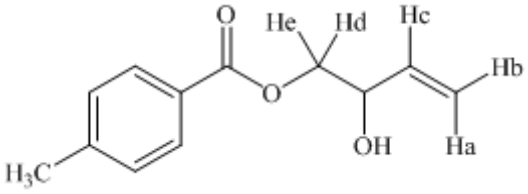
The title compound was prepared following the method outlined by Trost without modification.[9] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar, pressure equalising dropping funnel, reflux condenser and Rotaflo tap and attached to a Schlenk line. The dropping funnel was charged with benzyloxyacetaldehyde (1.40 cm^3, 10 mmol) and anhydrous THF (5 cm^3). The reaction flask was charged with a solution of vinylmagnesium bromide (0.83 M (12 cm^3 1M soln + 2.4 cm^3 THF)). Benzyloxyacetaldehyde was added to the reaction flask dropwise, causing the temperature to rise to 60 °C. After 30 minutes at reflux the reaction was left to cool. Aqueous ammonium chloride was added and the organic layer was decanted off and the precipitate washed with THF. The solvent was removed *in vacuo* to give a crude oil. This residue was then dissolved in diethyl ether (60 cm^3) and dried over $MgSO_4$. After removal of the solvent, the product was purified by chromatography [hexane: ethyl acetate (80:20)] to yield the product as a yellow oil, (1.43 g, 81 %). δ_H 2.35 (1H, bs, O*H*), 3.31 (1H, dd, $^2J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 7.8 Hz, *Hd*), 3.48 (1H, dd, $^2J_{HH}$ = 9.8 Hz, $^3J_{HH}$ = 3.5 Hz, *He*), 4.25-4.32 (1H, m, C*H*OH), 4.51 (2H, AB, $^2J_{AB}$ = 12.1 Hz, CH_AH_BAr), 5.13 (1H, ap.dt, $^3J_{HH}$ = 10.6 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.6 Hz, *Hb*), 5.29 (1H, ap.dt, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.6 Hz, *Ha*), 5.76 (1H, ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.5 Hz, *Hc*), 7.21-7.31 (5H, m, ArH); δ_C 71.5 (*CH*OH), 73.4 (*CH*$_2$Ar), 74.0 (O*CH*$_2$), 116.5 (CH*CH*$_2$), 127.8 (*ArCH-3*), 127.9 (*ArCH-4*), 128.5 (*ArCH-2*), 136.6 (*CH*CH$_2$), 137.9 (*ArC-1*).

6.2.28 Preparation of 2-hydroxybut-3-enyl benzoate (100)[10]



The title compound was prepared following the method outlined by Ziegler *et al.* without modification.[10] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar, pressure equalising dropping funnel and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The funnel was charged with benzoyl chloride (3.94 g, 3.26 cm^3, 28.03 mmol) and pyridine (2 cm^3). The reaction flask was charged with (±)3-butene-1,2-diol (1.99 g, 1.91 cm^3, 22.66 mmol) and pyridine (10 cm^3). The reaction flask was cooled to -35 ºC (isopropanol: dry ice mixture). The benzoyl chloride solution was then dropped into the cooled reaction flask, and the reaction mixture was stirred for 17 h. After which the reaction mixture was poured into water and then extracted with DCM. The extracts were then washed with 2M HCl and $NaHCO_3$ solution, after which it was dried over Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography [chloroform: hexane (80:20)] afforded the product as an oil (1.34 g, 31 %). δ_H 2.27 (1H, bd, J_{HH} = 4.3 Hz, O*H*), 4.33 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 7.0 Hz *Hd*), 4.45 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 3.5 Hz, *He*), 4.53-4.60 (1H, m, C*H*OH), 5.31 (1H, ap.dt, $^3J_{HH}$ = 10.6 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.6 Hz, *Hb*), 5.48 (1H, ap.dt, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.6 Hz, *Ha*), 5.97 (1H, ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.5 Hz, *Hc*), 7.47 (2H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-3*), 7.60 (1H, tt, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 2.0 Hz, *ArH-4*), 8.08 (2H, dm, $^3J_{HH}$ = 8.6 Hz, *ArH-2*); δ_C 68.3 (O*C*H_2), 71.0 (*C*HOH), 117.1 (CH*C*H_2), 128.4 (*ArCH-3*), 129.7 (*ArCH-2*), 129.8 (*ArC-1*), 133.2 (*ArCH-4*), 136.3 (*C*HCH_2), 166.7 (C=O).

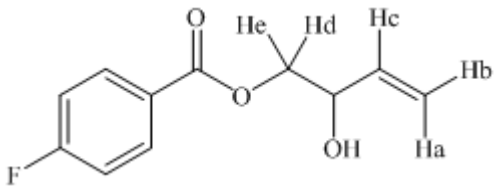
6.2.29 Preparation of *p*-methyl-2-hydroxybut-3-enyl benzoate (105)[10]



The title compound was prepared following the method outlined by Ziegler *et al.* without modification.[10] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar, pressure equalising dropping funnel and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with (±)-3-buten-2-ol (1.05 g, 1cm^3, 11.88 mmol) and pyridine (2 cm^3). The reaction mixture was stirred and cooled to – 15 ºC, after which *p*-methylbenzoyl chloride (1.67 g, 1.43 cm^3, 10.8 mmol) was added and the reaction mixture stirred at -15 ºC for 15 h. After 15 h, the reaction mixture was hydrolysed by the addition of

water (0.5 cm^3) and the solvent was removed *in vacuo*. The residue was then redissolved in DCM and washed with aqueous 2M HCl and $NaHCO_3$ solution, after which it was dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. Purification by chromatography [chloroform: hexane (80:20)] afforded the product as a white solid (0.89 g, 40 %). δ_H 1.90-2.14 (1H, bs, O*H*), 2.34 (3H, s, *CH₃*), 4.20 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 7.0 Hz, *Hd*), 4.34 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 3.5 Hz, *He*), 4.43-4.48 (1H, m, C*H*OH), 5.20 (1H, ap.dt, $^3J_{HH}$ = 10.6 Hz, $^2J_{HH}$ = 1.6 Hz, *Hb*), 5.37 (1H, ap.dt, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = 1.6 Hz, *Ha*), 5.87 (1H, ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.5 Hz, *Hc*), 7.17 (2H, d, $^3J_{HH}$ = 7.8 Hz, *ArH-3*) 7.87 (2H, dm, $^3J_{HH}$ = 8.6 Hz, *ArH-2*); δ_C 21.7 (*CH₃*), 68.2 (O*CH₂*), 71.2 (*CH*OH), 117.1 (CH*CH₂*), 127.1 (*ArC-1*), 129.2 (*ArCH-3*), 129.7 (*ArCH-2*), 136.2 (*CH*CH_2), 144.0 (*ArC-4*), 166.8 (C=O). m/z (EI^+) 206 ($[M]^+$, 52 %) 119 ($[M\text{-}OCH_2CHOHCH{=}CH_2]^+$, 100 %). HRMS (EI) 206.09402 ($C_{12}H_{14}O_3$ requires 206.09394).

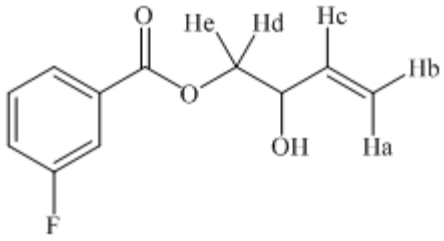
6.2.30 Preparation of 2-hydroxybut-3-enyl 4-fluorobenzoate (101)



The novel compound was prepared following the method outlined by Ziegler *et al.*[10] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar, pressure equalising dropping funnel and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The funnel was charged with 4-fluorobenzoyl chloride (2.33 g, 1.74 cm^3, 14.69 mmol) and pyridine (1.3 cm^3). The reaction flask was charged with (±)-3-butene-1,2-diol (1.05 g, 1 cm^3, 11.88 mmol) and pyridine (5 cm^3). The reaction flask was cooled to -35 ºC (isopropanol: dry ice mixture). The 4-fluorobenzoyl chloride solution was then dropped into the cooled reaction flask, and the reaction mixture was stirred for 17 h. After which the reaction mixture was poured into water and extracted with DCM. The extracts were then washed with 2M HCl and $NaHCO_3$ solution, after which it was dried over Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography [chloroform: hexane (80:20)] afforded the product as a white solid (1.47 g, 59 %). δ_H 2.35-2.55 (1H, bs, O*H*), 4.21 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 7.0 Hz, *Hd*), 4.32 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 3.5 Hz, *He*), 4.41-4.47 (1H, m, C*H*OH), 5.20 (1H, ap.dt, $^3J_{HH}$ = 10.6 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.6 Hz, *Hb*), 5.36 (1H, ap.dt, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.6 Hz, *Ha*), 5.86 (1H, ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.5 Hz, *Hc*), 7.02 (2H, ap.t, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, *ArH-3*), 7.98 (2H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HF}$ = 5.5 Hz, *ArH-2*); δ_C 68.3 (O*CH₂*), 71.1 (*CH*OH), 115.6 (d, $^2J_{CF}$ = 22.1 Hz, *ArCH-3*), 117.2 (CH*CH₂*), 126.1 (d, $^4J_{CF}$ = 2.0 Hz, *ArC-1*), 132.3 (d, $^3J_{CF}$ = 10.1 Hz, *ArCH-2*), 136.2 (*CH*CH_2), 165.7 (C=O), 165.9 (d,

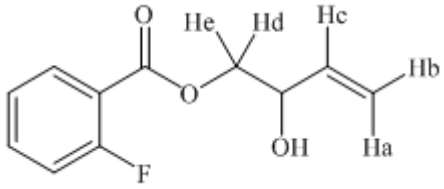
$^{1}J_{CF}$ = 253.5 Hz, *ArCF*); δ_F –105.2 (1F, s, CF). m/z (EI$^+$) 210 ([M]$^+$, 4 %) 123 ([M-$OCH_2CHOHCH{=}CH_2$]$^+$, 100 %). HRMS (EI) 210.06895 ($C_{11}H_{11}O_3F$ requires 210.06895).

6.2.31 Preparation of 2-hydroxybut-3-enyl 3-fluorobenzoate (102)



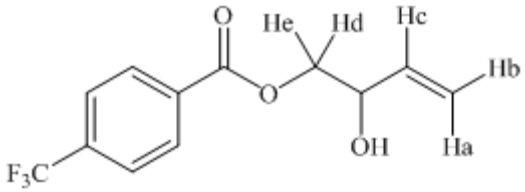
The novel compound was prepared following the method outlined by Ziegler *et al.*[10] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar, pressure equalising dropping funnel and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The funnel was charged with 3-fluorobenzoyl chloride (2.33 g, 1.79 cm^3, 14.69 mmol) and pyridine (1.3 cm^3). The reaction flask was charged with (±)3-butene-1,2-diol (1.05 g, 1 cm^3, 11.88 mmol) and pyridine (5 cm^3). The reaction flask was cooled to -35 ºC (isopropanol: dry ice mixture). The 3-fluorobenzoyl chloride solution was then dropped into the cooled reaction flask, and the reaction mixture was stirred for 17 h. After which the reaction mixture was poured into water and extracted with DCM. The extracts were then washed with 2M HCl and $NaHCO_3$ solution, after which it was dried over Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography [chloroform: hexane (80:20)] afforded the product as a white solid (1.05 g, 42 %). δ_H 2.08-2.11 (1H, bs, O*H*), 4.23 (1H, dd, $^{2}J_{HH}$ = 11.3 Hz, $^{3}J_{HH}$ = 7.0 Hz, *Hd*), 4.36 (1H, dd, $^{2}J_{HH}$ = 11.3 Hz, $^{3}J_{HH}$ = 3.5 Hz, *He*), 4.44-4.50 (1H, m, C*H*OH), 5.23 (1H, ap.dt, $^{3}J_{HH}$ = 10.6 Hz, $^{2}J_{HH}$ = $^{4}J_{HH}$ = 1.6 Hz, *Hb*), 5.38 (1H, ap.dt, $^{3}J_{HH}$ = 17.2 Hz, $^{2}J_{HH}$ = $^{4}J_{HH}$ = 1.6 Hz, *Ha*), 5.88 (1H, ddd, $^{3}J_{HH}$ = 17.2 Hz, $^{3}J_{HH}$ = 10.6 Hz, $^{3}J_{HH}$ = 5.9 Hz, *Hc*), 7.21 (1H, ap.tdd, $^{3}J_{HH}$ = $^{3}J_{HF}$ = 8.2 Hz, $^{4}J_{HH}$ = 2.7 Hz, $^{4}J_{HH}$ = 1.2 Hz, *ArH-4*), 7.36 (1H, td, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HF}$ = 5.5 Hz, *ArH-5*), 7.66 (1H, ddd, $^{3}J_{HF}$ = 9.4 Hz, $^{4}J_{HH}$ = 2.7 Hz, $^{4}J_{HH}$ = 1.6 Hz, *ArH-2*), 7.77 (1H, dt, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.6 Hz, *ArH-6*); δ_C 68.5 (O*C*H_2), 71.1 (*C*HOH), 116.6 (d, $^{2}J_{CF}$ = 24.1 Hz, *ArCH-2*), 117.4 (CH*C*H_2), 120.3 (d, $^{2}J_{CF}$ = 19.1 Hz, *ArCH-4*), 125.4 (*ArC-6*), 130.1 (d, $^{3}J_{CF}$ = 7.0 Hz, *ArCH-5*), 132.0 (d, $^{3}J_{CF}$ = 7.0 Hz, *ArC-1*), 136.1 (*C*HCH_2), 162.5 (d, $^{1}J_{CF}$ = 246.5 Hz, *ArCF*), 165.5 (C=O); δ_F –112.2 (1F, s, CF). m/z (EI$^+$) 210 ([M]$^+$, 8 %) 123 ([M-$OCH_2CHOHCH{=}CH_2$]$^+$, 100 %). HRMS (EI) 210.06900 ($C_{11}H_{11}O_3F$ requires 210.06895).

6.2.32 Preparation of 2-hydroxybut-3-enyl 2-fluorobenzoate (103)



The novel compound was prepared following the method outlined by Ziegler *et al.*[10] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar, pressure equalising dropping funnel and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The funnel was charged with 2-fluorobenzoyl chloride (2.33 g, 1.75 cm^3, 14.69 mmol) and pyridine (1.3 cm^3). The reaction flask was charged with (±)-3-butene-1,2-diol (1.05 g, 1 cm^3, 11.88 mmol) and pyridine (5 cm^3). The reaction flask was cooled to -35 ºC (isopropanol: dry ice mixture). The 2-fluorobenzoyl chloride solution was then dropped into the cooled reaction flask, and the reaction mixture was stirred for 17 h. After which the reaction mixture was poured into water and extracted with DCM. The extracts were then washed with 2M HCl and $NaHCO_3$ solution, after which it was dried over Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography [chloroform: hexane (80:20)] afforded the product as a white solid (1.09 g, 44 %). δ_H 1.80-2.00 (1H, bs, O*H*), 4.22 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 7.0 Hz, *Hd*), 4.32 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 3.5 Hz, *He*), 4.43-4.49 (1H, m, C*H*OH), 5.22 (1H, ap.dt, $^3J_{HH}$ = 10.6 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.6 Hz, *Hb*), 5.36 (1H, ap.dt, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.6 Hz, *Ha*), 5.86 (1H, ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.5 Hz, *Hc*), 7.08 (1H, ddd, $^3J_{HF}$ = 11.0 Hz, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-3*), 7.15 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-5),* 7.47 (1H, dddd, $^3J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 7.4 Hz, $^4J_{HF}$ = 4.7 Hz, $^4J_{HH}$ = 2.0 Hz, *ArH-4*), 7.89 (1H, td, $^3J_{HH}$ = $^4J_{HF}$ = 7.4 Hz, $^4J_{HH}$ = 2.0 Hz, *ArH-6*); δ_C 68.6 (O*C*H_2), 70.9 (*C*HOH), 117.0 (d, $^2J_{CF}$ = 243.1 Hz, *ArCH-3*) 117.3 (CH*C*H_2), 118.4 (d, $^2J_{CF}$ = 10.1 Hz, *ArC-1*), 124.1 (d, $^3J_{CF}$ = 4.0 Hz, *ArCH-4*), 132.3 (*ArCH-5*), 134.8 (d, $^3J_{CF}$ = 9.1 Hz, *ArCH-6*), 135.9 (*C*HCH_2), 162.0 (d, $^1J_{CF}$ = 259.6 Hz, *ArCF*), 164.5 (C=O); δ_F -109.0 (1F, s, CF). m/z (EI$^+$) 210 ([M]$^+$, 8 %) 123 ([M-$OCH_2CHOHCH{=}CH_2$]$^+$, 100 %). HRMS (EI) 210.06901 ($C_{11}H_{11}O_3F$ requires 210.06895).

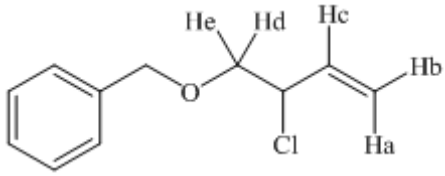
6.2.33 Preparation of 2-hydroxybut-3-enyl 4-(trifluoromethyl)benzoate (104)



The novel compound was prepared following the method outlined by Ziegler *et al.*[10] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar, pressure equalising dropping funnel and Rotaflo tap and attached to a Schlenk line. After flame-

drying under high vacuum, the flask was cooled and filled with nitrogen. The funnel was charged with 4-(trifluoromethyl)benzoyl chloride (3.06 g, 2.17 cm^3, 14.69 mmol) and pyridine (1.3 cm^3). The reaction flask was charged with (±)3-butene-1,2-diol (1.05 g, 1 cm^3, 11.88 mmol) and pyridine (5 cm^3). The reaction flask was cooled to -35 ºC (isopropanol: dry ice mixture). The 4-(trifluoromethyl)benzoyl chloride solution was then dropped into the cooled reaction flask, and the reaction mixture was stirred for 17 h. After which the reaction mixture was poured into water and extracted with DCM. The extracts were then washed with 2M HCl and $NaHCO_3$ solution, after which it was dried over Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography [chloroform: hexane (80:20)] afforded the product as a white solid (2.03 g, 66 %). δ_H 2.34-2.41 (1H, bs, O*H*), 4.25 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 7.0 Hz, *Hd*), 4.35 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 3.5 Hz, *He*), 4.44-4.49 (1H, m, C*H*OH), 5.20 (1H, ap.dt, $^3J_{HH}$ = 10.6 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.6 Hz, *Hb*), 5.36 (1H, ap.dt, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.6 Hz, *Ha*), 5.86 (1H, ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 5.9 Hz, *Hc*), 7.61 (2H, tm, $^3J_{HH}$ = 8.2 Hz, *ArH-3*), 8.07 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-2*); δ_C 68.6 (O*C*H_2), 71.0 (*C*HOH), 117.4 (CH*C*H_2), 123.6 (q, $^1J_{CF}$ = 272.9 Hz, *ArCF*$_3$), 125.5 (*ArCH-3*), 130.1 (*ArCH-2*), 133.0 (*ArC-1*), 134.7 (q, $^2J_{CF}$ = 32.7 Hz, *ArC-4*), 136.1 (*C*HCH_2), 165.5 (C=O); δ_F – 63.1 (3F, s, CF_3). m/z (FAB^+) 261 ($[MH]^+$, 32 %) 123 ($[M\text{-}OCH_2CHOHCH{=}\ CH_2]^+$, 100 %). HRMS (FAB) 261.07357 ($C_{12}H_{12}O_3F_3$ requires 261.07355).

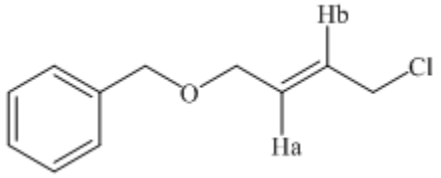
6.2.34 Preparation of ((2-chlorobut-3-enyloxy)methyl)benzene (106)



The novel compound was prepared following the method outlined by Munyemana *et al.*[11] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was then charged with 1-(benzyloxy)but-3-en-2-ol (0.37 g, 2.07 mmol) and anhydrous DCM (7 cm^3). The flask was then cooled to 0 ºC using an ice bath. Once cooled tetramethyl-α-chloroenamine was added (0.28 g, 0.28 cm^3, 2.07 mmol) *via* syringe. The reaction mixture was then stirred at room temperature for 3 h. After which purification by chromatography [DCM/cyclohexane (50/50)] afforded the product as an oil (0.21 g, 52 %). Elemental analysis: Found: C, 67.07; H, 6.55. Calc. for $C_{11}H_{13}OCl$: C, 67.18; H, 6.66 %. δ_H 3.58 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 6.3 Hz, *Hd*), 3.61 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 6.7 Hz, *He*), 4.41-4.46 (1H, m, *C*HCl), 4.53 (2H, AB, $^2J_{AB}$ = 12.1 Hz, CH_AH_BAr), 5.18 (1H, ap.dt, $^3J_{HH}$ = 10.2 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 0.8 Hz, *Hb*), 5.32 (1H, ap.dt, $^3J_{HH}$

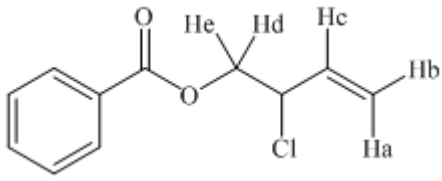
= 16.8 Hz, $^{2}J_{HH}$ = $^{4}J_{HH}$ = 0.8 Hz, *Ha*), 5.85 (1H, ddd, $^{3}J_{HH}$ = 17.2 Hz, $^{3}J_{HH}$ = 10.2 Hz, $^{3}J_{HH}$ = 7.8 Hz, *Hc*), 7.20–7.31 (5H, *ArH*); δ_C 60.1 (*CH*Cl), 73.4 (*CH*$_2$Ar), 73.6 (O*CH*$_2$), 118.6 (CH*CH*$_2$), 127.7 (*ArCH-3*), 127.9 (*ArCH-4*), 128.5 (*ArCH-2*), 135.5 (*CH*CH$_2$), 137.7 (*ArC-1*). m/z (EI$^+$) 196 ([M]$^+$, 15 %) 91 ([M-OCH$_2$CHClCH=CH$_2$]$^+$, 100 %). HRMS (EI) 196.06512 ($C_{11}H_{13}OCl$ requires 196.06517).

6.2.35 Preparation of ((4-chlorobut-2-enyloxy)methyl)benzene (107)[12]



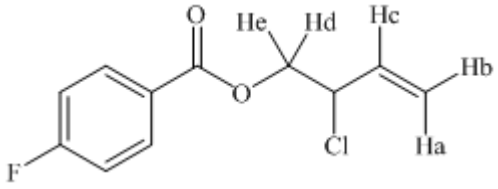
The rearranged chloride product was also isolated from the synthesis of ((4-chlorobut-2-enyloxy)methyl) benzene, as an oil (0.06 g, 15 %); δ_H 3.96 (2H, dm, $^{2}J_{HH}$ = 11.7 Hz), 3.99 (2H, dm, $^{3}J_{HH}$ = 5.5 Hz,), 4.44 (2H, AB, $^{2}J_{AB}$ = 12.5 Hz, *CH$_A$H$_B$Ar*), 5.73-5.87 (2H, m, *Ha and Hb*), 7.18–7.30 (5H, *ArH*); δ_C 44.4 (*CH*$_2$Cl), 69.5 (*CH*$_2$Ar), 72.4 (O*CH*$_2$), 127.7 (*ArCH-3*), 127.8 (*ArCH-4*), 128.4 (*CH*CH$_2$Cl), 128.5 (*ArCH-2*), 1 31.2 (*CH*CH$_2$O), 138.1 (*ArC-1*).

6.2.36 Preparation of 2-chlorobut-3-enyl benzoate (108)



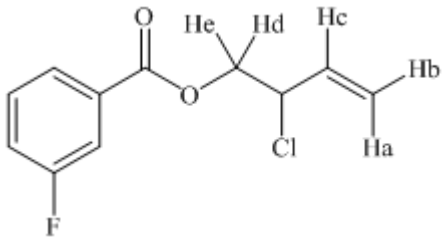
The title compound was prepared following the method outlined by Munyemana *et al.*[11] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was then charged with 2-hydroxybut-3-enyl benzoate (1.24 g, 6.45 mmol) and anhydrous DCM (25 cm^3). The flask was cooled to 0 ºC using an ice bath. Once cooled tetramethyl-α-chloroenamine was added (0.88 cm^3, 6.45 mmol) *via* syringe. The reaction mixture was then stirred at room temperature for 3 h. After which purification by chromatography [DCM: cyclohexane (50:50)] afforded the product as an oil (0.88 g, 65 %). δ_H 4.38 (1H, dd, $^{2}J_{HH}$ = 11.3 Hz, $^{3}J_{HH}$ = 7.0 Hz, *Hd*), 4.42 (1H, dd, $^{2}J_{HH}$ = 11.3 Hz, $^{3}J_{HH}$ = 5.9 Hz, *He*), 4.55-4.61 (1H, m, *CH*Cl), 5.20 (1H, ap.dt, $^{3}J_{HH}$ = 10.2 Hz, $^{2}J_{HH}$ = $^{4}J_{HH}$ = 0.8 Hz, *Hb*), 5.35 (1H, ap.dt, $^{3}J_{HH}$ = 16.8 Hz, $^{2}J_{HH}$ = $^{4}J_{HH}$ = 0.8 Hz, *Ha*), 5.86 (1H, ddd, $^{3}J_{HH}$ = 16.8 Hz, $^{3}J_{HH}$ = 10.2 Hz, $^{3}J_{HH}$ = 7.8 Hz, *Hc*), 7.34 (2H, tm, $^{3}J_{HH}$ = 7.8 Hz, *ArH-3*), 7.46 (1H, tt, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 2.0 Hz, *ArH-4*), 7.34 (2H, dm, $^{3}J_{HH}$ = 8.2 Hz, *ArH-2*); δ_C 58.8 (*CH*Cl), 67.1 (O*CH*$_2$), 119.4 (CH*CH*$_2$), 128.5 (*ArCH-3*), 129.7 (*ArC-1*), 129.8 (*ArCH-2*), 133.3 (*CH*CH$_2$), 134.5 (*ArCH-4*), 165.9 (C=O). m/z (EI$^+$) 210 ([M]$^+$, 5 %) 105 ([M-OCH$_2$CHClCH=CH$_2$]$^+$, 100 %). HRMS (EI) 210.04455 ($C_{11}H_{11}O_2Cl$ requires 210.04448).

