# The Preparation and Reactivity of a Fluoroiodane Reagent Derived from Fluoride

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By

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Gemma Geary

The fluoraza reagents are selective, shelf stable and easy to handle sources of electrophilic fluorine but their applications are limited because they are normally made from elemental fluorine making them very expensive. In Chapter 2, the synthesis of a new electrophilic fluorinating reagent derived from cheap and readily available sources of the fluoride anion is described. The air and moisture stable fluoroiodane was prepared on a 6–10 g scale using TREAT-HF with no complicated purifications and without the need for dry or inert conditions. The fluoroiodane could also be prepared using TBAF, which is a commonly used source of fluoride for the production of [$^{18}$F]-labelled radiotracers for positron emission tomography (PET). Preliminary reactivity studies showed that the fluoroiodane could be used to fluorinate 1,3-ketoesters and 1,3-diketones in good yields (45–88%). It was subsequently found in Chapter 3 that, in these reactions, the fluoroiodane simulated an electrophilic fluorination *via* an addition-substitution mechanism.

In Chapter 4, the fluoroiodane was also used for the intramolecular fluorocyclisation of unsaturated carboxylic acids to prepare novel fluorinated γ-lactones under mild conditions in the presence of $AgBF_4$. This reaction combined a cyclization, an aryl migration and a fluorination to deliver lactones which contain a tertiary alkyl fluoride. The fluoroiodane could also be used without a metal catalyst to give moderate yields in just 1 h demonstrating that it is a suitable reagent for developing new $^{18}$F-labelled radiotracers for PET imaging.

Finally, the synthesis of an acid derived fluoroiodoxolone species was attempted in Chapter 5. Unfortunately, however, the fluoroiodoxolone was difficult to prepare, insoluble, and unstable. It was also found that the fluoroiodoxolone was considerably less reactive than the fluoroiodane in the fluorination of 1,3-dicarbonyl compounds.

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## Contents

**Abbreviations**

| | |
|---|---|
| Ac | Acetyl |
| ASAP | Atmospheric solids analysis probe |
| Bn | Benzyl |
| BOC | *tert*-butyloxycarbonyl |
| Bu | Butyl |
| d | Doublet |
| DAST | Diethylaminosulfur trifluoride |
| DCE | Dichloroethane |
| DCM | Dichloromethane |
| DIB | (Diacetoxyiodo)benzene |
| DMF | Dimethylformamide |
| DMSO | Dimethylsulfoxide |
| DSC | Differential Scanning Calorimetry |
| ee | Enantiomeric excess |
| EI | Electron Impact |
| eq. | Equivalents |
| ES | Electrospray |
| Et | Ethyl |
| h | hours |
| HMBC | Heteronuclear multiple bond correlation |
| J | Coupling Constant |
| LCD | Liquid crystal display |
| m | Multiplet |

| | |
|---|---|
| m/z | Mass/charge ratio |
| Me | Methyl |
| MeCN | Acetonitrile |
| mp | Melting point |
| MS | Mass spectrometry |
| NBS | N-bromosuccinimide |
| NF reagents | Fluoraza reagents |
| NFSi | N-fluorobenzenesulfonimide |
| NMR | Nuclear magnetic resonance |
| PET | Positron emission tomography |
| Ph | Phenyl |
| ppm | Parts per million |
| Pr | Propyl |
| q | Quartet |
| RT | Room temperature |
| s | singlet |
| t | triplet |
| TBAF | Tetrabutylammonium fluoride |
| TEAB | Tetraethylammonium bicarbonate |
| TBAT | Tetrabutylammonium difluorotriphenylsilicate |
| $^{t}$Bu | *tert*-butyl |
| TCICA | Trichloroisocyanuric acid |
| TEMPO | 2,2,6,6-Tetramethyl-1-piperidinyloxy |
| TFA | Trifluoroacetic acid |

| | |
|---|---|
| THF | Tetrahydrofuran |
| TMEDA | N,N,N’,N’-tetramethylethylenediamine |
| TREAT-HF | Triethylamine trihydrofluoride |

# Chapter 1

# Introduction

## 1.1 Organofluorine Chemistry

Organofluorine compounds are not generally found in nature, however, the incorporation of fluorine into an organic molecule can have a profound effect on its biological activity. This has meant that organofluorine compounds have found wide applications in both the pharmaceutical and agrochemical industries.[1] They are also used as radiotracers in positron emission tomography, refrigerants, surface coatings and liquid crystals for LCD applications.[2] For this reason, there is considerable interest in finding new, greener and more efficient ways to introduce fluorine into organic molecules.

## 1.2 Fluorine in Pharmaceuticals

The importance of fluorine in the pharmaceutical industry is demonstrated by the fact that 30% of the leading thirty blockbuster drugs contain at least one fluorine atom.[3] The biological effects resulting from the incorporation of a fluorine atom are wide ranging. For example, fluorination can allow the lipophilicity of a drug molecule to be fine-tuned. Monofluorination or trifluoromethylation of saturated alkyl groups usually decreases lipophilicity due to the strong electronegativity of fluorine. In contrast, aromatic fluorination, per- or poly- fluorination and fluorination alpha to atoms with π bonds generally increases lipophilicity. This is a result of the excellent overlap between the 2s and 2p orbitals on the fluorine atom with the corresponding orbitals on carbon, making the C-F bond highly non-polarisable.

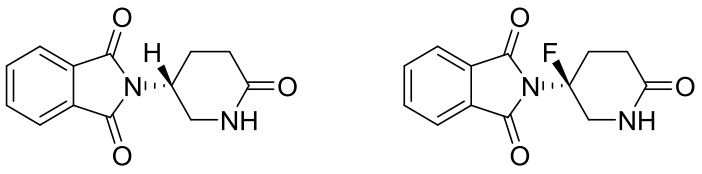
The fluorine atom is intermediate in size between oxygen (1.57 Å) and hydrogen (1.20 Å) at 1.47 Å.[4] Substitution of a hydrogen atom for a fluorine atom has little steric effect, however, the electronic effects of this substitution are dramatic, causing changes to the $pK_a$ of adjacent functional groups. This can in turn have an effect on the bioavailability, pharmacokinetic properties and binding affinity of a drug molecule. Substitution of an oxygen atom for a fluorine atom has less of an electronic effect since both are electronegative atoms. The subsequent loss of a hydrogen bond donor on substitution of a hydroxyl group for a fluorine atom, however, can be useful in probing hydrogen bonding interactions.

The high electronegativity of fluorine means that carbon-fluorine bonds are highly polarised and, therefore, have a less covalent and more electrostatic nature. This results in a large dipole and the interaction of this dipole with other dipoles can be a useful tool

to exploit in medicinal chemistry. For example, increased electrostatic interactions can help to increase the binding affinity of a molecule with a target receptor. Another consequence of the strong electrostatic nature of a carbon fluorine bond is that fluorinated molecules will often adopt very different preferred conformations to the corresponding non-fluorinated analogues.

One of the main problems associated with many active compounds is that they are metabolised and excreted by the body before they have time to have any therapeutic effect. A solution to this problem can be to block the metabolically labile site with a fluorine atom. This can prevent degradation pathways such as oxidation by cytochrome P450 monooxygensases.[1]

Most drug molecules are required as single enantiomers. Thalidomide, the anti-sickness drug given to pregnant women in the 1950s and 60s, exists as two enantiomers. The (*R*)-enantiomer **1** was responsible for the clinically useful effects whereas the (*S*)-enantiomer was responsible for the teratogenic side effects. Rapid epimerisation occurs under physiological conditions, however, replacement of the acidic hydrogen atom adjacent to the carbonyl group with a fluorine atom **2** prevented this epimerisation process (Figure 1).[1] This meant that research could continue into the use of thalidomide as a therapeutic agent in areas such as the treatment of cancer and inflammatory diseases such as rheumatoid arthritis, Crohn's disease and asthma.




**1** (3*R*)-thalidomide **2** (3*S*)-fluorothalidomide

**Figure 1** *Prevention of epimerisation by substitution with fluorine*

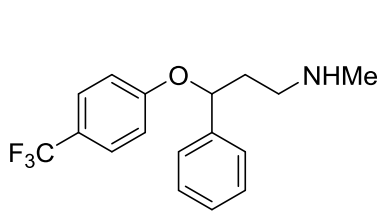
Finally, fluorinated molecules can have the effect of preventing a particular mechanism from proceeding. For example, the anti-cancer drug 5-fluorouracil, blocks a key biological pathway involved in DNA synthesis. This, therefore, prevents DNA replication and leads to programmed cell death.

Some examples of popular fluorinated drugs are shown in Figure 2. Prozac **3** is one of the most prescribed anti-depressants worldwide. It acts by selectively inhibiting the reuptake of serotonin.[1] The inclusion of an aryl-$CF_3$ group was found to increase

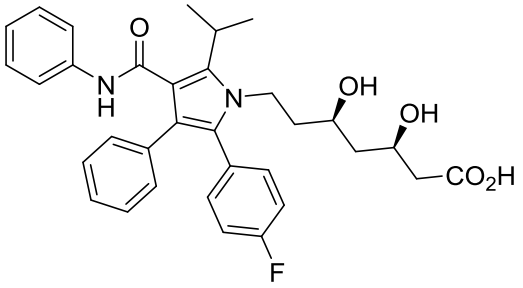
potency 6-fold because the steric bulk of the $CF_3$ group allowed the phenoxy group to adopt a conformation with favoured binding to the serotonin transporter protein.

Lipitor **4** is one of the biggest selling drugs globally and is a member of the statin class. It reduces the amount of cholesterol produced by the body and prevents other problems associated with high blood pressure.[3] It is a potent competitive inhibitor of the enzyme HMG-CoA reductase, which is the rate-limiting enzyme involved in cholesterol biosynthesis.

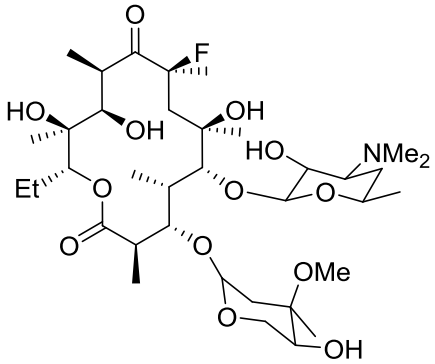
The antibiotic flurithromycin **5** was developed as an alternative to erthryomycin.[1] Erythromycin is a useful antibiotic in the treatment of infections such as bronchitis and Legionnaires disease. It was found, however, that it could not be used to treat Helicobacter pylori infection, which causes gastritis, due to the acidic conditions in the stomach. Addition of a fluorine atom alpha to the ketone functionality resulted in a longer biological half-life, better bioavailability and higher tissue concentrations *in vivo*.




**3**
Fluoxetine
(Prozac)




**4**
Atorvastin
(Lipitor)




**5**
Flurithromycin

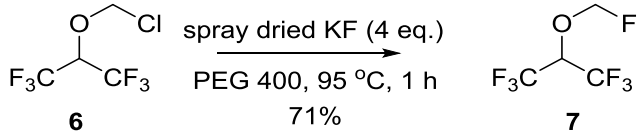
**Figure 2** *Fluorinated drug molecules*

## 1.3 Fluorination of Organic Molecules

### 1.3.1 Nucleophilic Fluorination

The easiest way to introduce fluorine into an organic molecule is using a nucleophilic source of fluoride since these are generally the cheapest and most readily available. Despite this, the formation of carbon-fluorine bonds is not a trivial task. Although there is a strong thermodynamic driving force for the formation of a carbon-fluorine bond, the strongest carbon-heteroatom single bond known, the high electronegativity of the fluorine atom means that there is a high kinetic barrier.[5] The tendency of fluoride to form strong hydrogen bonds means that the nucleophilicity of fluoride is reduced in the presence of hydrogen bond donors. In order to promote nucleophilic fluorination, rigorous exclusion of hydrogen bond donors is required. This in turn, however, increases the basicity of fluoride meaning that competing elimination reactions are common.

Alkali metal fluorides are amongst the most commonly used nucleophilic sources of fluoride due to their low cost. For example, potassium fluoride has been used for the synthesis of the inhalation anaesthetic sevoflurane **7** in high yield (Scheme 1).[6] The strong lattice energy of alkali metal fluorides means that the nucleophilicity of the fluoride anion is low and they have a poor solubility in organic solvents. The addition of a crown ether helps to increase the solubility and therefore the reactivity of the fluoride anion. In general, polar, aprotic solvents are preferred in these reactions.




**6** **7**

**Scheme 1** *Preparation of sevoflurane using KF*

Deoxofluorination reagents are useful for the direct conversion of a hydroxyl group into fluoride, thus eliminating the need for prefunctionalisation.[5] Examples include DAST **8**, Deoxo-Fluor **9**, PhenoFluor **10** and the XtalFluor reagents **11** and **12** (Figure 3). DAST **8** is moisture sensitive and can explode on heating. Deoxo-Fluor **9** is a more thermally stable alternative to DAST which participates in reactions such as the fluorination of ketones, carboxylic acids and secondary alcohols (Scheme 2).[7] The XtalFluor reagents **11** and **12**, have a similar reactivity profile to those of both DAST and Deoxo-Fluor but

are more thermally stable and are amenable to short term handling in the open atmosphere.

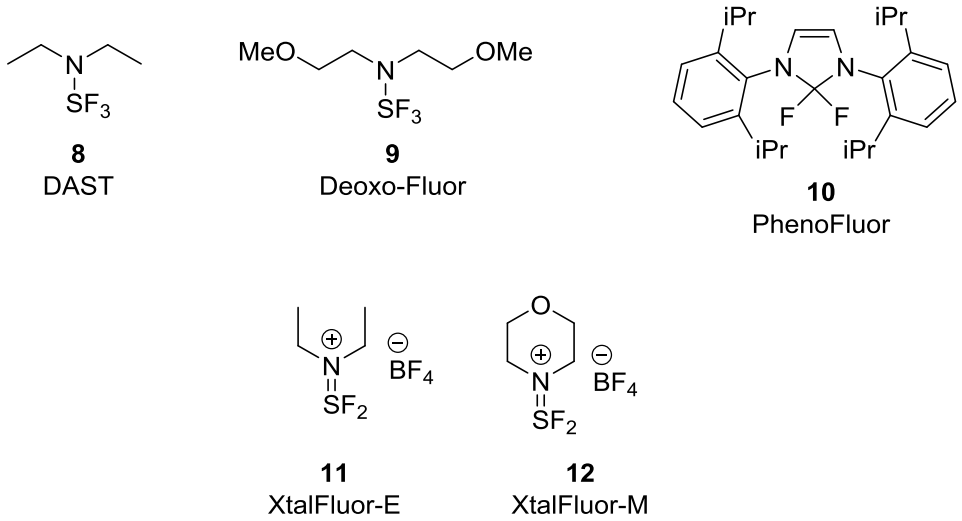
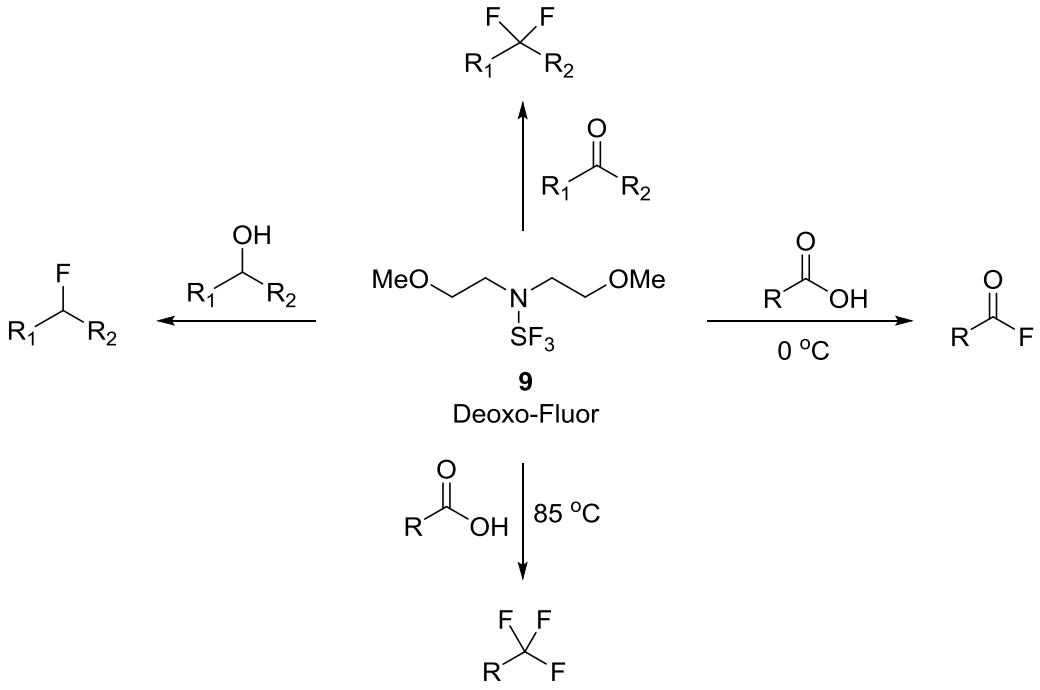


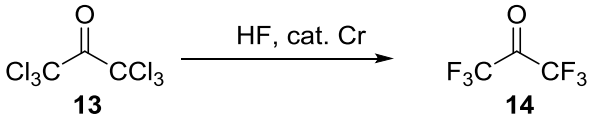

**Figure 3** *Examples of deoxofluorination reagents*




**Scheme 2** *Reactions of Deoxo-Fluor*

Reagents such as aqueous HF, pyridine-HF and triethylamine-HF (TREAT-HF) represent an additional class of cheap, nucleophilic fluorinating reagents. Aqueous HF and pyridine-HF are extremely dangerous reagents which cannot be used in normal glassware. Despite this, they are used in a number of industrial processes, including the synthesis of hexafluoroacetone **14** from hexachloroacetone (Scheme 3).[8]

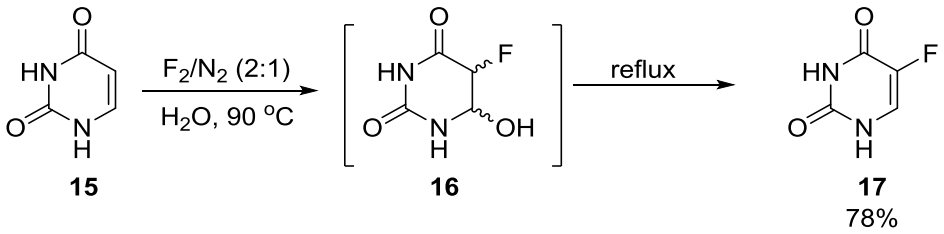
Hexafluoroacetone is used in the manufacture of hexafluoro-2-propanol and high performance fluoropolymers.



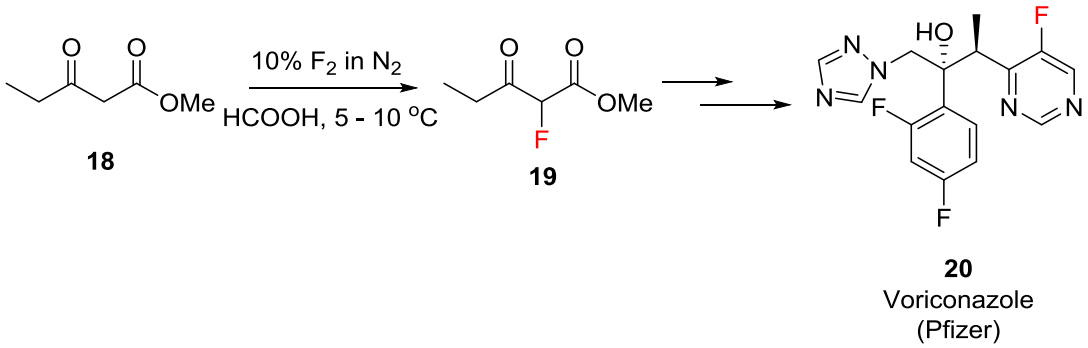

**Scheme 3** *Preparation of hexafluoroacetone using aqueous HF*

### 1.3.2 Electrophilic Fluorination

Nucleophilic sources of fluoride cannot be used to fluorinate electron rich substrates and for this an electrophilic source of fluorine is required. This is not easily achieved since fluorine is the most electronegative element. Elemental fluorine can be used as an electrophilic source of fluorine and is usually diluted with nitrogen gas in order to achieve selectivity. For example, it is used in the industrial scale synthesis of the anti-cancer drug 5-fluorouracil **17** (Scheme 4).[2] It has also been used, by Sandford and $F_2$ chemicals, for the synthesis of fluorinated 1,3-dicarbonyl derivatives **19** as intermediates for the pharmaceutical industry (Scheme 5).[9] Although selectivity can be achieved when using elemental fluorine, the extremely dangerous nature of the reagent means that specialist equipment and expertise are required.




**Scheme 4** *Preparation of 5-fluorouracil using elemental fluorine*

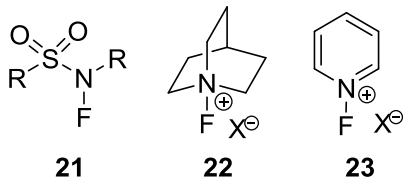



**Scheme 5** *Preparation of a fluoroketoester using elemental fluorine*

Early examples of electrophilic fluorinating reagents included hypofluorites, such as $CF_3OF$ and perchloryl fluoride, however, the use of these reagents was challenging due to their high reactivity. $XeF_2$ can also be used as an electrophilic fluorinating reagent although its strong oxidising capabilities preclude its use in the presence of sensitive functional groups.[5, 10]

Fluoraza (NF) reagents are generally viewed as safer, more stable, easier to handle and more selective sources of electrophilic fluorine.[11] They are prepared from either neutral secondary amines or tertiary amines to give neutral $R_2NF$ compounds or $R_3NF^+A^-$ salts respectively. In these reagents, the $R_2N$ or $R_3N^+$ components are specifically chosen to be good leaving groups in order to promote the transfer of fluorine to the nucleophile.

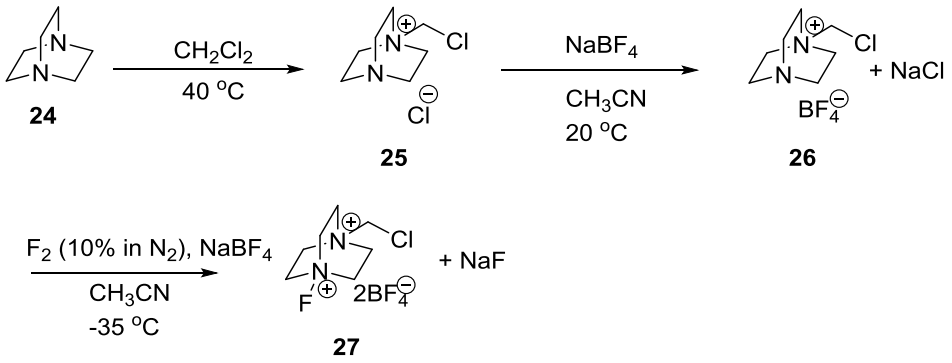
The first commercially available examples of NF reagents included *N*-fluoro-*p*-toluenesulfonimides (Barnette reagents, **21**),[12] *N*-fluoroquinuclidinium fluorides and triflates (Banks reagents, **22**)[13, 14] and *N*-fluoropyridinium salts (Umemoto reagents, **23**) (Figure 4).[15]




**21** **22** **23**

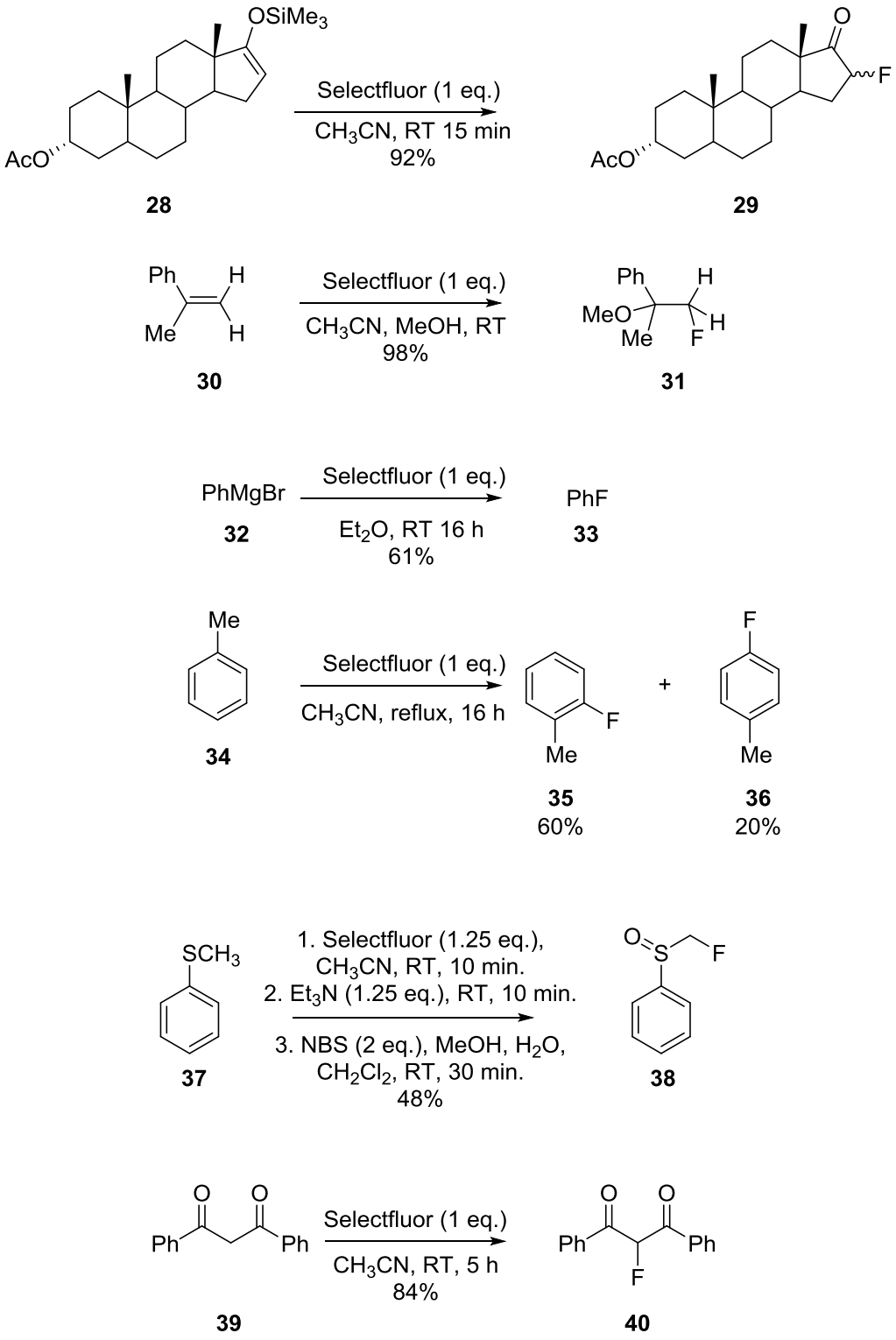
**Figure 4** *Early examples of NF reagents*

Selectfluor **27** is an example of a highly reliable, commercially available NF reagent.[16, 17] It is an exceptionally stable, virtually non-hygroscopic, crystalline white solid which is made on the multiton scale in a simple, efficient and flexible synthesis (Scheme 6). In the first step of the synthesis triethylene diamine **24** undergoes chloromethylation in dichloromethane. Anion metathesis incorporates $BF_4^-$ with the precipitation of sodium chloride. Finally, low temperature fluorination in the presence of $BF_4^-$ gives Selectfluor **27** with high yields and purity.[16]

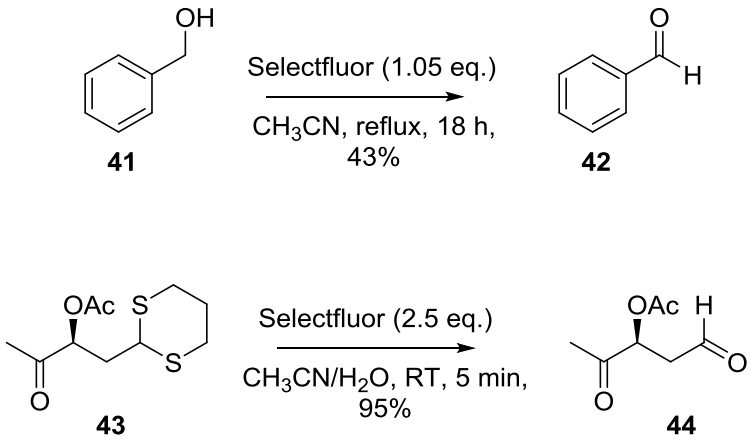



**Scheme 6** *Preparation of Selectfluor*

Selectfluor can be used as an electrophilic fluorinating reagent in a wide variety of reactions, including the fluorination of silyl enol ethers **28**, the fluorination of alkenes **30**, carbanions **32**, activated aromatic compounds **34**, sulphides **37** and 1,3-dicarbonyl compounds **39** (Scheme 7).[18, 19] Selectfluor can also react to give non-fluorinated products, for example, it acts as an oxidant with benzylic alcohols **41** and can be used to remove common protecting groups, such as dithianes **43** reducing the need for highly toxic and environmentally damaging mercury salts (Scheme 8). [20, 21]



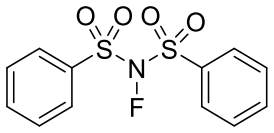

**Scheme 7** *Fluorination reactions of Selectfluor*




**Scheme 8** *Other reactions of Selectfluor*

More recently, an $^{18}$F-derivative of Selectfluor has been prepared and used for fluorination reactions, including the silver triflate mediated $^{18}$F-fluorination of electron rich aryl stannanes and the $^{18}$F-fluorination of silyl enol ethers.[22] A chiral analogue of Selectfluor has also been prepared and this has been used to prepare enantioenriched fluorocarbocyclised products with good enantioselectivities (70-73%).[23]

Another example of an extremely popular NF reagent is *N*-fluorobenzenesulfonimide (NFSi) **45** (Figure 5).[11, 24] This is a much milder electrophilic source of fluorine than Selectfluor and can be used for the fluorination of nucleophiles such as enolates, silyl enol ethers and activated aromatics.[24, 25] As with Selectfluor, both $^{18}$F and chiral versions of NFSi have been prepared and are useful for the preparation of $^{18}$F-radiolabelled and enantioenriched products respectively.[26-28]



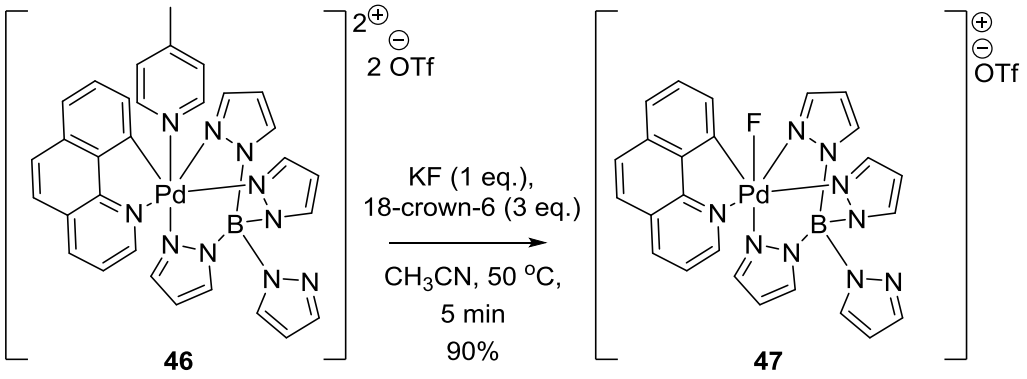

**45**
NFSi

**Figure 5** *Structure of N-fluorobenzenesulfonimide (NFSi)*

Despite the wide variety of applications of NF reagents such as Selectfluor and NFSi, there are also several disadvantages. They must, in the first instance, be made from elemental fluorine and this means that they are expensive to prepare. They also only contain a small amount of active fluorine. Finally, the high polarity of Selectfluor means that it is only soluble in polar solvents such as acetonitrile and water.

### 1.4 Strategies for Electrophilic Fluorination

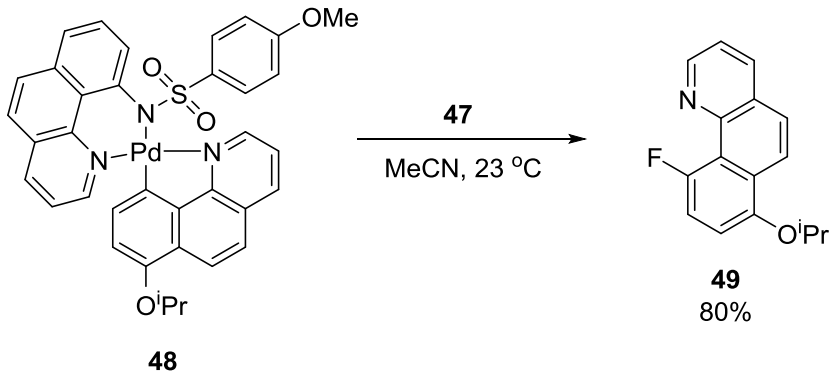
In late 2011, Ritter reported the synthesis of an organometallic electrophilic fluorinating reagent **47**, from a nucleophilic source of fluoride (Scheme 9).[29] The palladium complex was specifically designed in order to favour transfer of fluorine to a nucleophile *via* an $S_N2$ process. The palladium centre of the initial complex **46** carried three formal positive charges, countered by two triflate anions and an anionic borate ligand. This meant that the complex had a high fluorophilicity thereby favouring capture of fluoride anions from solution. The palladium centre in complex **47** was in a +4 oxidation state which is high for palladium. This meant that oxidative transfer of fluorine with concomitant reduction to palladium(II) was favoured. The supporting ligands were designed to stabilise the palladium centre, thereby reducing the likelihood of carbon-fluorine reductive elimination. The palladium-fluorine bond was polarised towards fluorine, with a partial negative charge on fluorine and a partial positive charge on palladium. Based on coulombic interactions, nucleophilic attack would be expected at palladium. This was disfavoured however due to the high energy of the available orbitals on palladium. Finally, the presence of multidentate ligands around the palladium centre blocks the trajectory of the nucleophile in any direction other than towards the fluoride ligand. This favoured nucleophilic attack at fluorine with palladium as a leaving group.




**46** **47**

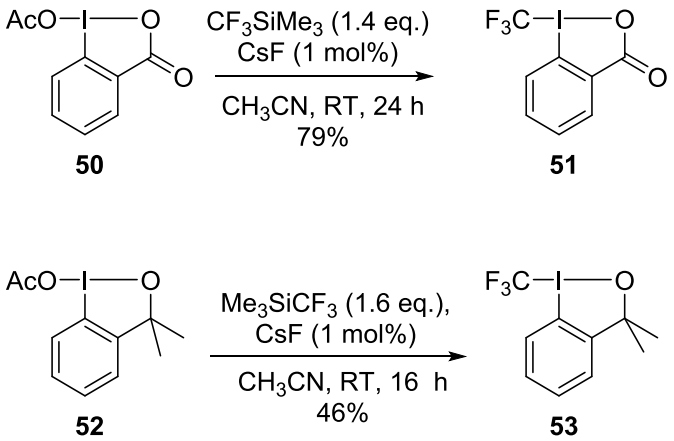
**Scheme 9** *Preparation of an electrophilic palladium-based fluorinating reagent from fluoride*

The fluorinated palladium complex **47** was formed in just five minutes from complex **46** in a 90% yield (Scheme 9). Fluorination of complex **48** using **47** and subsequent reductive elimination gave the fluorinated product **49** (Scheme 10).



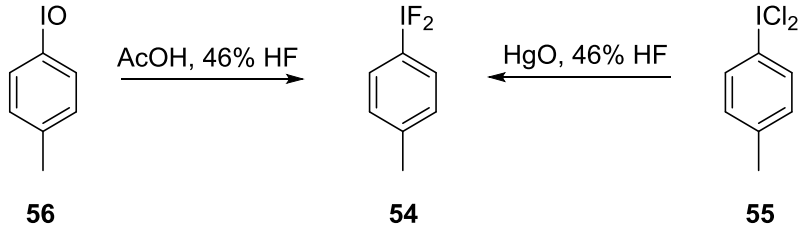

**Scheme 10** *Electrophilic fluorination using a palladium(IV)fluoride*

Togni has successfully employed a similar approach for the preparation of electrophilic trifluoromethylating reagents from a source of the trifluoromethyl anion. In this case, the reagents were based on a hypervalent iodine core skeleton, rather than a metal complex. They were prepared using the Ruppert-Prakash reagent, as the source of the trifluoromethyl anion (Scheme 11) and they have been used as electrophilic trifluoromethylating reagents for a variety of transformations which will be discussed in more detail later in this chapter. [30, 31]




**Scheme 11** *Synthesis of Togni's reagents*

There has also been a significant amount of work in the area of electrophilic fluorination using hypervalent iodine compounds. These reagents can be prepared from cheap and readily available sources of the fluoride anion such as aqueous HF (Scheme 12).[32, 33] Again, the preparation and reactivity of these reagents will be discussed in more detail later in this chapter.




**Scheme 12** *Preparation of difluoroiodoarenes*

### 1.5 Hypervalent Iodine Reagents

Hypervalent iodine compounds have, over recent years, seen a surge in interest due to their useful oxidising properties, benign environmental character and commercial availability.[34, 35] All known organic hypervalent iodine species belong to two general structural groups, iodine(III) compounds ($\lambda^3$-iodanes **57** and **58**) and iodine(V) compounds ($\lambda^5$-iodanes **59**). In iodine(III) compounds such as **57** (Figure 6) the central iodine atom has a share in 10 electrons and adopts a distorted trigonal bipyramidal structure. Two heteroatoms occupy the apical positions with the least electronegative carbon ligand occupying an equatorial position along with the two lone pairs. Iodine(III) compounds such as **58** have two carbon ligands along with a closely associated anionic ligand and are named iodonium salts. These compounds also adopt a distorted trigonal bipyramidal structure. Bonding in $RIX_2$ compounds uses the iodine non-hybridised 5p orbital in a linear X-I-X bond. This 3c-4e bond is highly polarised and is, therefore, longer and weaker than a normal covalent bond. This means that hypervalent iodine(III) compounds have a high electrophilic reactivity.

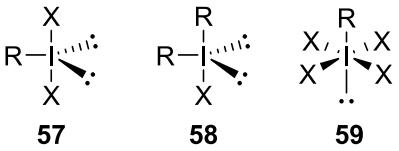



**Figure 6** *Types of hypervalent iodine structures*

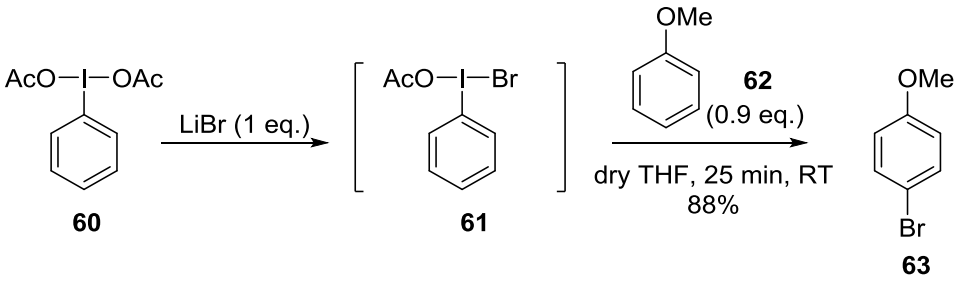
Iodine(V) compounds **59** adopt a distorted octahedral shape with an organic ligand and a lone pair occupying the apical positions and four heteroatom ligands in the equatorial positions. There are two orthogonal 3c-4e bonds accommodating all of the heteroatom ligands whilst the carbon ligand is attached via a normal covalent bond using a 5sp-hybridised orbital.

The use of hypervalent iodine compounds for reactions such as oxidations is well documented. For example, the Dess-Martin periodinane is one of the most widely used

oxidants in organic synthesis.[35, 36] Hypervalent iodine compounds have also been widely used as oxidative atom transfer reagents, for example, for electrophilic bromination, trifluoromethylation and fluorination.[37]

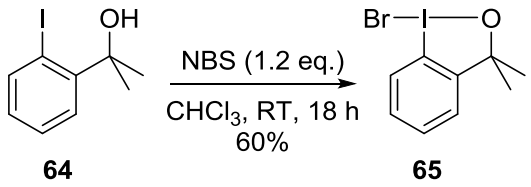
### 1.6 Electrophilic Bromination using Hypervalent Iodine Compounds

In 2004, Braddock and co-workers demonstrated that (diacetoxyiodo)benzene (DIB) could be used as a co-reagent with anionic bromide for the electrophilic bromination of arenes and alkenes.[38] It was suggested that '$Br^+$' was generated *in situ* by the reaction of the bromide anion with DIB **60** with subsequent displacement of acetate to give the non-isolable intermediate **61** (Scheme 13). In the presence of a nucleophile, such as anisole **62**, this intermediate acted as an electrophilic brominating reagent, giving 4-bromoanisole **63** in an 88% yield.




**Scheme 13** *In situ preparation of an electrophilic brominating reagent*

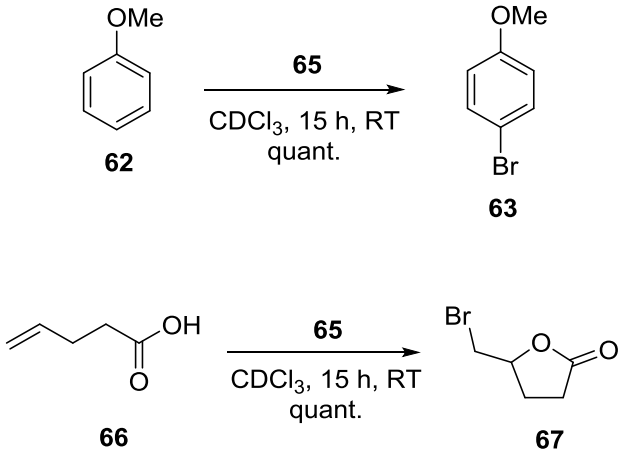
It was later found that, when the iodine atom was enclosed within a chelate ring, the resultant bromoiodane **65** was much more stable and could be isolated from the reaction between iodoalcohol **64** and *N*-bromosuccinimide (Scheme 14).[39] The increased stability of the bromoiodane **65** was thought to arise from the inclusion of the iodine atom in a five membered ring, the Thorpe-Ingold effect of the *gem*-dimethyl groups and the presence of an additional stabilising electronegative atom, oxygen.




**Scheme 14** *Preparation of a bromoiodane*

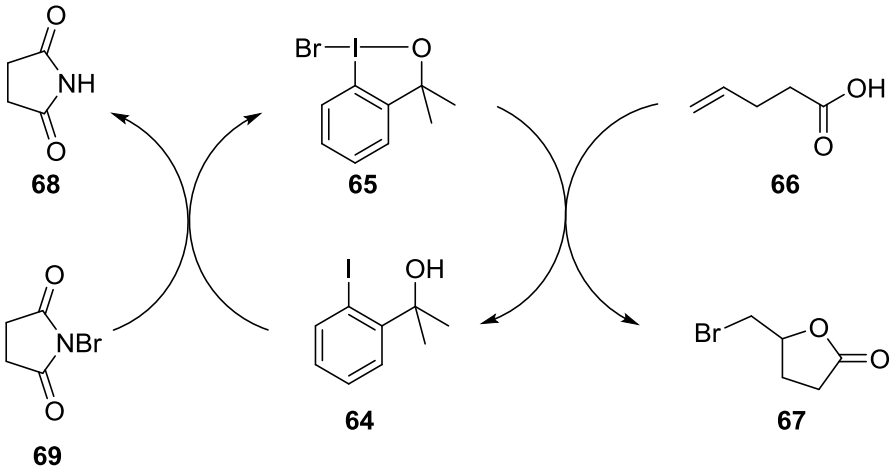
The bromoiodane **65** acted as a stoichiometric source of electrophilic bromine in reactions such as the conversion of anisole **62** to 4-bromoanisole **63** and 4-pentenoic acid, **66**, to the bromolactone, **67** (Scheme 15) under mild conditions. Significantly, the

attempted bromolactonisation of **66** using molecular bromine resulted in the formation of the 1,2-dibrominated alkene as a significant by-product. This suggested that molecular bromine was not generated in the reactions of the bromoiodane **65**.




**Scheme 15** *Brominations with the bromoiodane*

A by-product of the bromination reaction using the bromoiodane **65** was the iodoalcohol **64**. This suggested that the bromolactonisation of **66** should proceed using only a catalytic amount of the iodoalcohol **64** in the presence of stoichiometric amounts of NBS (Scheme 16).[40] In fact, when the iodoalcohol was used as the organocatalyst, the conversion after 15 hours was only slightly higher than the background reaction with NBS (entry 2 vs entry 1, Table 1). When 2-iodobenzoic acid **70** (Figure 7) was used as the organocatalyst, however, a 100% conversion was achieved in just 6 hours (entry 3). This was further improved by the use of the amidine **71** as the organocatalyst, achieving a 100% conversion in less than 30 minutes (entry 4).

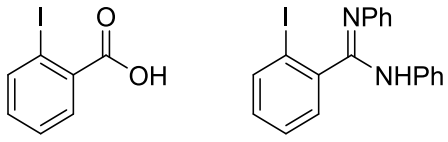



**Scheme 16** *Catalytic cycle involving bromoiodane*

**Table 1** *Catalytic bromolactonisation of* ***66***

| Entry | Organocatalyst | Loading (mol%) | Time (h) | Conversion[a] (%) |
|---|---|---|---|---|
| 1 | **-** | - | 15 | 20 |
| 2 | **64** | 25 | 15 | 32 |
| 3 | **70** | 10 | 6 | 100 |
| 4 | **71** | 10 | <0.5 | 100 |

[a] Conversion calculated by $^{1}$H NMR spectroscopy.