6.2.37 Preparation of 2-chlorobut-3-enyl 4-fluorobenzoate (109)



The novel compound was prepared following the method outlined by Munyemana *et al.*[11] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was then charged with 2-hydroxybut-3-enyl 4-fluorobenzoate (1.0 g, 4.75 mmol) and anhydrous DCM (25 cm^3). The flask was then cooled to 0 ºC using an ice bath. Once cooled tetramethyl-α-chloroenamine was added (0.64 cm^3, 4.75 mmol) *via* syringe. The reaction mixture was then stirred at room temperature for 3 h. After which purification by chromatography [DCM: cyclohexane (50:50)] afforded the product as an oil (0.80 g, 74 %). δ_H 4.38 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 7.0 Hz, *Hd*), 4.42 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 5.9 Hz, *He*), 4.55-4.61 (1H, m, *CH*Cl), 5.20 (1H, ap.dt, $^3J_{HH}$ = 10.2 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 0.8 Hz, *Hb*), 5.35 (1H, ap.dt, $^3J_{HH}$ = 16.8 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 0.8 Hz, *Ha*), 5.86 (1H, ddd, $^3J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 7.8 Hz, *Hc*), 7.05 (2H, ap.t, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, *ArH-3*), 8.00 (2H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HF}$ = 5.1 Hz, *ArH-2*); δ_C 58.7 (*CH*Cl), 67.2 (O*CH*$_2$), 115.7 (d, $^2J_{CF}$ = 22.1 Hz, *ArCH-3*), 119.5 (CH*CH*$_2$), 125.9 (d, $^4J_{CF}$ = 3.0 Hz, *ArC-1*), 132.3 (d, $^3J_{CF}$ = 10.1 Hz, *ArCH-2*), 134.4 (*CH*CH$_2$), 165.0 (C=O), 166.0 (d, $^1J_{CF}$ = 254.6 Hz, *ArCF*); δ_F -105.4 (1F, s, CF). m/z (EI^+) 228 ($[M]^+$, 22 %) 123 ($[M\text{-}OCH_2CHClCH{=}CH_2]^+$, 100 %). HRMS (EI) 228.03504 ($C_{11}H_{10}O_2ClF$ requires 228.03509).

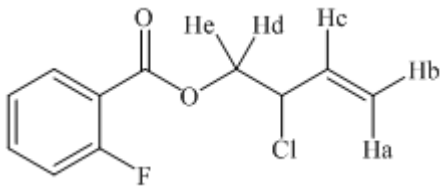
6.2.38 Preparation of 2-chlorobut-3-enyl 3-fluorobenzoate (110)



The novel compound was prepared following the method outlined by Munyemana *et al.*[11] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was then charged with 2-hydroxybut-3-enyl 3-fluorobenzoate (0.2 g, 2.46 mmol) and anhydrous DCM (15 cm^3). The flask was then cooled to 0 ºC using an ice bath. Once cooled tetramethyl-α-chloroenamine was added (0.36 cm^3, 2.71 mmol) *via* syringe. The reaction mixture was then stirred at room temperature for 3 h. After which purification by chromatography [DCM: cyclohexane

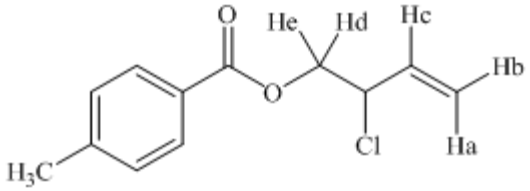
(50:50)] afforded the product as an oil (0.19 g, 34 %). δ_H 4.51 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 7.0 Hz, *Hd*), 4.55 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 5.9 Hz, *He*), 4.67-4.73 (1H, m, *CH*Cl), 5.34 (1H, d, $^3J_{HH}$ = 10.2 Hz, *Hb*), 5.48 (1H, ap.dt, $^3J_{HH}$ = 16.8 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 0.8 Hz, *Ha*), 5.98 (1H, ddd, $^3J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 7.8 Hz, *Hc*), 7.30 (1H, ap.tdd, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, $^4J_{HH}$ = 2.7 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-4*), 7.46 (1H, td, $^3J_{HH}$ = 8.2 Hz, $^4J_{HF}$ = 5.5 Hz, *ArH-5*), 7.75 (1H, ddd, $^3J_{HF}$ = 9.4 Hz, $^4J_{HH}$ = 2.7 Hz, $^4J_{HH}$ = 1.6 Hz, *ArH-2*), 7.87 (1H, dt, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-6*); δ_C 58.6 (*CH*Cl), 67.4 (O*CH*$_2$), 116.7 (d, $^2J_{CF}$ = 22.6 Hz, *ArCH-2*), 119.6 (CH*CH*$_2$), 120.4 (d, $^2J_{CF}$ = 21.4 Hz, *ArCH-4*), 125.5 (d, $^4J_{CF}$ = 2.5 Hz, *ArCH-6*), 130.2 (d, $^3J_{CF}$ = 8.8 Hz, *ArCH-5*), 131.8 (d, $^3J_{CF}$ = 7.5 Hz, *ArC-1*), 134.3 (*CH*CH$_2$), 162.6 (d, $^1J_{CF}$ = 246.5 Hz, *ArCF*), 164.9 (d, $^4J_{CF}$ = 3.8 Hz, C=O); δ_F –112.1. m/z (EI$^+$) 228 ([M]$^+$, 33 %) 123 ([M-OCH$_2$CHClCH=CH$_2$]$^+$, 90 %). HRMS (EI) 228.03509 ($C_{11}H_{10}O_2ClF$ requires 228.03509).

6.2.39 Preparation of 2-chlorobut-3-enyl 2-fluorobenzoate (111)



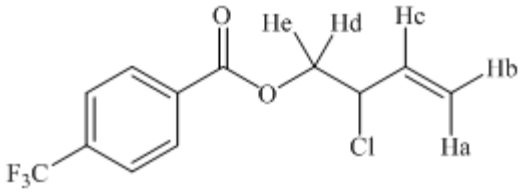
The novel compound was prepared following the method outlined by Munyemana *et al.*[11] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was then charged with 2-hydroxybut-3-enyl 2-fluorobenzoate (0.30 g, 1.43 mmol) and anhydrous DCM (15 cm^3). The flask was then cooled to 0 ºC using an ice bath. Once cooled tetramethyl-α-chloroenamine was added (0.19 cm^3, 1.43 mmol) *via* syringe. The reaction mixture was then stirred at room temperature for 3 h. After which purification by chromatography [DCM: cyclohexane (50:50)] afforded the product as an oil (0.15 g, 47 %). δ_H 4.43 (1H, dd, $^2J_{HH}$ = 11.7 Hz, $^3J_{HH}$ = 7.0 Hz, *Hd*), 4.47(1H, dd, $^2J_{HH}$ = 11.7 Hz, $^3J_{HH}$ = 5.9 Hz, *He*), 4.58-4.64 (1H, m, *CH*Cl), 5.24 (1H, d, $^3J_{HH}$ = 10.2 Hz, *Hb*), 5.39 (1H, ap.dt, $^3J_{HH}$ = 16.8 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 0.8 Hz, *Ha*), 5.90 (1H, ddd, $^3J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 7.8 Hz, *Hc*), 7.08 (1H, ddd, $^3J_{HF}$ = 11.0 Hz, $^4J_{HH}$ = 8.2 Hz, $^5J_{HH}$ = 1.2 Hz, *ArH-3*), 7.15 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-5),* 7.47 (1H dddd, $^3J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 7.4 Hz, $^4J_{HF}$ = 4.7 Hz, $^4J_{HH}$ = 2.0 Hz,, *ArH-4*), 7.88 (1H, td, $^3J_{HH}$ = $^4J_{HF}$ = 7.4 Hz, $^4J_{HH}$ = 2.0 Hz, *ArH-6*); δ_C 57.6 (*CH*Cl), 66.3 (O*CH*$_2$), 116.0 (d, $^2J_{CF}$ = 22.1 Hz, *ArCH-3*), 117.1 (d, $^2J_{CF}$ = 9.1 Hz, *ArC-1*), 118.4 (CH*CH*$_2$), 123.0 (d, $^4J_{CF}$ = 5.0 Hz, *ArCH-5*), 131.1 (*ArCH-6*), 133.4 (*CH*CH$_2$), 133.8 (d, $^3J_{CF}$ = 9.1 Hz, *ArCH-4*), 161.1 (d, $^1J_{CF}$ = 261.6 Hz, *ArCF*), 162.7 (C=O); δ_F -109.0 (1F, s, CF). m/z (EI$^+$) 228 ([M]$^+$, 23 %) 123 ([M-OCH$_2$CHClCH=CH$_2$]$^+$, 100 %). HRMS (EI) 228.03507 ($C_{11}H_{10}O_2ClF$ requires 228.03509).

6.2.40 Preparation of 2-chlorobut-3-enyl 4-(methyl)benzoate (113)



The novel compound was prepared following the method outlined by Munyemana *et al.*[11] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was then charged with 2-hydroxybut-3-enyl 4-methylbenzoate (1.19 g, 5.80 mmol) and anhydrous DCM (5 cm^3). The flask was then cooled to 0 ºC using an ice bath. Once cooled tetramethyl-α-chloroenamine was added (0.77 cm^3, 5.80 mmol) *via* syringe. The reaction mixture was then stirred at room temperature for 3 h. After which purification by chromatography [DCM: cyclohexane (50: 50)] afforded the product as an oil (0.41 g, 32 %). δ_H 2.44 (3H, s, *CH*$_3$), 4.49 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 7.0 Hz, *Hd*), 4.54 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 5.9 Hz, *He*), 4.67-4.73 (1H, m, *CH*Cl), 5.32 (1H, d, $^3J_{HH}$ = 10.2 Hz, *Hb*), 5.47 (1H, ap.dt, $^3J_{HH}$ = 16.8 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.2 Hz, *Ha*), 5.98 (1H, ddd, $^3J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 7.8 Hz, *Hc*), 7.27 (2H, d, $^3J_{HH}$ = 8.6 Hz, *ArH-3*), 7.96 (1H, dm, $^3J_{HH}$ = 8.6 Hz, *ArH-2*); δ_C 21.7 (*CH*$_3$), 58.8 (*CH*Cl), 66.9 (O*CH*$_2$), 119.3 (CH*CH*$_2$), 126.9 (*ArC-1*), 129.2 (*ArCH-3*), 129.8 (*ArCH-2*), 134.6 (*CH*CH$_2$), 144.0 (*ArC-4*), 166.0 (C=O). m/z (EI^+) 224 ($[M]^+$, 32 %) 119 ($[M\text{-}OCH_2CHClCH{=}CH_2]^+$, 100 %). HRMS (EI) 224.06006 ($C_{12}H_{13}O_2Cl$ requires 224.06008).

6.2.41 Preparation of 2-chlorobut-3-enyl 4-(trifluoromethyl)benzoate (112)

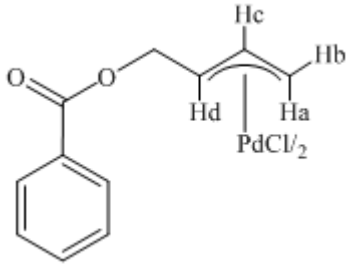


The novel compound was prepared following the method outlined by Munyemana *et al.*[11] A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was then charged with 2-hydroxybut-3-enyl 4-(trifluoromethyl)benzoate (0.50 g, 1.93 mmol) and anhydrous DCM (25 cm^3). The flask was then cooled to 0 ºC using an ice bath. Once cooled tetramethyl-α-chloroenamine was added (0.28 cm^3, 2.13 mmol) *via* syringe. The reaction mixture was then stirred at room temperature for 3 h. After which purification by chromatography [DCM: cyclohexane (50:50)] afforded the product as an oil (0.20 g, 37 %). δ_H 4.45 (1H, dd, $^2J_{HH}$ =

11.7 Hz, $^3J_{HH}$ = 7.0 Hz, *Hd*), 4.49 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 5.9 Hz, *He*), 4.59-4.65 (1H, m, *CH*Cl), 5.25 (1H, d, $^3J_{HH}$ = 10.2 Hz, *Hb*), 5.39 (1H, ap.dt, $^3J_{HH}$ = 16.8 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.2 Hz, *Ha*), 5.89 (1H, ddd, $^3J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 7.8 Hz, *Hc*), 7.65 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-3*), 8.10 (1H, dm, $^3J_{HH}$ = 8.6 Hz, *ArH-2*); δ_C 58.6 (*CH*Cl), 67.5 (O*CH*$_2$), 119.6 (CH*CH*$_2$), 123.6 (q, $^1J_{CF}$ = 272.9 Hz, *ArCF*$_3$), 125.5 (*ArCH-3*), 130.2 (*ArCH-2*), 132.8 (*ArC-1*), 134.2 (*CH*CH$_2$), 134.8 (q, $^2J_{CF}$ = 32.7 Hz, *ArC-4*), 164.8 (C=O); δ_F -63.2 (3F, s, CF_3). m/z (EI$^+$) 278 ([M]$^+$, 6 %), 173 ([M-$OCH_2CHClCH{=}CH_2$]$^+$, 68 %), 88 ([M-$CF_3C_6H_4COOH$]$^+$, 100 %). HRMS (EI) 278.03186 ($C_{12}H_{10}O_2ClF_3$ requires 278.03189).

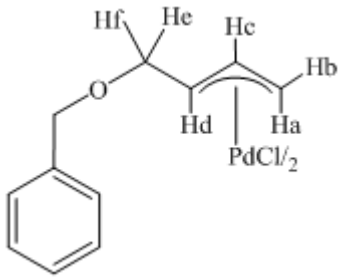
6.3 Experimental Details for Chapter 3

6.3.1 Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)-benzoate]dipalladium (125)



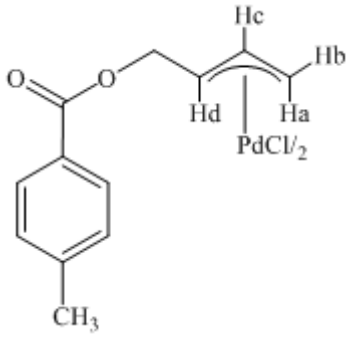
The novel compound was prepared following the method outlined by Granberg *et al.*[13] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (1.23 g, 2.13 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with 2-chlorobut-3-enyl benzoate (0.45 g, 2.13 mmol) and DMSO (30 cm^3). The reaction mixture was stirred for 2 h and then quenched with water (30 cm^3) and chloroform (30 cm^3). The organic phase was separated, washed with water (3 x 20 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid. Purification by column chromatography [DCM: hexane (70:30)] afforded the product as a yellow solid (0.48 g, 71 %). Elemental analysis: Found: C, 41.71; H, 3.45. Calc. for $C_{22}H_{22}Cl_2O_4Pd_2$: C, 41.67; H, 3.50 %. δ_H 2.98 (1H, d, $^3J_{HH}$ = 12.1 Hz, *Ha*), 3.79 (1H, dt, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.5 Hz, *Hd*), 4.01 (1H, d, $^3J_{HH}$ = 6.7 Hz, *Hb*), 4.41 (2H, m, O*CH*$_A$*H*$_B$), 5.54 (1H, ddd, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 7.0 Hz, *Hc*), 7.38 (2H, tm, $^3J_{HH}$ = 7.8 Hz, *ArH-3*), 7.51 (1H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-4*), 8.01 (2H, dm, $^3J_{HH}$ = 7.0 Hz, *ArH-2*); δ_C 61.4 (CH*CH*$_2$), 63.7 (O*CH*$_2$), 75.9 (OCH$_2$*CH*), 110.7 (*CH*CH$_2$), 128.4 (*ArCH-3*), 129.7 (*ArC-1*), 129.8 (*ArCH-2*), 133.2 (*ArCH-4*), 166.1 (C=O). m/z (FAB$^+$) 599 ([M-Cl]$^+$, 100 %), 634 ([M]$^+$, 8 %).

6.3.2 Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)oxy)methyl) benzene] dipalladium (126)



The novel compound was prepared following the method outlined by Granberg *et al.*[13] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (0.85 g, 1.47 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with ((2-chlorobut-3-enyloxy)methyl)benzene (0.29 g, 1.47 mmol) and DMSO (15 cm^3). The reaction mixture was stirred for 2 h and then quenched with water (15 cm^3) and chloroform (20 cm^3). The organic phase was separated, washed with water (3 x 10 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid. Purification by column chromatography [DCM: hexane (70:30)] afforded the product as a yellow solid (0.28 g, 63 %). δ_H 2.91 (1H, d, $^3J_{HH}$ = 12.1 Hz, *Ha*), 3.51 (1H, dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 6.3 *He*), 3.62 (1H, dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 3.1 Hz, *Hf*), 3.78 (1H, ddd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 3.1 Hz, *Hd*), 3.93 (1H, d, $^3J_{HH}$ = 6.7 Hz, *Hb*), 4.48 (1H, d, $^2J_{HH}$ = 11.7 Hz, CH*HAr*), 4.57 (1H, d, $^2J_{HH}$ = 11.7 Hz, *CH*HAr), 5.45 (1H, ddd, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 6.7 Hz, *Hc*), 7.22-7.30 (5H, m, *ArH*); δ_C 60.3 (CH*CH_2*), 69.0 (O*CH_2*), 73.2 (Ar*CH_2*), 79.5 (OCH_2*CH*), 109.5 (*CH*CH_2), 127.8 (*ArCH-3*), 128.0 (*ArCH-2*), 128.5 (*ArCH-4*), 138.0 (*ArC-1*). m/z (FAB^+) 571 ($[M\text{-}Cl]^+$), 100 %, 606 ($[M]^+$, 10 %).

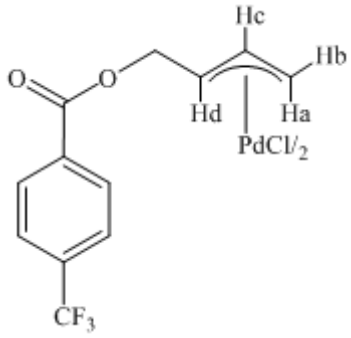
6.3.3 Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)-4-methylbenzoate] dipalladium (131)



The novel compound was prepared following the method outlined by Granberg *et al.*[13] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (0.56 g, 0.97 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with 2-chlorobut-3-enyl 4-

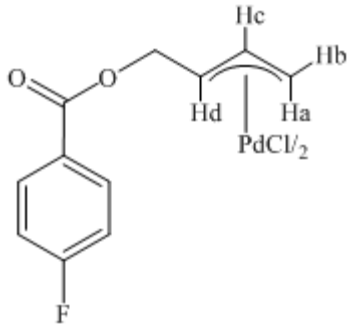
methylbenzoate (0.21g, 0.92 mmol) and DMSO (17 cm^3). The reaction mixture was stirred for 2 h and then quenched with water (15 cm^3) and chloroform (20 cm^3). The organic phase was separated, washed with water (3 x 20 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid. Purification by column chromatography [DCM: hexane (70:30)] afforded the product as a yellow solid (0.12 g, 39 %). Elemental analysis: Found: C, 43.57; H, 3.85. Calc. for $C_{24}H_{26}Cl_2O_4Pd_2$: C, 43.53; H, 3.96 %. δ_H 2.34 (3H, s, *CH*$_3$), 2.98 (1H, d, $^3J_{HH}$ = 12.1 Hz, *Ha*), 3.79 (1H, dt, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.5 Hz, *Hd*), 4.00 (1H, d, $^3J_{HH}$ = 6.3 Hz, *Hb*), 4.39 (2H, m, OC*H*$_A$*H*$_B$), 5.52 (1H, ddd, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 6.7 Hz, *Hc*), 7.17 (2H, dm, $^3J_{HH}$ = 8.6 Hz, *ArH-3*), 7.89 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-2*); δ_C 21.7 (CH_3), 61.4 (CH*C*H$_2$), 63.5 (O*C*H$_2$), 76.1 (OCH$_2$*C*H), 110.7 (*C*HCH$_2$), 126.9 (*ArC-1*), 129.2 (*ArCH-3*), 129.8 (*ArCH-2*), 144.0 (*ArC-4*), 166.2 (C=O). m/z (FAB^+) 627 ($[M\text{-}Cl]^+$, 100 %), 662 ($[M]^+$, 12 %).

6.3.4 Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)-4-(trifluoromethyl)benzoate] dipalladium (130)



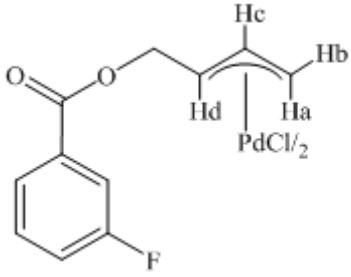
The title compound was prepared following the method outlined by Granberg *et al.*[13] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (0.21g, 0.36 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with 2-chlorobut-3-enyl-4-(trifluoromethyl)benzoate (0.10 g, 0.36 mmol) and DMSO (10 cm^3). The reaction mixture was stirred for 2 h and then quenched with water (15 cm^3) and chloroform (20 cm^3). The organic phase was separated, washed with water (3 x 10 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid. Purification by column chromatography [DCM: hexane (70:30)] afforded the product as a yellow solid (0.07 g, 53 %). δ_H 3.01 (1H, d, $^3J_{HH}$ = 12.1 Hz, *Ha*), 3.79 (1H, dt, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.5 Hz, *Hd*), 4.03 (1H, d, $^3J_{HH}$ = 7.0 Hz, *Hb*), 4.44 (2H, m, OC*H*$_A$*H*$_B$), 5.53 (1H, ddd, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 7.0 Hz, *Hc*), 7.64 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-3*), 8.11 (2H, dm, $^3J_{HH}$ = 7.8 Hz, *ArH-2*); δ_C 60.7 (CH*C*H$_2$), 63.2 (O*C*H$_2$), 74.3 (OCH$_2$*C*H), 109.7 (*C*HCH$_2$), 122.6 (q, $^1J_{CF}$ = 272.7 Hz, *ArCF*$_3$), 124.5 (*ArCH-3*), 129.2 (*ArCH-2*), 131.9 (*ArC-1*), 133.7 (q, $^2J_{CF}$ = 32.2 Hz, *ArC-4*), 163.9 (C=O); δ_F -63.12 (3F, s, CF_3). m/z (FAB^+) 735 ($[M\text{-}Cl]^+$, 100 %), 770 ($[M]^+$, 12 %).

6.3.5 Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)-4-fluorobenzoate]dipalladium (127)



The novel compound was prepared following the method outlined by Granberg *et al.*[13] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (0.53 g, 0.92 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with 2-chlorobut-3-enyl-4-fluorobenzoate (0.21 g, 0.90 mmol) and DMSO (17 cm^3). The reaction mixture was stirred for 2 h and then quenched with water (15 cm^3) and chloroform (20 cm^3). The organic phase was separated, washed with water (3 x 20 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid. Purification by column chromatography [DCM: hexane (70:30)] afforded the product as a yellow solid (0.22 g, 73 %). Elemental analysis: Found: C, 39.51; H, 3.07. Calc. for $C_{22}H_{20}Cl_2F_2O_4Pd_2$: C, 39.43; H, 3.01 %. δ_H 2.99 (1H, d, $^3J_{HH}$ = 12.5 Hz, *Ha*), 3.80 (1H, dt, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.5 Hz, *Hd*), 4.01 (1H, d, $^3J_{HH}$ = 6.7 Hz, *Hb*), 4.40 (2H, m, OCH_AH_B), 5.52 (1H, ddd, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 6.7 Hz, *Hc*), 7.05 (2H, ap.t, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, *ArH-3*), 8.02 (2H, dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HF}$ = 5.5 Hz, *ArH-2*); δ_C 61.5 ($CHCH_2$), 63.8 (OCH_2), 75.8 (OCH_2CH), 110.6 ($CHCH_2$), 115.6 (d, $^2J_{CF}$ = 22.6 Hz, *ArCH-3*), 125.9 (*ArC-1*), 132.4 (d, $^3J_{CF}$ = 9.1 Hz, *ArCH-2*), 165.2 (C=O), 165.9 (d, $^1J_{CF}$ = 254.2 Hz, *ArCF*); δ_F -105.02 (1F, s, CF). m/z (FAB^+) 635 ($[M\text{-}Cl]^+$, 100 %).