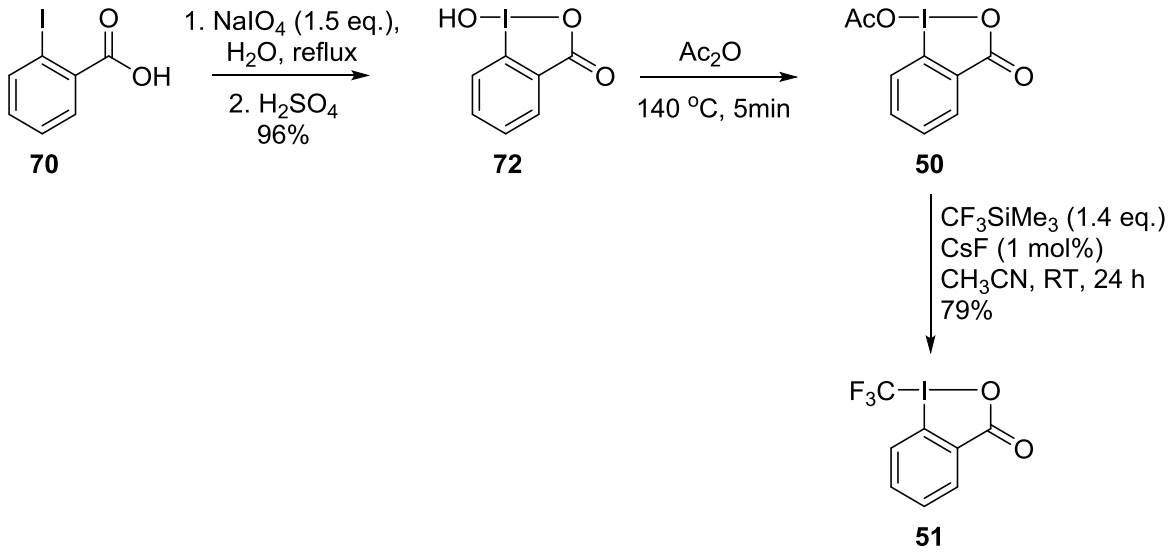

**70** **71**

**Figure 7** *Alternative organocatalysts*

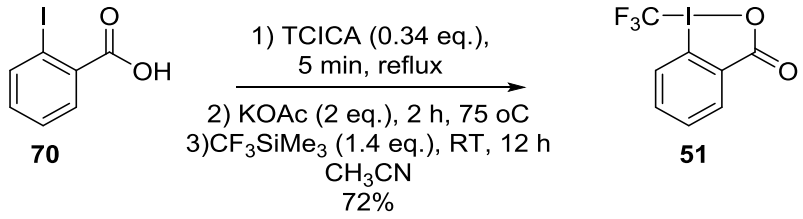
## 1.7 Electrophilic Trifluoromethylation using Hypervalent Iodine Compounds

### 1.7.1 Preparation of Togni's Reagents

Togni has prepared two hypervalent iodine electrophilic trifluoromethylating reagents, an acid derived reagent **51** and an alcohol derived reagent **53**. The acid derived reagent **51** was prepared in three steps from commercially available 2-iodobenzoic acid **70**.[30] In the first step 2-iodobenzoic acid **70** was oxidised to the hydroxyiodoxolone **72** using sodium metaperiodate. This was then acetylated using acetic anhydride before the final umpolung step was carried out using the Ruppert-Prakash reagent as the source of the trifluoromethyl anion (Scheme 17). This procedure was later optimised to a one-pot protocol, which was suitable for large-scale synthesis, using trichloroisocyanuric acid (TCICA) as a cheap oxidant (Scheme 18).

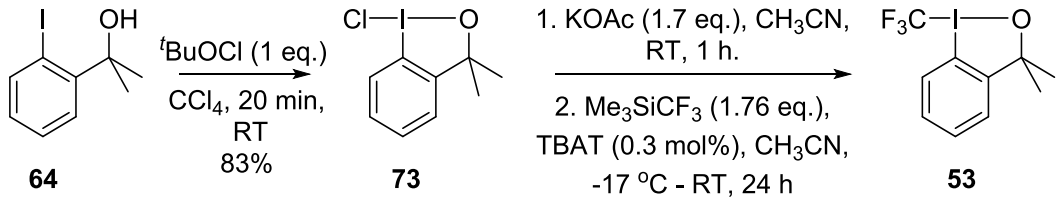



**Scheme 17** *Initial synthesis of Togni's acid reagent*




**Scheme 18** *Improved one-pot synthesis of Togni's acid reagent*

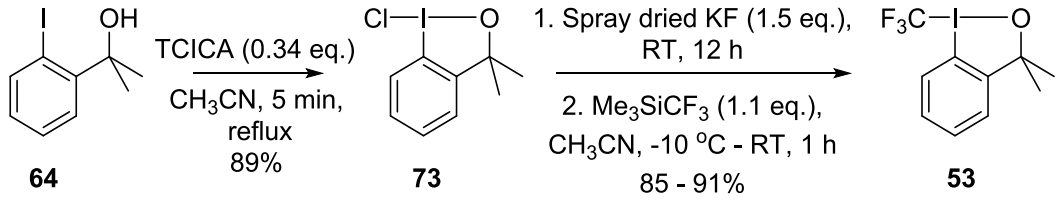
Togni's alcohol reagent **53** was prepared from 2-(2-iodophenyl)propan-2-ol **64** in two steps. In the first step the iodoalcohol **64** was oxidised using *tert*-butyl hypochlorite.[30] The chloroiodane **73** was then converted to the acetoxyiodane using KOAc. This was reacted *in situ* in the final umpolung step using the Ruppert-Prakash reagent as the source of the trifluoromethyl anion to give the trifluoromethyliodane **53**.




**Scheme 19** *Initial synthesis of Togni's alcohol reagent*

The initial synthesis of the trifluoromethyliodane **53** suffered a number of drawbacks. *Tert*-butyl hypochlorite is a light sensitive reagent with a short shelf life. It is also a potent lachrymator and has been responsible for a number of documented violent explosions. For this reason, its commercial availability is restricted. It was found that

the same transformation could be acheived using the much cheaper and safer alternative trichloroisocyanuric acid (TCICA) (Scheme 20).[30] A further problem of the initial synthesis was that the final umpolung step required a carefully controlled temperature gradient and more than 20 hours to obtain a good conversion. This problem was solved by the use of a fluoroiodane intermediate, instead of the acetoxyiodane. In the improved synthesis, the chloroiodane **73** was reacted with 1.5 equivalents of spray dried KF at room temperature for 12 hours. The product was then reacted *in situ* with the Ruppert-Prakash reagent to give the trifluoromethyliodane **53** in just one hour.



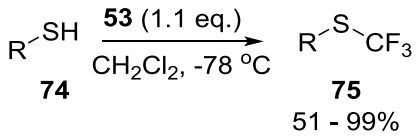

**64** **73** **53**

**Scheme 20** *Improved synthesis of Togni's alcohol reagent*

### 1.7.2 Reactions of Togni's Reagents

The use of Togni's reagents as electrophilic trifluoromethylating reagents has increased exponentially in the last three to four years. It would not be possible to give a complete overview of these reactions here. Instead, a brief summary of the reactivity of the two reagents will be discussed. A more in depth discussion can be found in Togni's recent review.[41]

Thiols were one of the first nucleophiles to be investigated as a substrate for trifluoromethylation. A range of both aromatic and aliphatic thiols were trifluoromethylated in good to excellent yields (Scheme 21).[42] A range of functional groups, such as amines, carboxylic acids, thioacetals, alcohols and alkynes were tolerated.

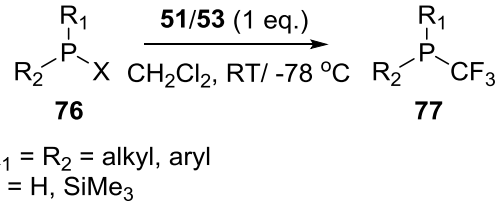



**74** **75**
51 - 99%

**Scheme 21** *Trifluoromethylation of thiols*

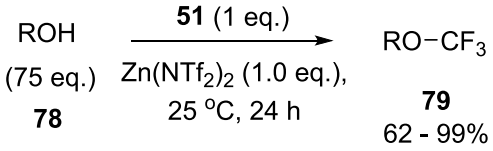
The trifluoromethylation of phosphines has a dramatic impact on their electronic properties and steric demand when compared to those of simple alkyl or aryl phosphines. It was found that the trifluoromethylation of dialkyl and diaryl phosphines

or trimethylsilyl dialkyl and diaryl phosphines could be achieved using both reagents **51** and **53** with good yields.[43] The resultant trifluoromethylated phosphines were found to act as suitable ligands for transitions metals such as Pd(II), Ru(II), Rh(I) and Ir(III).



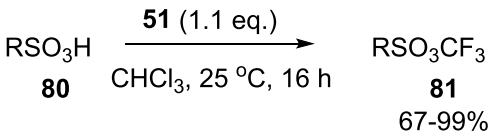

**Scheme 22** *Trifluoromethylation of phosphines*

The introduction of the trifluoromethoxy group usually requires harsh conditions and hazardous reagents such as $CCl_4$/HF, $COF_2$, $SF_4$ and $SbF_5$. Using reagent **51** and/or reagent **53**, however, this process could be achieved under significantly milder conditions. For example, the zinc(II) catalysed trifluoromethylation of alcohols using **51** (Scheme 23).[44] The substrate was usually used as the solvent for the reaction, however, in the case of solid or precious substrates the reaction could be carried out in chloroform with slightly lower yields.

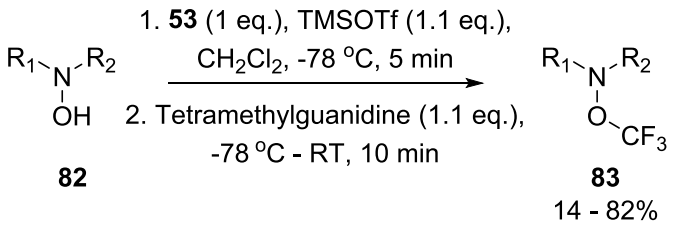



**Scheme 23** Trifluoromethylation of alcohols

The acid reagent **51** was also found to be suitable for the trifluoromethylation of sulphonic acids (Scheme 24) whilst the alcohol reagent **53** could be used for the trifluoromethylation of hydroxylamines (Scheme 25).[45, 46]

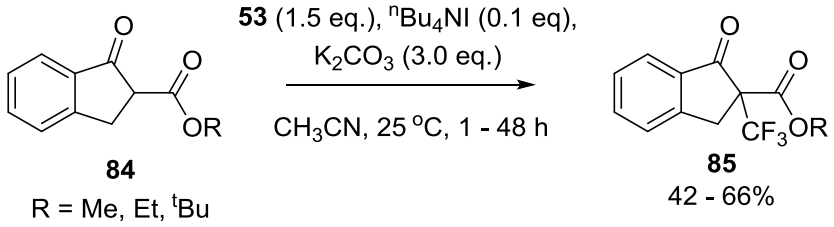



**Scheme 24** *Trifluoromethylation of sulphonic acids*



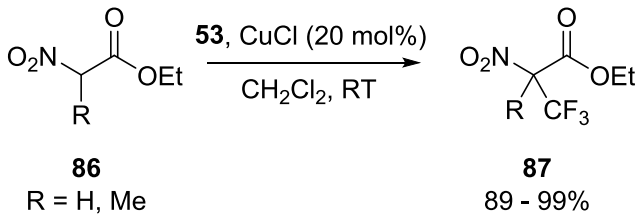

**Scheme 25** *Trifluoromethylation of hydroxylamines*

The trifluoromethylation of 1,3-dicarbonyl compounds was initially investigated using reagent **53** under phase transfer catalysis conditions (Scheme 26). The downside of this process, however, was that a large excess of base was required for deprotonation and only 5- or 6-membered cyclic substrates were reactive.[42] An enantioselective version of this reaction was later published which used a copper(II) salt and a chiral pincer ligand. Good enantioselectivities of 80-99% *ee* were achieved, however, this process was also limited to cyclic substrates.[47]



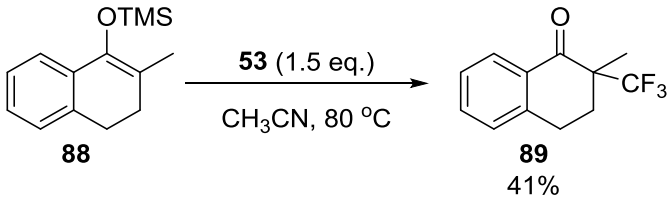

**Scheme 26** *Trifluoromethylation of 1,3-dicarbonyl compounds*

A similar type of substrate, α-nitro esters were trifluoromethylated using reagent **53** in the presence of a copper(I) catalyst (Scheme 27).[42] Following trifluoromethylation, the nitro group could be reduced to give α-$CF_3$-α-amino acids.[41] In an attempt to prepare enantioenriched α-$CF_3$-α-amino acids, an enantioselective trifluoromethylation procedure was sought. The use of Cu(I) salts and a chiral ligand only gave disappointing enantioselectivities of up to 24% *ee*. The use of a chiral auxiliary, however, achieved diastereoselectivities of up to 6:1.[41]

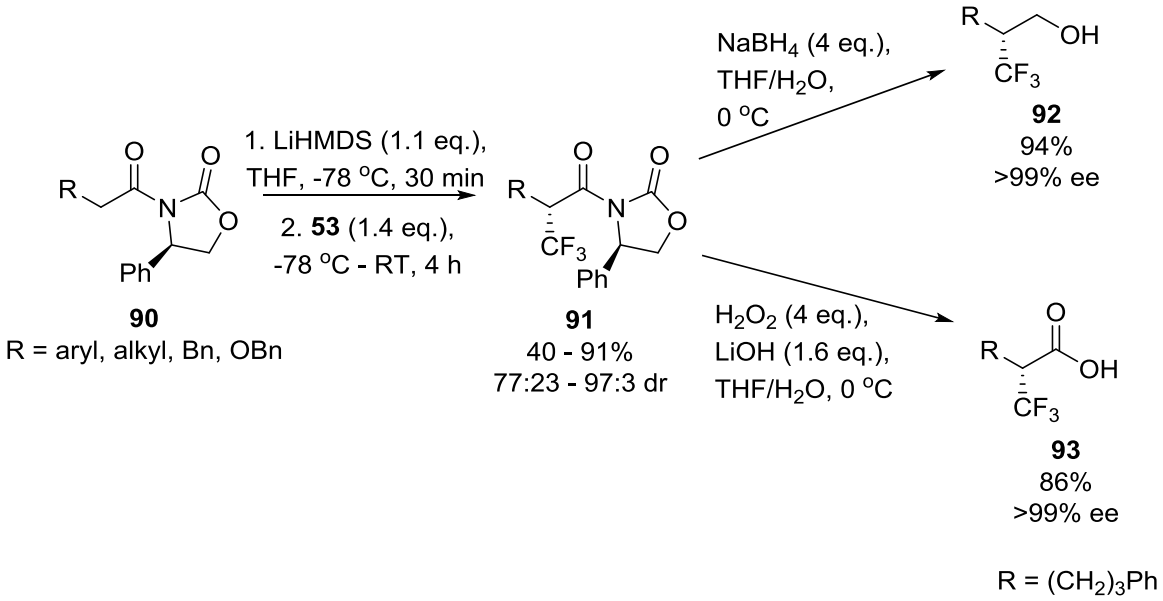



**Scheme 27** *Trifluoromethylation of α-nitro esters*

The key to success in the trifluoromethylation of ketones was found to be a two-step process in which a silyl enol ether was first made and isolated, followed by trifluoromethylation under mild conditions (Scheme 28).[48] A stereoselective α-trifluoromethylation of carbonyl compounds has also been carried out using chiral oxazolidinones as chiral auxiliaries (Scheme 29).[49] The products of this reaction could then be derivatised to give either β-trifluoromethyl alcohols or α-trifluoromethyl carboxylic acids with no degradation in enantiomeric excess. Enantioselective trifluoromethylation of simple aldehydes was also possible in the presence of a copper(I) salt and an organocatalyst.[50]



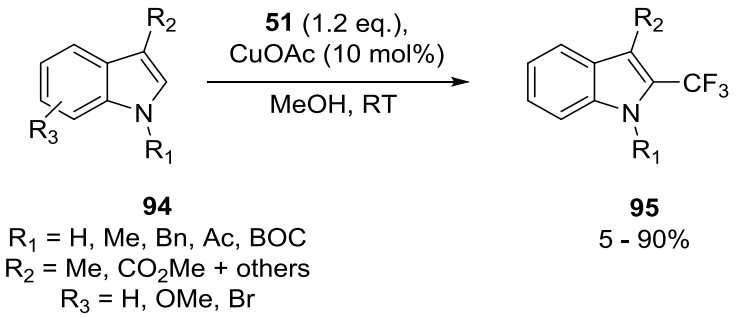

**Scheme 28** *Trifluoromethylation of silyl enol ethers*




**Scheme 29** *Stereoselective α-trifluoromethylation of carbonyls*

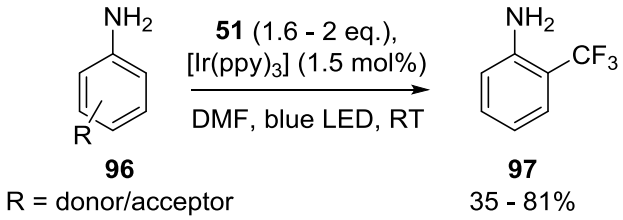
The trifluoromethylation of aromatic compounds is a desirable target due to the abundance of these building blocks in biologically active molecules. Togni reported a direct trifluoromethylation of pyrroles, indoles, imidazoles, pyridines and phenyl derivatives.[51] It was limited, however, by a lack of generality. A general approach for the trifluoromethylation of indoles was published by Sodeoka *et al.* (Scheme 30).[52] This

procedure was subsequently used by MAP pharmaceuticals for the scalable synthesis of an active pharmaceutical ingredient which is currently in clinical trials for the treatment of migraine.[53]



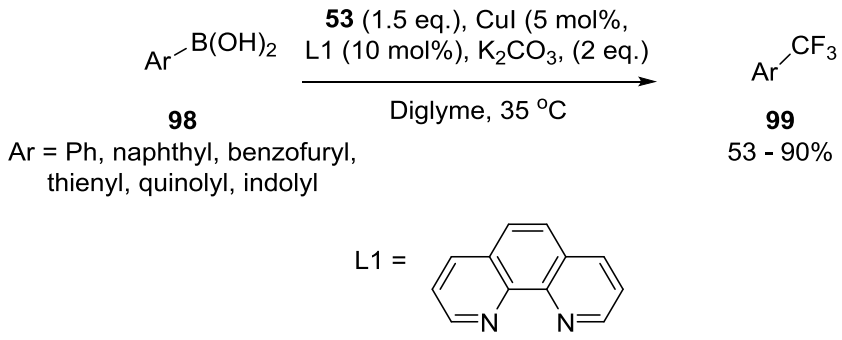

**Scheme 30** *Trifluoromethylation of indoles*

The *ortho*-trifluoromethylation of anilines could be achieved using a pivalamido directing group under copper(I) catalysis.[54] Further work showed that the trifluoromethylation of unprotected anilines was possible using [Ir(ppy)$_3$] as a photoredox catalyst (Scheme 31).[55] The trifluoromethylated anilines formed in these reactions could be converted into a range of pharmaceutically relevant building blocks including quinolones, tetrazoles, isatins, benzoxazoles, benzotriazoles and azides.



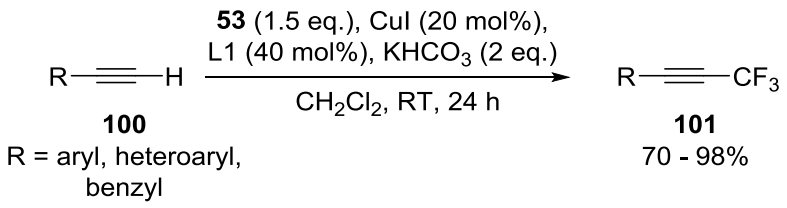

**Scheme 31** *Trifluoromethylation of anilines*

The trifluoromethylation of boronic acids was reported by Shen (Scheme 32).[56] Subsequent studies showed that the same transformation was possible using trifluoroborates.[57] These more reactive substrates required milder conditions allowing for the trifluoromethylation of more sensitive substrates.



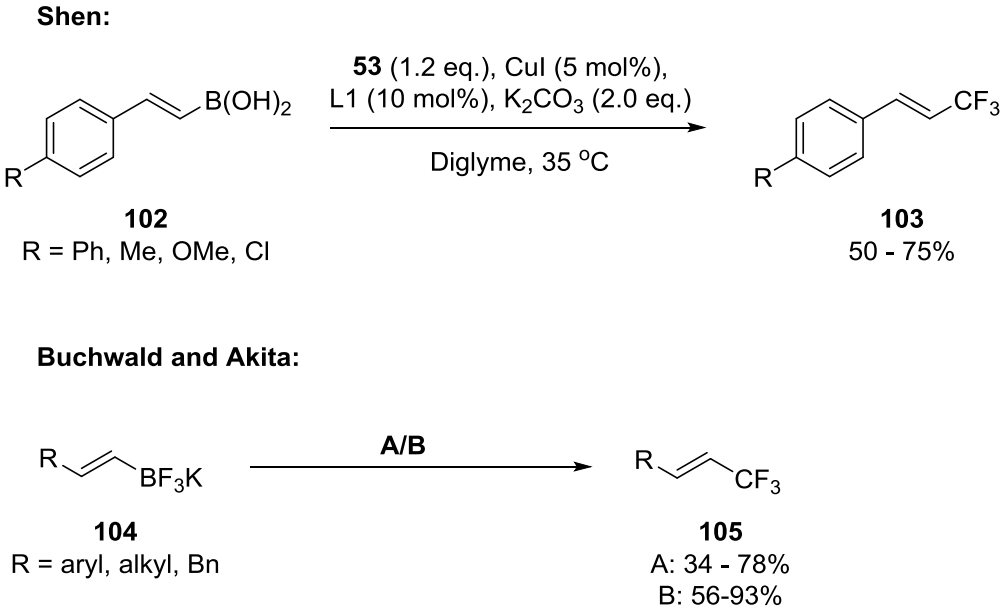

**Scheme 32** Trifluoromethylation of boronic acids

Trifluoromethylated acetylenes could be prepared using reagent **53**, a copper(I) catalyst and an excess of base (Scheme 33).[58] Up to 98% yields were obtained for electron rich aryl substituted acetylenes. Functional groups such as amines and bromides were tolerated in the aromatic fragments, raising the possibility of further derivatisation. The trifluoromethylation of alkynyl trifluoroborates was also possible.[59] In this case, the need to prefunctionalise the alkyne was offset by the fact that i) less of the fluorinating reagent was required; ii) milder conditions could be used, allowing for the trifluoromethylation of more sensitive substrates; iii) non-aryl acetylenes could also be used.



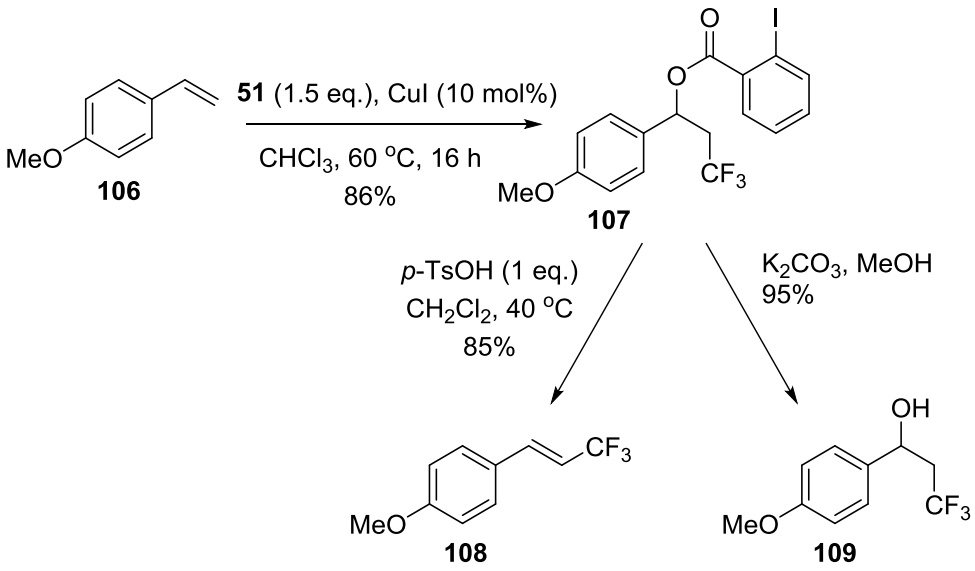

**Scheme 33** *Trifluoromethylation of alkynes*

Shen, Buchwald and Akita used similar approaches to prepare trifluoromethylated alkenes using vinyl boronic acids and trifluoroborates (Scheme 34). Shen used a copper(I) catalysed protocol for the trifluoromethylation of vinyl boronic acids.[56] Buchwald used an iron(II) catalysed approach for the trifluoromethylation of vinyl trifluoroborates, whilst Akita used a Ru photo-redox catalyst for the same transformation.[60, 61]



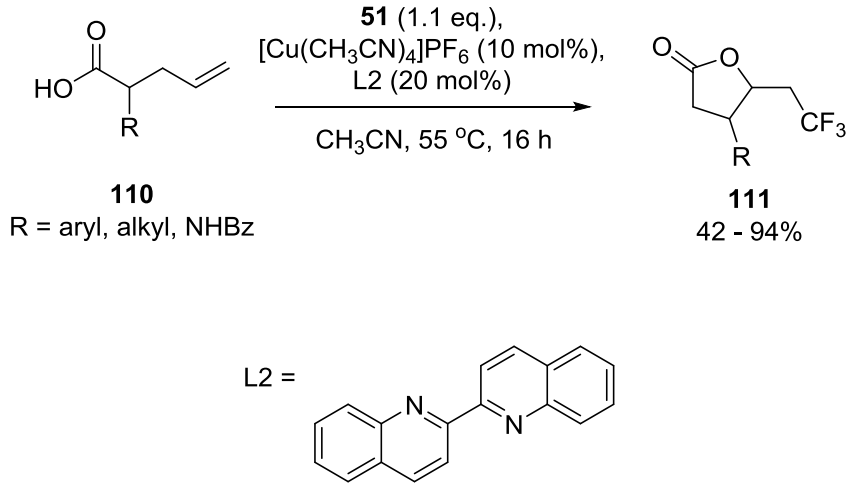

**Scheme 34** *Trifluoromethylation of alkenes*

There have also been several examples of addition reactions to alkenes where vinylic trifluoromethylated products were obtained after elimination or hydrolysis. For example, Szabó and Sodeoka both demonstrated very similar copper(I) catalysed additions to styrenes in which 2-iodobenzoate acted as the nucleophile (Scheme 35).[62, 63] The products of these reactions could undergo Brønsted acid catalysed elimination to give vinylic trifluoromethylated products.[63] Alternatively, base promoted hydrolysis gave β-trifluoromethylated alcohols.[62] Szabo also demonstrated that other, external nucleophiles could be added to the reaction mixture in order to give β-iodo, -bromo and -cyano trifluoromethylated products.[62, 64]




**Scheme 35** *Addition of Togni's reagent to alkenes*

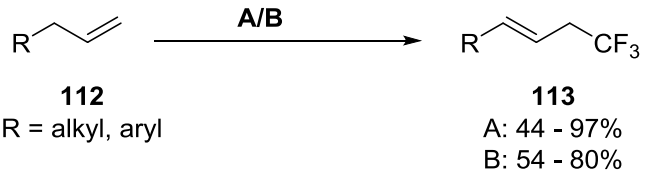
When an alkene and a nucleophile were present within the same substrate a heterocyclisation reaction took place. For example, Buchwald prepared trifluoromethyl substituted lactones in a copper(I) catalysed process (Scheme 36).[65] This protocol was later developed into an asymmetric version using a $C_2$-symmetric bis(oxazoline)-type ligand for enantioinduction and enantiomeric excesses of up to 88% were observed.[66]




**Scheme 36** *Synthesis of trifluoromethylated lactones*

Allylic trifluoromethylation has been carried out using two key approaches. Both Buchwald and Wang attempted copper(I) catalysed trifluoromethylation of simple terminal olefins (Scheme 37).[67, 68] They found that the thermodynamically favoured E olefin was formed with a high stereoselectivity. Alkyl substituted allylic substrates gave

good yields and various functional groups such as esters, epoxides, amides, alcohols and aldehydes were tolerated. Aryl substituted substrates, however, gave poor yields.



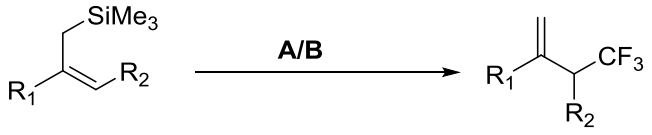

**112**
R = alkyl, aryl

**113**
A: 44 - 97%
B: 54 - 80%

Wang (A): Substrate (1.25 eq.), **51** (1 - 2 eq.), CuCl (10 mol%), MeOH, 70 °C.
Buchwald (B): Substrate (1 - 1.6 eq.), **51** (1.0 eq.), $[Cu(CH_3CN)_4]PF_6$ (15 mol%), MeOH, 0 °C - RT.

**Scheme 37** *Allylic trifluoromethylation with simple alkenes*

Gouverneur and Sodeoka on the other hand used allyl silanes as the starting materials to prepare allyl trifluoromethylated products (Scheme 38).[69, 70] This approach gave different product substitution patterns to those obtained by Buchwald and Wang. An additional advantage of Gouverneur's procedure was that internally substituted olefins could be trifluoromethylated. Gouverneur's method was later extended to a stereoselective protocol using a photoredox catalyst.[71]




**114**
$R_1$ = alkyl, aryl, alkynyl
$R_2$ = H, alkyl

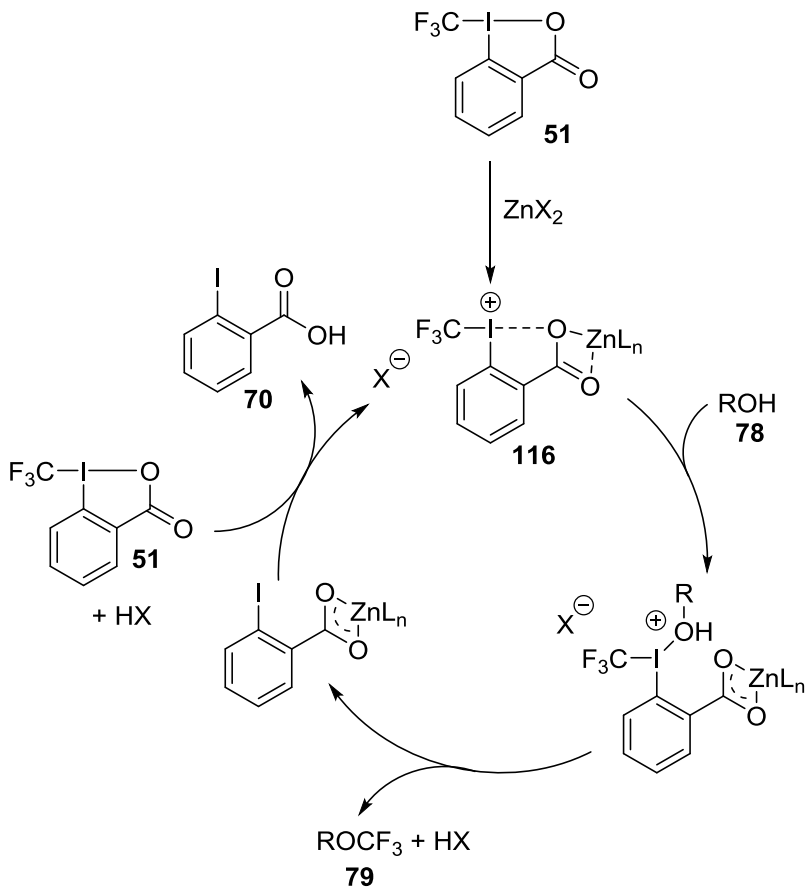
**115**
A: 63 - 84%
B: 6 - 84%

Sodeoka (A): **51** (1.2 eq.), CuI (10 mol%), MeOH, RT.
Gouverneur (B): **51** (1.2 eq.), CuCl (20 mol%), MeOH, 70 °C.

**Scheme 38** *Allylic trifluoromethylation with allylsilanes*

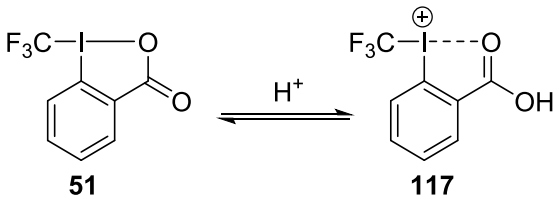
### 1.7.3 Mode of Action of Togni's Reagents

In many of the reactions in the previous section, activation of Togni's reagents was achieved using either a Lewis or a Brønsted acid. For example, in the trifluoromethylation of alcohols (Scheme 23), the acid reagent **51** was activated by Lewis acids such as $Zn(OTf)_2$ and $Zn(NTf)_2$.[41] It was shown that the presence of a zinc(II) salt caused the elongation of the I-O bond to form complex **116** (Scheme 39). This facilitated ligand exchange with the alcohol substrate and subsequent reductive elimination gave the product **79**.




**Scheme 39** *Activation of Togni's reagent with a Lewis acid.*

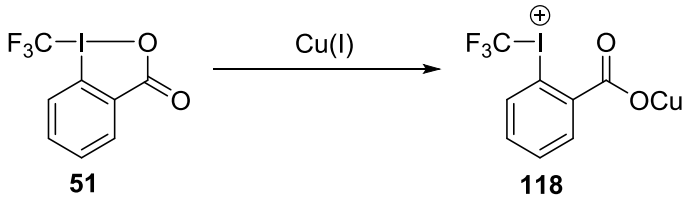
Activation of Togni's acid reagent **51** by Brønsted acids was also possible. For example, in the trifluoromethylation of sulphonic acids using **51** (Scheme 24) it was proved that the trifluoromethylating reagent was activated by protonation of the carbonyl oxygen (Scheme 40).[41, 45, 72] This caused a weakening of the I-O bond and facilitated coordination of the substrate at iodine. Product formation then occurred *via* reductive elimination from iodine. A similar mechanism for the reaction of **53** with sulphonic acids was proposed, in which protonation occurred at the alcohol oxygen.




**Scheme 40** *Bronsted acid activation of Togni's acid reagent*

One of the most widely used catalysts for the activation of Togni's reagents are copper(I) salts, with 35 examples in this area between 2012 and 2013.[41] In most cases, the acid reagent **51** was used, however, this was thought to be a consequence of the

shorter synthesis, price and commercial availability of this reagent, rather than any improved reactivity when compared to that of the alcohol reagent **53**. Despite the large number of reactions carried out using copper(I) salts, there is very little mechanistic information available. Most groups suggest that the formation of an iodonium cation **118** is a key mechanistic step (Scheme 41), although there is little proof of this. Togni has proposed that this is unlikely due to the poor affinity of Cu(I) for a $\kappa^2$-carboxylate group. Since I(III) interactions are usually loose and bond distances are long, an elongation of the I-O bond is in fact the more likely scenario, rather than full cleavage.




**Scheme 41** *Proposed Acitvation of Togni's acid reagent by copper*

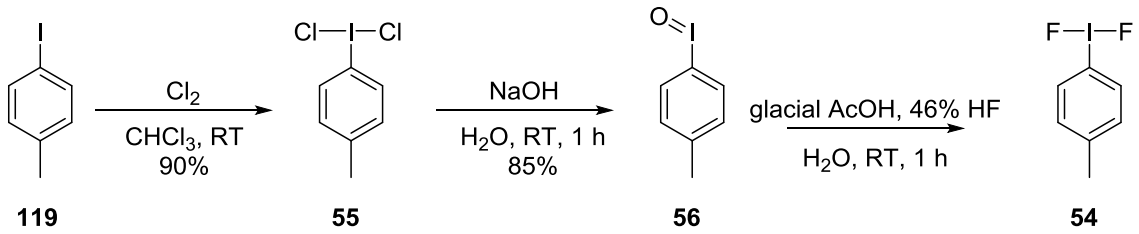
Most reports suggest that, in the case of Cu(I) catalysis, a radical mechanism was occurring as proved by the addition of TEMPO and subsequent formation of TEMPO-$CF_3$ adducts. [41] In fact, however, it was shown by Togni, that both reagents **51** and **52** were capable of trifluoromethylating TEMPO even without the addition of a substrate.[46] The only study which seemed to prove a radical mechanism was a reaction involving the trifluoromethylation of allylic alcohols, in which products corresponding to radical rearrangements were observed, rather than a semi-pinacol rearrangement.[73] It is clear that more mechanistic investigation is required in this area.

## 1.8 Electrophilic Fluorination using Hypervalent Iodine Reagents

### 1.8.1 Preparation of Difluoroiodoarenes

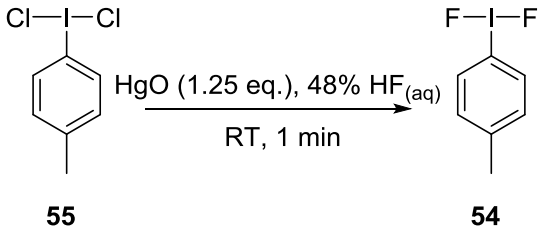
The first example of the preparation of a difluoroiodoarene was more than eighty years ago.[74] Despite this, the preparation of hypervalent iodine derived electrophilic fluorinating reagents compounds is poorly developed, due to the difficulties involved in their preparation and storage. One of the earliest examples of the preparation of a difluoroiodoarene involved a three step synthesis from 4-iodotoluene (Scheme 42).[32] 4-Iodotoluene **119** was first oxidised to dichloroiodotoluene **55**, followed by hydrolysis to give iodosotoluene **56**. This was then reacted with glacial acetic acid and 46% HF to give difluoroiodotoluene **54**. Due to the instability of difluoroiodotoluene it was

immediately dissolved in chloroform after isolation. In chloroform, difluoroiodotoluene was stable for up to 2 days. This method was later improved, using the stable, crystalline (diacetoxyiodo)toluene instead of dichloroiodotoluene **55** which was found to be unstable and light and heat sensitive.[75]



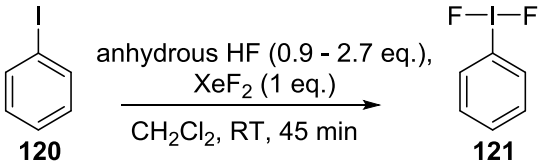

**Scheme 42** *Preparation of difluoroiodotoluene from iodosotoluene*

An alternative synthesis, in which dichloroiodotoluene **55** was converted directly to difluoroiodotoluene **54** using HgO and 48% HF, eliminated the requirement to prepare iodosotoluene **56** which disproportionates on standing (Scheme 43).[33] Although shorter, the disadvantage of this synthesis was the need to use toxic mercury salts.



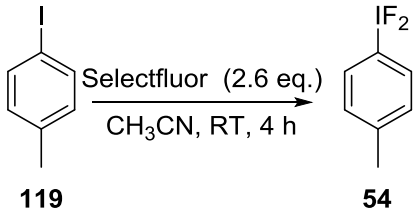

**Scheme 43** *Preparation of difluoroiodotoluene from dichloroiodotoluene*

An improved synthesis which did not use toxic mercury salts or proceed *via* iodosotoluene **56** has been reported. In this case, difluoroiodobenzene **121** was formed in one step from iodobenzene **120** using $XeF_2$ and anhydrous HF (Scheme 44).[76] The preparation of difluoroiodotoluene **54** was also possible directly from 4-iodotoluene **119** by direct electrochemical fluorination using $Et_3N.5HF$.[77]




**Scheme 44** *Preparation of difluoroiodobenzene from iodobenzene*

In all of the above syntheses of difluoroiodoarenes, the use of aqueous HF was required. This is an extremely corrosive reagent that cannot be used in normal glassware. Shreeve developed an alternative synthesis of difluoroiodotoluene **54** from 4-iodotoluene **119** in one step using Selectfluor (Scheme 45).[78] It was noted that the addition of trace amounts of $Et_3N.3HF$ before work up could help stabilize the difluoroiodotoluene **54**. A disadvantage of this synthesis is the high cost of Selectfluor.




**Scheme 45** *Preparation of difluoroiodotoluene using Selectfluor*

Alternatively, difluoroiodobenzene **121** could be prepared in one step from commercially available DIB **60** and a cheap and readily available source of the fluoride anion, TBAF (Scheme 46).[79]


**Scheme 46** *Preparation of difluoroiodobenzene using TBAF*

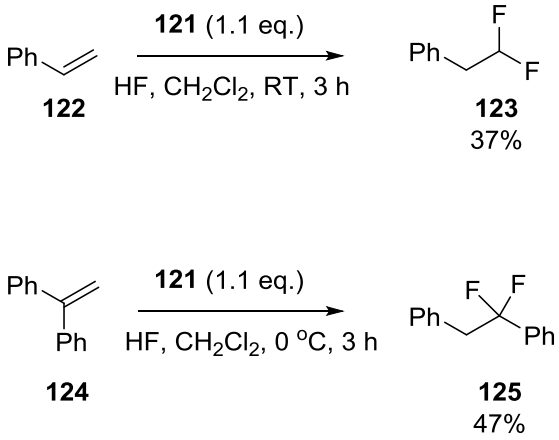
Having surveyed the literature relating to the preparation and reactivity of difluoroiodoarenes, it is clear that there is significant confusion and disagreement associated with the stability of the difluoroiodoarenes. In many cases difluoroiodoarenes derived from toluene are prepared in preference to those derived from benzene, suggesting that they are more stable. One report states that difluoriodotoluene is an 'easily purified solid' and that 'its chloroform solution is stable for several days'[32] whereas other mention the 'intrinsic instability of iodine(III) difluorides'.[78, 80] It is true that stability is a relative concept and this could account for some of the disagreement. Over the course of my PhD, I have had some experience in the preparation of difluoroiodotoluene **54** and have found it to be unstable in air for any length of time. In all cases, it has been prepared under nitrogen and used immediately.

### 1.8.2 Reactions of Difluoroiodoarenes

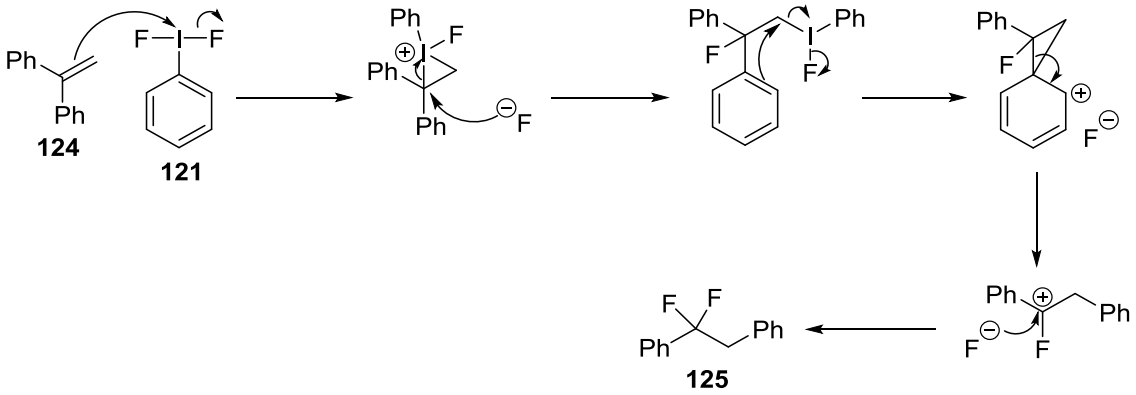
Difluoroiodoarenes have been used as electrophilic fluorinating reagents with a large range of different substrates. The key advantage of the difluoroiodoarenes over other electrophilic fluorinating reagents such as Selectfluor is that they are, in most cases, prepared from cheap and readily available sources of the fluoride anion. In some cases, it has also been shown that the difluoroiodoarenes are complementary to reagents such as Selectfluor, in that different products can be obtained with the same substrates. Some of the key reactions of the difluoroiodoarenes are discussed in this section.

Difluoroiodoarenes can be used for the fluorination of phenyl substituted alkenes, such as styrene **122** and 1,1-diphenylethene **124**.[81] It was found that fluorination was accompanied by a rearrangement of the carbon skeleton (Scheme 47).[33, 78, 82, 83] This is in contrast to Selectfluor, where a simple 1,2 addition was observed.[18]

The mechanism was proposed to proceed first by nucleophilic attack of the alkene **124** at the iodine atom of difluoroiodobenzene **121**, with subsequent release of fluoride (Scheme 48).[33, 83] The fluoride anion then attacked at the more substituted carbon which was best able to stabilise the positive charge, followed by migration of the phenyl group. Following rearomatisation, a second fluoride anion attacked to give the difluorinated product **125**.