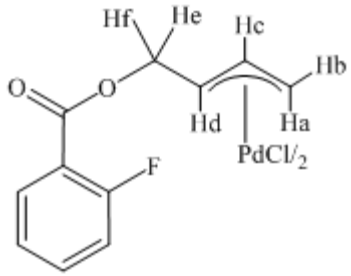
6.3.6 Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)-3-fluorobenzoate]dipalladium (128)



The novel compound was prepared following the method outlined by Granberg *et al.*[13] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (0.26 g, 0.45 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with 2-chlorobut-3-enyl-3-fluorobenzoate (0.10g, 0.44 mmol)

and DMSO (10 cm^3). The reaction mixture was stirred for 2 h and then quenched with water (15 cm^3) and chloroform (20 cm^3). The organic phase was separated, washed with water (3 x 10 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid. Purification by column chromatography [DCM: hexane (70:30)] afforded the product as a yellow solid (0.09 g, 60 %). Elemental analysis: Found: C, 39.61; H, 2.97. Calc. for $C_{22}H_{20}Cl_2F_2O_4Pd_2$: C, 39.43; H, 3.01. δ_H 2.99 (1H, d, $^3J_{HH}$ = 12.5 Hz, *Ha*), 3.8 (dt, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.5 Hz, *Hd*), 4.01 (1H, d, $^3J_{HH}$ = 6.7 Hz, *Hb*), 4.40 (2H, AB, $^2J_{AB}$ = 13.3 Hz, OCH_AH_B), 5.52 (1H, ddd, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 11.3, $^3J_{HH}$ = 6.7 Hz, *Hc*), 7.20 (1H, ap.tdd, $^3J_{HH} = {}^3J_{HF}$ = 8.2 Hz, $^4J_{HH}$ = 2.7 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-4*), 7.35 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HF}$ = 5.5 Hz, *ArH-5*), 7.68 (1H, ddd, $^3J_{HF}$ = 9.4 Hz, $^4J_{HH}$ = 2.7 Hz, $^4J_{HH}$ = 1.6 Hz, *ArH-2*), 7.79 (1H, dt, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.6 Hz, *ArH-6*); δ_C 60.6 ($CHCH_2$), 61.7 (OCH_2), 74.5 (OCH_2CH), 109.6 ($CHCH_2$), 115.7 (d, $^2J_{CF}$ = 23.1 Hz, *ArCH-2*), 119.3 (d, $^2J_{CF}$ = 20.1 Hz, *ArCH-4*), 124.5 (d, $^3J_{CF}$ = 3.0 Hz, *ArCH-6*), 129.1 (d, $^4J_{CF}$ = 8.0 Hz, *ArCH-5*), 130.8 (d, $^3J_{CF}$ = 7.0 Hz, *ArC-1*), 161.5 (d, $^1J_{CF}$ = 247.5 Hz, *ArCF*), 164.0 (d, $^4J_{CF}$ = 3.0 Hz, C=O); δ_F -112.06 (1F, s, CF). m/z (FAB$^+$) 635 ($[M\text{-}Cl]^+$, 100 %), 670 ($[M]^+$, 17 %).

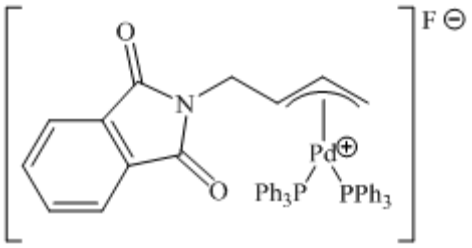
6.3.7 Preparation of Bis[μ-chloro-bis(butenyl-(1,2,3-η)-2-fluorobenzoate]dipalladium (129)



The novel compound was prepared following the method outlined by Granberg *et al.*[13] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (0.25 g, 0.44 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with 2-chlorobut-3-enyl-2-fluorobenzoate (0.10g, 0.44 mmol) and DMSO (10 cm^3). The reaction mixture was stirred for 2 h and then quenched with water (15 cm^3) and chloroform (20 cm^3). The organic phase was separated, washed with water (3 x 10 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid. Purification by column chromatography [DCM: hexane (70:30)] afforded the product as a yellow solid (0.11 g, 71 %). Elemental analysis: Found: C, 39.45; H, 2.94. Calc. for $C_{22}H_{20}Cl_2F_2O_4Pd_2$: C, 39.43; H, 3.01 %. δ_H 2.99 (1H, d, $^3J_{HH}$ = 12.1 Hz, *Ha*), 3.78 (1H, ddd, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 4.3 Hz, *Hd*), 4.00 (1H, d, $^3J_{HH}$ = 6.7 Hz, *Hb*), 4.24 (1H, dd, $^2J_{HH}$ = 13.3, $^3J_{HH}$ = 4.3 Hz, *He*), 4.43 (1H, dd, $^2J_{HH}$ = 13.3, $^3J_{HH}$ = 6.7 Hz, *Hf*), 5.56 (1H, ddd, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 6.7 Hz, *Hc*), 7.07 (1H, ddd, $^3J_{HF}$ = 11.0 Hz, $^3J_{HH}$ = 8.2 Hz,

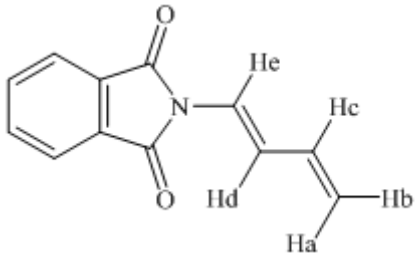
$^4J_{HH}$ = 1.2 Hz, *ArH-3*), 7.14 (1H, td, $^3J_{HH}$ = 78 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-5),* 7.46 (1H, dddd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 7.4 Hz, $^4J_{HF}$ = 5.1 Hz, $^4J_{HH}$ = 2.0 Hz, *ArH-4*), 7.90 (1H, td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 2.0 Hz, *ArH-6*); δ_C 61.4 (CH*CH*$_2$), 63.9 (O*CH*$_2$), 75.5 (OCH$_2$*CH*), 110.7 (*CH*CH$_2$), 117.0 (d, $^2J_{CF}$ = 22.1 Hz, *ArCH-3*), 118.2 (d, $^2J_{CF}$ = 9.1 Hz, *ArC-1*), 124.1 (d, $^4J_{CF}$ = 3.0 Hz, *ArCH-5*), 132.3 (*ArCH-6*), 134.8 (d, $^3J_{CF}$ = 9.1 Hz, *ArCH-4*), 162.0 (d, $^1J_{CF}$ = 260.6 Hz, *ArCF*), 163.2 (d, $^3J_{CF}$ = 3.0 Hz, C=O); δ_F -108.84 (1F, s, CF). m/z (FAB$^+$) 635 ([M-Cl]$^+$, 100 %), 670 ([M]$^+$, 22 %).

6.3.8 Preparation of ((butenyl-(1,2,3-η)-isoindoline-1,3-dione)bis(triphenylphosphine) palladium fluoride (132)



The novel compound was prepared following the method outlined by Gouverneur *et al.*[14] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. Pd(dba)$_2$ (0.05 g, 0.09 mmol), PPh$_3$ (0.24 g, 0.91 mmol) and anhydrous CDCl$_3$ were added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione (0.10 g, 0.46 mmol), after stirring the reaction for 1 minute a small aliquot was transferred into an NMR tube. The progress of the reaction was monitored by ^{1}H and ^{19}F{^{1}H} NMR (see Table 6.1 and Table 6.2) and after 1 h electrospray mass spectrometry indicated the formation of the allylpalladium cationic complex, (ES$^+$) 830 (M$^+$, 23 %) 568 (M$^+$-PPh$_3$, 100 %). However, starting material had not been fully consumed, hence, the reaction mixture was stirred overnight, solvent then removed *in vacuo*, and reaction mixture purified by column chromatography [DCM: hexane (70:30)]. No desired product was isolated but an elimination product; 2-(buta-1,3-dienyl)isoindoline-1,3-dione **(133)**, had also formed and was isolated as a yellow solid (45 mg, 50 %).

6.3.9 Experimental Data for 2-(buta-1,3-dienyl)isoindoline-1,3-dione (133)[15]



δ_H 5.12 (1H, d, $^3J_{HH}$ = 10.2 Hz, *Hb*), 5.30 (1H, d, $^3J_{HH}$ = 16.8 Hz, *Ha*), 6.31 (1H, ddd, $^3J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 10.2 Hz, *Hc*), 6.80 (1H, d, $^3J_{HH}$ = 14.9 Hz, *He*), 7.19 (1H, dd, $^3J_{HH}$ = 14.9 Hz, $^3J_{HH}$ = 11.0 Hz, *Hd*), 7.67 (2H, dd, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 3.1 Hz, *ArH-5*), 7.81 (2H, dd, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 3.1 Hz, *ArH-5*); δ_C 117.1 (*CH*$_2$), 119.4 (CH*CH*), 120.2 (N*CH*), 122.6 (*ArCH-4*), 130.7 (*ArC-3*), 133.5 (*ArCH-5*), 134.0 (*CH*CH$_2$), 165.2 (C=O). m/z (EI$^+$) 199 ([M]$^+$, 100 %). HRMS (EI) 199.06311 ($C_{12}H_9NO_2$ requires 199.06310).

Time (minutes)	Selective ^{1}H data (ppm)	Assignment
3	3.76 (ddd), 5.02 – 5.25 (dm), 5.87 (dddd) 7.00 – 7.82 (m)	Starting material **(74)** PPh_3 and dba
43	3.76 (ddd), 3.96 (ddd), 5.87 (dddd) 5.12 (1H, d), 5.30 (1H, d), 6.31 (1H, ddd) 7.00 – 7.82 (m) 3.00 (m), 3.86 (t), 4.11 (t), 4.52 (dd)	Starting material **(74)** 2-(buta-1,3-dienyl)isoindoline-1,3-dione) **(133)**, PPh_3 and dba **(132)**
73	3.76 (ddd), 3.96 (ddd), 5.87 (dddd) 5.12 (1H, d), 5.30 (1H, d), 6.31 (1H, ddd) 7.00 – 7.82 (m) 3.00 (m), 3.86 (t), 4.11 (t), 4.52 (dd)	Starting material **(74)** 2-(buta-1,3-dienyl)isoindoline-1,3-dione) **(133)** PPh_3 and dba **(132)**
185	5.12 (1H, d), 5.30 (1H, d), 6.31 (1H, ddd) 7.00 – 7.82 (m) 3.00 (m), 3.86 (t), 4.11 (t), 4.52 (dd)	2-(buta-1,3-dienyl)isoindoline-1,3-dione) **(133)** PPh_3 and dba **(132)**
320	5.12 (1H, d), 5.30 (1H, d), 6.31 (1H, ddd) 7.00 – 7.82 (m) 3.00 (m), 3.86 (t), 4.11 (t), 4.52 (dd)	2-(buta-1,3-dienyl)isoindoline-1,3-dione) **(133)** PPh_3 and dba **(132)**

Table 6.1

Time (minutes)	$^{19}F\{^{1}H\}$ (ppm)	Time (minutes)	$^{31}P\{^{1}H\}$ (ppm)
4	-184.7 (allylic fluoride starting material peak) and small broad bump -157.9	7	33.2, 29.1, 24.9, 22.0, 18.9
11	-184.7 and small broad bump -157.9	13	33.2, 29.1, 24.9, 22.0, 18.7
18	-184.7 and small broad bump -157.9	20	33.2, 29.1, 24.9, 22.0, 18.7
25	-184.7 and small broad bump -157.9	27	33.2, 29.1, 24.9, 22.0, 18.7
31	-184.7 and broad bump -157.9	34	33.2, 29.1, 24.9, 22.0, 18.7
38	-184.7 and broad bump -157.9	40	33.2, 29.1, 24.9, 22.0, 18.7
47	-184.7 and broad bump -157.9	49	33.2, 29.1, 24.9, 22.0, 18.7
54	-184.7 and broad bump -157.9	56	33.2, 29.1, 24.9, 22.0, 18.7
60	-184.7 and broad peak -157.9	63	33.2, 29.1, 24.9, 22.0, 18.7
67	-184.7 and broad peak -157.9		33.2, 29.1, 24.9, 22.0, 18.7
79	-184.7 and broad peak -157.9	82	33.2, 29.1, 24.9, 22.0, 18.7
88	-184.1 and large broad peak-157.9	90	33.2, 29.1, 24.9, 22.0, 18.7
97	-184.7 and large broad peak at -160.0	99	33.2, 29.1, 24.9, 22.0, 18.7
103	-184.7 and large broad peak at -161.0	106	33.2, 29.1, 24.9, 22.0, 18.7
191	-184.7 and large broad peak at -158.9	194	33.2, 29.1, 23.4, 21.9, 18.6
323	-184.7 very weak peak and large broad peak at -163.6	319	33.2, 29.1, 23.4, 21.9, 18.6

Table 6.2

General procedure for NMR experiments following reactions of allyl halides with palladium (0)

A series of products were prepared but not isolated following the method outlined by Gouverneur *et al.*[14] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (l equiv.), PPh_3 (2 equiv.) and anhydrous $CDCl_3$ were added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with allyl halide (2 equiv.), after stirring the reaction for 1 minute a small aliquot was transferred into an NMR tube. The progress of the reactions were monitored by ^1H, $^{19}F\{^1H\}$, $^{31}P\{^1H\}$ NMR and electrospray mass spectrometry. However, due to the excess of PPh_3 in the reaction mixtures the ^1H NMR spectra were largely uninterpretable.

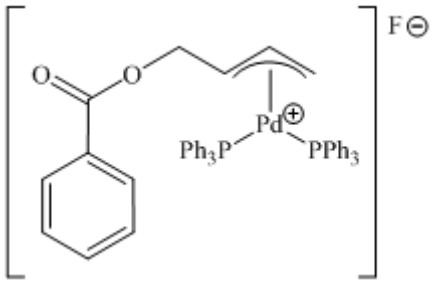
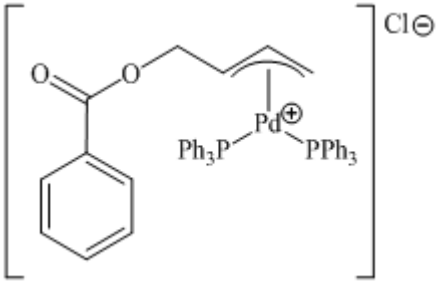
	Experiment 1	**Experiment 2**
Allyl halide	2-fluorobut-3-enyl benzoate **(75)**, 10 mg, 0.051 mmol	2-chlorobut-3-enyl benzoate **(108)**, 10 mg, 0.047 mmol
$Pd(dba)_2$	14.8 mg, 0.026 mmol	13.7 mg, 0.024 mmol
PPh_3	13.5 mg, 0.051 mmol	12.4 mg, 0.047 mmol
Product		
m/z	805 ($[M\text{-}F]^+$, 53 %), 543 ($[M\text{-}PPh_3]^+$, 100 %).	805 ($[M\text{-}Cl]^+$, 14 %), 543 ($[M\text{-}PPh_3]^+$, 29 %).
NMR Spectra	See Table 6.4	See Table 6.5

Table 6.3

Time (minutes)	$^{19}F\{^{1}H\}$ (ppm)	Time (minutes)	$^{31}P\{^{1}H\}$ (ppm)
4	-187.5 (allyl fluoride peak)	7	29.1, 27.1, 24.9, 24.1, 19.7
10	-187.5 and bs -170.8	14	29.1, 27.1, 24.9, 24.1, 19.7
17	-186.0 and bs -167.4	20	29.2, 27.1, 24.9, 23.9, 19.6
24	-186.6 and bs -166.7	27	29.2, 27.1, 24.9, 23.9, 19.6
33	Broad bump -185.6 - 197.6 and bs -167.1	37	29.2, 27.1, 24.9, 23.9, 19.6
49	Broad bump -186.6 - 197.7 and bs -168.6	51	29.3, 27.1, 24.9, 24.2, 23.9, 19.6
54	Broad bump -185.9 – 199.8 and bs -168.6	58	29.4, 27.1, 24.9, 24.2, 23.9, 19.6
61	Broad bump -184.3 – 199.6 and bs -168.7		
67	Broad bump -183.5 – 197.6 and bs -168.7	70	29.5, 27.1, 24.9, 24.2, 23.9, 21.3, 19.6
73	Bs -169.0 (allyl fluoride peak completely gone)	77	29.5, 27.1, 24.9, 24.2, 23.9, 19.6
80	Bs -169.1	83	29.6, 27.1, 24.9, 24.2, 23.9, 21.3, 19.6

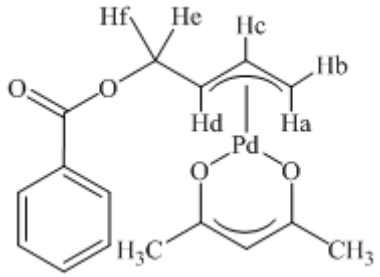
Table 6.4

Time (minutes)	$^{31}P\{^{1}H\}$ (ppm)
3	29.2, 23.4, 21.9, 21.2, 20.1
9	29.2, 23.4, 21.9, 21.2, 20.4
14	29.2, 23.4, 21.9, 21.2, 20.4
69	29.3, 24.7, 23.4, 21.9, 21.2, 20.0, 19.3
421	29.3, 24.7, 23.6, 23.4, 21.9, 21.2, 20.0, 19.3

Table 6.5

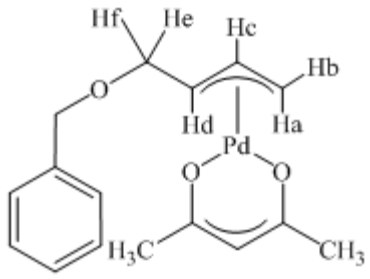
6.4 Experimental Details for Chapter 4

6.4.1 Preparation of Acetylacetonato[(butenyl-(1,2,3-η)-benzoate]palladium (145)



The novel compound was prepared following the method outlined by Hayashi *et al.* without modification.[16] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. Bis[μ-chloro-bis(butenyl-(1,2,3-η)-benzoate]dipalladium (154 mg, 0.49 mmol) and anhydrous THF (5 cm^3) were added to the reaction flask and then cooled to 0 ºC. A suspension of sodium acetylacetonate (1.5 cm^3 of a 0.32 M solution in THF, 0.49 mmol) was added and the reaction mixture stirred at 0 ºC for 1 h. After which, the reaction was quenched with water (5 cm^3), and extracted with diethyl ether (10 cm^3). The diethyl ether extracts were then washed with water, dried over $MgSO_4$ and solvent removed *in vacuo* to give the product (61 mg, 66 %). δ_H 1.87 (3H, s, CH_3), 1.93 (3H, s, CH_3), 2.88 (1H, ap.dt, $^3J_{HH}$ = 12.1 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 3.56 (1H, ddd, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 4.3 Hz, *Hd*), 3.78 (1H, d, $^3J_{HH}$ = 6.7 Hz, *Hb*), 4.44 (1H, dd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 7.8 Hz *He*), 4.51 (1H, dd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 4.3 Hz *Hf*), 5.29 (1H, s, *CH*CO), 5.56 (1H, ddd, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 11.0, $^3J_{HH}$ = 7.0 Hz, *Hc*), 7.37 (2H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-3*), 7.50 (1H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-4*), 8.01 (2H, dm, $^3J_{HH}$ = 7.0 Hz, *ArH-2*); δ_C 26.8 (*CH_3*), 27.0 (*CH_3*), 54.0 (CH*CH_2*), 63.4 (O*CH_2*), 66.2 (OCH_2*CH*), 99.0 (*CH*CH_3), 110.1 (*CH*CH_2), 127.4 (*ArCH-3*), 128.7 (*ArCH-2*), 129.1 (*ArC-1*), 132.0 (*ArCH-4*), 165.1 (*C=O*), 186.2 (CH_3*CO*), 187.1 (CH_3*CO*).

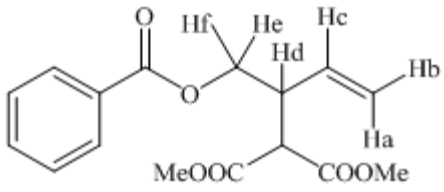
6.4.2 Preparation of Acetylacetonato[(butenyl-(1,2,3-η)-oxy)methyl)benzene]palladium (146)



The novel compound was prepared following the method outlined by Hayashi *et al.* without modification.[16] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. Bis[μ-chloro) bis(butenyl-(1,2,3-η)- oxy) methyl) benzene] dipalladium (147 mg, 0.49 mmol) and anhydrous THF (5 cm^3) were added to the reaction flask and then cooled to 0 ºC. A

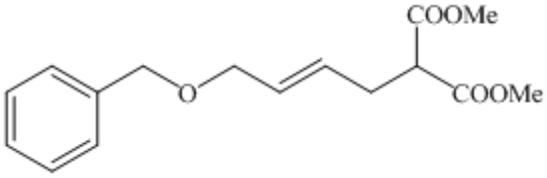
suspension of sodium acetylacetonate (1.5 cm^3 of a 0.32 M solution in THF, 0.49 mmol) was added and the reaction mixture stirred at 0 ºC for 1 h. After which, the reaction was quenched with water (5 cm^3), and extracted with diethyl ether (10 cm^3). The diethyl ether extracts were then washed with water, dried over $MgSO_4$ and solvent removed *in vacuo* to give the product (59 mg, 66 %). δ_H 1.89 (3H, s, *CH₃*), 1.92 (3H, s, *CH₃*), 2.78 (1H, d, $^3J_{HH}$ = 12.1 Hz, *Ha*), 3.55 (2H, dm, $^2J_{HH}$ = 13.3 Hz, *He and Hf*), 3.67 (1H, m, *Hd*) 3.72 (1H, d, $^3J_{HH}$ = 6.7 Hz, *Hb*), 4.53 (1H, d, $^2J_{HH}$ = 11.7 Hz, CH*HAr*), 4.57 (1H, d, $^2J_{HH}$ = 11.7 Hz, *CH*HAr), 5.28 (1H, s, *CH*CO), 5.40-5.50 (1H, m, *Hc*), 7.20-7.32 (5H, m, *ArH*); δ_C 26.8 (CH3), 27.2 (CH3), 53.0 (CH*CH₂*), 68.1 (O*CH₂*), 70.0 (OCH_2CH), 71.9 (Ar*CH₂*), 98.9 (*CH*CO), 109.6 (*CH*CH_2), 126.6 (*ArCH-4*), 126.7 (*ArCH-3*), 127.4 (*ArCH-2*), 137.2 (*ArC-1*), 186.3 (CO), 187.0 (CO).

6.4.3 Preparation of dimethyl 2-(1-(benzoyloxy)but-3-en-2-yl)malonate (148)



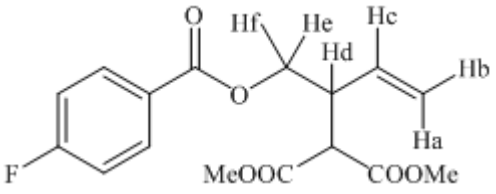
The novel compound was prepared following the method outlined by Hayashi *et al*.[17] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with bis[μ-chloro–bis-(butenyl-(1,2,3-η)-benzoate]dipalladium (83 mg, 0.13 mmol) and anhydrous THF (5 cm^3). The reaction mixture was stirred at room temperature for 15 minutes, after which PPh_3 (136 mg, 0.52 mmol) and sodium dimethylmalonate (81 mg, 0.52 mmol) were added and the mixture stirred overnight. The formed precipitate was filtered off and solvent removed *in vacuo* to give the crude product which was purified by column chromatography [hexane: ethyl acetate (70:30)], affording the product as a colourless oil (7 mg, 37 %). δ_H 3.27 (1H, m, *Hd*), 3.61 (1H, d, $^3J_{HH}$ = 8.6 Hz, *CH*$(COOMe)_2$), 3.65 (6H, s, CH_3), 4.32 (1H, dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.9 Hz, *He*), 4.40 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 5.9 Hz, *Hf*), 5.14 (1H, d, $^3J_{HH}$ = 10.2 Hz, *Hb*), 5.20 (1H, d, $^3J_{HH}$ = 17.2 Hz, *Ha*), 5.81 (1H, ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 8.6 Hz, *Hc*), 7.38 (2H, tm, $^3J_{HH}$ = 7.8 Hz, *ArH-3*), 7.50 (1H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-4*), 7.95 (2H, dm, $^3J_{HH}$ = 8.6 Hz, *ArH-2*); δ_C 43.0 (OCH_2CH), 52.6 (*CH*$(COOMe)_2$), 53.3 (CH_3), 65.2 (O*CH₂*), 119.1 (CH*CH₂*), 128.3 (*ArCH-3*), 129.6 (*ArCH-2*), 129.9 (*ArC-1*), 133.1 (*ArCH-4*), 134.4 (*CH*CH_2), 166.2 (Ar*C=O*), 168.1 (C=O). m/z (EI^+) 306 ($[M]^+$, 5 %), 175 ($[M\text{-}CH(COOMe)_2]^+$, 90 %). HRMS (EI) 306.10984 ($C_{16}H_{18}O_6$ requires 306.10989).

6.4.4 Preparation of Dimethyl 2-(4-(benzyloxy)but-2-enyl)malonate (147)



The novel compound was prepared following the method outlined by Hayashi *et al*.[17] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with bis[μ-chloro) bis(butenyl-(1,2,3-η)-oxy)methyl)benzene]dipalladium (79 mg, 0.13 mmol) and anhydrous THF (5 cm^3). The reaction mixture was stirred at room temperature for 15 minutes, after which PPh_3 (136 mg, 0.52 mmol) and sodium dimethylmalonate (78 mg, 0.52 mmol) were added and the mixture stirred overnight. The formed precipitate was filtered off and solvent removed *in vacuo* to give the crude product which was purified by column chromatography [hexane: ethyl acetate (70:30)], affording the product as a colourless oil (8 mg, 44 %). δ_H 2.59 (2H, dd, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 5.5 Hz, $CH_2CH(COOMe)_2$), 3.39 (1H, t, $^3J_{HH}$ = 7.4 Hz, $CH(COOMe)_2$), 3.66 (6H, s, CH_3), 3.88 (2H, d, $^3J_{HH}$ = 4.7 Hz, OCH_2CH), 4.40 (2H, AB, $^2J_{AB}$ = 13.3 Hz, CH_AH_BAr), 5.56- 5.67 (2H, m, -*CH*=*CH*-), 7.22-7.30 (5H, m, *ArH*). m/z (EI^+) 292 ($[M]^+$, 30 %).

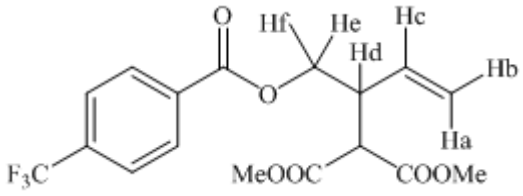
6.4.5 Preparation of dimethyl 2-(1-(4-fluorobenzoyloxy)but-3-en-2-yl)malonate (150)



The novel compound was prepared following the method outlined by Hayashi *et al*.[17] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with bis[μ-chloro-bis(butenyl-(1,2,3-η)-4-fluoro benzoate] dipalladium (87 mg, 0.13 mmol) and anhydrous THF (5 cm^3). The reaction mixture was stirred at room temperature for 15 minutes, after which PPh_3 (136 mg, 0.52 mmol) and sodium dimethylmalonate (81 mg, 0.52 mmol) were added and the mixture stirred overnight. The formed precipitate was filtered off and solvent removed *in vacuo* to give the crude product which was purified by column chromatography [hexane: ethyl acetate (70:30)], affording the product as a colourless oil (4 mg, 21 %). δ_H 3.25 (1H, m, *Hd*), 3.58 (1H, d, $^3J_{HH}$ = 8.2 Hz, $CH(COOMe)_2$), 3.65 (6H, s, CH_3), 4.31 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 6.3 Hz, *He*), 4.43 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 5.9 Hz, *Hf*), 5.13 (1H, d, $^3J_{HH}$ = 11.0

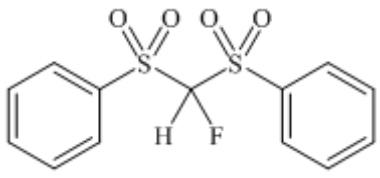
Hz, *Ha*), 5.19 (1H, d, $^3J_{HH}$ = 17.2 Hz, *Hb*), 5.81 (1H, ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 8.6 Hz, *Hc*), 7.05 (2H, tm, $^3J_{HH}$ = 9.0 Hz, *ArH-3*), 7.96 (2H, dm, $^3J_{HH}$ = 9.0 Hz, *ArH-2*); δ_F -105.3 (1F, s, CF).

6.4.6 Preparation of dimethyl 2-(1-(4-(trifluoromethyl)benzoyloxy)but-3-en-2-yl) malonate (149)



The novel compound was prepared following the method outlined by Hayashi *et al*.[17] A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with bis[μ-chloro) bis(butenyl-(1,2,3-η)-4-(trifluoromethyl)benzoate]dipalladium (100 mg, 0.13 mmol) and anhydrous THF (5 cm^3). The reaction mixture was stirred at room temperature for 15 minutes, after which PPh_3 (136 mg, 0.52 mmol) and sodium dimethylmalonate (81 mg, 0.52 mmol) were added and the mixture stirred overnight. The formed precipitate was filtered off and solvent removed *in vacuo* to give the crude product which was purified by column chromatography [hexane: ethyl acetate (70:30)], affording the product as a colourless oil (5 mg, 21 %). δ_H 3.27 (1H, m, *Hd*), 3.58 (1H, d, $^3J_{HH}$ = 8.6 Hz, *CH(COOMe)$_2$*), 3.65 (6H, s, CH_3), 4.36 (1H, dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.9 Hz, *He*), 4.43 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 6.3 Hz, *Hf*), 5.15 (1H, d, $^3J_{HH}$ = 11.0 Hz, *Ha*), 5.20 (1H, dt, $^3J_{HH}$ = 17.2 Hz, *Hb*), 5.81 (1H, ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 8.6 Hz, *Hc*), 7.65 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-3*), 8.06 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-2*); δ_F -63.1 (3F, s, CF_3).

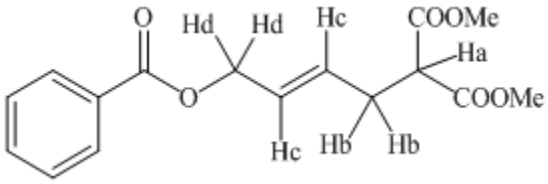
6.4.7 Preparation of 1-fluoro-bis(phenylsulfonyl)methane (140)[18]



The title compound was prepared using a method outlined by Shibata *et al*. without modification.[18] A 100 cm^3, three-necked round-bottomed flask was equipped with a magnetic stirring bar, pressure equalising dropping funnel and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with NaH (60 % oil dispersion, 135 mg, 3.38 mmol) and anhydrous THF (15 cm^3). The mixture was cooled to 0 °C using an ice bath and bis(phenylsulfonyl)methane (1.00 g, 3.38 mmol) added. The reaction mixture was then stirred at room temperature for 30 min. Selectfluor (1.20 g, 3.38 mmol) and anhydrous

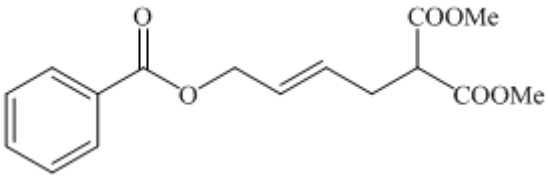
MeCN (5 cm^3) were added to the dropping funnel, the temperature of the flask cooled to 0 °C, and the solution of Selectfluor added dropwise. The mixture was stirred for 3 h at room temperature. The reaction was quenched by addition of saturated aqueous ammonium chloride. The mixture was then extracted with DCM, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography [hexane: DCM (20:80)] affording the product as a white solid (0.62 g, 58 %). δ_H 5.64 (1H, d, $^2J_{HF}$ = 45.8 Hz, *CHF*), 7.55 (4H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-3*), 7.70 (2H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-4*), 7.92 (4H, dm, $^3J_{HH}$ = 7.4 Hz, *ArH-2*); δ_C 104.8 (d, J_{CF} = 266.6 Hz, CHF), 128.5 (*ArCH-3*), 129.2 (*ArCH-2*), 134.4 (*ArC-1*), 134.7 (*ArCH-4*); δ_F -168.1 (1F, s, CHF). m/z (EI^+) 314 ($[M]^+$, 5 %), 141 ($[M\text{-}C_6H_5SO_2CHF]^+$, 55 %). HRMS (EI) 314.00814 ($C_{13}H_{11}O_4FS_2$ requires 314.00801).

6.4.8 Preparation of Dimethyl 2-(4-(benzoyloxy)but-2-enyl)malonate (151)[19]



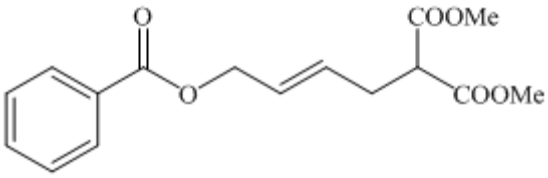
The title compound was prepared using a method outlined by Gouverneur *et al.*[14] A 50 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $[Pd(C_3H_5)Cl]_2$ (3 mg, 0.008 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with PPh_3 (83 mg, 0.32 mmol) and anhydrous DCM (3 cm^3) and stirred at room temperature for 15 minutes. After which, 2-fluorobut-3-enyl benzoate (62 mg, 0.32 mmol), sodium dimethylmalonate (148 mg, 0.96 mmol) and 15-crown-5 (0.19 cm^3, 0.96 mmol) were added and the reaction mixture left to stir. After stirring overnight, the reaction was quenched with water (10 cm^3) and the aqueous phase extracted with diethyl ether (3 x 10 cm^3). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and was purified by column chromatography [hexane: ethyl acetate (70:30)] affording the product as a colourless oil (45 mg, 46 %). δ_H 2.62 (2H, dd, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 5.5 Hz, *Hb*), 3.41 (1H, t, $^3J_{HH}$ = 7.4 Hz, *Ha*), 3.66 (6H, s, CH_3), 4.68 (2H, d, $^3J_{HH}$ = 4.7 Hz, *Hd*), 5.74 (2H, m, *Hc*), 7.40 (2H, tm, $^3J_{HH}$ = 7.8 Hz, *ArH-3*), 7.55 (1H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-2*), 8.05 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-4*); δ_C 31.5 ($CH_2CH(COOMe)_2$), 51.3 (*CH*(COOMe)), 52.6 (CH_3), 64.9 (OCH_2), 127.4 (*CH*CH_2COOMe), 128.5 (*ArCH-3*), 130.2 (*ArC-1*), 130.2 (*ArCH-2*), 130.8 (OCH_2CH), 133.8 (*ArCH-4*), 166.3 (Ar*C=O*), 169.2 (C=O). m/z (FAB^+) 307 ($[MH]^+$, 100 %). HRMS (FAB) 307.11768 $C_{16}H_{19}O_6$ requires 307.11769).

6.4.9 Preparation of Dimethyl 2-(4-(benzoyloxy)but-2-enyl)malonate (151)[19]



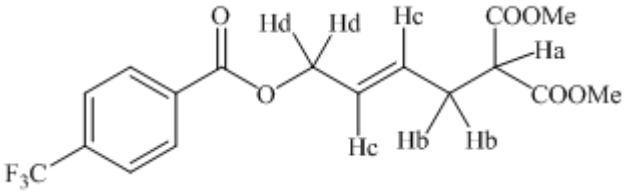
The title compound was prepared using a method outlined by Gouverneur *et al.*[14] A 50 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $[Pd(C_3H_5)Cl]_2$ (3 mg, 0.008 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with PPh_3 (83 mg, 0.32 mmol) and anhydrous DCM (3 cm^3) and stirred at room temperature for 15 minutes. After which, 2-chlorobut-3-enyl benzoate (67 mg, 0.32 mmol), sodium dimethyl malonate (148 mg, 0.96 mmol) and 15-crown-5 (0.19 cm^3, 0.96 mmol) were added and the reaction mixture left to stir. After stirring overnight, the reaction was quenched with water (10 cm^3) and the aqueous phase extracted with diethyl ether (3 x 10 cm^3). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography [hexane: ethyl acetate (70:30)], affording the product as a colourless oil (39 mg, 40 %). NMR data as for **(151)**.

6.4.10 Preparation of Dimethyl 2-(4-(benzoyloxy)but-2-enyl)malonate (151)[19]



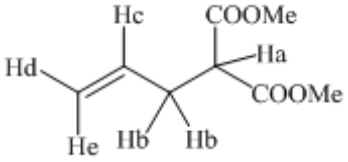
The title compound was prepared using a method outlined by Gouverneur *et al.* without modification.[14] A 50 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $[Pd(C_3H_5)Cl]_2$ (35 mg, 0.10 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with PPh_3 (100 mg, 0.38 mmol) and anhydrous DCM (10 cm^3) and stirred at room temperature for 15 minutes. After which, 2-chlorobut-3-enyl benzoate (200 mg, 0.95 mmol), dimethyl malonate (151 mg, 0.13 cm^3, 1.14 mmol) and BSA (232 mg, 0.28 cm^3, 1.14 mmol) were added and the reaction mixture left to stir. After stirring overnight, the reaction was quenched with water (10 cm^3) and the aqueous phase extracted with diethyl ether (3 x 10 cm^3). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography [hexane: ethyl acetate (70:30)], affording the product as a colourless oil (110 mg, 34 %). NMR as for **(151)**.

6.4.11 Preparation of Dimethyl 2-(4-(4-(trifluoromethyl)benzoyloxy)but-2-enyl) malonate (152)



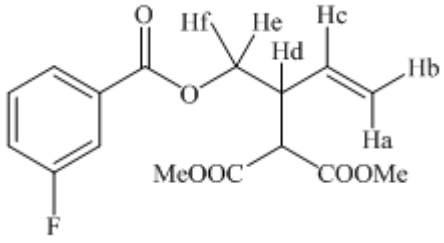
The novel compound was prepared using a method outlined by Gouverneur *et al.*[14] A 50 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $[Pd(C_3H_5)Cl]_2$ (3 mg, 0.008 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with PPh_3 (83 mg, 0.32 mmol) and anhydrous DCM (5 cm^3) and stirred at room temperature for 15 minutes. After which, 2-chlorobut-3-enyl 4-(trifluoromethyl)benzoate (89 mg, 0.32 mmol), sodium dimethyl malonate (148 mg, 0.96 mmol) and 15-crown-5 (0.19 cm^3, 0.96 mmol) were added and the reaction mixture left to stir. After stirring overnight, the reaction was quenched with water (10 cm^3) and the aqueous phase extracted with diethyl ether (3 x 10 cm^3). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography [hexane: ethyl acetate (70:30)], affording the product as a pale yellow oil (34 mg, 29 %). δ_H 2.63 (2H, dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 5.8 Hz, *Hb*), 3.42 (1H, t, $^3J_{HH}$ = 7.6 Hz, *Ha*), 3.67 (6H, s, CH_3), 4.71 (2H, d, $^3J_{HH}$ = 5.0 Hz, *Hd*), 5.75 (2H, m, *Hc*), 7.64 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-3*), 8.08 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-2*); δ_C 31.5 (*CH_2*CH(COOMe)$_2$), 51.3 (*CH*(COOMe)), 52.6 (*CH_3*), 65.5 (O*CH_2*), 125.4 (*ArCH-3*), 126.9 (*CH*CH_2COOMe), 130.0 (*ArCH-2*), 130.1 (*ArC-1*), 131.5 (OCH_2*CH*), 165.0 (Ar*C=O*), 169.1 (*C=O*); δ_F – 63.1 (3F, s, CF_3). [^{13}C spectrum too weak to see quaternary *CF_3* quartet and *ArC-4* quartet]

6.4.12 Experimental Data for Dimethyl 2-allylmalonate (154)[20]



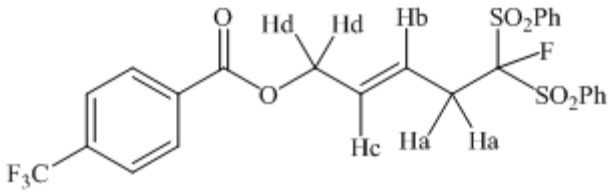
The co-product allyl dimethyl malonate **(154)** was also isolated from the synthesis of dimethyl 2-(4-(benzoyloxy)but-2-enyl)malonate **(151)**, as an oil (25 mg, 15 %). δ_H 2.58 (2H, dd, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 6.7 Hz, *Hb*), 3.40 (1H, t, $^3J_{HH}$ = 7.4 Hz, *Ha*), 3.65 (6H, s, *CH_3*), 4.99 (1H, ddt, $^3J_{HH}$ = 10.2 Hz, $^2J_{HH}$ = 1.6 Hz, $^4J_{HH}$ = 1.2 Hz, *Hd*), 5.05 (1H, d, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = 1.6 Hz, $^4J_{HH}$ = 1.6 Hz, *He*), 5.70 (1H, ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 6.7 Hz, *Hc*); δ_C 32.9 (*CH_2*CH(COOMe)$_2$), 51.4 (*CH*(COOMe)$_2$), 52.5 (*CH_3*), 117.7 (*CH_2*CH), 133.9 (CH_2*CH*), 169.3 (*C=O*).

6.4.13 Preparation of dimethyl 2-(1-(3-fluorobenzoyloxy)but-3-en-2-yl)malonate (153)



The title compound was prepared using a method outlined by Gouverneur *et al.*[14] A 50 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $[Pd(C_3H_5)Cl]_2$ (3 mg, 0.008 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with PPh_3 (83 mg, 0.32 mmol) and anhydrous DCM (5 cm^3) and stirred at room temperature for 15 minutes. After which, 2-chlorobut-3-enyl 3-fluoro benzoate (73 mg, 0.32 mmol), sodium dimethyl malonate (148 mg, 0.96 mmol) and 15-crown-5 (0.19 cm^3, 0.96 mmol) were added and the reaction mixture left to stir. After stirring overnight, the reaction was quenched with water (10 cm^3) and the aqueous phase extracted with diethyl ether (3 x 10 cm^3). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography [hexane: ethyl acetate (70:30)], affording the product as a pale yellow oil (25 mg, 24 %). δ_H 3.26 (1H, m, *Hd*), 3.59 (1H, d, $^3J_{HH}$ = 8.2 Hz, *CH*(COOMe)$_2$), 3.65 (6H, s, CH_3), 4.32 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 5.9 Hz, *He*), 4.40 (1H, dd, $^2J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 6.3 Hz, *Hf*), 5.14 (1H, d, $^3J_{HH}$ = 10.6 Hz, *Hb*), 5.19 (1H, d, $^3J_{HH}$ = 17.2 Hz, *Ha*), 5.80 (1H, ddd, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 8.2 Hz, *Hc*), 7.22 (1H, m, *ArH-4*), 7.36 (1H, td, $^3J_{HH}$ = 8.2 Hz, $^4J_{HF}$ = 5.5 Hz, *ArH-5*), 7.62 (1H,ddd, $^3J_{HF}$ = 9.4 Hz, $^4J_{HH}$ = 1.6 Hz, *ArH-2*), 7.74 (1H, dt, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.2 Hz, *ArH-2*); δ_C 42.9 (OCH$_2$*CH*), 52.6 (*CH*(COOMe)$_2$), 53.3 (CH_3), 65.6 (O*CH$_2$*), 116.5 (d, $^2J_{CF}$ = 22.1 Hz, *ArCH-2*), 119.3 (CH*CH$_2$*), 120.2 (d, $^2J_{CF}$ = 20.1 Hz, *ArCH-4*), 125.4 (*ArCH-6*), 130.1 (d, $^4J_{CF}$ = 8.0 Hz, *ArCH-5*), 131.5 (d, $^3J_{CF}$ = 6.0 Hz, *ArC-1*), 134.3 (*CH*CH$_2$), 161.1 (d, $^1J_{CF}$ = 247.0 Hz, *ArCF*), 161.6 (Ar*C=O*), 168.1 (C=O). δ_F -112.2 (1F, s, CF).

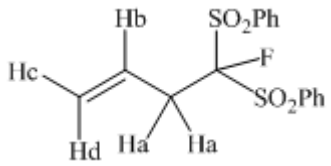
6.4.14 Preparation of 5-fluoro-5,5-bis(phenylsulfonyl)pent-2-enyl 4-(trifluoromethyl) benzoate (155)



The title compound was prepared using a method outlined by Shibata *et al.* without modification.[18] A 50 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying

under high vacuum, the flask was cooled and filled with nitrogen. $[Pd(C_3H_5)Cl]_2$ (3 mg, 0.009 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with PPh_3 (10 mg, 0.036 mmol), 2-chlorobut-3-enyl 4-(trifluoromethyl)benzoate (100 mg, 0.359 mmol) and anhydrous DCM (5 cm^3) and stirred at room temperature for 15 minutes. After which, 1-fluoro-bis(phenylsulfonyl)methane (124 mg, 0.395 mmol) and cesium carbonate (129 mg, 0.395 mmol) were added and the reaction mixture at 0 ºC and left to stir for 6 h. After which, the reaction mixture was poured into saturated ammonium chloride solution (15 cm^3), extracted with DCM (2 x 10 cm^3). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography [hexane: ethyl acetate (70:30)], affording the product as colourless oil (30 mg, 15 %). δ_H 3.15 (2H, dd, $^3J_{HF}$ = 16.6 Hz, $^3J_{HH}$ = 6.7 Hz, *Ha*), 4.68 (2H, d, $^3J_{HH}$ = 5.6 Hz, *Hd*), 5.65-5.80 (2H, m, *Hb and Hc*), 7.49 (4H, tm, $^3J_{HH}$ = 7.8 Hz, *ArH-3'*), 7.65 (4H, m, *ArH-4' and ArH-3*), 7.85 (4H, dm, $^3J_{HH}$ = 7.8 Hz, *ArH-2*), 8.08 (2H, dm, $^3J_{HH}$ = 7.8 Hz, *ArH-2*); δ_C 33.3 (d, $^2J_{CF}$ = 18.9 Hz, $CH_2CF(SO_2Ph)_2$), 64.9 (OCH_2), 114.0 (d, $^1J_{CF}$ = 269.0 Hz, $CF(SO_2Ph)_2$), 123.8 ($CHCH_2CF(SO_2Ph)_2$), 125.5 (*ArCH-3*), 129.0 (*ArCH-3'*), 130.1 (*ArCH-2*), 130.3 (OCH_2CH), 130.9 (*ArCH-2'*), 135.1 (*ArC-1'*), 135.2 (*ArC-1*), 135.3 (*ArCH-4'*), 165.0 (C=O); δ_F – 63.0 (3F, s, CF_3), -142.0 (1F, s, CF). [^{13}C spectrum too weak to see quaternary CF_3 quartet and *ArC-4* quartet]

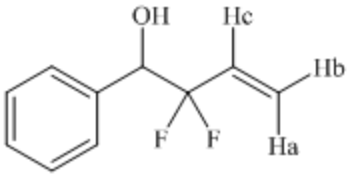
6.4.15 Preparation of Allyl 1-fluoro-bis (phenylsulfonyl)methane (156)



The novel co-product allyl 1-fluoro-bis (phenylsulfonyl)methane **(156)** was also isolated from the synthesis of 5-fluoro-5,5-bis (phenylsulfonyl)pent-2-enyl 4-(trifluoromethyl) benzoate **(155)**, as an oil (20 mg, 14 %). δ_H 3.08 (2H, dd, $^3J_{HF}$ = 17.2 Hz, $^3J_{HH}$ = 7.0 Hz, *Ha*), 5.03 (1H, d, $^3J_{HH}$ = 17.0 Hz, *Hd*), 5.10 (1H, d, $^3J_{HH}$ = 10.2 Hz, *Hc*), 5.73 (1H, d, $^3J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 7.0 Hz, *Hb*), 7.50 (4H, tm, $^3J_{HH}$ = 7.6 Hz, *ArH-3*), 7.66 (2H, tm, $^3J_{HH}$ = 7.6 Hz, *ArH-4*), 7.86 (4H, dm, $^3J_{HH}$ = 7.6 Hz, *ArH-2*); δ_C 34.6 (d, $^2J_{CF}$ = 18.9 Hz, $CH_2CF(SO_2Ph)_2$), 114.5 (d, $^1J_{CF}$ = 267.9 Hz, $CF(SO_2Ph)_2$), 121.5 (CH_2CH), 124.7 (d, $^3J_{CF}$ = 10.1 Hz, CH_2CH), 128.5 (*ArCH-3*), 130.9 (*ArCH-2*), 133.8 (*ArC-1*), 135.3 (*ArCH-4*); δ_F (1F, s, CF).

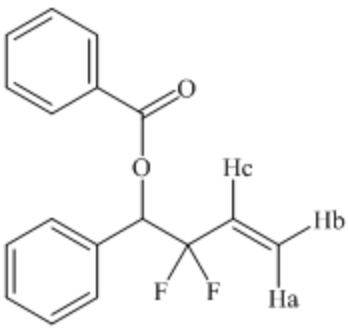
6.5 Experimental Details for Chapter 5

6.5.1 Preparation of 2,2-difluoro-1-phenylbut-3-en-1-ol (158)



The title compound was prepared using a method outlined by Audouard *et al.*[21] A 25 cm^3 round-bottomed flask was set up in a sonicating bath, 3-bromo-3,3-difluoroprop-1-ene (0.07 cm^3, 0.69 mmol), benzaldehyde (0.05 cm^3, 0.50 mmol), indium powder (0.05 g, 0.41 mmol) and water (7 cm^3) were added successively, and the reaction mixture sonicated for 4 h at room temperature. After 4 h the reaction mixture was quenched with HCl (10 cm^3 of a 1M aqueous solution), extracted with DCM and the combined organic layers washed with brine (20 cm^3) and dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [diethyl ether: light petroleum ether (15:85)], affording the product as a yellow oil (49 mg, 54 %). δ_H 2.36-2.54 (1H, bs, OH), 4.79 (1H, ap.t, $^3J_{HF}$ = 9.0 Hz, *CHOH*), 5.36 (1H, ddt, $^3J_{HH}$ = 11.0 Hz, $^4J_{HF}$ = 0.8 Hz, $^2J_{HH}$ = 0.8 Hz, *Hb*), 5.49 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 2.3 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.75 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HF}$ = 11.1 Hz, *Hc*), 7.22-7.34 (5H, m, *ArH*); δ_C 75.9 (t, $^3J_{CF}$ = 30.2 Hz, *CH*OH), 119.6 (t, $^1J_{CF}$ = 244.5 Hz, CF_2), 121.6 (t, $^3J_{CF}$ = 10.1 Hz, CHCH_2), 127.7 (*ArCH-3*), 128.2 (*ArCH-2*), 128.6 (*ArCH-4*), 129.4 (t, $^2J_{CF}$ = 25.2 Hz, *CH*CH_2), 136.1 (*ArC-1*); δ_F -107.8 (1F, d, $^2J_{FF}$ = 246.4 Hz, CF), -109.3 (1F, d, $^2J_{FF}$ = 249.1 Hz, CF). m/z (EI^+) 184 ($[M]^+$, 36 %) 107 ($[M-CF_2CH=CH_2]^+$, 100 %). HRMS (EI) 184.06960 ($C_{10}H_{10}OF_2$ requires 184.06972).