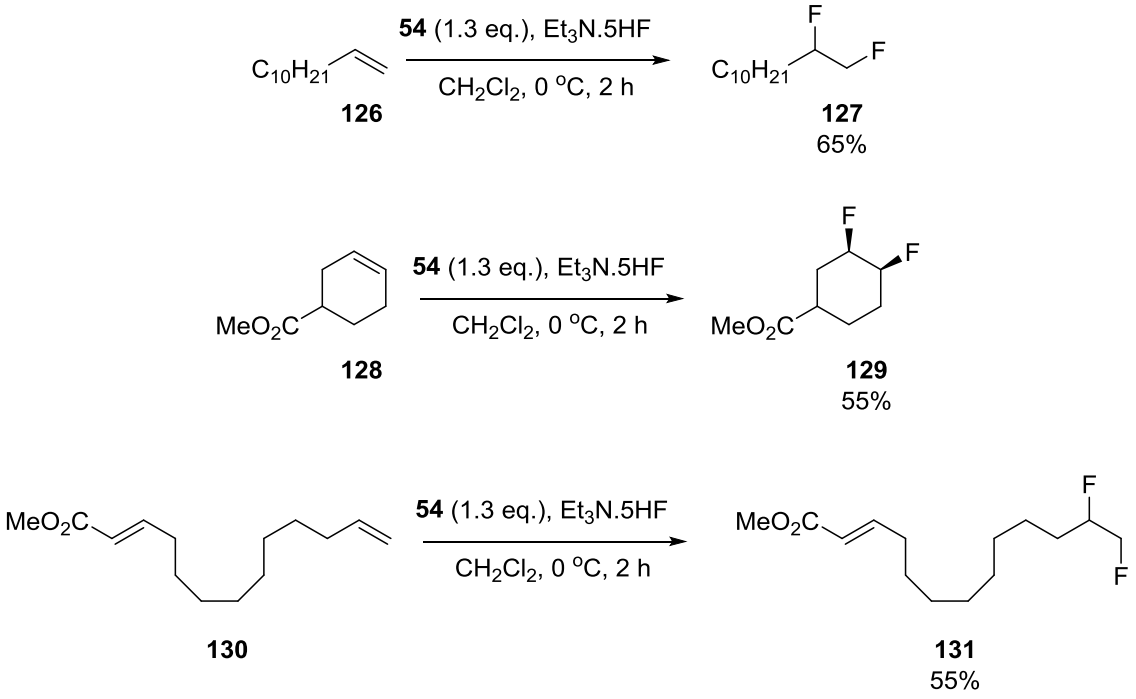



**Scheme 47** *Fluorination of phenyl-substituted alkenes using difluoroiodobenzene*



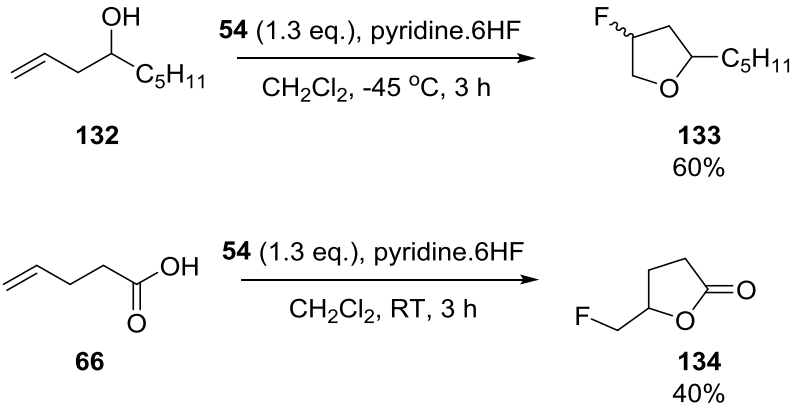

**Scheme 48** *Mechanism for the reaction between 1,1-diphenylethene and difluoroiodobenzene*

When the difluoroiodoarenes were reacted with non-phenyl substituted, terminal alkenes, a simple 1,2-addition was observed, instead of a rearrangement (Scheme 49).[84] Ester, acetoxy, chloro and free hydroxyl groups were found to survive the reaction conditions. In the case of a cyclohexene **128**, the *cis*-product was formed stereoselectively. An alkene substituted by an ester functionality **130** was found to be considerably less reactive and was left unchanged during the reaction of a terminal double bond in the same molecule. The reaction of internal alkenes was also sluggish and resulted in the formation of complex mixtures of products.

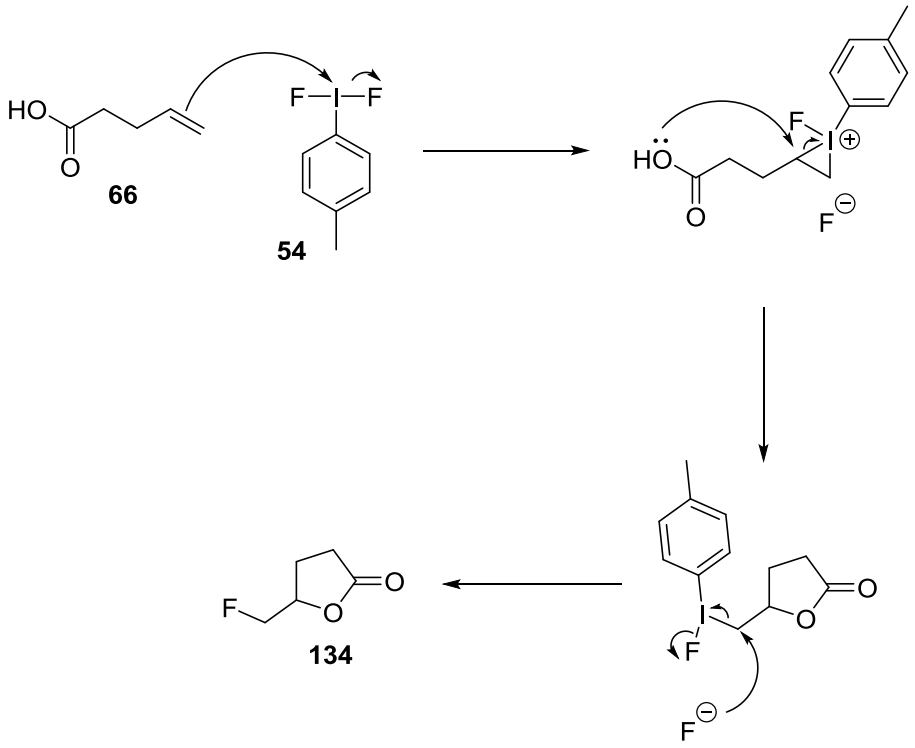



**Scheme 49** *Fluorination of aliphatic alkenes with difluoroiodotoluene*

When an alkene functionality and an additional nucleophile, such as an alcohol or carboxylic acid, were present in the same molecule, intramolecular cyclisation reactions were observed to form cyclic ethers **133** and lactones **134** (Scheme 50).[85] These are useful compounds as intermediates in the synthesis of fluorinated carbohydrates which have significant biological activity and are useful in probing biological mechanisms. The mechanism of this reaction was thought to be similar to that shown in Scheme 48 but without a rearrangement (Scheme 51).



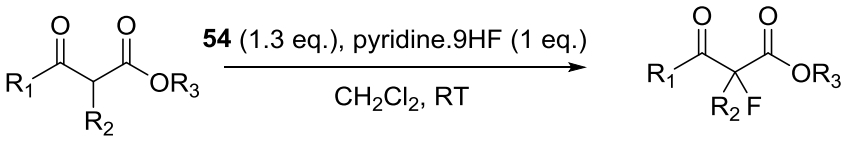

**Scheme 50** *Fluorocyclisation using difluoroiodotoluene*




**Scheme 51** *Mechanism for the fluorocyclisation reaction using difluoroiodotoluene*

Another area in which the use of difluoroiodoarenes has been particularly popular is the fluorination of 1,3-dicarbonyl compounds. In the first example of the fluorination of 1,3-dicarbonyl compounds, difluoroiodotoluene **54** in the presence of pyridine.9HF was found to be the optimum fluorinating reagent and a series of 1,3-ketoesters were fluorinated in good to excellent yields (Table 2).[86] Very similar results could also be achieved electrochemically using $Et_3N.5HF$ as the fluoride additive.[77]

**Table 2** *Fluorination of 1,3-ketoesters with difluoroiodotoluene and pyridine.9HF*




**135** **136**

| Entry | 140 | $R_1$ | $R_2$ | $R_3$ | Time (h) | Yield of 136[a] (%) |
|---|---|---|---|---|---|---|
| 1 | a | Me | H | Et | 2 | 80[b] |
| 2 | b | Me | H | Bu | 3 | 79 |
| 3 | c | Pr | H | Et | 3 | 72 |
| 4 | d | Ph | H | Et | 3 | 73 |
| 5 | e | Me | Me | Bu | 3 | 62 |
| 6 | f | Ph | Ph | Et | 5 | 50[b] |

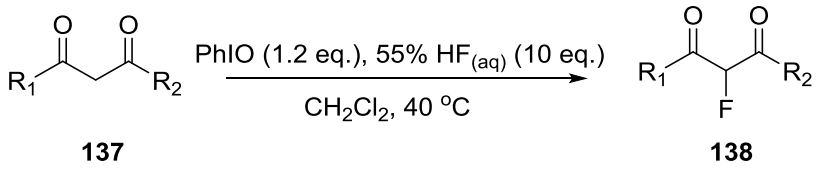
[a] Isolated yield; [b] Yield calculated by GLPC.

Under neutral conditions, in the absence of pyridine-HF, the fluorination of 1,3-dicarbonyl compounds was considerably slower.[87] For example, in the fluorination of ethyl 3-oxo-3-phenylpropanoate **136d** under acidic conditions, a 73% yield was obtained after just three hours. Under neutral conditions, the same transformation took 10 hours. The neutral conditions were better suited to the more reactive 1,3-diketone substrates. For example, in the fluorination of 1,3-diphenylpropane-1,3-dione under acidic conditions, moderate yields were obtained along with a number of unidentifiable by-products. Under neutral conditions a longer reaction time was required but the fluorinated product was obtained in a good yield of 71%.

Since both the preparation of the difluoroiodoarene and the reaction with 1,3-dicarbonyls required the addition of HF, Kitamura proposed a protocol in which difluoroiodobenzene **121** was made and used *in situ*.[88] It was found that iodosobenzene,

in the presence of aqueous HF, gave the optimum conversions to the products. 1,3-Ketoesters, 1,3-diketones and 1,3-ketoamides gave the corresponding monofluorinated products in moderate to excellent yields (Table 3).

**Table 3** *Fluorination of 1,3-dicarbonyls with iodosobenzene and aqueous HF*

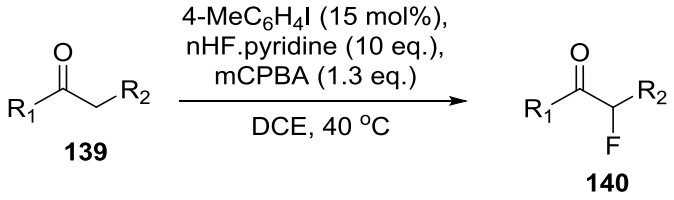



**137** **138**

| Entry | 142 | $R_1$ | $R_2$ | Time (h) | Yield of 138 (%) |
|---|---|---|---|---|---|
| 1 | a | Bu | OEt | 1 | 73 |
| 2 | b | Pr | OEt | 1 | 93 |
| 3 | c | 2,3,4,5-tetrafluorophenyl | OEt | 24 | 70 |
| 4 | d | 4-($NO_2$)$C_6H_4$ | OEt | 24 | 58 |
| 5 | e | Ph | Me | 24 | 47 |
| 6 | f | Ph | Ph | 36 | 90 |
| 7 | g | Et | Et | 2 | 34 |
| 8 | h | Me | $NEt_2$ | 2 | 52 |
| 9 | i | Me | $NMe_2$ | 2 | 25 |

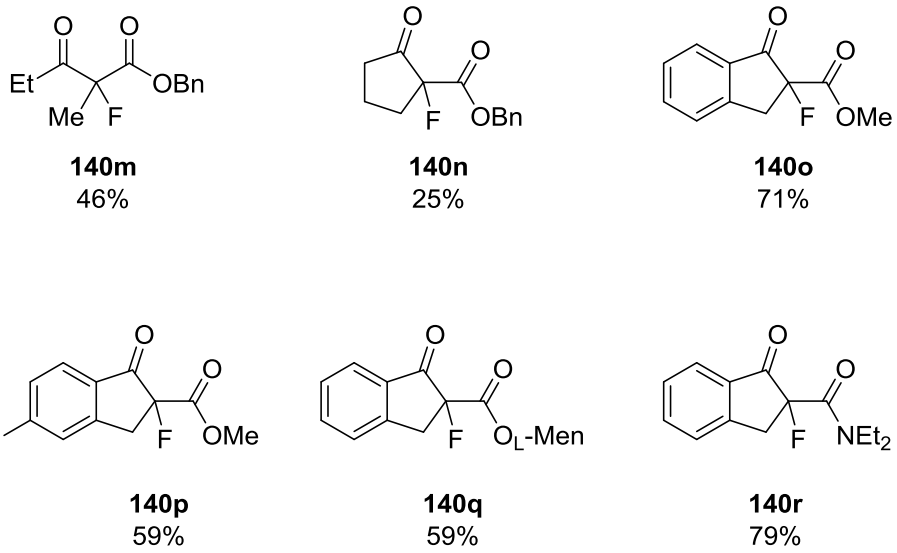
One of the key disadvantages of the use of difluoroiodoarenes as electrophilic fluorinating reagents is the low percentage molecular weight of fluorine. This was addressed by both Kitamura and Shibata, by the development of a process using only catalytic amounts of the iodoarene.[89, 90] Of the two methods, the one developed by Shibata was the more general, using the same iodoarene for all transformations. In his procedure just 15 mol% of the iodoarene was required, in addition to 10 equivalents of pyridine.nHF and 1.3 equivalents of the oxidant, *m*CPBA. When tested in the fluorination of 1,3-dicarbonyl compounds it was found that monofluorinated products **140** could be obtained with very short reactions times of between 30 minutes and one hour (Table 4). Shibata also showed that the procedure was applicable to a number of 1,3-dicarbonyl compounds with substituents at the α-position (Scheme 52).

**Table 4** *Fluorination of 1,3-dicarbonyls using a catalytic amount of the iodoarene*[90]



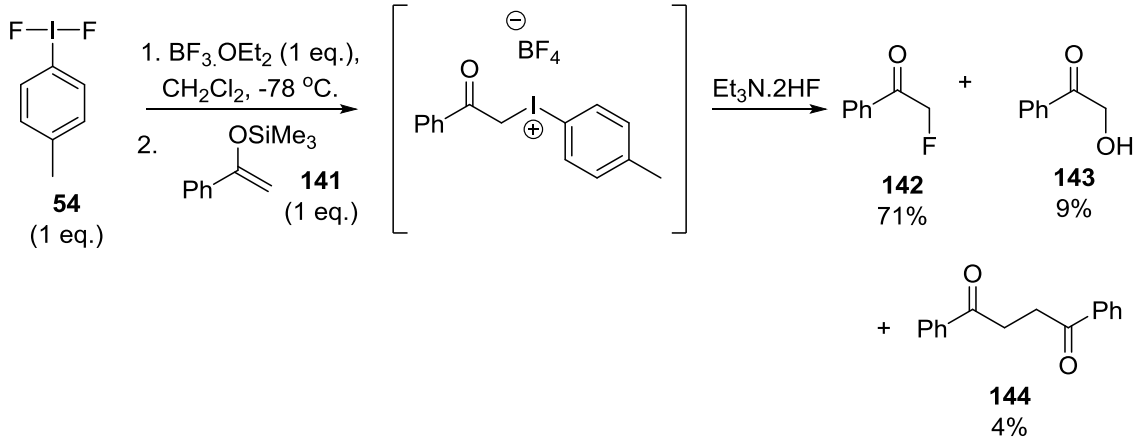

| Entry | 144 | $R_1$ | $R_2$ | Time (h) | Yield of 140[a] (%) |
|---|---|---|---|---|---|
| 1[b] | a | Ph | $CO_2Et$ | 0.5 | 98 |
| 2[b] | b | 2-$MeC_6H_4$ | $CO_2Me$ | 0.5 | 74 |
| 3[b] | c | 3-$MeC_6H_4$ | $CO_2Me$ | 0.5 | 62 |
| 4[b] | d | 4-$MeC_6H_4$ | $CO_2Me$ | 0.5 | 53 |
| 5[b] | e | 3-$MeOC_6H_4$ | $CO_2Me$ | 0.5 | 61 |
| 6[b] | f | 4-$MeOC_6H_4$ | $CO_2Me$ | 0.5 | 72 |
| 7[b] | g | 4-$ClC_6H_4$ | $CO_2Me$ | 0.5 | 59 |
| 8[b] | h | 4-$BrC_6H_4$ | $CO_2Me$ | 0.5 | 78 |
| 9[b] | i | Cyclohexyl | $CO_2Me$ | 1 | 91 |
| 10[b] | j | 3-Furanyl | $CO_2Et$ | 0.5 | 64 |
| 11[b] | k | Ph | $CONEt_2$ | 0.5 | 66 |
| 12[c] | l | Ph | $SO_2Ph$ | 24 | 71 |

[a] Isolated yield; [b] mCPBA was divided into 2 aliquots before addition; [c] mCPBA was divided into 3 aliquots before addition.



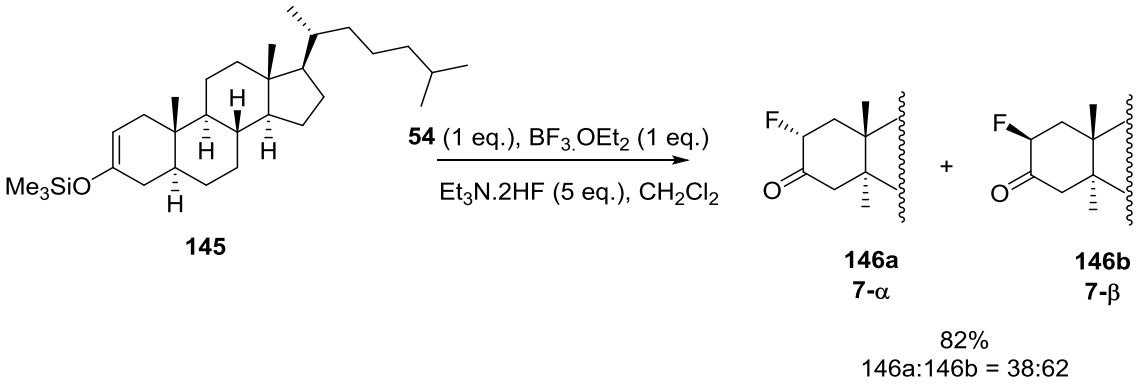

**Scheme 52** *Fluorination of substituted 1,3-dicarbonyl compounds*[90]

The fluorination of monocarbonyl compounds is a more difficult task due to their decreased reactivity when compared to 1,3-dicarbonyl compounds. Hara attempted the fluorination of ketones using difluoroiodotoluene **54**.[91] When difluoroiodotoluene **54** was reacted directly with the silyl enol ether of acetophenone **141**, only acetophenone and its dimer **144** were recovered. Alternatively, when difluoroiodotoluene **54** was first activated using $BF_3.OEt_2$, followed by addition of the silyl enol ether **141** and finally the addition of a fluoride source, the reaction was much more successful (Scheme 53). $Et_3N.2HF$ was the most successful fluoride source. $Et_3N.3HF$ gave a similar yield, however, $Et_3N.HF$ and basic sources of fluoride such as TBAF, $Et_4NF$, CsF and KF gave only poor yields of the desired product. Using this method, a variety of both aryl and alkyl substituted cyclic and acyclic ketones were fluorinated in good yields.



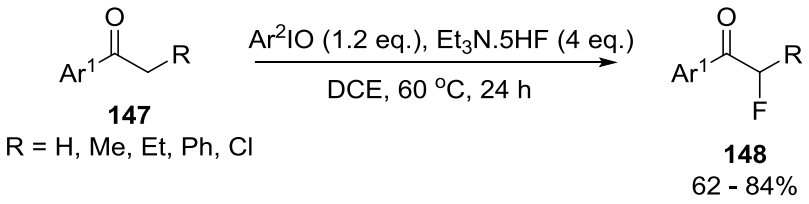

**Scheme 53** *Fluorination of silyl enol ethers with difluoroiodotoluene*

Hara's method was applied to the fluorination of steroids. Using conventional electrophilic fluorination methods, the kinetically and thermodynamically favoured α-isomers were usually favoured. Using difluoroiodotoluene **54**, however, the β-isomer was the major product. This could be explained by the attack of difluoroiodotoluene **54** at the less hindered α-face to give the α-isomer of the iodonium intermediate, followed by nucleophilic substitution by fluoride with inversion of configuration to give the β-isomer (Scheme 54).




**Scheme 54** *Fluorination of steroids with difluoroiodotoluene*

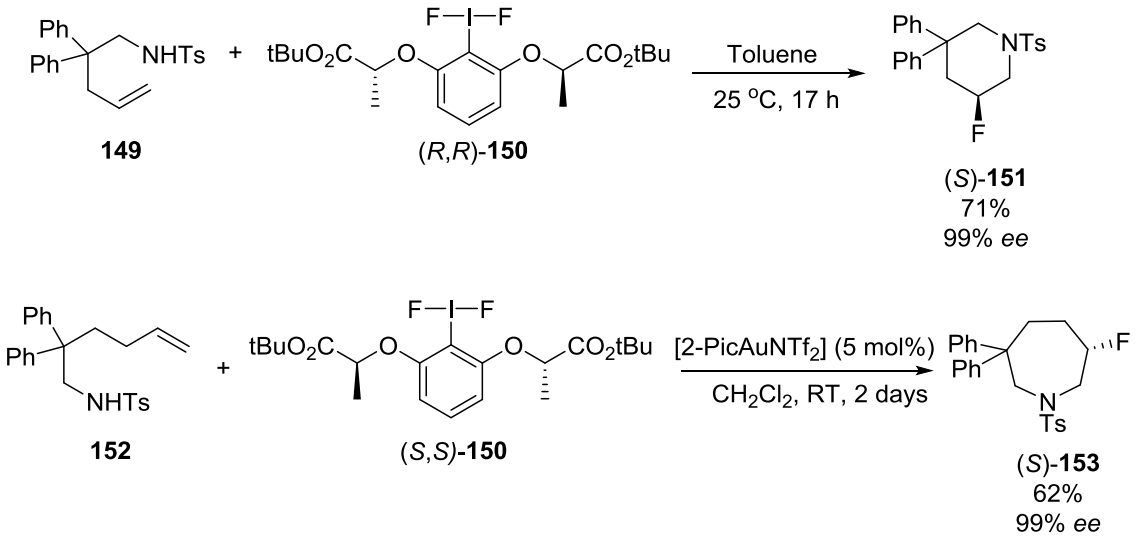
Kitamura also developed a direct synthesis of fluorinated aromatic ketones using a similar procedure to the one used for the fluorination of 1,3-dicarbonyl compounds (Scheme 55).[88, 92] In this case, however, a non-aqueous fluoride source, $Et_3N.5HF$, was used in order to increase the nucleophilicity of the fluoride anion.




**Scheme 55** *Fluorination of ketones using iodosoarenes and $Et_3N.5HF$*

In the last three years, several procedures for the intramolecular aminofluorination of alkenes using difluoroiodoarenes have been reported. In 2012, Li and Meng developed a regio- and stereoselective procedure for the preparation of 2-fluoropiperidines using $PhI(OPiv)_2$ and HF.pyridine.[93] A further development by Zhang prepared 2-fluoropyrrolidines using PhIO as the iodoarene and $BF_3.OEt_2$ as the fluoride source.[94]

Nevado published an enantioselective procedure for the preparation of 2-fluoropiperidines and azepanes with high enantioselectvities (Scheme 56).[80] This was achieved by the use of a chiral difluoroiodoarene **150**. Whilst the preparation of 2-fluoropiperidines **151** was possible without the requirement for a catalyst, the reaction to form 2-fluoroazepanes **153** was more difficult. This was thought to be due to the decreased favourability of a 7-endo-trig cyclisation. It was found, however, that the addition of a Lewis acid catalyst in order to activate the olefin, overcame this problem.




**Scheme 56** *Enantioselective aminocyclisation using a difluoroiodoarene*

The Nevado method for aminocyclisation used a large excess (2.5 equivalents) of the chiral difluoroiodoarene **150**. This could be recovered in 50-60% yield in its initial enantiopurity at the end of the reaction. Shibata carried out an enantioselective aminocyclisation reaction in which the difluoroiodoarene was prepared *in situ* using only catalytic amounts (15 mol%) of the chiral iodoarene.[90] This reaction gave moderate enantioselectivities (45 – 70% *ee*) using (*R*)-binapthyldiiodide as the iodoarene. The same method was also applied to the fluorination of 1,3-dicarbonyl compounds, again, with moderate enantioselectivities.

### 1.9 Project Aims

Difluoroiodoarenes can be prepared from cheap and readily available sources of the fluoride anion and act as electrophilic fluorinating reagents. Their widespread use, however, is limited by the fact that they are usually prepared *in situ* because they are unstable and moisture sensitive. Another disadvantage of the difluoroiodoarenes is that both their preparation and use often requires the addition of reagents such as aqueous HF and pyridine-HF. These reagents are extremely dangerous and cannot be used in normal glassware because they are so corrosive.