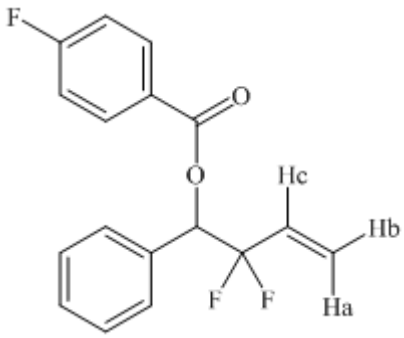
6.5.2 Preparation of 2,2-difluoro-1-phenylbut-3-enyl benzoate (159)



The novel compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluoro-1-phenylbut-3-en-1-ol (0.09 g, 0.51 mmol) and pyridine (1 cm^3) and cooled to 0 ºC. Benzoyl chloride (0.065 cm^3, 0.51 mmol) was added and the reaction mixture warmed to room temperature and stirred for 2 h. After which the reaction was quenched with brine (6 cm^3) and diethyl ether (5 cm^3). The organic layer was then separated and washed with HCl (1 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in*

vacuo the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the product as an oil (39 mg, 27 %). δ_H 5.45 (1H, d, $^3J_{HH}$ = 11.0 Hz, *Hb*), 5.62 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 2.7 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.87 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HF}$ = 11.4 Hz, *Hc*), 6.15 (1H, ap.t, $^3J_{HF}$ = 9.8 Hz, *CHO*), 7.26-7.33 (3H, m, *ArH-3 and ArH-4'*), 7.37-7.45 (4H, m, *ArH'*), 7.50-7.55 (1H, tm, $^3J_{HH}$ = 7.4 Hz, *ArH-4*), 8.04 (2H, dm, $^3J_{HH}$ = 8.6 Hz, *ArH-2*); δ_C 75.8 (t, $^3J_{CF}$ = 31.4 Hz, *CH*CF_2), 118.2 (t, $^1J_{CF}$ = 245.2 Hz, *CF_2*), 122.0 (t, $^3J_{CF}$ = 8.8 Hz, CH*CH_2*), 128.2 (*ArCH-3*), 128.4 (*ArCH-2*), 128.6 (*ArCH-3'*), 129.2 (*ArCH-2'*), 129.4 (*ArC-1'*), 129.6 (t, $^2J_{CF}$ = 26.1 Hz, *CH*CH_2), 129.8 (*ArCH-4*), 133.3 (*ArC-1*), 133.5 (*ArCH-4'*), 164.8 (C=O); δ_F -106.1 (1F, d, $^2J_{FF}$ = 249.1 Hz, CF), -109.1 (1F, d, $^2J_{FF}$ = 249.1 Hz, CF). m/z (EI^+) 288 ($[M]^+$, 15 %) 105 ($[M\text{-}OCH(C_6H_5)CF_2CH{=}CH_2]^+$, 84 %). HRMS (EI) 288.09577 ($C_{17}H_{14}O_2F_2$ requires 288.09584).

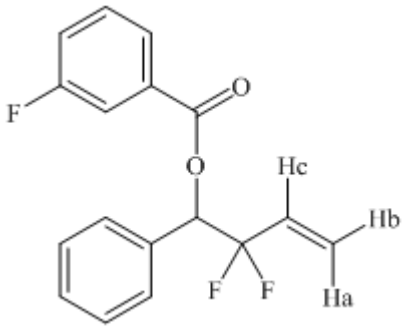
6.5.3 Preparation of 2,2-difluoro-1-phenylbut-3-enyl 4-fluorobenzoate (160)



The novel compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluoro-1-phenylbut-3-en-1-ol (0.06 g, 0.34 mmol) and pyridine (1 cm^3) and cooled to 0 ºC. 4-fluorobenzoyl chloride (0.04 cm^3, 0.34 mmol) was added and the reaction mixture warmed to room temperature and stirred for 2 h. After which the reaction was quenched with brine (5 cm^3) and diethyl ether (5 cm^3). The organic layer was then separated and washed with HCl (1 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the product as an oil (44 mg, 43 %). δ_H 5.45 (1H, d, $^3J_{HH}$ = 11.0 Hz, *Hb*), 5.62 (1H, ddt, $^3J_{HH}$ = 17.6 Hz, $^4J_{HF}$ = 2.7 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.85 (1H, ddt, $^3J_{HH}$ = 17.6 Hz, $^3J_{HF}$ = 12.1 Hz, $^3J_{HH}$ = 11.0 Hz, *Hc*), 6.12 (1H, ap.t, $^3J_{HF}$ = 10.6 Hz, *CHO*), 7.08 (2H, tm, $^3J_{HH}$ = 9.0 Hz, *ArH-3*), 7.28-7.34 (3H, m, *ArH'*), 7.39-7.44 (2H, m, *ArH'*), 8.05 (2H, dm, $^3J_{HH}$ = 9.0 Hz, *ArH-2*); δ_C 77.3 (t, $^3J_{CF}$ = 31.4 Hz, *CH*CF_2), 117.2 (d, $^2J_{CF}$ = 22.6 Hz, *ArCH-3*), 119.6 (t, $^1J_{CF}$ = 245.2 Hz, *CF_2*), 123.4 (t, $^3J_{CF}$ = 8.8 Hz, CH*CH_2*), 127.0 (*ArC-1*), 129.6 (*ArCH-3'*), 129.8 (*ArCH-2'*), 129.2 (*ArCH-4'*), 130.6 (*ArCH-4*), 131.1 (t, $^2J_{CF}$ = 25.2 Hz,

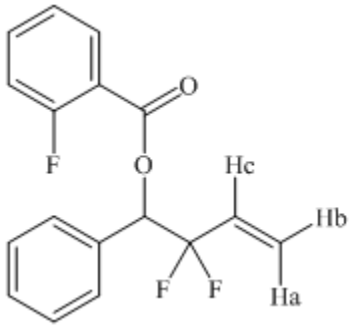
CHCH_2), 133.9 (d, $^3J_{CF}$ = 8.8 Hz, *ArCH-2*), 134.6 (*ArC-1*), 165.2 (C=O), 167.5 (d, $^1J_{CF}$ = 255.3 Hz, CF); δ_F -104.5 (1F,s), -106.4 (1F, d, $^2J_{FF}$ = 249.1 Hz, *ArCF*), -109.0 (1F, d, $^2J_{FF}$ = 251.9 Hz, CF). m/z (EI^+) 306 ($[M]^+$, 4 %) 123 ($[M\text{-}OCH(C_6H_5)CF_2CH{=}CH_2]^+$, 100 %). HRMS (EI) 306.08639 ($C_{17}H_{13}O_2F_3$ requires 306.08644).

6.5.4 Preparation of 2,2-difluoro-1-phenylbut-3-enyl 3-fluorobenzoate (161)



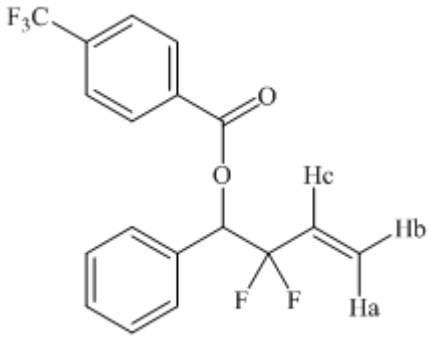
The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluoro-1-phenylbut-3-en-1-ol (0.07 g, 0.40 mmol) and pyridine (1 cm^3) and cooled to 0 ºC. 3-fluorobenzoyl chloride (0.05 cm^3, 0.40 mmol) was added and the reaction mixture stirred for 4 h at 0 ºC. After which the reaction was quenched with brine (5 cm^3) and diethyl ether (5 cm^3). The organic layer was then separated and washed with HCl (7 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the product as an oil (67 mg, 55 %). δ_H 5.46 (1H, d, $^3J_{HH}$ = 11.0 Hz, *Hb*), 5.63 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 2.7 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.85 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 12.5 Hz, $^3J_{HH}$ = 11.0 Hz, *Hc*), 6.14 (1H, ap.t, $^3J_{HF}$ = 10.6 Hz, *CHO*), 7.23 (1H, tdd, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 2.7 Hz, $^3J_{HH}$ = 0.8 Hz, *ArH-4*), 7.29-7.45 (6H, m, *ArH-5 and ArH'*), 7.70 (1H, dm, $^3J_{HH}$ = 9.4 Hz, $^3J_{HH}$ = 1.2 Hz, *ArH-2*), 7.83 (1H, dt, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 1.2 Hz, *ArH-6*); δ_C 76.1 (t, $^3J_{CF}$ = 30.2 Hz, *CH*CF_2), 116.7 (d, $^2J_{CF}$ = 23.9 Hz, *ArCH-2*), 118.1 (t, J_{CF} = 245.2 Hz, *CF_2*),120.7 (d, $^2J_{CF}$ = 21.4 Hz, *ArCH-4*), 122.1 (t, $^3J_{CF}$ = 8.8 Hz, CH*CH_2*), 125.7 (d, $^4J_{CF}$ = 2.5 Hz, *ArCH-6*), 128.2 (*ArCH-3'*), 128.4 (*ArCH-2'*), 129.3 (*ArCH-4'*), 129.6 (t, $^2J_{CF}$ = 23.9 Hz, *CH*CH_2), 130.3 (d, $^4J_{CF}$ = 8.8 Hz, *ArCH-5*), 131.5 (d, $^3J_{CF}$ = 7.5 Hz, *ArC-1*), 133.0 (*ArC-1'*), 162.6 (d, $^1J_{CF}$ = 247.7 Hz, CF), 163.7 (C=O); δ_F -106.5 (1F, d, $^2J_{FF}$ = 251.9 Hz, *ArCF*), -109.6 (1F, d, $^2J_{FF}$ = 249.1 Hz, CF), -111.9 (1F,s). m/z (EI^+) 306 ($[M]^+$, 3 %) 123 ($[M\text{-}OCH(C_6H_5)CF_2CH{=}CH_2]^+$, 94 %). HRMS (EI) 306.08639 ($C_{17}H_{13}O_2F_3$ requires 306.08644).

6.5.5 Preparation of 2,2-difluoro-1-phenylbut-3-enyl 2-fluorobenzoate (162)



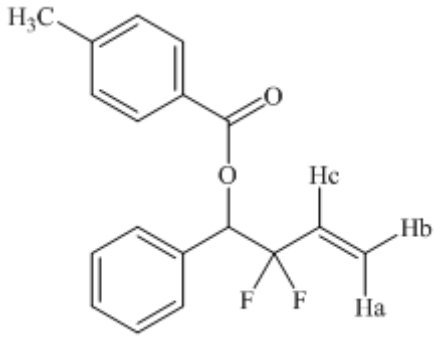
The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluoro-1-phenylbut-3-en-1-ol (0.05 g, 0.27 mmol) and pyridine (1 cm^3) and cooled to 0 ºC. 2-fluorobenzoyl chloride (0.03 cm^3, 0.26 mmol) was added and the reaction mixture stirred for 3 h at 0 ºC. After which the reaction was quenched with brine (5 cm^3) and diethyl ether (5 cm^3). The organic layer was then separated and washed with HCl (7 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (30:70)], affording the product as an oil (29 mg, 37 %). δ_H 5.45 (1H, d, $^3J_{HH}$ = 11.0 Hz, *Hb*), 5.59 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 2.7 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.85 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HF}$ = 10.6 Hz, *Hc*), 6.18 (1H, ap.t, $^3J_{HF}$ = 9.8 Hz, *CHO*), 7.10 (1H, $^3J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 1.2 Hz, *ArH-3*), 7.16 (1H, dt, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 1.2 Hz, *ArH-5*), 7.27 - 7.33 (3H, m, *ArH*), 7.40-7.45 (2H, m, *ArH*), 7.46-7.52 (1H, m, *ArH-4*), 7.93 (1H, dt, $^3J_{HH}$ = 9.4 Hz, $^3J_{HH}$ = 2.0 Hz, *ArH-6*); δ_C 76.1 (t, $^3J_{CF}$ = 31.4 Hz, *CH*CF_2), 117.2 (d, $^2J_{CF}$ = 22.6 Hz, *ArCH-3*), 117.9 (d, $^2J_{CF}$ = 10.1 Hz, *ArC-1*), 118.2 (t, $^1J_{CF}$ = 245.2 Hz, *CF_2*), 122.0 (t, $^3J_{CF}$ = 8.8 Hz, CH*CH_2*), 124.1 (d, $^4J_{CF}$ = 2.5 Hz, *ArCH-5*), 128.3 (*ArCH-3'*), 128.3 (*ArCH-2'*), 129.2 (*ArCH-4'*), 129.5 (t, $^2J_{CF}$ = 25.2 Hz, *CH*CH_2), 132.4 (*ArCH-6*), 133.1 (*ArC-1*), 135.2 (d, $^3J_{CF}$ = 8.8 Hz, *ArCH-4*), 162.2 (d, $^1J_{CF}$ = 261.6 Hz, *ArCF*), 162.6 (d, $^3J_{CF}$ = 3.7 Hz, C=O); δ_F -105.9 (1F, d, $^2J_{FF}$ = 249.1 Hz, CF), -108.0 (1F,s), -109.5 (1F, d, $^2J_{FF}$ = 249.1 Hz, CF). m/z (EI^+) 306 ($[M]^+$, 8 %) 123 ($[M\text{-}OCH(C_6H_5)CF_2CH{=}CH_2]^+$, 100 %). HRMS (EI) 306.08636 ($C_{17}H_{13}O_2F_3$ requires 306.08644).

6.5.6 Preparation of 2,2-difluoro-1-phenylbut-3-enyl 4-(trifluoromethyl)benzoate (163)



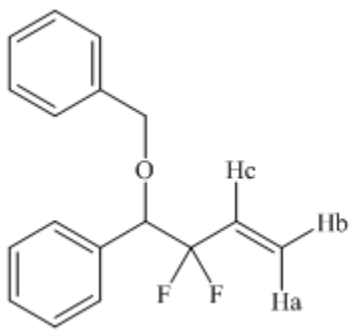
The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluoro-1-phenylbut-3-en-1-ol (0.05 g, 0.27 mmol) and pyridine (1 cm^3) and cooled to 0 ºC. 4-(trifluoromethyl)benzoyl chloride (0.03 cm^3, 0.26 mmol) was added and the reaction mixture warmed to room temperature and stirred for 4 h. After which the reaction was quenched with brine (5 cm^3) and diethyl ether (5 cm^3). The organic layer was then separated and washed with HCl (1 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (30:70)], affording the product as an oil (27 mg, 34 %). δ_H 5.47 (1H, d, $^3J_{HH}$ = 11.0 Hz, *Hb*), 5.63 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 2.7 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.84 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HF}$ = 10.6 Hz, *Hc*), 6.15 (1H, ap.t, $^3J_{HF}$ = 10.6 Hz, *CHO*), 7.29-7.34 (3H, m, *ArH*), 7.39-7.45 (2H, m, *ArH*), 7.67 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-3'*), 8.15 (1H, dm, $^3J_{HH}$ = 9.0 Hz, *ArH-2'*); δ_C 76.3 (t, $^3J_{CF}$ = 31.4 Hz, *CH*CF_2), 118.1 (t, $^1J_{CF}$ = 245.2 Hz, *CF_2*), 122.2 (t, $^3J_{CF}$ = 8.8 Hz, CH*CH_2*), 123.5 (q, $^1J_{CF}$ = 272.9 Hz, *$ArCF_3$*), 125.7 (d, *ArCH-3'*), 128.2 (*ArCH-2*), 128.5 (*ArCH-3*), 129.4 (*ArCH-4*), 129.6 (t, $^2J_{CF}$ = 26.4 Hz, *CH*CH_2), 130.3 (*ArCH-2'*), 132.6 (*ArC-1*), 132.9 (*ArC-1'*), 135.0 (q, $^2J_{CF}$ = 36.5 Hz, *ArCH-4*), 163.7 (C=O); δ_F -64.5. (3F, s) -106.8 (d, $^2J_{FF}$ = 249.1 Hz, CF), -108.9 (1F, d, $^2J_{FF}$ = 249.1 Hz, CF). m/z (EI^+) 356 ($[M]^+$, 8 %) 173 ($[M\text{-}OCH(C_6H_5)CF_2CH{=}CH_2]^+$, 100 %). HRMS (EI) 356.08323 ($C_{18}H_{13}O_2F_5$ requires 356.08325).

6.5.7 Preparation of 2,2-difluoro-1-phenylbut-3-enyl 4-methylbenzoate (164)



The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluoro-1-phenylbut-3-en-1-ol (0.05 g, 0.27 mmol) and pyridine (1 cm^3) and cooled to 0 ºC. 4-methylbenzoyl chloride (0.03 cm^3, 0.26 mmol) was added and the reaction mixture warmed to room temperature and stirred for 4 h. After which the reaction was quenched with brine (5 cm^3) and diethyl ether (5 cm^3). The organic layer was then separated and washed with HCl (1 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (30:70)], affording the product as an oil (16 mg, 20 %). δ_H 5.44 (1H, d, $^3J_{HH}$ = 11.0 Hz, *Hb*), 5.62 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 2.7 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.86 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 11.4Hz, $^3J_{HH}$ = 11.0 Hz, *Hc*), 6.13 (1H, ap.t, $^3J_{HF}$ = 9.8 Hz, *CHO*), 7.20 (2H, d, $^3J_{HH}$ = 8.2 Hz, *ArH-3*), 7.27-7.32 (3H, m, *ArH'*), 7.40-7.45 (2H, m, *ArH'*), 7.93 (2H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-2*); δ_C 21.7 (CH_3), 75.6 (t, $^3J_{CF}$ = 30.2 Hz, *CH*CF_2), 118.2 (t, $^1J_{CF}$ = 244.0 Hz, *CF_2*), 121.9 (t, $^3J_{CF}$ = 8.8 Hz, CH*CH_2*), 126.7 (*ArC-1*), 128.2 (*ArCH-3'*), 128.3 (*ArCH-2'*), 129.1 (*ArCH-4'*), 129.3 (*ArCH-3*), 129.9 (t, $^2J_{CF}$ = 26.1 Hz, *CH*CH_2), 130.0 (*ArCH-2*), 133.5 (*ArC-1*), 144.4 (*ArC-4'*), 164.8 (C=O); δ_F -106.0 (d, $^2J_{FF}$ = 249.1 Hz, CF), -109.2 (1F, d, $^2J_{FF}$ = 249.1 Hz, CF). m/z (EI$^+$) 302 ([M]$^+$, 5 %) 119 ([M-OCH(C_6H_5)CF_2CH=CH_2]$^+$, 100 %). HRMS (EI) 302.11153 ($C_{18}H_{16}O_2F_2$ requires 302.11144).

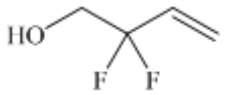
6.5.8 Preparation of (1-(benzyloxy)-2,2-difluorobut-3-enyl)benzene (165)



The title compound was prepared using a method outlined by Wu *et al.*[22] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, dropping funnel and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with a suspension of NaH in anhydrous DMF *via* syringe, and stirred at 0 ºC. 2,2-difluoro-1-phenylbut-3-en-1-ol

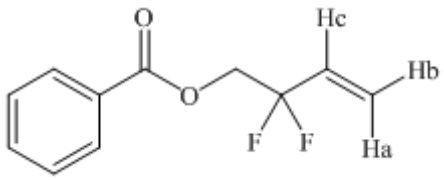
(5 mg, 0.27 mmol) and anhydrous DMF were syringed into the dropping funnel and added to the reaction mixture dropwise. The mixture was stirred at room temperature for 1 h, after which benzyl bromide (0.04 cm^3, 0.33 mmol) was added and the reaction stirred for a further 20 h. the reaction was then quenched with water (30 cm^3) and extracted with diethyl ether (4 x 25 cm^3). The organic layers were combined, washed with water and brine and dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [hexane: chloroform (50:50)], affording the product as an oil (29 mg, 15 %). δ_H 4.34 (1H, d, $^2J_{HH}$ = 12.1 Hz, CH*HAr*), 4.50 (1H, ap.t, $^3J_{HH}$ = 9.0 Hz, *CHOCF*$_2$), 4.55 (1H, d, $^2J_{HH}$ = 12.1 Hz, *OCH*H), 5.36 (1H, d, $^3J_{HH}$ = 11.0 Hz, *Hb*), (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 2.7 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.90 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 12.5 Hz, $^3J_{HH}$ = 11.0 Hz, *Hc*), 7.20-7.36 (10H, m, *ArH*); δ_C 71.3 (OCH_2), 82.1 (t, $^2J_{CF}$ = 30.2 Hz, *CH*CF_2), 118.9 (t,$^1J_{CF}$ = 244.0 Hz, *CF*$_2$), 120.9 (t, $^3J_{CF}$ = 8.8 Hz, CH*CH*$_2$), 127.8 (*ArCH-3'*), 127.8 (*ArCH-4'*), 128.2 (*ArCH-3*), 128.4 (*ArCH-2*), 128.7 (*ArCH-2'*), 128.8 (*ArCH-4*), 130.2 ((t, $^2J_{CF}$ = 25.2 Hz, *CH*CH_2), 134.6 (*ArC-1*), 137.3 (*ArC-1*); δ_F -104.0 (1F, d, $^2J_{FF}$ = 249.1 Hz), -109.2 (1F, d, $^2J_{FF}$ = 249.1 Hz). m/z (EI^+) 197 ($[M-(C_6H_5)]^+$, 78 %).

6.5.9 Attempted Preparation of 2,2-difluorobut-3-en-1-ol (174)



The title compound was prepared using a method outlined by Audouard *et al.*[21] A 25 cm^3 round-bottomed flask was set up in a sonicating bath, 3-bromo-3,3-difluoroprop-1-ene (0.1 cm^3, 0.98 mmol), formaldehyde (0.3 cm^3, 0.49 mmol), indium powder (0.14 g, 0.98 mmol) and water (7 cm^3) were added successively, and the reaction mixture sonicated for 20 h. After 20 h the reaction mixture was quenched with HCl (10 cm^3 of a 1M aqueous solution), extracted with DCM and the combined organic layers washed with brine (20 cm^3) and dried over magnesium sulphate. After removal of solvent *in vacuo*, NMR spectroscopy of the crude product showed no product to be present.

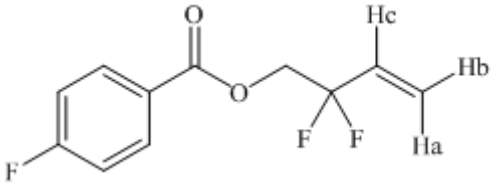
6.5.10 Preparation of 2,2-difluorobut-3-enyl benzoate (175)



The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluorobut-3-en-1-ol (*ca.* 0.15 g in 40 cm^3 DCM, 1.48 mmol) and pyridine (1 cm^3) and cooled to 0 ºC. Benzoyl chloride (1 cm^3, 7.31 mmol)

was added and the reaction mixture stirred at 0 ºC for 4 h. After which the reaction was quenched with brine (5 cm^3) and the organic layer separated and washed with HCl (10 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the product as an oil (134 mg, 86 %). δ_H 4.59 (2H, ap.t, $^3J_{HF}$ = 12.5 Hz, *CHO*), 5.61 (1H, d, $^3J_{HH}$ = 10.9 Hz, $^2J_{HH}$ = 0.6 Hz, *Hb*), 5.83 (1H, ddt, $^3J_{HH}$ = 17.3 Hz, $^4J_{HF}$ = 3.5 Hz, $^2J_{HH}$ = 0.6 Hz, *Ha*), 6.04 (1H, ddt, $^3J_{HH}$ = 17.3 Hz, $^3J_{HF}$ = 11.2 Hz, $^3J_{HH}$ = 10.9 Hz, *Hc*),), 7.49 (2H, tm, $^3J_{HH}$ = 8.0 Hz, *ArH-3*), 7.62 (1H, tm, $^3J_{HH}$ = 7.7 Hz, *ArH-4*), 8.09 (1H, ddm, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 1.3 Hz, *ArH-2*); δ_C 64.5 (t, $^2J_{CF}$ = 34.1 Hz, O*CH*$_2$), 117.7 (t, $^1J_{CF}$ = 240.9 Hz, *CF*$_2$), 121.7 (t, $^3J_{CF}$ = 10.0 Hz, CH*CH*$_2$), 128.5 (*ArCH-3*), 129.1 (*ArC-1*), 129.9 (*ArCH-2*), 130.1 (t, $^2J_{CF}$ = 25.1 Hz, *CH*CH$_2$), 133.5 (*ArCH-4*), 165.5 (C=O); δ_F -105.7 (2F, s, CF_2). m/z (EI^+) 212 ($[M]^+$, 25 %) 105 ($[M\text{-}OCH_2CF_2CH{=}CH_2]^+$, 100 %). HRMS (EI) 212.06468 ($C_{11}H_{10}O_2F_2$ requires 212.06464).