The aim of this project is to prepare a new hypervalent iodine based electrophilic fluorinating **154** reagent with a cyclic structure, similar to both Togni's **53** and Braddock's **65** reagents (Figure 8). The inclusion of the hypervalent iodine atom in a 5 membered ring, the Thorpe-Ingold effect of the *gem*-dimethyl groups and the inclusion

of an additional electronegative atom, oxygen, should all help to increase the stability of **154** relative to the difluoroiodoarenes **54**.[39]

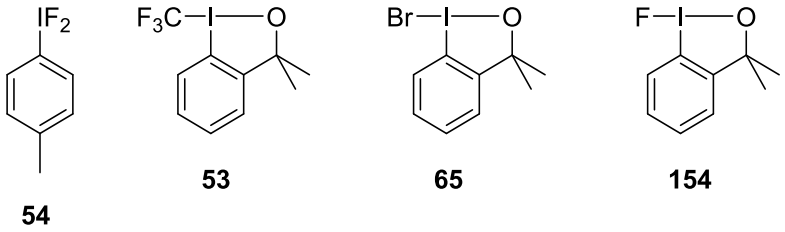



**Figure 8** *Comparison of Hypervalent Iodine Reagents*

The key benefit of the new fluoroiodane **154** over pre-existing electrophilic fluorinating reagents would be that it could be prepared from cheap and readily available sources of the fluoride anion rather than elemental fluorine. The new reagent should be shelf stable, react as an electrophilic fluorinating reagent with a wide variety of substrates and be soluble in a range of organic solvents. Ideally, the fluoroiodane **154** will also act as a complementary electrophilic fluorinating reagent to those that already exist and participate in new and interesting reactions.

Positron emission tomography (PET) is a non-invasive imaging technology used to probe and observe biological processes.[29] Several positron emitting isotopes can be used for PET imaging, however, $^{18}F$ is the most clinically relevant. In general, the incorporation of $^{18}F$ into radiotracers relies on nucleophilic substitution chemistry, since [$^{18}F$]-fluoride is both easier to make and handle than [$^{18}F$]-$F_2$. [$^{18}F$]-fluoride can also be prepared in a substantially higher specific activity than [$^{18}F$]-$F_2$. If an electrophilic fluorinating reagent could be made using fluoride, a whole new array of PET tracers could be developed which are currently inaccessible using conventional nucleophilic methodologies. For this reason, another aim of this project is to look at ways in which the fluoroiodane **154** could be prepared, which would make it more applicable to the preparation of PET radiotracers.

In chapter 2 of this thesis, the preparation of fluoroiodane **154** from different sources of the fluoride anion will be discussed. Preliminary studies into the reactivity of the fluoroiodane **154** as an electrophilic fluorinating reagent with 1,3-dicarbonyl substrates and other nucleophiles will be presented.

In chapter 3, the mechanism of the reaction between the fluoroiodane and 1,3-dicarbonyl compounds will be explored in more detail. A proposed mechanism is

presented in addition to the preparation of a series of new, stable iodonium ylides, the reactivity of which was used as evidence to substantiate the mechanism.

In chapter 4, the intramolecular fluorocyclization of unsaturated alkenes using the fluoroiodane **154** will be presented. In this interesting reaction, tertiary alkyl fluoride functionalised γ-lactones were prepared. This is in contrast to the fluoraza reagents which give primary alkyl fluoride functionalised γ-lactones with the same substrates.

Finally, in chapter 5 of this thesis, attempts to prepare a new acid derived fluoroiodoxolone reagent will be presented. The preparation of the new reagent and its reactivity with 1,3-dicarbonyl compounds will be discussed.

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# Chapter 2

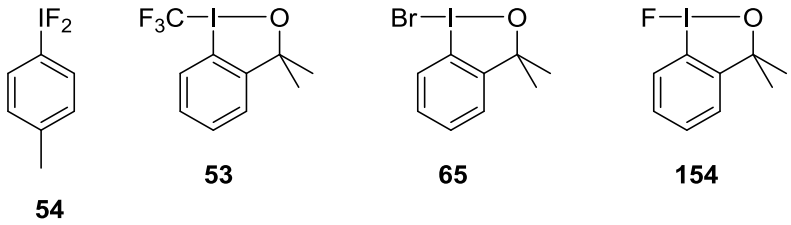
# Synthesis of a Fluoroiodane and Initial Testing as an Electrophilic Fluorinating Reagent

## 2.1 Introduction

The most popular reagents used for electrophilic fluorination are the fluoraza reagents, examples of which include Selectfluor and NFSi. These reagents are selective, shelf stable and easy to handle sources of electrophilic fluorine.[1, 2] One of the drawbacks associated with these reagents, however, is that they must be made, in the first instance, from elemental fluorine and this means that they are very expensive.

Electrophilic fluorinating reagents based on a hypervalent iodine skeleton can be prepared from cheap and readily available, nucleophilic sources of fluoride.[3, 4] These difluoroiodoarene reagents **54** are limited, however, by their poor stability and moisture sensitivity and the fact that dangerous reagents such as aqueous HF and pyridine HF are required for their preparation and/or use.

The aim of this chapter was to prepare a stable, electrophilic fluorinating reagent **154** based on a hypervalent iodine core skeleton, which could be prepared from different sources of the fluoride anion. It was hoped that a cyclic structure similar to that of Togni's trifluoromethylating reagent **53** and Braddock's brominating reagent **65** would infer increased stability due to i) the inclusion of the iodine atom in a 5-membered ring, ii) the Thorpe-Ingold effect of the *gem*-dimethyl groups and iii) the inclusion of a second electronegative atom, oxygen, bonded to the hypervalent iodine atom.[5] The new reagent needed to be air and moisture stable, soluble in a variety of organic solvents and react as an electrophilic fluorinating reagent with a broad substrate scope.




**54** **53** **65** **154**

**Figure 1** *Hypervalent iodine atom transfer reagents*

Towards the main aim of this chapter, the preparation of the fluoroiodane **154** from both electrophilic and cheap and readily available, nucleophilic sources of fluoride will be discussed.[6] Towards the secondary aim of this chapter, the preparation of the fluoroiodane **154** from sources of fluoride, such as potassium fluoride or tetrabutylammonium fluoride, which are commonly used in PET chemistry, will be

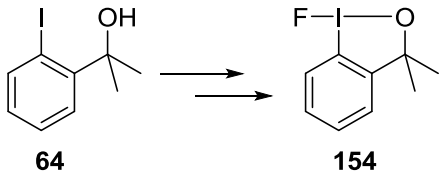
presented. This would potentially provide a route for the synthesis of a fluorinating reagent that would be suitable for the production of $^{18}$F-labelled radiotracers for Positron Emission Tomography (PET).

The final aim of this chapter was to test the reactivity of the fluoroiodane **154** as an electrophilic fluorinating reagent with a range of nucleophiles. The results of the initial testing with 1,3-dicarbonyl compounds in addition to other substrates such as silyl enol ethers, alkenes and aromatic compounds will also be presented in this chapter.[6]

As a brief overview, the chapter will be presented in four sections:

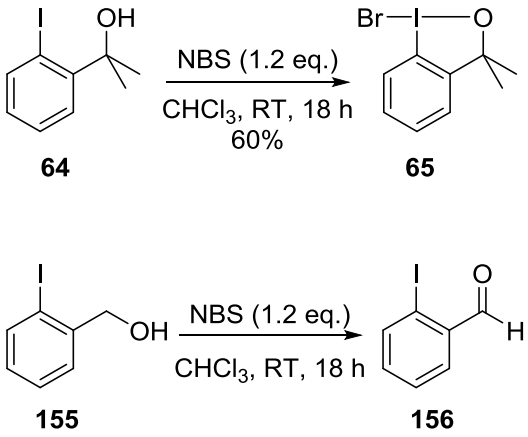
1. Preparation of a key starting material for the synthesis of the fluoroiodane; the iodoalcohol **64**.
2. Preparation of the fluoroiodane **154** using
    i. Selectfluor
    ii. $Et_3N.3HF$ (TREAT-HF)
    iii. TBAF.
3. Testing the reactivity of the fluoroiodane **154** with 1,3-dicarbonyl compounds.
4. Testing the reactivity of the fluoroiodane **154** with other substrates.

## 2.2 Preparation of the Iodoalcohol



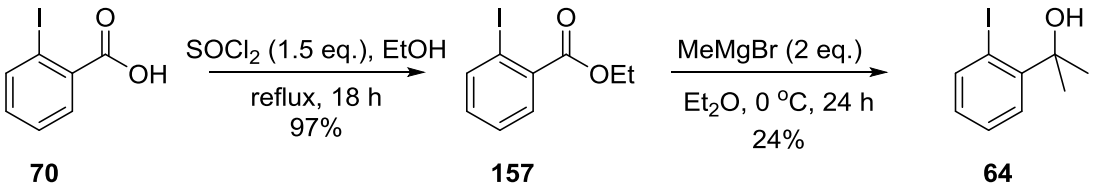

**Scheme 1** *The fluoroiodane and iodoalcohol*

The key starting material required for the preparation of the fluoroiodane **154** was the iodoalcohol, 2-(2-iodophenyl)propan-2-ol **64** (Scheme 1). The iodoalcohol **64** was known to react with *N*-bromosuccinimide (NBS) to give the bromoiodane **65** (Scheme 2).[5] Since 2-iodobenzyl alcohol **155** was commercially available, it was reacted with NBS to see if this alcohol could be used instead of **64** to prepare an iodine(III) species. The only observed product from this reaction, however, was the aldehyde **156**. This showed that the *gem*-dimethyl groups in **64** were essential to prevent oxidation of the alcohol during oxidation from iodine(I) to iodine(III).




**Scheme 2** *Attempted oxidation reactions*

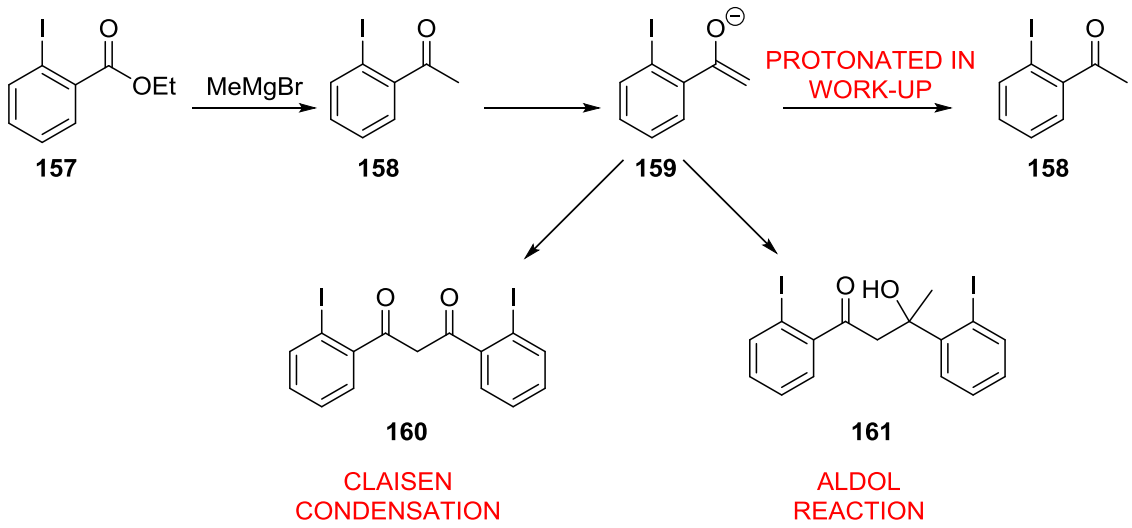
A literature route to the iodoalcohol **64** is the esterification of 2-iodobenzoic acid **70** followed by a Grignard reaction using methyl magnesium bromide (Scheme 3).[7-9] The iodoester **157** was prepared according to the literature procedure from 2-iodobenzoic acid **70** with thionyl chloride and ethanol. A yield of 97% was obtained which was higher than the reported literature value of 79% and the characterisation data was in agreement with the literature.[7] The iodoester **157** was then reacted with commercially available methyl magnesium bromide in diethyl ether to give the iodoalcohol **64** in a yield of approximately 24%. This was significantly lower than the literature value of 85% but it was not possible to reproduce the literature results.[9] Purification by column chromatography was extremely difficult due to the large number of by-products.



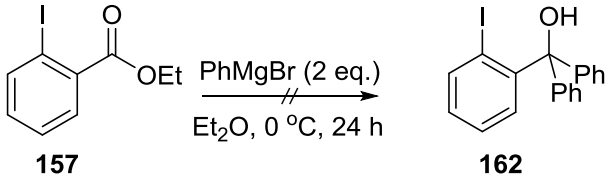

**Scheme 3** *Preparation of the iodoalcohol via a Grignard reaction*

It was presumed that the yield and purity of this reaction was so low due to deleterious side reactions such as enolisation of the intermediate ketone **158** followed by aldol or Claisen condensation reactions (Scheme 4). Although these products were not isolated, the ability of Grignard reagents to act as bases is well known.[10] To prevent enolisation, phenyl magnesium bromide was used as the Grignard reagent, in order to prepare an iodoalcohol with two phenyl groups **162** instead of two methyl groups (Scheme 5). This

reaction, however, resulted in the formation of a complex mixture of products from which the desired product **162** could not be isolated.

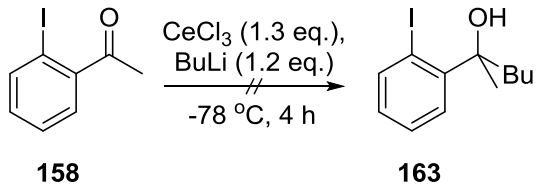



**Scheme 4** *Potential pathways to by-product formation in the Grignard reaction*



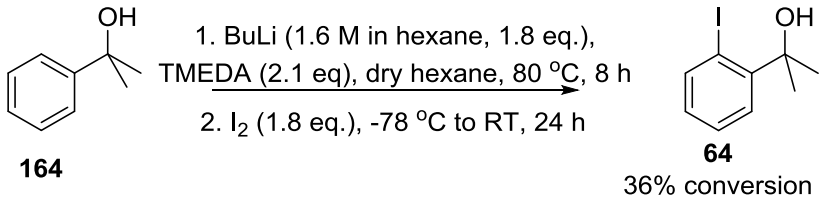

**Scheme 5** *Reaction of the iodoester with PhMgBr*

Organocerium reagents have been shown to act as non-basic nucleophiles and can therefore be useful when enolisation is a problem with traditional Grignard reagents.[11] The reaction between the iodoketone **158** and an organocerium reagent was attempted (Scheme 6). The organocerium reagent, $BuCeCl_2$ was prepared *in situ* by the reaction of butyl lithium with $CeCl_3$. This reaction was unsuccessful and the starting iodoketone **158** was recovered unreacted. The same was true when the iodoester **157** was used as the starting material and when $MeCeCl_2$ was used instead of $BuCeCl_2$.



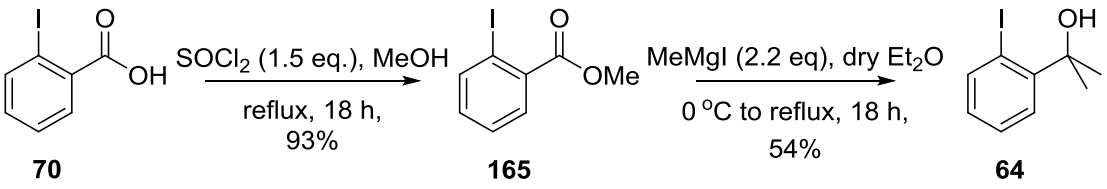

**Scheme 6** *Reaction of the iodoketone with an organocerium reagent*

In an alternative approach for the preparation of **64** an *ortho*-lithiation reaction was attempted (Scheme 7). Despite several modifications to the procedure, the highest conversion to **64** was 36%. Since the iodinated product **64** and non-iodinated starting material **164** could not be separated by column chromatography or distillation, this method was abandoned.




**Scheme 7** *Preparation of the iodoalcohol in an ortholithiation reaction*

During the course of this work, a new procedure was published in which the iodoalcohol **64** was prepared in a Grignard reaction.[12] The starting material **165** was prepared from 2-iodobenzoic acid **70** using thionyl chloride and methanol in 93% yield (Scheme 8). The characterisation data for this known compound was in agreement with the literature.[13] The procedure for the new Grignard reaction varied in five subtle ways from the original procedure: i) the Grignard reagent was freshly prepared rather than using the commercially available pre-prepared solution, ii) the methyl ester starting material **165** was used instead of the ethyl ester **157** iii) methyl magnesium iodide was used instead of methyl magnesium bromide iv) in an effort to prevent unwanted side reactions such as deprotonation of the intermediate ketone, an inverse addition procedure was used in which the Grignard reagent was added to an ice cold solution of the ester **165** in diethyl ether v) after stirring at room temperature for 17 hours, the reaction mixture was heated to reflux for an hour.




**Scheme 8** *Final synthesis of the iodoalcohol*

When the new procedure was attempted, 100% conversion of the starting material was achieved. The crude product was much cleaner and, therefore, purification by column chromatography was significantly easier resulting in a higher isolated yield of 54%

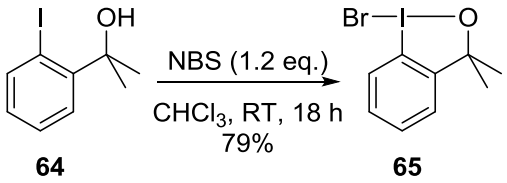
(Scheme 8). Higher yields were obtained in the literature (83% yield, 90% purity) since the crude product was deemed sufficiently pure to not require further purification. Here, although the $^{1}$H NMR spectrum of the crude product was quite clean, purification by column chromatography was essential. When the crude product was used without purification, subsequent reactions did not work as efficiently. Using this new method, approximately 9 g of the iodoalcohol **64** could be prepared in each reaction. It was, therefore, possible to prepare large quantities of the iodoalcohol **64** in sufficient purity for further reactions.

## 2.3 Preparation of the Fluoroiodane

### 2.3.1 Preparation of Fluoroiodane using Selectfluor

Since Braddock and co-workers had prepared the bromoiodane **65** from the iodoalcohol **64** and an electrophilic source of bromine, NBS,[5] a similar strategy was investigated for the initial preparation of the fluoroiodane **154** using Selectfluor as the electrophilic source of fluorine. This was chosen as a simple method for the preparation of the fluoroiodane **154** in one step so that its properties could be established.

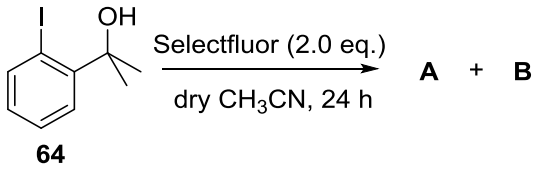
Before attempting to synthesise the fluoroiodane **154**, the bromoiodane **65** was prepared using NBS (Scheme 9). 100% Conversion of the starting material was achieved and the bromoiodane **65** was isolated in a 79% yield after recrystallization from ethyl acetate. The characterisation data was in agreement with the literature.[5] It was important not to let the bromoiodane **65** be exposed to temperatures higher than approximately 30 $^{o}$C since this resulted in decomposition. The bromoiodane **65** was stable at -18 $^{o}$C for a period of several months. It was noted that fresh (< 1 year) *N*-bromosuccinimide was essential for a clean reaction to occur. When an older sample was used the reaction did not work and the iodoalcohol **64** was recovered.




**Scheme 9** *Preparation of the bromoiodane*

The reaction between the iodoalcohol **64** and Selectfluor was attempted in dry acetonitrile at 30 $^{o}$C (entry 1, Table 1). This resulted in the formation of two products **A** ($\delta_F$ = -142.4 ppm) and **B** ($\delta_F$ = -25.0 ppm). When the temperature of the reaction was decreased, **A** became the dominant product (entries 2 to 4) and at -8 $^{o}$C, there was a 96% conversion to product **A** which was purified by extraction into hexane and identified as the fluoroiodane **154** (entry 4).

**Table 1** *Optimisation of the reaction between the iodoalcohol and Selectfluor*




| Entry | Temperature ($^{o}$C) | Conversion to A[a,b] (%) | Conversion to B[a] (%) |
|---|---|---|---|
| 1 | 30 | 50 | 50 |
| 2 | 16 | 80 | 20 |
| 3 | 5 | 91 | 9 |
| 4 | -8 | 96 (34) | 4 |

[a] Determined by $^{19}$F NMR spectroscopy; [b] Isolated yield in parenthesis.

The identity of **A** was confirmed as the fluoroiodane **154** by $^{1}$H, $^{19}$F and $^{13}$C NMR spectroscopy as well as by X-ray crystallography, mass spectrometry and elemental analysis. The $^{1}$H NMR spectrum of **154** was similar to that for the bromoiodane **65** (Figure 2) and a downfield shift of $H_b$ from 6.77 ppm in **64** to 7.47 ppm in **154** was observed. This was consistent with oxidation from I(I) to I(III).[14] In the $^{13}$C NMR spectrum a downfield shift of the carbon directly attached to iodine was observed from 92.2 ppm in **64** to 114.9 ppm in **154**, again, indicating an oxidation from I(I) to I(III).[15] The $^{19}$F NMR spectrum showed a single peak at -142.4 ppm and ASAP mass spectrometry showed a molecular ion peak at 280.9855 corresponding to $MH^+$. Elemental analysis confirmed the empirical formula of the fluoroiodane **154**.

The by-product **B** was thought to be an I(V) fluoride since the corresponding peak in the $^{19}$F NMR spectrum was in a similar place to other I(V) fluorides.[16, 17] The identity of **B**, however, was not investigated further.