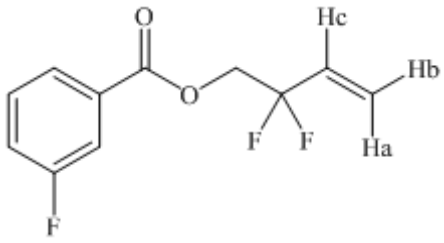
6.5.11 Preparation of 2,2-difluorobut-3-enyl 4-fluorobenzoate (176)



The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluorobut-3-en-1-ol (*ca.* 0.05 g in 40 cm^3 DCM, 0.49 mmol) and pyridine (1 cm^3) and cooled to 0 ºC. 4-fluorobenzoyl chloride (0.4 cm^3, 2.46 mmol) was added and the reaction mixture stirred at 0 ºC for 4 h. After which the reaction was quenched with brine (5 cm^3) and the organic layer separated and washed with HCl (10 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the product as an oil (64 mg, 28 %). δ_H 4.58 (2H, ap.t, $^3J_{HF}$ = 12.5 Hz, *CHO*), 5.61 (1H, d, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = 0.6 Hz, *Hb*), 5.83 (1H, dt, $^3J_{HH}$ = 17.4 Hz, $^4J_{HF}$ = 3.4 Hz, *Ha*), 6.03 (1H, ddt, $^3J_{HH}$ = 17.4 Hz, $^3J_{HF}$ = 11.3 Hz, $^3J_{HH}$ = 11.0 Hz, *Hc*),), 7.16 (2H, tm, $^3J_{HH}$ = 8.5 Hz, *ArH-3*), 8.11 (1H, dd, $^3J_{HH}$ = 9.2 Hz, $^4J_{HF}$ = 5.5 Hz, *ArH-2*); δ_C 64.5 (t, $^2J_{CF}$ = 34.1 Hz, O*CH*$_2$), 115.8 (d, $^2J_{CF}$ = 22.1 Hz, *ArCH-3*), 117.7 (t, $^1J_{CF}$ = 242.9 Hz, *CF*$_2$), 121.8 (t, $^3J_{CF}$ = 10.0 Hz, CH*CH*$_2$), 125.4 (*ArC-1*), 130.1 (t, $^2J_{CF}$ = 26.1 Hz, *CH*CH$_2$), 132.5 (d, $^3J_{CF}$ = 10.0 Hz, *ArCH-2*), 164.5 (C=O), 166.1

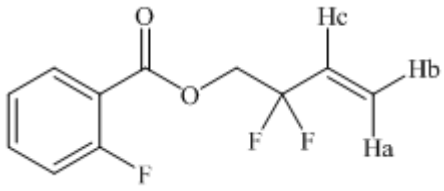
(d, $^{1}J_{CF}$ = 255.0 Hz, *ArCF*); δ_F -104.6 (1F, s, CF), -105.7 (2F, s, CF_2). m/z (EI^+) 230 ($[M]^+$, 68 %) 123 ($[M\text{-}OCH_2CF_2CH{=}CH_2]^+$, 100 %). HRMS (EI) 230.05521 ($C_{11}H_9O_2F_3$ requires 230.05524).

6.5.12 Preparation of 2,2-difluorobut-3-enyl 3-fluorobenzoate (177)



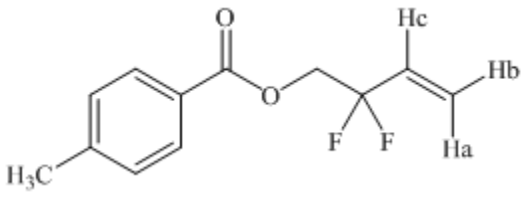
The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluorobut-3-en-1-ol (*ca.* 0.05 g in 40 cm^3 DCM, 0.49 mmol) and pyridine (1 cm^3) and cooled to 0 ºC. 3-fluorobenzoyl chloride (0.4 cm^3, 2.45 mmol) was added and the reaction mixture stirred at 0 ºC for 4 h. After which the reaction was quenched with brine (5 cm^3) and the organic layer separated and washed with HCl (10 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the product as an oil (49 mg, 36 %). δ_H 4.59 (2H, ap.t, $^{3}J_{HF}$ = 12.4 Hz, *CHO*), 5.62 (1H, d, $^{3}J_{HH}$ = 11.1 Hz, $^{2}J_{HH}$ = 0.8 Hz, *Hb*), 5.83 (1H, ddt, $^{3}J_{HH}$ = 17.4 Hz, $^{4}J_{HF}$ = 2.6 Hz, $^{2}J_{HH}$ = 0.6 Hz, *Ha*), 6.03 (1H, ddt, $^{3}J_{HH}$ = 17.6 Hz, $^{3}J_{HF}$ = 11.1 Hz, $^{3}J_{HH}$ = 11.0 Hz, *Hc*), 7.22 (1H, ddt, $^{3}J_{HF}$ = 8.4 Hz, $^{3}J_{HH}$ = 2.7 Hz, $^{4}J_{HH}$ = 1.1 Hz, *ArH-4*), 7.47 (1H, dt, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HF}$ = 5.5 Hz, *ArH-5*), 7.75 (1H, ddd, $^{3}J_{HF}$ = 9.4 Hz, $^{4}J_{HH}$ = 2.9 Hz, $^{5}J_{HH}$ = 1.7 Hz, *ArH-2*), 7.88 (1H, dt, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.5 Hz, *ArH-6*); δ_C 64.7 (t, $^{2}J_{CF}$ = 34.0 Hz, O*CH*$_2$), 116.7 (d, $^{2}J_{CF}$ = 23.9 Hz, *ArCH-2*), 117.6 (t, $^{1}J_{CF}$ = 241.5 Hz, *CF*$_2$), 120.7 (d, $^{2}J_{CF}$ = 21.4 Hz, *ArCH-4*), 121.9 (t, $^{3}J_{CF}$ = 10.1 Hz, CH*CH*$_2$), 125.6 (d, $^{4}J_{CF}$ = 2.5 Hz, *ArCH-6*), 130.0 (t, $^{2}J_{CF}$ = 25.2 Hz, *CH*CH_2), 130.2 (d, $^{3}J_{CF}$ = 7.5 Hz, *ArCH-5*), 131.2 (d, $^{3}J_{CF}$ = 7.5 Hz, C *ArC-1*), 162.6 (d, $^{1}J_{CF}$ = 247.7 Hz, *ArCF*), 164.4 (d, $^{4}J_{CF}$ = 3.8 Hz, C=O); δ_F -105.8 (2F, s, CF_2), -111.9 (1F, s, CF). m/z (EI) 230 (M^+, 40 %), 123 ($[M\text{-}OCH_2CF_2CH{=}CH_2]^+$, 100 %). HRMS (EI) 230.05526 ($C_{11}H_9O_2F_3$ requires 230.05524).

6.5.13 Preparation of 2,2-difluorobut-3-enyl 2-fluorobenzoate (178)



The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluorobut-3-en-1-ol (*ca.* 0.05 g in 40 cm^3 DCM, 0.49 mmol) and pyridine (1 cm^3) and cooled to 0 ºC. 2-fluorobenzoyl chloride (0.4 cm^3, 2.45 mmol) was added and the reaction mixture stirred at 0 ºC for 4 h. After which the reaction was quenched with brine (5 cm^3) and the organic layer separated and washed with HCl (10 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the product as an oil (35 mg, 25 %). δ_H 4.49 (2H, ap.t, $^3J_{HF}$ = 12.1 Hz, *CHO*), 5.51 (1H, d, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = 0.8 Hz, *Hb*), 5.73 (1H, ddt, $^3J_{HH}$ = 17.6 Hz, $^4J_{HF}$ = 3.1 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.96 (1H, ddt, $^3J_{HH}$ = 17.6 Hz, $^3J_{HF}$ = 11.3 Hz, $^3J_{HH}$ = 11.0 Hz, *Hc*), 7.18 (1H, m, *ArH-3*), 7.25 (1H, m, *ArH-5*), 7.59 (1H, m, *ArH-4*), 7.98 (1H, m, *ArH-6*); δ_C 64.7 (t, $^2J_{CF}$ = 32.1 Hz, O*CH*$_2$), 117.2 (d, $^2J_{CF}$ = 24.1 Hz, *ArCH-3*), 117.6 (t, $^1J_{CF}$ = 240.9 Hz, *CF*$_2$), 121.7 (t, $^3J_{CF}$ = 10.0 Hz, CH*CH*$_2$), 124.1 (d, $^4J_{CF}$ = 4.0 Hz, *ArCH-5*), 130.0 (t, $^2J_{CF}$ = 26.1 Hz, *CH*CH_2), 132.2 (*ArCH-6*), 134.5 (d, $^2J_{CF}$ = 10.0 Hz, *ArC-1*), 135.1 (d, $^3J_{CF}$ = 10.0 Hz, *ArCH-4*), 162.12 (d, $^1J_{CF}$ = 253.0 Hz, *ArCF*), 163.2 (C=O); δ_F, -105.7 (2F, s, CF_2), -108.6 (1F, s, CF). m/z (EI) 230 (M^+, 12 %), 123 ([M-$OCH_2CF_2CH{=}CH_2]^+$, 100 %). HRMS (EI) 230.05519 ($C_{11}H_9O_2F_3$ requires 230.05524).

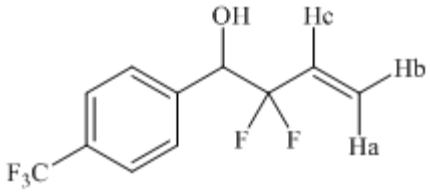
6.5.14 Preparation of 2,2-difluorobut-3-enyl 4-methylbenzoate (180)



The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluorobut-3-en-1-ol (*ca.* 0.05 g in 40 cm^3 DCM, 0.49 mmol) and pyridine (1 cm^3) and cooled to 0 ºC. 4-methylbenzoyl chloride (0.3 cm^3, 2.45 mmol) was added and the reaction mixture stirred at 0 ºC for 4 h. After which the reaction was quenched with brine (5 cm^3) and the organic

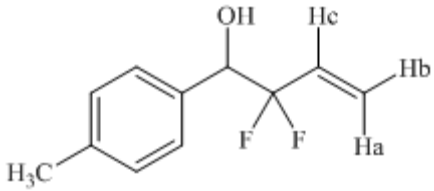
layer separated and washed with HCl (10 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the product as an oil (0.012 g, 11 %). δ_H 4.47 (2H, ap.t, $^3J_{HF}$ = 12.5 Hz, O*CH*$_2$), 5.49 (1H, dd, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = 0.8 Hz, *Hb*), 5.72 (1H, dt, $^3J_{HH}$ = 17.6 Hz, $^4J_{HF}$ = 2.7 Hz, *Ha*), 5.94 (1H, ddt, $^3J_{HH}$ = 17.6 Hz, $^3J_{HF}$ = 11.3 Hz, $^3J_{HH}$ = 11.0 Hz, *Hc*), 7.18 (2H, dm, $^3J_{HH}$ = 7.8 Hz, *ArH-3*), 7.87 (1H, dm, $^3J_{HH}$ = 8.2 Hz, *ArH-2*); δ_C 21.7 (*CH*$_3$), 64.3 (t, $^2J_{CF}$ = 34.0 Hz, O*CH*$_2$), 117.8 (t, $^1J_{CF}$ = 240.2 Hz, *CF*$_2$), 121.6 (t, $^3J_{CF}$ = 10.1 Hz, CH*CH*$_2$), 126.4 (*ArC-1*), 129.2 (*ArCH-3*), 129.9 (*ArCH-2*), 130.2 (t, $^2J_{CF}$ = 26.4 Hz, *CH*CH_2), 144.3 (*ArC-4*), 165.6 (C=O); δ_F -105.3 (2F, s, CF_2). m/z (EI^+) 226 ($[M]^+$, 76 %). HRMS (EI) 226.08020 ($C_{12}H_{12}O_2F_2$ requires 226.08024).

6.5.15 Preparation of 2,2-difluoro-1-(4-(trifluoromethyl)phenyl)but-3-en-1-ol (166)



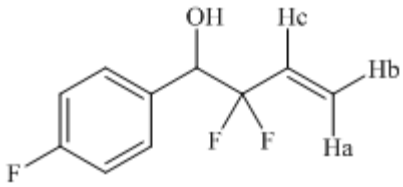
The novel compound was prepared using a method outlined by Audouard *et al.*[21] A 25 cm^3 round-bottomed flask was set up in a sonicating bath, 3-bromo-3,3-difluoro prop-1-ene (0.30 cm^3, 2.94 mmol), 4-(trifluoromethyl) benzaldehyde (0.27 cm^3, 1.96 mmol), indium powder (0.34 g, 2.94 mmol) and water (15 cm^3) were added successively, and the reaction mixture sonicated for 4 h at room temperature. After 4 h the reaction mixture was quenched with HCl (20 cm^3 of a 1M aqueous solution), extracted with DCM and the combined organic layers washed with brine (20 cm^3) and dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [hexane: ethyl acetate (80:20)], affording the product as a white solid (88 mg, 18 %). δ_H 2.45-2.65 (1H, bs, OH), 4.90 (1H, ap.t, $^3J_{HF}$ = 9.0 Hz, *CHOH*), 5.41 (1H, d, $^3J_{HH}$ = 11.0 Hz, *Hb*), 5.51 (1H, ddt, $^3J_{HH}$ = 17.6 Hz, $^4J_{HF}$ = 2.7 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.84 (1H, ddt, $^3J_{HH}$ = 17.6 Hz, $^3J_{HF}$ = 12.5 Hz, $^3J_{HH}$ = 11.0 Hz, *Hc*), 7.47 (2H, d, $^3J_{HH}$ = 8.2 Hz, *ArH-3*), 7.55 (2H, d, $^3J_{HH}$ = 8.2 Hz, *ArH-2*); δ_C 75.3 (t, $^2J_{CF}$ = 30.2 Hz, *CH*OH), 119.4 (t, $^1J_{CF}$ = 244.0 Hz, *CF*$_2$), 122.3 (t, $^3J_{CF}$ = 8.8 Hz, CH*CH*$_2$), 124.0 (q, $^1J_{CF}$ = 271.6 Hz, *ArCF*$_3$), 125.1 (*ArCH-2*), 128.0 (*ArCH-3*), 128.8 (t, $^2J_{CF}$ = 25.2 Hz, *CH*CH_2), 130.9 (q, $^2J_{CF}$ = 32.7 Hz, *ArC-4*), 139.7 (*ArC-1*); δ_F -62.7 (3F, s, CF_3), -107.1 (1F, d, $^2J_{FF}$ = 251.3 Hz, CF), -109.5 (1F, d, $^2J_{FF}$ = 254.1 Hz, CF).

6.5.16 Preparation of 2,2-difluoro-1-*p*-tolylbut-3-en-1-ol (167)



The title compound was prepared using a method outlined by Audouard *et al.*[21] A 25 cm^3 round-bottomed flask was set up in a sonicating bath, 3-bromo-3,3-difluoroprop-1-ene (0.30 cm^3, 2.94 mmol), 4-methyl benzaldehyde (0.23 cm^3, 1.96 mmol), indium powder (0.34 g, 2.94 mmol) and water (15 cm^3) were added successively, and the reaction mixture sonicated for 4 h at room temperature. After 4 h the reaction mixture was quenched with HCl (20 cm^3 of a 1M aqueous solution), extracted with DCM and the combined organic layers washed with brine (20 cm^3) and dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [hexane: ethyl acetate (80:20)], affording the product as an oil (118 mg, 30 %). δ_H 2.28 (3H, s, C*H*$_3$), 4.80 (1H, ap.t, $^3J_{HF}$ = 9.0 Hz, *CHOH*), 5.39 (1H,dd, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = 0.8 Hz, *Hb*), 5.51 (1H, ddt, $^3J_{HH}$ = 17.6 Hz, $^4J_{HF}$ = 3.1 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.78 (1H, ddt, $^3J_{HH}$ = 17.6 Hz, $^3J_{HF}$ = 12.5 Hz, $^3J_{HH}$ = 11.0 Hz, *Hc*), 7.10 (2H, d, $^3J_{HH}$ = 7.8 Hz, *ArH-3*), 7.23 (2H, d, $^3J_{HH}$ = 7.8 Hz, *ArH-2*); δ_C 21.2 (*CH*$_3$), 75.8 (t, $^2J_{CF}$ = 30.2 Hz, *CH*OH), 119.7 (t, $^1J_{CF}$ = 244.2 Hz, *CF*$_2$), 121.5 (t, $^3J_{CF}$ = 8.8 Hz, CH*CH*$_2$), 127.6 (*ArCH-2*), 129.2 (*ArCH-3*), 129.6 (t, $^2J_{CF}$ = 25.2 Hz, *CH*CH$_2$), 133.1 (*ArC-4*), 138.6 (*ArC-1*); δ_F -108.0 (d, $^2J_{FF}$ = 246.4 Hz, CF), -109.4 (d, $^2J_{FF}$ = 246.4 Hz, CF). m/z (EI$^+$) 198 ([M]$^+$, 12 %), 121 ([M-$CF_2CH{=}CH_2$]$^+$, 100 %). HRMS (EI) 198.08534 ($C_{11}H_{12}O_1F_2$ requires 198.08532).

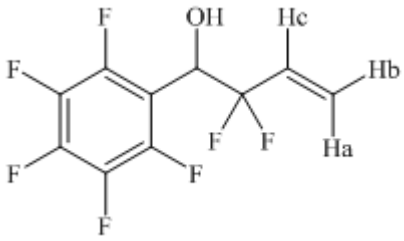
6.5.17 Preparation of 2,2-difluoro-1-(4-fluorophenyl)but-3-en-1-ol (168)



The title compound was prepared using a method outlined by Audouard *et al.*[21] A 25 cm^3 round-bottomed flask was set up in a sonicating bath, 3-bromo-3,3-difluoroprop-1-ene (0.25 cm^3, 2.46 mmol), 4-fluoro benzaldehyde (0.21 cm^3, 1.78 mmol), indium powder (0.34 g, 2.94 mmol) and water (15 cm^3) were added successively, and the reaction mixture sonicated for 4 h at room temperature. After 4 h the reaction mixture was quenched with HCl (20 cm^3 of a 1M aqueous solution), extracted with DCM and the combined organic layers washed with brine (20 cm^3) and dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [hexane: ethyl acetate (90:10)], affording the product as an oil (164 mg, 41 %). δ_H 2.55 (1H, bd, $^3J_{HH}$ = 3.8 Hz, OH), 4.90 (1H, ap.td, $^3J_{HF}$ = 9.4 Hz, $^3J_{HH}$ = 3.5 Hz, *CHOH*), 5.47 (1H, ddt, $^3J_{HH}$ = 11.1 Hz, $^2J_{HH}$ = 0.8 Hz, *Hb*), 5.57 (1H, ddt, $^3J_{HH}$ = 17.2

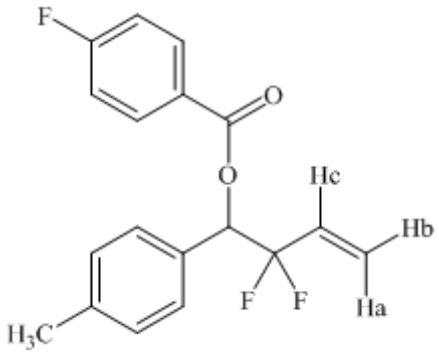
Hz, $^{4}J_{HF}$ = 3.2 Hz, $^{2}J_{HH}$ = 0.9 Hz, *Ha*), 5.84 (1H, ddt, $^{3}J_{HH}$ = 17.2 Hz, $^{3}J_{HF}$ = 12.6 Hz, $^{3}J_{HH}$ = 10.8 Hz, *Hc*), 7.05 (2H, tm, $^{3}J_{HH}$ = 8.8 Hz, *ArH-3*), 7.39 (2H, ddm, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HF}$ = 5.3 Hz, *ArH-2*); δ_C 76.7 (t, $^{2}J_{CF}$ = 30.2 Hz, *CH*OH), 116.6 (d, $^{2}J_{CF}$ = 22.6 Hz, *ArCH-3*), 120.9 (t, $^{1}J_{CF}$ = 244.0 Hz, *CF_2*), 123.3 (t, $^{3}J_{CF}$ = 10.1 Hz, CH*CH_2*), 130.5 (t, $^{2}J_{CF}$ = 25.2 Hz, *CH*CH_2), 130.8 (d, $^{3}J_{CF}$ = 8.8 Hz, *ArCH-2*), 133.1 (*ArC-1*), 164.4 (d, $^{1}J_{CF}$ = 247.7 Hz, *ArCF*); δ_F -107.9 (d, $^{2}J_{FF}$ = 249.1 Hz, CF), -109.6 (d, $^{2}J_{FF}$ = 246.4 Hz, CF), -113.2 (1F, s, CF). m/z (EI^+) 202 ($[M]^+$, 14 %), 125 ($[M\text{-}CF_2CH{=}CH_2]^+$, 100 %). HRMS (EI) 202.06045 ($C_{10}H_9O_1F_3$ requires 202.06032).

6.5.18 Preparation of 2,2-difluoro-1-(perfluorophenyl)but-3-en-1-ol (169)



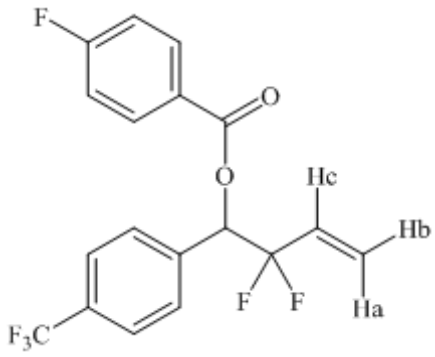
The novel compound was prepared using a method outlined by Audouard *et al.*[21] A 25 cm^3 round-bottomed flask was set up in a sonicating bath, 3-bromo-3,3-difluoroprop-1-ene (0.10 cm^3, 0.98 mmol), 2,3,4,5,6-pentafluoro- benzaldehyde (0.13 g, 0.66 mmol), indium powder (0.11 g, 0.98 mmol) and water (7 cm^3) were added successively, and the reaction mixture sonicated for 4 h at room temperature. After 4 h the reaction mixture was quenched with HCl (20 cm^3 of a 1M aqueous solution), extracted with DCM and the combined organic layers washed with brine (20 cm^3) and dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [hexane: ethyl acetate (90:10)], affording the product as a solid (0.117 g, 65 %). δ_H 3.61 (1H, bd, $^{5}J_{HF}$ = 9.1 Hz, OH), 5.24 (1H, ap.dt, $^{4}J_{HF}$ = 14.0 Hz, $^{3}J_{HF}$ = 8.5 Hz, *CHOH*), 5.60 (1H, dd, $^{3}J_{HH}$ = 11.1 Hz, $^{2}J_{HH}$ = 0.6 Hz, *Hb*), 5.75 (1H, ddt, $^{3}J_{HH}$ = 17.2 Hz, $^{4}J_{HF}$ = 3.2 Hz, $^{2}J_{HH}$ = 0.9 Hz, *Ha*), 6.05 (1H, ddt, $^{3}J_{HH}$ = 17.2 Hz, $^{3}J_{HF}$ = 11.7 Hz, $^{3}J_{HH}$ = 11.1 Hz, *Hc*); δ_C 68.4 (t, $^{2}J_{CF}$ = 32.2 Hz, *CH*OH), 109.1 (tm, $^{2}J_{CF}$ = 13.6 Hz, *ArC-1*) 117.6 (t, $^{1}J_{CF}$ = 246.5 Hz, *CF_2*), 121.6 (t, $^{3}J_{CF}$ = 9.1 Hz, CH*CH_2*), 127.9 (t, $^{2}J_{CF}$ = 25.2 Hz, *CH*CH_2), 136.6 (dm, $^{1}J_{CF}$ = 253.5 Hz, *ArCF-3*), 140.5 (dm, $^{1}J_{CF}$ = 255.6 Hz, *ArCF-4*), 144.5 (dm, $^{1}J_{CF}$ = 249.5 Hz, *ArCF-2*) δ_F -108.2 (d, $^{2}J_{FF}$ = 249.3 Hz, *CF*), -112.5 (d, $^{2}J_{FF}$ = 249.3 Hz, CF), -140.7 (2F,dm $^{3}J_{FF}$ = 21.8 Hz, *ArF-2*), -153.1 (1F, t, $^{3}J_{FF}$ = 21.8 Hz, *ArF-2*), -161.9 (2F, m, *ArF-3*); m.p 51-52 ºC.

6.5.19 Preparation of 2,2-difluoro-1-*p*-tolylbut-3-enyl 4-fluorobenzoate (170)



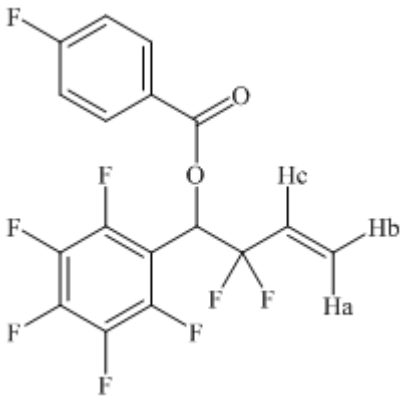
The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluoro-1-*p*-tolylbut-3-en-1-ol (42 mg, 0.21 mmol) and pyridine (0.63 cm^3) and cooled to 0 ºC. 4-Fluorobenzoyl chloride (0.025 cm^3, 0.21 mmol) was added and the reaction mixture warmed to room temperature and stirred for 2 h. After which the reaction was quenched with brine (6 cm^3) and diethyl ether (5 cm^3). The organic layer was then separated and washed with HCl (1 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the product as an oil (12 mg, 18 %). δ_H 2.27 (3H, s, CH_3), 5.44 (1H,d, $^3J_{HH}$ = 11.0 Hz, *Hb*), 5.62 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 2.7 Hz, $^2J_{HH}$ = 0.8 Hz, *Ha*), 5.85 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 12.1 Hz, $^3J_{HH}$ = 11.0 Hz, *Hc*), 6.08 (1H, ap.t, $^3J_{HF}$ = 10.6 Hz, *CHO*), 7.07 (2H, tm, $^3J_{HH}$ = 9.0 Hz, *ArH-3'*), 7.11 (2H, d, $^3J_{HH}$ = 7.8 Hz, *ArH-3*), 7.30 (2H, d, $^3J_{HH}$ = 7.8 Hz, *ArH-2*), 8.04 (2H, ddm, $^3J_{HH}$ = 9.0 Hz, $^4J_{HF}$ = 5.1 Hz *ArH-2'*); δ_C 21.3 (CH_3), 75.9 (t, $^2J_{CF}$ = 30.2 Hz, *CH*CF_2), 115.8 (d, $^2J_{CF}$ = 21.4 Hz, *ArCH-3*), 118.2 (t, $^1J_{CF}$ = 245.2 Hz, *CF_2*), 121.9 (t, $^3J_{CF}$ = 8.8 Hz, CH*CH_2*), 125.7 (d, $^4J_{CF}$ = 2.5 Hz, *ArC-1'*), 128.2 (*ArCH-2*), 129.1 (*ArCH-3*), 129.8 (t, $^2J_{CF}$ = 23.9 Hz, *CH*CH_2), 130.2 (*ArC-1)*, 132.5 (d, $^3J_{CF}$ = 10.1 Hz, *ArCH-2'*), 139.2 (*ArC-4*), 163.9 (C=O), 166.1 (d, $^1J_{CF}$ = 255.3 Hz, *ArCF*); δ_F -104.6 (1F, s, CF), -106.7 (d, $^2J_{FF}$ = 250.4 Hz, CF), -109.0 (d, $^2J_{FF}$ = 250.4 Hz, CF). m/z (EI^+) 320 ($[M]^+$, 7 %), 243 ($[M\text{-}CF_2CH{=}CH_2]^+$, 80 %), 123 ($[M\text{-}CHO(C_6H_4CH_3)$ $CF_2CH{=}CH_2]^+$, 100 %). HRMS (EI) 320.10211 ($C_{18}H_{15}O_2F_3$ requires 320.10204).