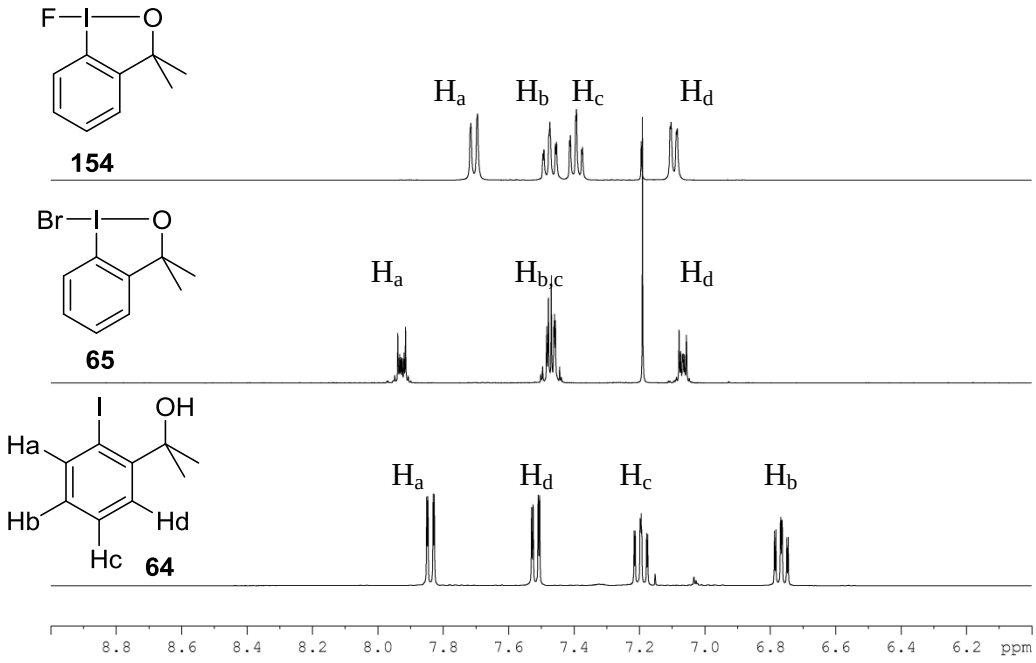



**Figure 2** *Typical [1]H NMR spectra for iodine(I) and iodine(III) species*

The solid state structure of **154** showed that there are two unique molecules in the unit cell (Figure 3). The molecule adopts a distorted T-shaped geometry about the iodine atom as expected for an iodine(III) species.[18-20] The F(1)-I(1)-C(1) bond angle is distorted from 180 $^{o}$ to 166.66(14)/166.71(14) $^{o}$ due to the repulsion and space requirements of the two iodine lone pairs (Table 2).[19] The I(1)-F(1) bond length is 2.048(3)/2.058(3) Å and is of a similar length to other I(III)-F bond lengths, for example, that found in difluoroiodotoluene **54** (Table 2). The O(1)-I(1)-C(1) bond angle of 80.65(18)$^{o}$ shows that there is significant strain in the 5-membered ring. This strain is partially relieved by the adoption of an envelope conformation in which the oxygen atom sits either above or below the plane of the aromatic ring. Short intermolecular interactions were observed between I(1) and O(1A)' and I(1A) and O(1)' of 2.938 Å and 3.039 Å respectively.

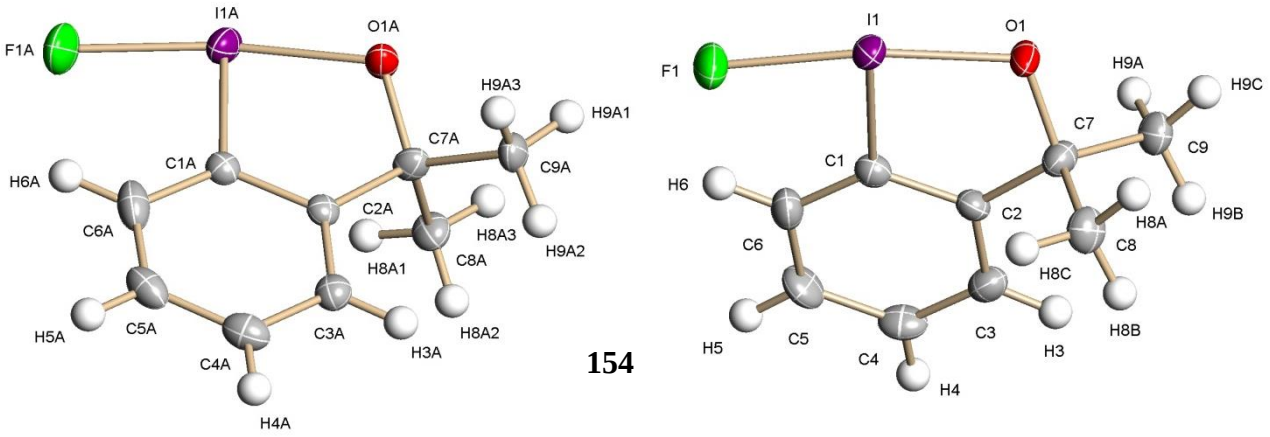


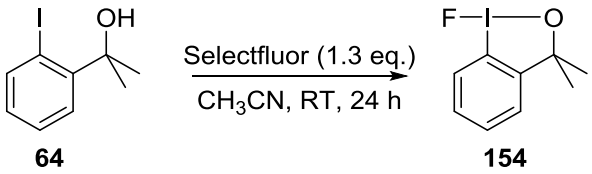

**Figure 3** *Solid-state structures for the fluoroiodane*

**Table 2** *Key bond lengths (Å) and angles (°) for fluoroiodane **154** and difluoroiodotoluene **54***

| | **154**[a] | | **54**[a,b] | |
|---|---|---|---|---|
| I(1)-O(1) | 2.029(3) | 2.028(3) | - | |
| I(1)-F(1) | 2.048(3) | 2.058(3) | 2.025, 1.995 | 2.023, 1.992 |
| I(1)-C(1) | 2.085(5) | 2.092(5) | 2.090 | 2.089 |
| O(1)-C(7) | 1.450(6) | 1.439(6) | - | - |
| O(1)-I(1)-F(1) | 166.66(14) | 166.71(14) | 171.0 | 174.4 |
| O(1)-I(1)-C(1) | 80.65(18) | 80.21(17) | - | - |
| F(1)-I(1)-C(1) | 86.39(17) | 87.20(17) | 87.9 | 86.0 |
| O(1)-I(1)-C(1)-C(6) | 11.2(4) | -13.6(4) | - | - |

[a] There are two unique molecules in the unit cell; [b] See reference [20].

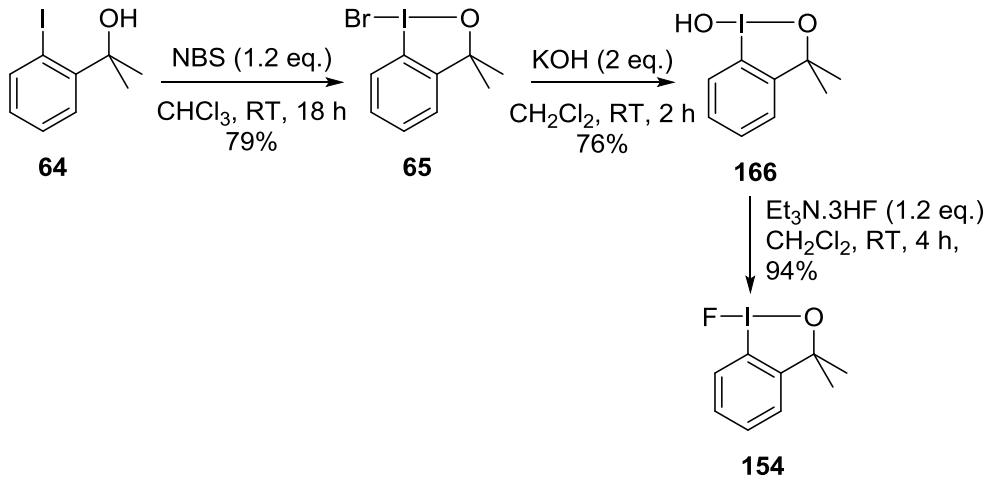
Shortly after this work was completed, this route, along with the crystal structure of the fluoroiodane **154**, were published by Legault *et al* (Scheme 10).[21] Surprisingly however, although their reaction was carried out at room temperature, no by-product (**B**, Table 1) was reported. This may be due to the fact that they used fewer equivalents of Selectfluor (1.3 vs. 2 equivalents). The data reported for the crystal structure of the fluoroiodane **154** was in agreement with our crystallographic data.




**Scheme 10** *Preparation of the fluoroiodane using Legault's method*

### 2.3.2 Preparation of Fluoroiodane using TREAT-HF

The preparation of the fluoroiodane **154** using Selectfluor, in just one step from the iodoalcohol **64**, allowed the properties to be established quickly. The main aim of this project, however, was to prepare the fluoroiodane **154** from a cheap and readily available source of the fluoride anion. Since the bromoiodane **65** had already been prepared it was used as the starting material from which to synthesise the fluoroiodane **154** *via* a nucleophilic pathway. Triethylamine tris(hydrogen fluoride) (TREAT-HF) was chosen as the nucleophilic source of fluoride since it is a cheap source of fluoride and it is a much safer alternative to aqueous HF.[22] Initially, the bromoiodane **65** was reacted with 1.2 equivalents of TREAT-HF in dichloromethane at room temperature for 2 hours. Unfortunately, this resulted in 100% conversion back to the iodoalcohol **64**. An alternative strategy was to convert the bromoiodane **65** to the hydroxyiodane **166** since the hydroxyl group should be protonated by TREAT-HF to form a good leaving group and aid displacement by fluoride. Hydroxyiodane **166** was prepared according to the literature procedure by reaction of the bromoiodane **65** with 2 equivalents of potassium hydroxide at room temperature in 79% yield (Scheme 11). The characterisation data for this known compound was in agreement with the literature.[9]




**Scheme 11** *Preparation of the fluoroiodane using TREAT-HF*

The hydroxyiodane **166** was then reacted with 1.2 equivalents of TREAT HF at room temperature overnight to give the fluoroiodane **154** with 100% conversion (Scheme 11). On a small scale, the reaction was very clean, however, when the reaction was scaled up, the crude product was contaminated by significant impurities. This was partially rectified by reducing the duration of the reaction from 18 to 4 hours. It was also found that the fluoroiodane **154** was particularly sensitive towards $MgSO_4$ and significant decomposition occurred when it was used as the drying agent. For this reason, the crude product was not dried over $MgSO_4$ but instead co-evaporated with toluene to remove any residual water.

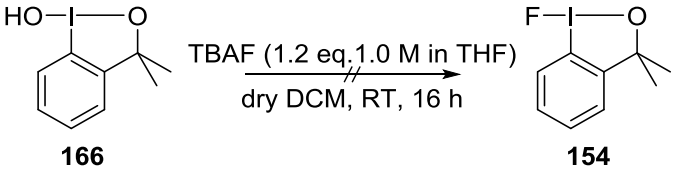
Under the optimised conditions, the hydroxyiodane **166** was reacted with 1.2 equivalents of TREAT-HF for 4 hours at room temperature. When the reaction was complete, the product was extracted into dichloromethane, concentrated on a rotary evaporator and co-evaporated with toluene. The crude product was recrystallized from hexane to give the fluoroiodane **154** as a white crystalline solid in a 94% yield (Scheme 11). The reaction was carried out on a 6 - 10 g scale with no deterioration in yield or purity. The fluoroiodane **154** was normally stored in air, at -18 $^{o}$C, because it became quite sticky over extended periods at room temperature. It was, however, still pure by $^{1}$H NMR spectroscopy. At -18 $^{o}$C, the fluoroiodane **154** was stable for several months.

### 2.3.3 Preparation of Fluoroiodane using TBAF

Having demonstrated that the fluoroiodane **154** could be prepared from a nucleophilic source of fluoride, TREAT HF, a secondary objective was the synthesis of the

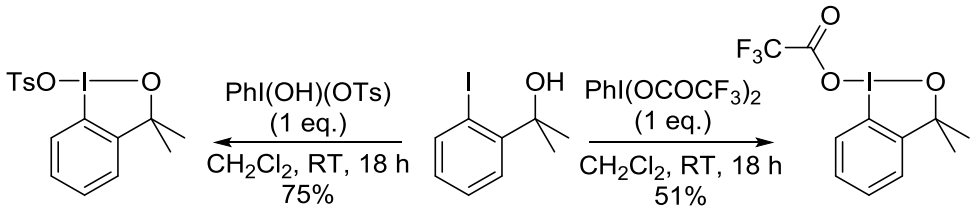
fluoroiodane **154** from other nucleophilic sources of fluoride. TBAF was chosen as a nucleophilic source of fluoride due to its applicability in the synthesis of [$^{18}$F]-labelled radiotracers for positron emission tomography.

The route used to prepare the fluoroiodane **154** using TREAT-HF was not suitable because the hydroxyiodane **166** did not react with TBAF (Scheme 12). An alternative strategy involved the generation of a new iodane species containing a good, non-nucleophilic leaving group which could be displaced by fluoride. Herein, two new hypervalent iodine species, trifluoroacetoxyiodane **167** and tosyliodane **168** were synthesised by the reaction of the iodoalcohol **64** with either PhI(OCOCF$_3$)$_2$ or PhI(OH)(OTs) respectively following Koser's procedure (Scheme 13).[23]




**166** **154**

**Scheme 12** *Attempted reaction between the hydroxyiodane and TBAF*




**168** **64** **167**

**Scheme 13** *Preparation of the trifluoroacetoxyiodane and tosyliodane*

The preparation of trifluoroacetoxyiodane **167** proceeded with 100% conversion. The by-product of the reaction was iodobenzene which was washed out of the crude reaction mixture using cold pentane to give **167** as a pale yellow solid in a 51% yield (Scheme 13). Since **167** was partially soluble in pentane, some of the product was lost at this stage. The trifluoroacetoxyiodane **167** was quite stable and no decomposition was observed at room temperature after several hours. Over longer periods it was stored at -18 $^{o}$C. The structure of the trifluoroacetoxyiodane **167** was confirmed by $^{1}$H, $^{19}$F and $^{13}$C NMR spectroscopy in addition to mass spectrometry, elemental analysis and X-ray crystallography. In the $^{1}$H NMR spectrum, $H_b$ underwent a downfield shift from 6.77 ppm in **64** to 7.51 ppm in **167** as is characteristic on oxidation from iodine(I) to

iodine(III) (Figure 4).[14] In the $^{13}C$ NMR spectrum a downfield shift of the carbon directly attached to iodine was observed from 92.2 ppm in **64** to 115.6 ppm in **167**.[15] The $^{19}F$ NMR spectrum showed a single peak at -74.4 ppm. As is common with iodine(III) compounds, only a peak corresponding to the loss of the trifluoroacetoxy group was observed in the electrospray mass spectrum at 260.9791. The empirical formula of **167** was, however, confirmed by elemental analysis.

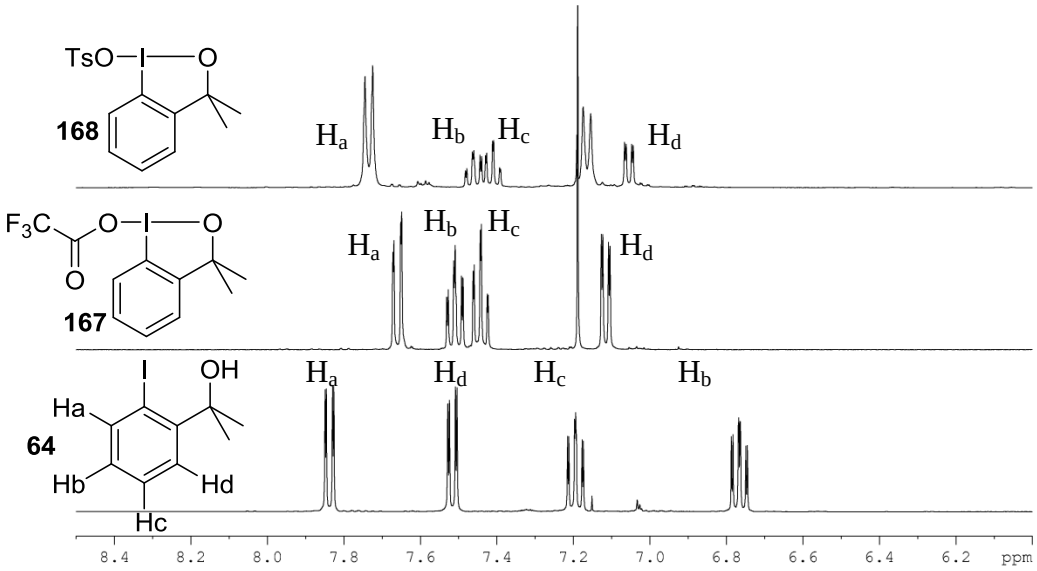
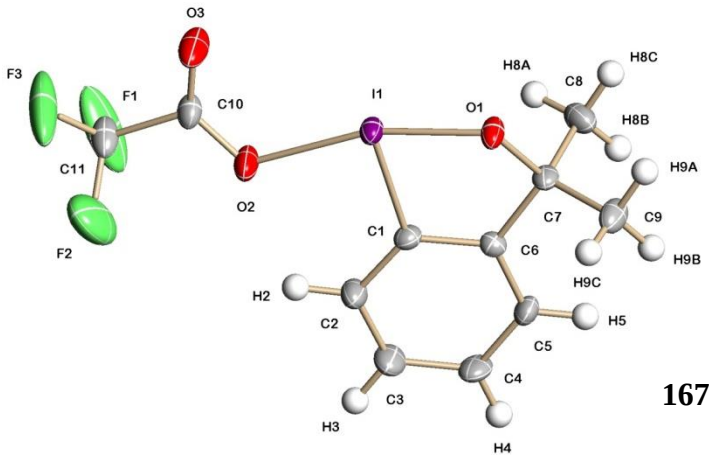



**Figure 4** *Typical $^{1}H$ NMR spectra for iodine(I) and iodine(III) species*

The preparation of the tosyliodane **168** from the iodoalcohol **64** also proceeded with a 100% conversion (Scheme 13). The iodobenzene by-product was removed by washing the crude product with hexane to give **168** as a yellow solid in 75% yield. The tosyliodane **168** was not as stable as the trifluoroacetoxyiodane **167** and so it was stored at -18 $^{o}C$ as soon as possible after purification. It was found that drying the tosyliodane **168** under high vacuum resulted in its decomposition to a complex mixture of products. Again, the identity of **168** was confirmed by the usual spectroscopic methods. In the $^{1}H$ NMR spectrum a downfield shift of $H_b$ from 6.77 ppm in **64** to 7.48 ppm in **168** was observed (Figure 4). In the $^{13}C$ NMR spectrum a downfield shift of the carbon directly attached to iodine was observed from 92.2 ppm to 116.6 ppm. In the electrospray mass spectrum, only a peak corresponding to loss of the tosylate group was observed at 260.9759. The empirical formula of **168** was confirmed by elemental analysis.

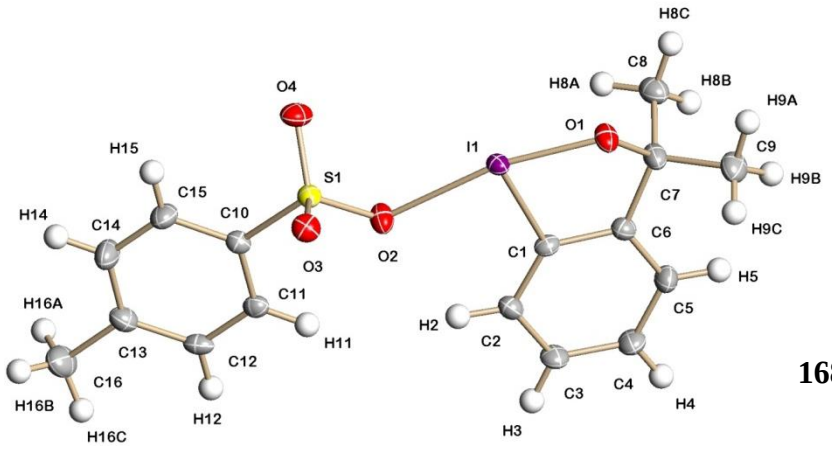
Crystals suitable for X-ray crystallography were obtained for both **167** (Figure 5) and **168** (Figure 6). In both cases there was one unique molecule in the unit cell. The key

bond lengths and angles for **167** and **168** are presented in Table 3 along with the data for the fluoroiodane **154** for comparison. Both structures **167** and **168** adopt the same distorted T-shaped structure around iodine that was observed for the fluoroiodane **154** and is normal for iodine(III) species.[18-20] The I-O bond lengths in **167** are approximately as expected in comparison to other I(III)-O bond lengths. In **167** I(1)-O(1) is 2.011(3) Å and I(1)-O(2) is 2.233(3) Å. The I(III)-O bond length in [bis(trifluoroacetoxy)iodo] benzene is 2.160 Å.[24] In **168**, however, the I(1)-O(1) bond length is slightly shorter at 1.9815(18) Å, whilst the I(1)-O(2) bond length is much longer at 2.3607(19) Å. This increased I(1)-O(2) bond length suggests that the I-OTs bond is quite weak and may explain why **168** is a less stable iodane species. As expected, the 5-membered rings for both **167** and **168** are quite strained, with bond angles in the range of 81-83 $^{o}$; the strain is reduced to an extent by the adoption of an envelope conformation, in which the oxygen atom sits just out of the plane of the aromatic ring. It was also found that short intermolecular interactions were present between I1 and O1' in **167** (3.019(3) Å, Figure 7) and between I1 and O3' in **168** (2.8774(19) Å, Figure 8). This was also observed in the crystal structure of $PhI(OCOCF_3)_2$ where the intermolecular iodine to oxygen distances were approximately 3.00 Å.[24]




**167**

**Figure 5** *Solid-state structure of the trifluoroacetoxyiodane*




**168**

**Figure 6** *Solid-state structure of the tosyliodane*

**Table 3** *Key bond lengths (Å) and angles (°) for* ***167***, ***168*** *and* ***154***

| | **167** | **168** | **154**[a] | |
|---|---|---|---|---|
| I(1)-O(1) | 2.011(3) | 1.9815(18) | 2.029(3) | 2.028(3) |
| I(1)-O(2) | 2.233(3) | 2.3607(19) | 2.048(3) | 2.058(3) |
| I(1)-C(1) | 2.094(4) | 2.100(3) | 2.085(5) | 2.092(5) |
| O(1)-C(7) | 1.442(5) | 1.450(3) | 1.450(6) | 1.439(6) |
| O(1)-I(1)-O(2) | 163.74(13) | 166.03(7) | - | - |
| O(1)-I(1)-F(1) | - | - | 166.66(14) | 166.71(14) |
| O(1)-I(1)-C(1) | 81.08(16) | 82.23(9) | 80.65(18) | 80.21(17) |
| O(2)-I(1)-C(1) | 82.18(15) | 83.80(9) | - | - |
| F(1)-I(1)-C(1) | - | - | 86.39(17) | 87.20(17) |
| O(1)-I(1)-C(1)-C(6) | -12.0(3) | -11.85(18) | 11.2(4) | -13.6(4) |

[a] There are two unique molecules in the unit cell.