6.5.20 Preparation of 2,2-difluoro-1-(4-(trifluoromethyl)phenyl)but-3-enyl 4-fluoro benzoate (171)



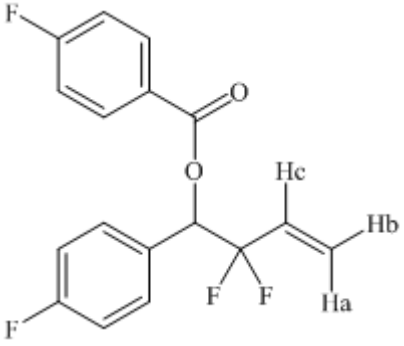
The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluoro-1-(4-(trifluoromethyl) phenyl)but-3-en-1-ol (42 mg, 0.17 mmol) and pyridine (0.5 cm^3) and cooled to 0 ºC. 4-Fluorobenzoyl chloride (0.02 cm^3, 0.17 mmol) was added and the reaction mixture warmed to room temperature and stirred for 2 h. After which the reaction was quenched with brine (6 cm^3) and diethyl ether (5 cm^3). The organic layer was then separated and washed with HCl (1 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the product as an oil (39 mg, 63%). δ_H 5.48 (1H,d, $^3J_{HH}$ = 11.0 Hz, *Hb*), 5.64(1H, dt, $^3J_{HH}$ = 17.6 Hz, $^4J_{HF}$ = 2.3 Hz, *Ha*), 5.85 (1H, ddt, $^3J_{HH}$ = 17.6 Hz, $^3J_{HF}$ = 12.5 Hz, $^3J_{HH}$ = 11.0 Hz, *Hc*), 6.08 (1H, dd, $^3J_{HF}$ = 11.3 Hz, $^3J_{HF}$ = 9.0 Hz, *CHO*), 7.08 (2H, tm, $^3J_{HH}$ = 9.0 Hz, *ArH-3'*), 7.53 (2H, d, $^3J_{HH}$ = 8.6 Hz, *ArH-3*), 7.57 (2H, d, $^3J_{HH}$ = 8.6 Hz, *ArH-2*), 8.04 (2H, ddm, $^3J_{HH}$ = 9.0 Hz, $^4J_{HF}$ = 5.5 Hz *ArH-2'*); δ_C 75.3 (t, $^2J_{CF}$ = 30.2 Hz, *CH*CF_2), 115.9 (d, $^2J_{CF}$ = 21.4 Hz, *ArCH-3'*), 117.9 (t, $^1J_{CF}$ = 246.5 Hz, *CF_2*), 122.6 (t, $^3J_{CF}$ = 8.8 Hz, CH*CH_2*), 123.8 (q, $^1J_{CF}$ = 271.6 Hz, *$ArCF_3$*), 125.2 (d, $^4J_{CF}$ = 2.5 Hz, *ArC-1'*), 125.4 (q, $^3J_{CF}$ = 3.8 Hz, *ArCH-3*), 128.6 (*ArCH-2*), 129.3 (t, $^2J_{CF}$ = 25.2 Hz, *CH*CH_2), 131.4 (q, $^2J_{CF}$ = 32.7 Hz, *ArCH-4*), 132.6 (d, $^3J_{CF}$ = 8.8 Hz, *ArCH-2'*), 137.1 (*ArC-1*), 163.7 (C=O), 166.3 (d, $^1J_{CF}$ = 255.3 Hz, *ArCF'*); δ_F -62.8 (3F, s, CF_3), -103.8 (1F, s, CF), -105.8 (d, $^2J_{FF}$ = 254.3 Hz, CF), -109.4 (d, $^2J_{FF}$ = 250.4 Hz, CF). m/z (EI^+) 374 ($[M]^+$, 13 %), 297 ($[M\text{-}CF_2CH{=}CH_2]^+$, 76 %), 123 ($[M\text{-}CHO(C_6H_4CH_3)\ CF_2CH{=}CH_2]^+$, 100 %). HRMS (EI) 374.07384 ($C_{18}H_{12}O_2F_6$ requires 374.07385).

6.5.21 Preparation of 2,2-difluoro-1-(perfluorophenyl)but-3-enyl 4-fluorobenzoate (173)



The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluoro-1-(perfluorophenyl) but-3-en-1-ol (100 mg, 0.37 mmol) and pyridine (1.1 cm^3) and cooled to 0 ºC. 4-Fluorobenzoyl chloride (0.043 cm^3, x mmol) was added and the reaction mixture warmed to room temperature and stirred for 2 h. After which the reaction was quenched with brine (6 cm^3) and diethyl ether (5 cm^3). The organic layer was then separated and washed with HCl (1 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the product as a white solid (137 mg, 95 %). δ_H 5.62 (1H, d, $^3J_{HH}$ = 10.8 Hz, *Hb*), 5.82 (1H, dt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 2.4 Hz, *Ha*), 6.05 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 12.3 Hz, $^3J_{HH}$ = 10.8 Hz, *Hc*), 6.17 (1H, dd, $^3J_{HF}$ = 14.6 Hz, $^3J_{HF}$ = 7.9 Hz *CHO*), 7.16 (2H, tm, $^3J_{HH}$ = 8.5 Hz, *ArH-3*), 8.10 (2H, ddm, $^3J_{HH}$ = 8.8 Hz, $^4J_{HF}$ = 5.3 Hz, *ArH-2*); δ_C 68.2 (t, $^2J_{CF}$ = 31.4 Hz, *CH*CF_2), 116.0 (d, $^2J_{CF}$ = 22.6 Hz, *ArCH-3'*), 117.6 (t, $^1J_{CF}$ = 248.9 Hz, *CF_2*), 123.1 (t, $^3J_{CF}$ = 10.1 Hz, CH*CH_2*), 124.5 (*ArC-1'*), 128.7 (t, $^2J_{CF}$ = 25.2 Hz, *CH*CH_2), 132.8 (d, $^3J_{CF}$ = 8.8 Hz, *ArCH-2'*), 163.6 (C=O), 166.4 (d, $^1J_{CF}$ = 255.3 Hz, *ArCF*), [quaternary pentafluoro C-F carbons not visible]. δ_F -103.2 (1F, s, CF), -105.1 (d, $^2J_{FF}$ = 245.0 Hz, CF), -110.4 (d, $^2J_{FF}$ = 251.4 Hz, CF), -138.6 (2F,dm $^3J_{FF}$ = 21.5 Hz, *ArF-2*), -151.2 (1F, t, $^3J_{FF}$ = 21.5 Hz, *ArF-2*), -160.9 (2F, m, *ArF-3*). m/z (EI^+) 396 ($[M]^+$, 25 %), 319 ($[M\text{-}CF_2CH{=}CH_2]^+$, 75 %). HRMS (EI) 396.03947 ($C_{17}H_8O_2F_8$ requires 396.03946).

6.5.22 Preparation of 2,2-difluoro-1-(4-fluorophenyl)but-3-enyl 4-fluorobenzoate (172)



The title compound was prepared using a method outlined by Nakamura *et al.*[7] A 100 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluoro-1-(4-fluorophenyl)but-3-en-1-ol (68 mg, 0.34 mmol) and pyridine (2 cm^3) and cooled to 0 ºC. 4-Fluorobenzoyl chloride (0.04 cm^3, 0.34 mmol) was added and the reaction mixture warmed to room temperature and stirred for 2 h. After which the reaction was quenched with brine (6 cm^3) and diethyl ether (5 cm^3). The organic layer was then separated and washed with HCl (1 cm^3, 5 % aqueous solution), saturated brine (10 cm^3), saturated $NaHCO_3$ (10 cm^3) and saturated brine (10 cm^3) successively, then dried over magnesium sulphate. After removal of solvent *in vacuo* the crude product was purified by column chromatography [chloroform: hexane (50:50)], affording the product as an oil (65 mg, 60 %) δ_H 5.53 (1H, d, $^3J_{HH}$ = 10.8 Hz, *Hb*), 5.69 (1H, dt, $^3J_{HH}$ = 17.2 Hz, $^4J_{HF}$ = 2.6 Hz, *Ha*), 5.84 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 12.3 Hz, $^3J_{HH}$ = 10.8 Hz, *Hc*), 6.17 (1H, ap.t, $^3J_{HF}$ = 10.5 Hz, *CHO*), 7.06 (2H, tm, $^3J_{HH}$ = 8.8 Hz, *ArH-3*), 7.14 (2H, tm, $^3J_{HH}$ = 8.8 Hz, *ArH-3'*), 7.47 (2H, ddm, $^3J_{HH}$ = 8.5 Hz, $^4J_{HF}$ = 5.6 Hz, *ArH-2*), 8.12 (2H, ddm, $^3J_{HH}$ = 9.1 Hz, $^4J_{HF}$ = 5.6 Hz, *ArH-2'*); δ_C 75.3 (t, $^2J_{CF}$ =31.4 Hz, *CH*CF_2), 115.5 (d, $^2J_{CF}$ = 21.4 Hz, *ArCH-3*), 115.9 (d, $^2J_{CF}$ = 22.6 Hz, *ArCH-3'*), 118.0 (t, $^1J_{CF}$ = 245.2 Hz, CF_2), 122.2 (t, $^3J_{CF}$ = 10.1 Hz, CHCH_2), 125.5 (*ArC-1'*), 129.1 (*ArC-1*), 129.6 (t, $^2J_{CF}$ = 25.2 Hz, *CH*CH_2), 130.9 (d, $^3J_{CF}$ = 8.8 Hz, *ArCH-2*), 132.5 (d, $^3J_{CF}$ = 10.1 Hz, *ArCH-2'*), 163.0 (d, $^1J_{CF}$ = 249.0 Hz, *ArCF*), 164.2 (C=O), 166.2 (d, $^1J_{CF}$ = 255.2 Hz, *ArCF'*); δ_F -104.2 (1F, s, CF), -106.5 (d, $^2J_{FF}$ = 249.1 Hz, CF), -109.4 (d, $^2J_{FF}$ = 249.1 Hz, CF), -112.0 (1F, s, CF). m/z (EI$^+$) 324 ([M]$^+$, 15 %), 123 ([M-CHO(C_6H_4F) $CF_2CH{=}CH_2$]$^+$, 100 %). HRMS (EI) 324.07709 ($C_{17}H_{12}O_2F_4$ requires 324.07704).

6.6 References

[1] A. Abulikemu, G. Halasz, A. Csampai, A. Gomory, J. Rabai, *J. Fluorine Chem* **2004**, *125*, 1143.

[2] K. Yasui, K. Fugami, S. Tanaka, Y. Tamaru, *J. Org. Chem.* **1995**, *60*, 1365.

[3] A. Bhattacharya, N. C. Patel, T. Vasques, R. Tichkule, G. Parmar, J. Wu, *Tetrahedron Lett.* **2006**, *47*, 565.

[4] I. Victor Paul Raj, A. Sudalai, *Tetrahedron Lett.* **2005**, *46*, 8303

[5] G. W. Ebert, W. L. Juda, R. H. Kosakowski, B. Ma, L. Dong, K. E. Cummings, M. V. B. Phelps, A. E. Mostafa, J. Luo, *J. Org. Chem.* **2005**, *70*, 4314

[6] T. J. Deming, B. M. Novak, *J. Am. Chem. Soc.* **1993**, *115*, 9101.

[7] K. Nakamura, K. Takenaka, *Tetrahedron: Asymmetry* **2002**, *13*, 415.

[8] S. Thibaudeau, V. Gouverneur, *Org. Lett.* **2003**, *5*, 4891.

[9] B. M. Trost, C. Nübling, *Carbohydr. Res.* **1990**, *202*, 1.

[10] T. Ziegler, F. Bien, C. Jurisch, *Tetrahedron: Asymmetry* **1998**, *9*, 765.

[11] F. Munyemana, A.-M. Frisque-Hesbain, A. Devos, L. Ghosez, *Tetrahedron Lett.* **1989**, *30*, 3077.

[12] M. Bandini, P. G. Cozzi, S. Licciulli, A. Umani-Ronchi, *Synthesis* **2004**, *3*, 409.

[13] K. L. Granberg, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1992**, *114*, 6858.

[14] A. Hazari, V. Gouverneur, J. Brown, *Angew. Chem. Int. Ed.* **2009**, *48*, 1296.

[15] A. Terada, *Nippon Kagaku Zasshi* **1960**, *81*, 1773.

[16] T. Hayashi, A. Yamamoto, Y. Ito, *J. Organomet. Chem.* **1988**, *338*, 261.

[17] T. Hayashi, M. Konishi, M. Kumada, *J. Chem. Soc. Chem. Commun.* **1984**, 107.

[18] T. Fukuzumi, N. Shibata, M. Sugiura, H. Yasui, S. Nakamura, T. Toru, *Angew. Chem. Int. Ed.* **2006**, *45*, 4973.

[19] H. Hrebabecky, M. Masojidkova, A. Holy, *Collect. Czech. Chem. Commun.* **1998**, *63*, 2044.

[20] G. H. Jeffrey, A. I. Vogel, *Journal of the Chemical Society* **1948**, 658.

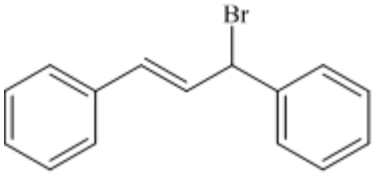
[21] C. Audouard, J. Fawcett, G. Griffiths, J. Percy, S. Pintat, C. Smith, *Org. Biomol. Chem.* **2004**, *2*, 528.

[22] Y. Wu, J. Gao, *Org. Lett.* **2008**, *10*, 1533.

APPENDIX

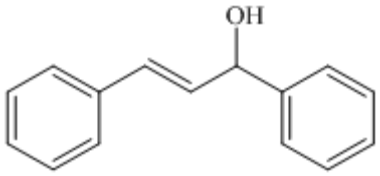
A1 Attempted Reactions in Chapter Two

Preparation of (3-bromoprop-1-ene-1,3-diyl)dibenzene



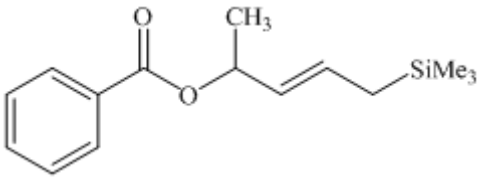
The title compound was prepared following the method outlined by Hintermann[1] without modification. A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 1,3-diphenylprop-2-en-1-ol (1.0 g, 4.76 mmol) and HBr in acetic acid (1.75 cm^3, 9 mmol), and stirred for 10 minutes at room temperature and then 1 h at 0 ºC. After which the brown product was dried *in vacuo*, to afford a brown powder.

Attempted preparation of 1,3-diphenylprop-2-en-1-ol



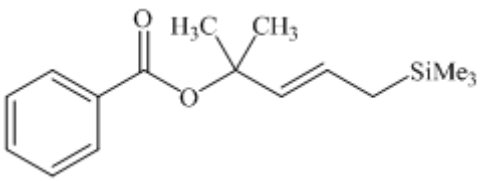
A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The flask was charged with 1,3-diphenylprop-2-en-1-ol (1.0 g, 4.76 mmol) triethylamine (0.66 cm^3) and anhydrous DCM (25 cm^3) and cooled to 0 ºC, a solution of *p*-toluenesulphonyl chloride (0.98 g, 5.23 mmol) in anhydrous DCM (25 cm^3) was added dropwise over 30 minutes, and the reaction mixture stirred for 3 h. Work up afforded a product as a pale yellow powder.

Attempted preparation of 5-(trimethylsilyl)pent-3-en-2-yl benzoate



The title compound was prepared following the method outlined by Gouverneur *et al.*[2] without modification. A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and condenser and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with argon. The flask was charged with but-3-en-2-yl benzoate (176 mg, 1 mmol), allyltrimethylsilane (0.48 cm^3, 3 mmol) and anhydrous DCM (3 cm^3). The reaction mixture was heated to reflux. Second generation Grubbs catalyst (5 % mol, 42 mg, 0.05 mmol) was weighed into a V-shaped dropping tube in a dry box and then transferred to the reaction flask, addition was in three portions over 48 h. The reaction was left to reflux for 48 h. Purification by flash column chromatography [diethyl ether/hexane (15:85)] and concentration *in vacuo* failed to afford the desired product.

Attempted preparation of 2-methyl-5-(trimethylsilyl)pent-3-en-2-yl benzoate

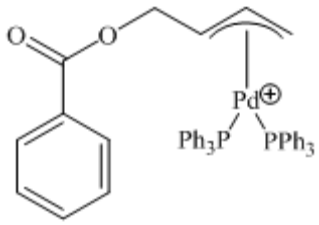


The title compound was prepared following the method outlined by Gouverneur *et al.*[2] without modification. A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and condenser and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with argon. The flask was charged with 2-methylbut-3-en-2-yl benzoate (380 mg, 2 mmol), allyltrimethylsilane (0.96 cm^3, 6 mmol) and anhydrous DCM (7 cm^3). The reaction mixture was heated to reflux.

Second generation Grubbs catalyst (5 % mol, 84 mg, 0.10 mmol) was weighed into a V-shaped dropping tube in a dry box and then transferred to the reaction flask, addition was in three portions over 48 h. The reaction was left to reflux for 48 h. Purification by flash column chromatography [diethyl ether/hexane (15:85)] and concentration *in vacuo* failed to afford the desired product.

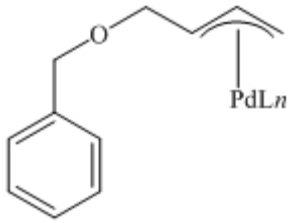
A2 Attempted reactions in Chapter Three

Reaction of 2-chlorobut-3-enyl benzoate with $Pd(PPh_3)_4$



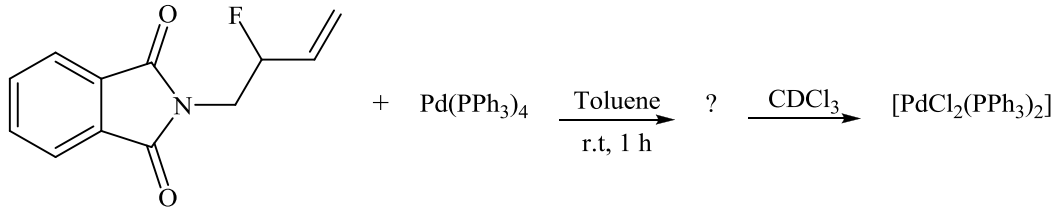
The title compound was prepared following the method outlined by Kurosawa *et al.* without modification. A 100 cm^3, three-necked round-bottom flask was equipped with a magnetic stirring bar and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with argon. $Pd(PPh_3)_4$ (193 mg, 0.17 mmol) was added to the flask in the dry box, and then reattached to the Schlenk line. Anhydrous DCM (2 cm^3) and 2-chlorobut-3-enyl benzoate (200 mg, 0.95 mmol) added and the reaction mixture was stirred at room temperature for 1 h. After which hexane was added to cause precipitation of the product, this was then isolated and dried *in vacuo*. Analysis by ^1H NMR revealed some product formation but predominantly starting material.

Reaction of ((2-fluorobut-3-enyloxy)methyl)benzene with $Pd(dba)_2$ at r.t in THF



The title compound was prepared following the method outlined by Togni *et al.* without modification. A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (55 mg, 0.10 mmol) was added to the flask in the dry box, and then reattached to the Schlenk line. Anhydrous THF (10 cm^3) and ((2-fluorobut-3-enyloxy)methyl)benzene (100 mg, 0.55 mmol) were added and the reaction mixture was stirred at room temperature for 12 h. Analysis by ^1H and ^{19}F NMR revealed no starting material to be present.

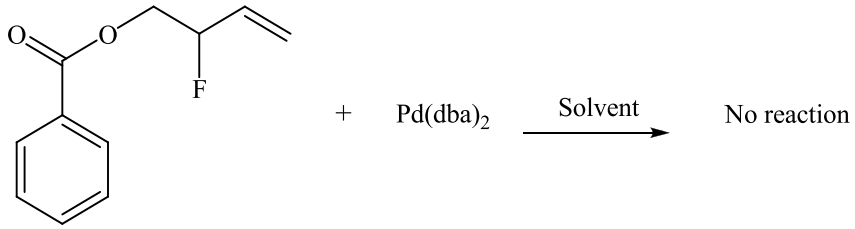
Reaction of 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione with $Pd(PPh_3)_4$ at r.t



A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(PPh_3)_4$ (140 mg, 0.12 mmol) was added to the flask in the dry box, and then reattached to the Schlenk line. Anhydrous toluene (10 cm^3) and 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione (156 mg, 0.71 mmol) were added and the reaction mixture was stirred at room temperature for 1 h, the precipitate formed was isolated and analysis by ^1H and ^{19}F NMR revealed no starting material to be present, however dominance

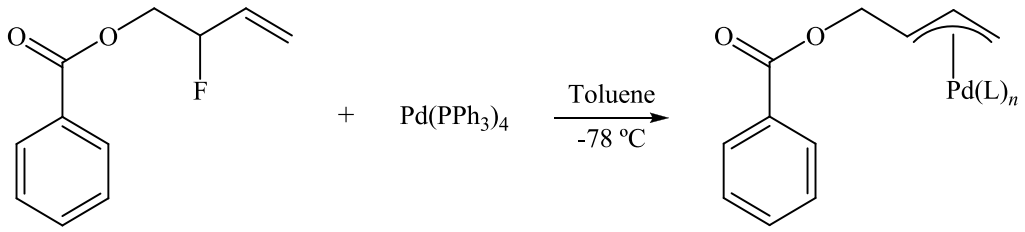
by PPh_3, hindered full analysis of the spectrum. After several days, the NMR sample became crystalline, analysis by X-ray crystallography determined the product to be $PdCl_2(PPh_3)_2$. Formation of this complex indicates that an intermediate product is forming which may then be decomposing, hence as NMR spectroscopy of the product was conducted in $CDCl_3$, formation of $PdCl_2(PPh_3)_2$ occurred.

Reaction of 2-fluorobut-3-enyl benzoate with $Pd(dba)_2$ at r.t



A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (50 mg, 0.09 mmol) was added to the flask in the dry box, and then reattached to the Schlenk line. Anhydrous DCM (10 cm^3) and 2-fluorobut-3-enyl benzoate (100 mg, 0.52 mmol) were added and the reaction mixture was stirred at room temperature for 12 h. Analysis by ^1H and ^{19}F NMR revealed no reaction had occurred.
Repeating the reaction with toluene also resulted in no reaction.
Conducting the reaction in THF at -78 ºC with warming to room temperature over 48 h, afforded only starting material

Reaction of 2-fluorobut-3-enyl benzoate with $Pd(PPh_3)_4$ at -78 ºC



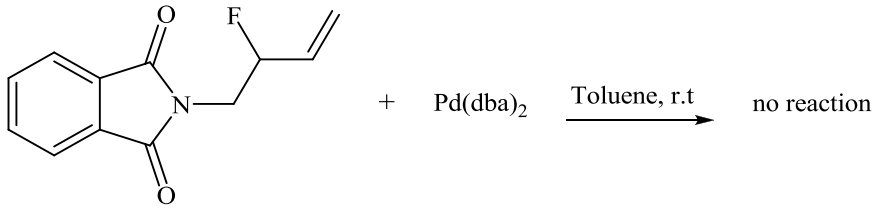
A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(PPh_3)_4$ (104 mg, 0.09 mmol) was added to the flask in the dry box, and then reattached to the Schlenk line. Anhydrous toluene (10 cm^3) and 2-fluorobut-3-enyl benzoate (100 mg, 0.52 mmol) were added and the reaction mixture was stirred at -78 ºC for 1 h, the precipitate formed was isolated and analysis by ^1H and ^{19}F NMR revealed no starting material to be present.

Reaction of 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione with $Pd(PPh_3)_4$ at -78 ºC

A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(PPh_3)_4$ (93 mg, 0.08 mmol) was added to the flask in the dry box, and then reattached to the Schlenk line. Anhydrous toluene (10 cm^3) and 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione (156 mg, 0.46 mmol) were added and the reaction

mixture was stirred at -78 ºC for 1h, the precipitate formed was isolated and analysis by ^{1}H and ^{19}F NMR revealed no starting material to be present, however dominance by PPh_3, hindered full analysis of the spectrum.

Reaction of 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione with $Pd(dba)_2$ at r.t



A 50 cm^3 two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (273 mg, 0.48 mmol) was added to the flask in the dry box, and then reattached to the Schlenk line. Anhydrous toluene (10 cm^3) and 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione (104 mg, 0.48 mmol) were added and the reaction mixture was stirred at room temperature for 6h. After removal of the reaction solvent the mixture analysed by ^{1}H and ^{19}F NMR spectroscopy confirming that no reaction had occurred as only starting material was observed. The same reaction conditions had simultaneously been applied to 2-fluorobut-3-enyl benzoate and unfortunately the same disappointing result was obtained.

Reaction of 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione with $Pd(dba)_2$ at 30 – 70 ºC

A 50 cm^3 two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (263 mg, 0.46 mmol) was added to the flask in the dry box, and then reattached to the Schlenk line. Anhydrous toluene (10 cm^3) and 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione (100 mg, 0.46 mmol) were added and the reaction mixture was stirred at 30 ºC overnight. The following day no precipitate or colour change was observed, therefore, the temperature was increased to 35 ºC, and stirred for a further 2 hours, however, no notable change was observed. Therefore, the temperature was increased further to 40 ºC for 1 hour and then stirred at 50 ºC for 3 hours, before finally refluxing at 70 ºC for 24 hours. After which a yellow solution was observed with a dark precipitate. The yellow solution was transferred *via* cannula and dried *in vacuo*. Both ^{1}H and ^{19}F NMR spectroscopy showed that only starting material and dba were present. The dark precipitate was also dried *in vacuo* and analysed by ^{1}H and ^{19}F NMR spectroscopy with some difficulty as it was not fully soluble in $CDCl_3$ or C_6D_6, therefore, deuterated toluene was used, however, only dba and starting material were present.

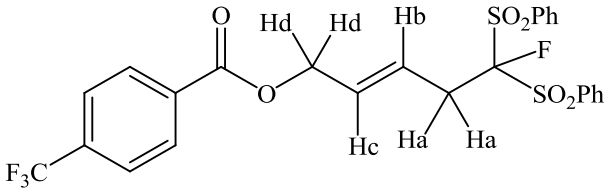
Reaction of 2-fluorobut-3-enyl benzoate with $Pd(dba)_2$ at 30 – 70 ºC

A 50 cm^3 two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (296 mg, 0.52 mmol) was added to the flask in the dry box, and then reattached to the Schlenk line. Anhydrous toluene (10 cm^3) and 22-fluorobut-3-enyl benzoate (100 mg, 0.52 mmol) were added and the reaction mixture was stirred at 30 ºC overnight. The following day no precipitate or colour change was observed,

therefore, the temperature was increased to 35 ºC, and stirred for a further 2 hours, however, no notable change was observed. Therefore, the temperature was increased further to 40 ºC for 1 hour and then stirred at 50 ºC for 3 hours, before finally refluxing at 70 ºC for 24 hours. After which a yellow solution was observed with a dark precipitate. The yellow solution was transferred *via* cannula and dried *in vacuo*. Both ^{1}H and ^{19}F NMR spectroscopy showed that only starting material and dba were present.

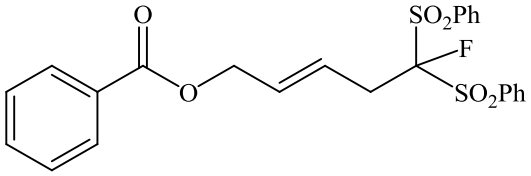
A3 Attempted reactions in Chapter 4

Synthesis of 5-fluoro-5,5-bis(phenylsulfonyl)pent-2-enyl 4-(trifluoromethyl) benzoate



A 50 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $[Pd(C_3H_5)Cl]_2$ (3 mg, 0.008 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with PPh_3 (83 mg, 0.32 mmol) and anhydrous DCM (3 cm^3) and stirred at room temperature for 15 minutes. After which, 2-chlorobut-3-enyl 4-(trifluoromethyl)benzoate (89 mg, 0.32 mmol), sodium 1-fluoro-bis(phenylsulfonyl)methane (323 mg, 0.96 mmol) and 15-crown-5 (0.19 cm^3, 0.96 mmol) were added and the reaction mixture left to stir. After stirring overnight, the reaction was quenched with water (10 cm^3) and the aqueous phase extracted with diethyl ether (3 x 10 cm^3). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo*. Purification by column chromatography failed to fully isolate the product.

Synthesis of 5-fluoro-5,5-bis(phenylsulfonyl)pent-2-enyl 4-(trifluoromethyl) benzoate



A 50 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $[Pd(C_3H_5)Cl]_2$ (3 mg, 0.008 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with PPh_3 (83 mg, 0.32 mmol) and anhydrous DCM (3 cm^3) and stirred at room temperature for 15 minutes. After which, 2-chlorobut-3-enyl benzoate (67 mg, 0.32 mmol), sodium 1-fluoro-bis (phenylsulfonyl)methane (323 mg, 0.96 mmol) and 15-crown-5 (0.19 cm^3, 0.96 mmol) were added and the reaction mixture left to stir. After stirring overnight, the reaction was quenched with water (10 cm^3) and the aqueous phase extracted with diethyl ether (3 x 10 cm^3). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo*. However no desired product was found.

Fluoride reactions

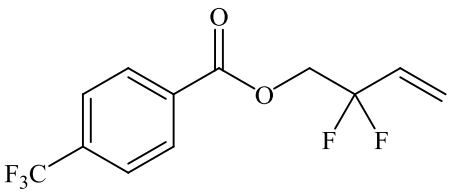
A 50 cm^3, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $[Pd(C_3H_5)Cl]_2$ (3 mg, 0.008 mmol) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with PPh_3 (83 mg, 0.32 mmol) and anhydrous DCM (3 cm^3) and

stirred at room temperature for 15 minutes. After which, 2-chlorobut-3-enyl benzoate (67 mg, 0.32 mmol), sodium fluoride (40 mg, 0.96 mmol) and 15-crown-5 (0.19 cm^3, 0.96 mmol) were added and the reaction mixture left to stir. After stirring overnight, the reaction was quenched with water (10 cm^3) and the aqueous phase extracted with diethyl ether (3 x 10 cm^3). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo*. Analysis by ^1H and ^{19}F NMR spectroscopy of the crude product revealed that no fluorinated product had formed.

A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (l equiv.), PPh_3 (2 equiv.) and anhydrous $CDCl_3$ were added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with allyl halide (2 equiv.), after stirring the reaction for 2 hours, fluoride (5 equivalents) was added to the reaction flask, a small aliquot was transferred to an NMR tube, and the reaction was monitored by ^1H and ^{19}F NMR spectroscopy. However, no desired product was formed when fluoride = TBAF, TASF, TREAT HF or HF.pyridine.

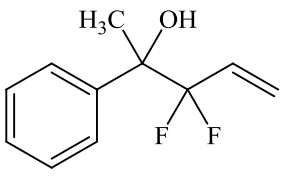
A4 Attempted reactions in Chapter 5

Attempted preparation of 2,2-difluorobut-3-enyl 4-methylbenzoate



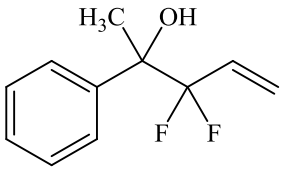
The title compound was prepared using a method outlined by Nakamura *et al.*[3] A 100 mL, two-necked round-bottomed flask was equipped with a magnetic stirring bar, and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. The reaction flask was charged with 2,2-difluorobut-3-en-1-ol (*ca.* 0.05 g in 40 mL DCM, 0.49 mmol) and pyridine (1 mL) and cooled to 0 ºC. 4-(trifluoromethyl)benzoyl chloride (0.6 mL, 2.45 mmol) was added and the reaction mixture stirred at 0 ºC for 4 h. After which the reaction was quenched with brine (5 mL) and the organic layer separated and washed with HCl (10 mL, 5 % aqueous solution), saturated brine (10 mL), saturated $NaHCO_3$ (10 mL) and saturated brine (10 mL) successively, then dried over magnesium sulphate. Purification by flash column chromatography [chloroform: hexane (50:50)] and concentration *in vacuo* failed to afford the desired product.

Attempted preparation of 3,3-difluoro-2-phenylpent-4-en-2-ol



The title compound was prepared using a method outlined by Audouard *et al.*[4] A 25 mL round-bottomed flask was set up in a sonicating bath, 3-bromo-3,3-difluoroprop-1-ene (0.3 cm^3, 2.95 mmol),acetophenone (0.17 cm^3, 1.48 mmol), indium powder (0.31 g, 2.95 mmol) and water (14 mL) were added successively, and the reaction mixture sonicated for 24 h at room temperature. After 24 h the reaction mixture was quenched with HCl (10 mL of a 1M aqueous solution), extracted with dichloromethane and the combined organic layers washed with brine (20 mL) and dried over magnesium sulphate. Purification by flash column chromatography [petroleum ether: diethyl ether (85:15)] and concentration *in vacuo* failed to afford the desired product.

Attempted preparation of 3,3-difluoro-2-phenylpent-4-en-2-ol



The title compound was prepared using a method outlined by Burton *et al.* A 100 mL, three-necked round-bottomed flask was equipped with a magnetic stirring bar, Rotaflo tap and dropping funnel were attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. Acetophenone (0.35 cm^3, 2.95 mmol) and anhydrous THF (10 mL) were added to the reaction flask containing acid washed zinc powder (0.39 g, 5.90 mmol). The reaction mixture was then cooled to 0 ºC and 3-bromo-3,3-difluoroprop-1-ene (0.3 cm^3, 2.95 mmol) in THF (10 mL) was added dropwise over 30 minutes. After which the reaction mixture was warmed to room temperature and stirred overnight. A small aliquot was removed and quenched by the addition of aqueous 5 % HCl extracted with diethyl ether (10 cm^3), washed with saturated $NaHCO_3$ and dried over magnesium sulphate. Analysis by ^1H NMR revealed only a small proportion of product to be present. Therefore the reaction mixture was heated at 45 ºC for 24 h. After which a small aliquot was then removed and worked up, however, analysis by ^1H NMR showed no further improvement in conversion to product, therefore, the reaction mixture was refluxed for 24 h and then sonicated for a further 24 h. After which the reaction mixture underwent work up and the crude product was analysed by ^1H NMR, however, the proportion of product was too small to purify by column chromatography.

Reaction of 2,2-difluorobut-3-enyl benzoate with $Pd(PPh_3)_4$

A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(PPh_3)_4$ (l equiv.), and anhydrous $CDCl_3$ were added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with 2,2-difluorobut-3-enyl benzoate (1 equiv.), after stirring the reaction for 5 minutes a small aliquot was transferred to an NMR tube, and the reaction was monitored by ^1H and ^{19}F NMR spectroscopy and mass spectrometry. However, no desired product was observed only starting material.

Reaction of 3-bromo-3,3-difluoroprop-1-ene with $Pd(dba)_2$ in $CDCl_3$

A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (l equiv.), PPh_3 (2 equiv.) and anhydrous $CDCl_3$ were added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with 3-bromo-3,3-difluoroprop-1-ene (2 equiv.), after stirring the reaction for 5 minutes a small aliquot was transferred to an NMR tube, and the reaction was monitored by ^1H and ^{19}F NMR spectroscopy and mass spectrometry. However no desired product was formed.

Reaction of 3-bromo-3,3-difluoroprop-1-ene with $Pd(dba)_2$ in DMSO

A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(dba)_2$ (1 equiv) was added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with 3-bromo-3,3-difluoroprop-1-ene (1 equiv) and DMSO (10 cm^3). The reaction mixture was stirred for 2 h and then quenched with water (10 cm^3) and chloroform (10 cm^3).

The organic phase was separated, washed with water (3 x 20 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid. However ^1H and ^{19}F NMR spectroscopy revealed no desired product to be present.

Reaction of 3-bromo-3,3-difluoroprop-1-ene with $Pd(PPh_3)_4$

A 50 cm^3, two-necked round-bottom flask was equipped with a magnetic stirring bar and Rotaflo tap and attached to a Schlenk line. After flame-drying under high vacuum, the flask was cooled and filled with nitrogen. $Pd(PPh_3)_4$ (l equiv.), and anhydrous $CDCl_3$ were added to the reaction flask in a dry box. Subsequently, the flask was reattached to the Schlenk line, filled with nitrogen and charged with 3-bromo-3,3-difluoroprop-1-ene (1 equiv.), after stirring the reaction for 5 minutes a small aliquot was transferred to an NMR tube, and the reaction was monitored by ^1H and ^{19}F NMR spectroscopy and mass spectrometry. The desired Pd cationic complex was observed by mass spectrometry, however, the main product formed was 3,3-difluoroallyltriphenylphosphonium bromide.

A5 Crystal data and structure refinement for 2-hydroxybut-3-enyl 4-(trifluoromethyl) benzoate (104)

Empirical formula	C12 H11 F3 O3	
Formula weight	260.21	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 17.452(3) Å	α= 90°
	b = 4.5964(7) Å	β= 99.270(3)°
	c = 29.576(5) Å	γ = 90°
Volume	2341.6(6) $Å^3$	
Z	8	
Density (calculated)	1.476 Mg/m^3	
Absorption coefficient	0.136 mm^{-1}	
F(000)	1072	
Crystal size	0.25 x 0.17 x 0.07 mm^3	
Theta range for data collection	1.27 to 25.00°.	
Index ranges	-20<=h<=20, -5<=k<=5, -34<=l<=35	
Reflections collected	15865	
Independent reflections	4138 [R(int) = 0.0711]	
Completeness to theta = 25.00°	99.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9906 and 0.9669	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4138 / 0 / 354	
Goodness-of-fit on F^2	0.917	
Final R indices [I>2sigma(I)]	R1 = 0.0568, wR2 = 0.1047	
R indices (all data)	R1 = 0.1138, wR2 = 0.1218	
Largest diff. peak and hole	0.458 and -0.237 $e.Å^{-3}$	

A6 Crystal data and structure refinement for 2-hydroxybut-3-enyl 4-methylbenzoate (105)

Empirical formula	C12 H14 O3	
Formula weight	206.23	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 17.373(4) Å	α= 90°
	b = 4.5935(10) Å	β= 90°
	c = 26.711(6) Å	γ = 90°
Volume	2131.6(8) $Å^3$	
Z	8	
Density (calculated)	1.285 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	880	
Crystal size	0.13 x 0.10 x 0.07 mm^3	
Theta range for data collection	2.34 to 24.99°.	
Index ranges	-20<=h<=20, -5<=k<=5, -31<=l<=31	
Reflections collected	14214	
Independent reflections	1934 [R(int) = 0.1315]	
Completeness to theta = 24.99°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9936 and 0.9882	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1934 / 1 / 276	
Goodness-of-fit on F^2	0.889	
Final R indices [I>2sigma(I)]	R1 = 0.0520, wR2 = 0.0879	
R indices (all data)	R1 = 0.0937, wR2 = 0.1006	
Absolute structure parameter	0(10)	
Largest diff. peak and hole	0.187 and -0.199 e.$Å^{-3}$	

A7 Crystal data and structure refinement for 2-hydroxybut-3-enyl 4-fluorobenzoate (101)

Empirical formula	C11 H11 F O3	
Formula weight	210.20	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 17.150(3) Å	α= 90°
	b = 4.5568(9) Å	β= 90°
	c = 25.694(5) Å	γ = 90°
Volume	2008.0(7) $Å^3$	
Z	8	
Density (calculated)	1.391 Mg/m^3	
Absorption coefficient	0.112 mm^{-1}	
F(000)	880	
Crystal size	0.27 x 0.18 x 0.03 mm^3	
Theta range for data collection	2.38 to 25.00°.	
Index ranges	-20<=h<=19, -5<=k<=5, -30<=l<=30	
Reflections collected	13196	
Independent reflections	1816 [R(int) = 0.1329]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9966 and 0.9703	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1816 / 1 / 273	
Goodness-of-fit on F^2	0.858	
Final R indices [I>2sigma(I)]	R1 = 0.0468, wR2 = 0.0771	
R indices (all data)	R1 = 0.1008, wR2 = 0.0911	
Absolute structure parameter	-10(10)	
Largest diff. peak and hole	0.172 and -0.156 e.$Å^{-3}$	

A8 Crystal data and structure refinement for Bis[μ-chloro-bis(butenyl-(1,2,3-η)-4-fluorobenzoate] dipalladium (127)

Empirical formula	C22 H20 Cl2 F2 O4 Pd2	
Formula weight	670.08	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	I4(1)/a	
Unit cell dimensions	a = 15.811(2) Å	α= 90°.
	b = 15.811(2) Å	β= 90°.
	c = 18.577(4) Å	γ = 90°.
Volume	4644.2(12) $Å^3$	
Z	8	
Density (calculated)	1.917 Mg/m^3	
Absorption coefficient	1.822 mm^{-1}	
F(000)	2624	
Crystal size	0.12 x 0.11 x 0.07 mm^3	
Theta range for data collection	1.69 to 25.98°.	
Index ranges	-19<=h<=19, -19<=k<=19, -22<=l<=22	
Reflections collected	17903	
Independent reflections	2273 [R(int) = 0.0815]	
Completeness to theta = 25.98°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.8831 and 0.8110	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2273 / 0 / 145	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0659, wR2 = 0.1543	
R indices (all data)	R1 = 0.1035, wR2 = 0.1699	
Largest diff. peak and hole	0.582 and -0.679 $e.Å^{-3}$	

A9 Crystal data and structure refinement for Bis[μ-chloro-bis(butenyl-(1,2,3-η)-3-fluorobenzoate] dipalladium (128)

Empirical formula	C22 H20 Cl2 F2 O4 Pd2	
Formula weight	670.08	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.756(4) Å	α= 71.839(9)°.
	b = 11.612(6) Å	β= 83.806(9)°.
	c = 13.575(8) Å	γ = 81.685(10)°.
Volume	1146.9(11) $Å^3$	
Z	2	
Density (calculated)	1.940 Mg/m^3	
Absorption coefficient	1.844 mm^{-1}	
F(000)	656	
Crystal size	0.18 x 0.16 x 0.04 mm^3	
Theta range for data collection	1.58 to 26.00°.	
Index ranges	-9<=h<=9, -14<=k<=14, -16<=l<=16	
Reflections collected	8902	
Independent reflections	4443 [R(int) = 0.0683]	
Completeness to theta = 26.00°	98.5 %	
Absorption correction	Empirical	
Max. and min. transmission	0.831 and 0.507	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4443 / 0 / 289	
Goodness-of-fit on F^2	1.000	
Final R indices [I>2sigma(I)]	R1 = 0.0715, wR2 = 0.1409	
R indices (all data)	R1 = 0.1270, wR2 = 0.1599	
Largest diff. peak and hole	1.138 and -0.825 e.$Å^{-3}$	

A10 Crystal data and structure refinement for 2-(2-fluorobut-3-enyl)isoindoline-1,3-dione (74)

Empirical formula	C12 H10 F N O2	
Formula weight	219.21	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.209(2) Å	α= 99.982(4)°.
	b = 8.316(2) Å	β= 109.527(5)°.
	c = 8.767(3) Å	γ = 104.789(4)°.
Volume	523.0(3) $Å^3$	
Z	2	
Density (calculated)	1.392 Mg/m^3	
Absorption coefficient	0.107 mm^{-1}	
F(000)	228	
Crystal size	0.17 x 0.16 x 0.03 mm^3	
Theta range for data collection	2.57 to 25.00°.	
Index ranges	-9<=h<=9, -9<=k<=9, -10<=l<=10	
Reflections collected	3799	
Independent reflections	1825 [R(int) = 0.0426]	
Completeness to theta = 25.00°	99.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9968 and 0.9820	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1825 / 0 / 154	
Goodness-of-fit on F^2	1.015	
Final R indices [I>2sigma(I)]	R1 = 0.0549, wR2 = 0.1407	
R indices (all data)	R1 = 0.0650, wR2 = 0.1482	
Largest diff. peak and hole	0.332 and -0.229 $e.Å^{-3}$	

A11 Crystal data and structure refinement for Palladium(II) Acetylacetonate (144)

Empirical formula	C10 H14 O4 Pd	
Formula weight	304.61	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 9.965(11) Å	α= 90°.
	b = 5.216(6) Å	β= 94.859(19)°.
	c = 10.487(12) Å	γ = 90°.
Volume	543.1(11) $Å^3$	
Z	2	
Density (calculated)	1.863 Mg/m^3	
Absorption coefficient	1.699 mm^{-1}	
F(000)	304	
Crystal size	0.25 x 0.06 x 0.02 mm^3	
Theta range for data collection	2.71 to 25.99°.	
Index ranges	-12<=h<=12, -6<=k<=6, -12<=l<=12	
Reflections collected	2632	
Independent reflections	1059 [R(int) = 0.1421]	
Completeness to theta = 25.99°	98.5 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9668 and 0.6761	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1059 / 0 / 72	
Goodness-of-fit on F^2	1.014	
Final R indices [I>2sigma(I)]	R1 = 0.0857, wR2 = 0.1924	
R indices (all data)	R1 = 0.1405, wR2 = 0.2165	
Largest diff. peak and hole	1.498 and -1.837 $e.Å^{-3}$	

A12 Lecture Courses Attended

Advanced Structural Determination	Prof. E. G. Hope
Clusters	Dr. G. Solan
Retrosynthetic Analysis	Dr. P. Jenkins

A13 Organic/Inorganic Seminar Programme
2005

10th October, Dr. Christopher Frost (University of Bath), *Exploring New Strategies in Organic Synthesis via Catalytic Conjugate addition Catalytic Organic Synthesis*

17th October, Prof. Gary Attard (University of Cardiff), *Aspects of Chiral Surface Chemisty: an Electrochemical Perspective*

26th October, Prof. R. H. Holm (Harvard University), *Structural and Functional Analogues of Molybdenum and Tungsten Oxotransferases/Hydroxylases: What can be Learned?*

31st October, Prof. Matthew Davidson (University of Bath), *Metal and Non-Metal Phenolates: Catalysts, Sensors and Surprises*

7th November, Prof. Richard Templar (Imperial College), *How Cells Survive - from Lipids to Liquid Crystals*

9th November, Prof. Peter H. Seeberger (ETH, Zurich), *Chemical Glycomics: Automated Synthesis of Carbohydrates as a Platform for Biological and Medical Research*

14th November, Dr. Richard Grainger (University of Birmingham), *Harnessing Reactive Intermediates for Organic Synthesis*

21st November, Prof. Paul Pringle (University of Bristol), *Synergic Effects in Catalysis with Phosphorus (III) Ligands*

29th November, Prof. Tim Softley (University of Oxford), *From Highly excited to Ultracold Molecules: Chemical Dynamics in the Extreme*

5th December, Prof. Tom Simpson (University of Bristol), *Fungal Polyketides: Tales of the Unexpected*

7th December, Dr Yasuhisa Ikeda (Research laboratory for Nuclear Reactors), *Studies on Solute-Solvent Interactions in Supercritical CO_2 by Using Raman Spectroscopy* and *Applications of Ionic Liquids to Pyrochemical Reprocessing Methods*

2006

22nd February - Leicester Half-day Symposium
Dr. Darren Dixon (University of Manchester), *Chiral Water from Chiral Relays: Stereocontrol in the Oxy-Michael and Related Reactions*
Dr. Bruno Linclau (University of Southampton), *Novel Approaches for the Enantioselective Total Synthesis of Steroids*
Prof. Tony Barrett (Imperial College), *Recent Advances in Methods for Parallel Synthesis*

6th March, Prof. M. Sodeoka (Tohoku University), *Enantioselective Catalysis Based on Palladium Enolate Chemistry*

22nd November - Leicester Green Chemistry Symposium
Dr Neil Winterton (University of Liverpool), *Green Chemistry and Ionic Liquids*
Dr Peter Licence (University of Nottingham), *Ionic Liquids In Vacuo*
Dr Paul Watts (University of Hull), *Application of Micro-reactors for Improving Atom Efficient Chemical Reactions*

2007

30th April - Metals In Medicine Symposium
Dr Sofia I Pascu (University of Oxford), *Designing Small-Molecule Based Probes for in vitro Fluorescence Imaging*
Prof. Nils Metzler-Nolte (Ruhr-Universitat Bochum), *Labelling of Bioactive Peptides with Organometallic Compounds: From Solid Phase Synthesis to Biomedical Applications*
Dr Gareth Williams (University of Durham), *Sensing and Imaging with Cells Permeable Luminescent Platinum Complexes*
Prof. Chris Orvig (University of British Columbia), *Carbohydrate Conjugates in Medicinal Inorganic Chemistry*

A14 Conferences Attended

RSC Organic Division, University of Warwick, April 2006

Organic Synthesis Symposium, University of Loughborough, March 2007

RSC Organic Division, University of Nottingham, April 2007

RSC Fluorine Subject Group Postgraduate Meeting, University of Leicester, September 2007

AstraZeneca R&D Charnwood & Loughborough University Organic Synthesis Symposium, October 2007

An Introduction to Process Chemistry, GSK Stevenage, October 2007

Dalton Division Midlands Postgraduate Symposium, University of Warwick, March 2008

RSC Industry Tour, July 2008

RSC Fluorine Subject Group Postgraduate Meeting, Newcastle University, September 2008

A15 Presentations

Presentation – "Transition Metal Centred Fluorination"- University of Leicester.

Presentation – "Synthesis of Metal Allyl Complexes"- University of Leicester.

Poster – "Transition Metal Centred Fluorination." K. Rakkar and E.G. Hope. Presented at postgraduate fluorine subject group meeting, Dalton division midlands postgraduate symposium and RSC industry tour.

Poster – "Synthesis of Metal allyl Complexes." K. Rakkar and E.G. Hope. Presented at postgraduate fluorine subject group meeting

A16 References

[1] L. Hintermann, PhD thesis, ETH-Zurich **2000**.

[2] S. Thibaudeau, V. Gouverneur, *Org. Lett.* **2003**, *5*, 4891.

[3] K. Nakamura, K. Takenaka, *Tetrahedron: Asymmetry* **2002**, *13*, 415.

[4] C. Audouard, J. Fawcett, G. Griffiths, J. Percy, S. Pintat, C. Smith, *Org. Biomol. Chem.* **2004**, *2*, 528.