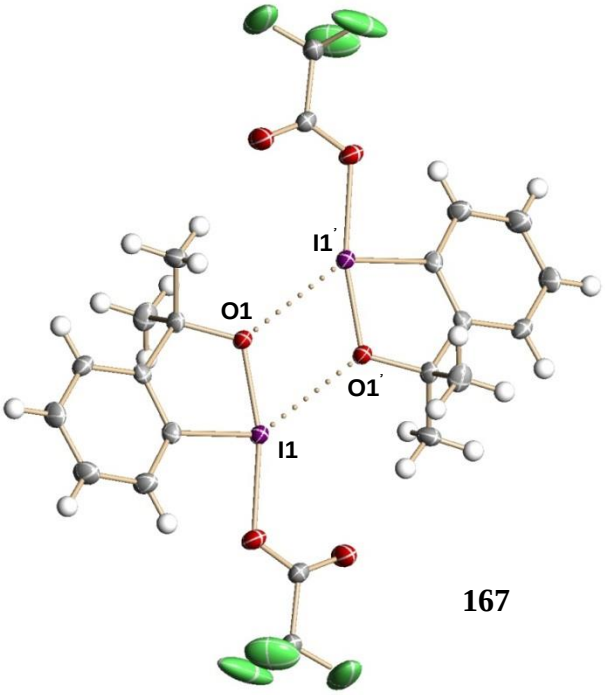



**Figure 7** *Intermolecular interactions in the solid-state structure of the trifluoroacetoxyiodane*

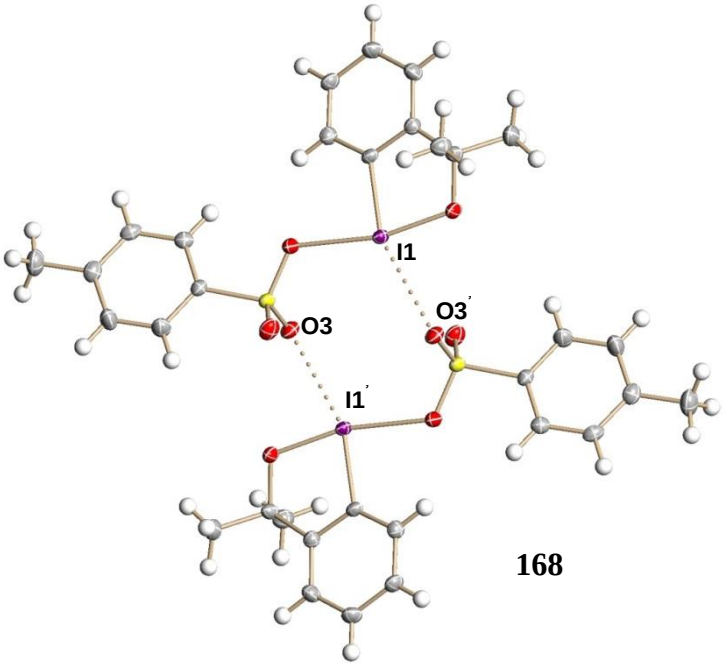
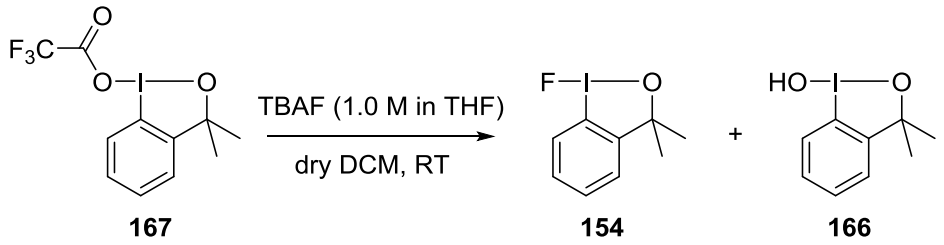



**Figure 8** *Intermolecular interactions in the solid-state structure of the tosyliodane*

The reaction to form the fluoroiodane **154** from the trifluoroacetoxyiodane **167** was first attempted under similar conditions to those used for the reaction between the hydroxyiodane **166** and TREAT-HF. When **167** was reacted at room temperature for 16

h with 1.2 equivalents of TBAF (1.0 M in THF), the fluoroiodane **154** and the hydroxyiodane **166** were both formed in 75% and 25% conversions respectively (entry 1, Table 4). Decreasing the reaction time to just 4 hours gave a similar result (entry 2). Increasing the amount of TBAF to 2 equivalents resulted in 100% conversion to the hydroxyiodane **166** (entry 3). It was thought that the formation of the hydroxyiodane **166** was due to the presence of tetrabutylammonium hydroxide in the TBAF solution. Since tetrabutylammonium hydroxide reacts with aqueous HF to give tetrabutylammonium fluoride[25] and the hydroxyiodane **166** reacts with TREAT-HF to give the fluoroiodane **154** (Scheme 11), 0.5 equivalents of TREAT-HF were added to the reaction mixture (entry 4, Table 4). This resulted in 100% conversion to the fluoroiodane **154** in just 4 hours. A test reaction between the trifluoroacetoxyiodane **167** and TREAT-HF showed that there was no reaction and only the starting materials were recovered. The amount of TREAT-HF added could be reduced to 0.2 equivalents with no detrimental effect on the conversion to the fluoroiodane **154** (entry 8). The reaction time could also be reduced to just 2 hours with the same conversion (entry 9) and 100% conversion to **154** was also obtained when the amount of TBAF was reduced to just 1.0 equivalent (entry 10). The addition of TREAT-HF, however, was still required and when it was left out under these conditions, the hydroxyiodane **166** was observed once again (entry 11).

**Table 4** *Formation of the fluoroiodane from the trifluoroacetoxyiodane*

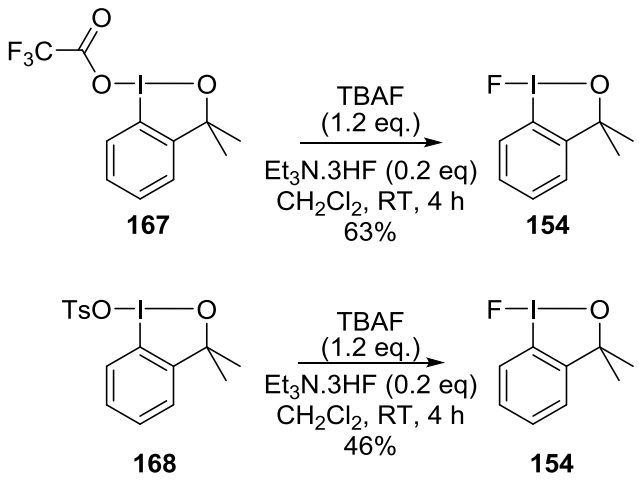



**167** **154** **166**

| Entry | TBAF (eq.) | $Et_3N.3HF$ (eq.) | Time (h) | Conversion to **154**[a] (%) | Conversion to **166**[a] (%) |
|---|---|---|---|---|---|
| 1 | 1.2 | 0 | 16 | 75 | 25 |
| 2 | 1.2 | 0 | 4 | 73 | 27 |
| 3 | 2.0 | 0 | 4 | 0 | 100 |
| 4 | 1.2 | 0.5 | 4 | 100 | 0 |
| 5 | 1.2 | 0.5 | 4 | 100 | 0 |
| 6 | 1.2 | 0.4 | 4 | 100 | 0 |
| 7 | 1.2 | 0.3 | 4 | 100 | 0 |
| 8 | 1.2 | 0.2 | 4 | 100 | 0 |
| 9 | 1.2 | 0.2 | 2 | 100 | 0 |
| 10 | 1.0 | 0.2 | 2 | 100 | 0 |
| 11 | 1.0 | 0 | 2 | 68 | 32 |

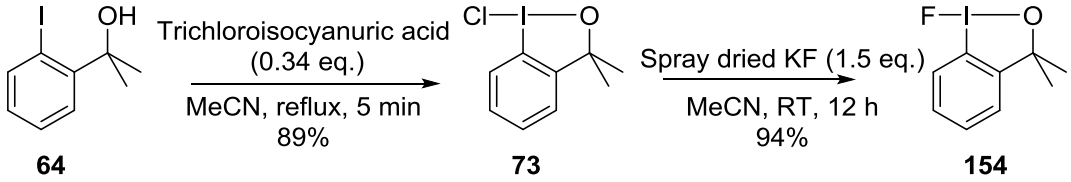
[a] Determined by $^1$H NMR spectroscopy.

With the optimum conditions in hand, the reaction was scaled up, using 1 g of **167** as the starting material (Scheme 14). After recrystallization from hexane, the fluoroiodane **154** was isolated in 63% yield. The optimum reaction conditions were also used to convert the tosyliodane **168** to the fluoroiodane **154** (Scheme 14). This reaction proceeded with 100% conversion and the fluoroiodane **154** was isolated in 46% yield after recrystallization from hexane.




**Scheme 14** *Preparation of the fluoroiodane using TBAF*

Whilst this work was being carried out, another route to the fluoroiodane **154** was reported by Togni (Scheme 15).[26] This route contained one less step than the TREAT-HF route and had a comparable yield. The fluoride source used, KF, can also be applied to PET chemistry.

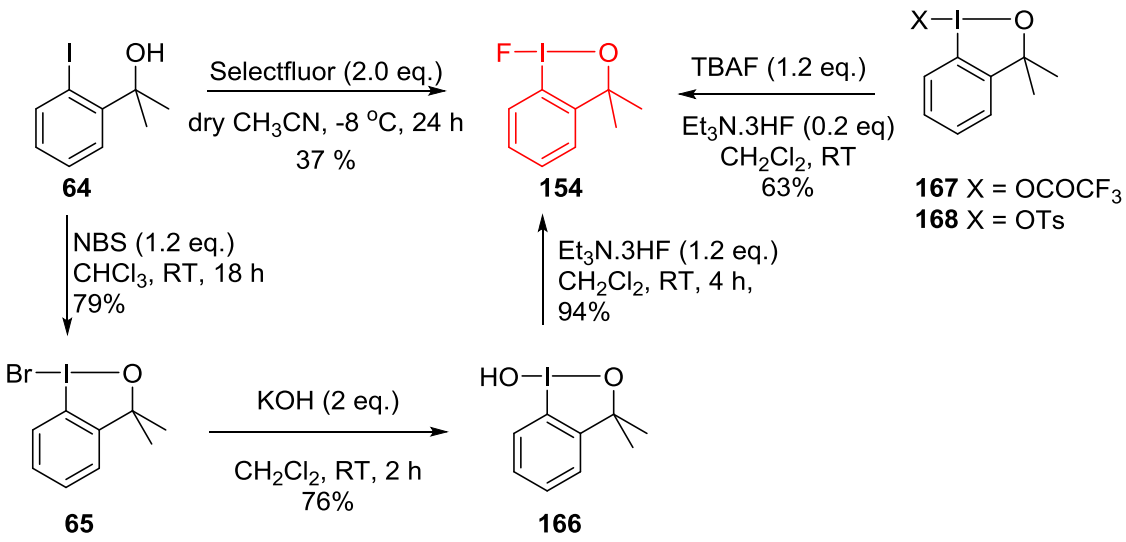



**Scheme 15** *Togni's route to the fluoroiodane*

### 2.3.4 Summary of the Preparation of the Fluoroiodane

In this section, the fluoroiodane **154** was prepared using three different routes which are summarised in Scheme 16.[6] In the first instance the fluoroiodane **154** was prepared in one step from the iodoalcohol **64** using Selectfluor. This route was not viable for the large scale synthesis of the fluoroiodane **154** due to the high cost of Selectfluor. It did, however, allow the fluoroiodane **154** to be prepared quickly so that its properties could be established. The fluoroiodane **154** was also prepared using two different, cheap and readily available sources of the fluoride anion, TREAT-HF and TBAF. The synthesis using TREAT-HF was suitable for the preparation of the fluoroiodane on a 6 – 10 g scale. The synthesis using TBAF was more suited to the small scale preparation of the fluoroiodane **154**, as requirement to remove the tetrabutylammonium salts at the end of the reaction made the work-up procedure more complicated. This route could

potentially be used for the preparation of an $^{18}F$ analogue of the fluoroiodane **154** for use in the synthesis of radiotracers for positron emission tomography.

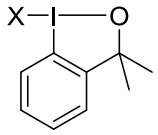



**Scheme 16** *Summary of the preparation of the fluoroiodane*

### 2.3.5 Safety Profile of the Fluoroiodane and other Hypervalent Iodine Compounds

A report published in 2013 showed that Togni's trifluoromethyliodoxolone **51** had explosive properties. It was also suggested that the trifluoromethyliodane **53** was a dangerous reagent which decomposed exothermically at a relatively low temperature (135 °C). In order to determine the safety profile of the fluoroiodane **154** and the other iodane species prepared in this chapter, the exothermic decomposition energy was measured by differential scanning calorimetry (DSC) and the results are shown in Table 5. These results showed that the fluoroiodane **154** decomposed at a higher temperature than either of Togni's reagents **51** or **53** and released considerably less energy when it decomposed (entry 1 vs. entries 6 and 7). From these results it was established that the fluoroiodane **154** is safe to use below temperatures of 100 °C. The other iodane species **65** and **166-168** all decomposed at higher temperatures than either of Togni's reagents **51** or **53**. Only the hydroxyiodoxolone **166** gave out a significant amount of energy on decomposition (506.4 J $g^{-1}$) and for this reason this reagent was never used at temperatures above 40 °C.

**Table 5** *DSC results for a series of hypervalent iodine reagents*



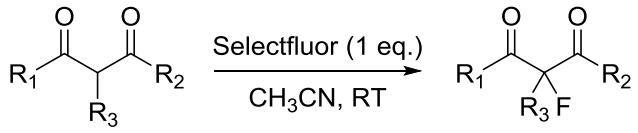
| Entry[a] | X | Onset ($^{o}$C) | Energy (J/g) |
|---|---|---|---|
| 1 | F (**154**) | 197.5 | 263.6 |
| 2 | Br (**65**) | 153.0 | 177.9 |
| 3 | OH (**166**) | 179.3 | 506.4 |
| 4 | $OCOCF_3$ (**167**) | 188.6 | 216.2 |
| 5 | OTs (**168**) | 177.5 | 144.6 |
| 6[b] | **51** | 149 | 502 |
| 7[b] | **53** | 135 | 790 |

[a] DSC calculations were carried out in an aluminium pan with a pierced lid and the heating rate was 10 $^{o}$C/min; [b] Result taken from reference [27]

### 2.4 Fluorination of 1,3-Dicarbonyl Compounds using the Fluoroiodane

Fluorinated 1,3-dicarbonyl compounds are useful building blocks in the synthesis of pharmaceuticals, such as the antifungal agent, Voriconazole.[28] There are a large number of examples in the literature of the fluorination of 1,3-dicarbonyl compounds using different electrophilic fluorinating reagents. For example, Banks and co-workers fluorinated a range of 1,3-dicarbonyl compounds using Selectfluor in generally good yields at room temperature although many of the reaction times were quite long (Table 6).[29] The disadvantage of Selectfluor as an electrophilic fluorinating reagent is that it is very expensive since it must be prepared in the first instance from elemental fluorine.

**Table 6** *Fluorination of dicarbonyl compounds using Selectfluor*



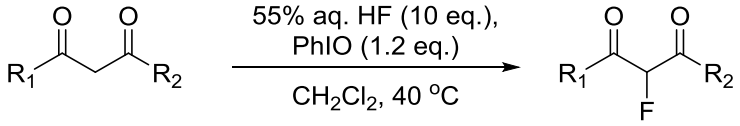

**169** **170**

| **23** | **$R_1$** | **$R_2$** | **$R_3$** | **Time (h)** | **Conversion to 170[a] (%)** |
|---|---|---|---|---|---|
| a | -$(CH_2)_3$ | | Me | 19 | - (84) |
| b | Ph | Ph | H | 5 | 100 (84) |
| c | Ph | OEt | H | 54 | 88 (22) |
| d | Me | OEt | H | 120 | 57 |
| e | OEt | OEt | Ph | 20 | 96 (93) |
| f | Ph | $NMe_2$ | H | 3 | 96 (87) |
| g | Ph | (±)-N(Me)CH(Ph)Me | H | 67 | 87 (80) |

[a] Isolated yields in parenthesis.

The fluorination of 1,3-dicarbonyl compounds has also been achieved using difluoroiodoarenes. Kitamura and co-workers showed that the fluorination of 1,3-dicarbonyl compounds could be achieved using difluoroiodobenzene, which was prepared *in situ* from iodosobenzene and aqueous HF (Table 7).[30] Moderate to good yields of the fluorinated products were obtained however the requirement for the use of a large excess of aqueous HF is not ideal from a safety perspective.

**Table 7** *Fluorination of dicarbonyl compounds using iodosobenzene and aqueous HF*




**137** **138**

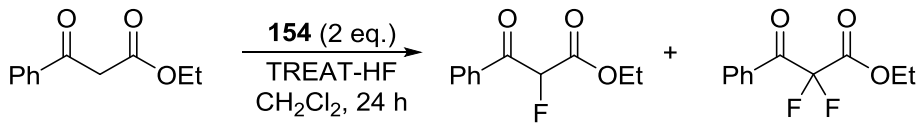
| **25** | **$R_1$** | **$R_2$** | **Time (h)** | **Yield of 138 (%)** |
|---|---|---|---|---|
| a | Bu | OEt | 1 | 73 |
| b | Pr | OEt | 1 | 93 |
| c | $C_6F_4H$ | OEt | 24 | 70 |
| d | *p*-$NO_2C_6H_4$ | OEt | 24 | 58 |
| e | Ph | Me | 24 | 47 |
| f | Ph | Ph | 36 | 90 |
| g | Et | Et | 2 | 34 |
| h | Me | $NEt_2$ | 2 | 52 |
| i | Me | $NMe_2$ | 2 | 25 |

### 2.4.1 Optimisation with Ethyl 3-oxo-3-phenylpropanoate

Since there had been a significant amount of investigation into the fluorination of 1,3-dicarbonyl compounds, these were chosen as the first class of substrates with which to test the reactivity of the fluoroiodane **154** as an electrophilic fluorinating reagent. The conversion in these reactions was calculated from the amount of fluorinated products **172** and **173** observed relative to the amount of starting material **171** remaining. When 2 equivalents of the fluoroiodane **154** were reacted with the model substrate, ethyl 3-oxo-3-phenylpropanoate **171** at 60 $^oC$ for 24 hours only an 8% conversion to the monofluorinated product **172** was obtained (entry 1, Table 8). The addition 0.9 equivalents of TREAT-HF, increased the conversion to the monofluorinated product **172** to 30% (entry 2). Increasing the equivalents of TREAT-HF from 0.9 to 2.7 increased the conversion to the monofluorinated product **172** to 65% but the reaction was less selective and more of the difluorinated product was formed (entry 4). No reaction was observed in the absence of the fluoroiodane **154** (entry 5) demonstrating that it is essential for the reaction to proceed. When the time of the reaction was increased from 24 to 48 hours, the overall conversion increased, but the reaction was

less selective (entry 6). When the temperature was reduced to 40 $^{o}$C, the overall conversion decreased and the reaction was more selective for the monofluorinated product **172** (entry 7). Increasing the temperature of the reaction to 80 $^{o}$C resulted in an increased conversion to the difluorinated product **173** (entry 8).

**Table 8** *Initial optimisation of the reaction between ethyl 3-oxo-3-phenylpropanoate and the fluoroiodane*




**171** **172** **173**

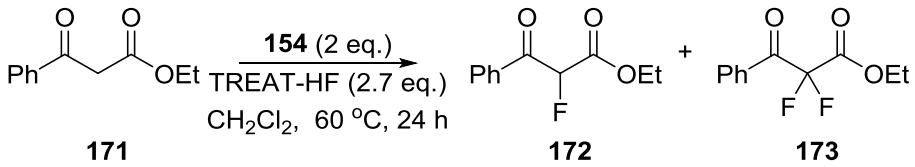
| Entry | Temperature ($^{o}$C) | TREAT-HF (eq.) | Conversion to 172[a] (%) | Conversion to 173[a] (%) |
|---|---|---|---|---|
| 1 | 60 | 0 | 8 | 0 |
| 2 | 60 | 0.9 | 30 | 4 |
| 3 | 60 | 1.8 | 48 | 7 |
| 4 | 60 | 2.7 | 65 | 19 |
| 5[b] | 60 | 2.7 | 0 | 0 |
| 6[c] | 60 | 2.7 | 54 | 28 |
| 7 | 40 | 2.7 | 54 | 4 |
| 8 | 80 | 2.7 | 49 | 36 |

[a] Determined by $^{1}$H and $^{19}$F NMR spectroscopy; [b] Control reaction without fluoroiodane **154**; [c] Reaction time was extended to 48 h.

The concentration of the reaction mixture proved to be an important factor. Due to the small scale of the reactions, it was not easy to control the concentration of the reaction using a standard round-bottomed flask and condenser arrangement. It was often found that all of the solvent had evaporated away from the reaction mixture and, therefore, the concentrations of reagents were difficult to calculate. For this reason all of the reactions were carried out in closed Schlenk flasks. When the concentration of the starting material was 0.12 M, only a 13% conversion to the monofluorinated product **172** was observed (entry 1, Table 9). On doubling the concentration of the substrate to 0.24 M, the conversion to the monofluorinated product **172** increased substantially to 65% (entry 2). Doubling the concentration again brought the reaction almost to completion, with a

67% conversion to the monofluorinated product **172** and a 25% conversion to the difluorinated product **173** (entry 3). When the fluoroiodane **4** was reacted with ethyl 3-oxo-3-phenylpropanoate **171**, the iodoalcohol **64** was formed as a by-product. The advantage of this was that it could be recovered and recycled to form more of the fluoroiodane **154**. The disadvantage was that the iodoalcohol **64** was difficult to separate from the products of the reaction. The crude reaction mixture contained unreacted fluoroiodane **154**, iodoalcohol **64**, both monofluorinated and difluorinated products **172** and **173** as well as any unreacted starting material **171**. Until this point, the purification of the crude reaction mixture had not been attempted since all of the components had very similar $R_f$ values. Having found conditions in which the reaction had gone almost to completion (entry 3, Table 9), however, it became easier to separate the individual components of the crude product. Purification of the crude product from entry 3 (Table 9) by column chromatography gave the monofluorinated product **172** in a 49% yield and the difluorinated product **173** in a 13% yield. The unreacted fluoroiodane **154** and $Et_3N.3HF$ were not recovered after column chromatography. The iodoalcohol **64** was collected (40% from fluoroiodane **154**) and recycled to reform the fluoroiodane **154**.

**Table 9** *The effect of concentration in the fluorination of ethyl 3-oxo-3-phenylpropanoate*




| Entry | Concentration of 171 (M) | Conversion to 172[a, b] (%) | Conversion to 173[a,b] (%) |
|---|---|---|---|
| 1 | 0.12 | 13 | 0 |
| 2 | 0.24 | 65 | 19 |
| 3 | 0.48 | 67 (49) | 25 (13) |

[a] Determined by $^1H$ and $^{19}F$ NMR spectroscopy; [b] Isolated yields in parenthesis.

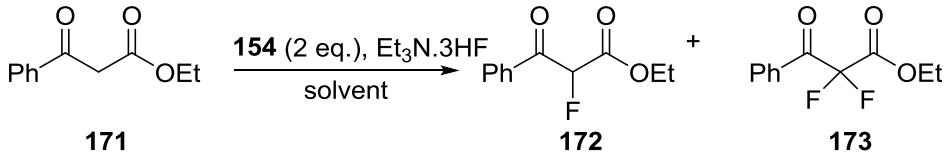
Having established the optimum concentration for the fluorination of ethyl 3-oxo-3-phenylpropanoate **171**, the reaction conditions were then examined in more detail (Table 10). It was found that on decreasing the temperature from 60 $^oC$ (entry 1) to 40

$^{o}$C (entry 2), the reaction was more selective for the monofluorinated product **172** which was isolated in a 63% yield. As was noted at the lower concentration, when the reaction time was extended to 48 hours (entry 3), the conversion to the difluorinated product **173** increased slightly to 11% whilst maintaining a high conversion to the monofluorinated product **172** of 83%. On decreasing the reaction time to 16 hours (entry 4), a comparable result was obtained to the 24 hour reaction. Further decreasing the time to 10 hours (entry 5) lowered the conversion to the monofluorinated product **172** to 78%. When the amount of TREAT-HF was decreased from 2.7 to 1.0 equivalent, the overall conversion to fluorinated products **172** and **173** decreased (entry 6, Table 10). This trend continued as the amount of TREAT-HF was decreased further (entries 7 and 8).

A solvent screen showed that both toluene and THF (entries 9 and 10, Table 10), gave essentially the same results as those achieved in dichloromethane (entry 1). In acetonitrile (entry 11), however, more of the competing difluorinated product **173** was formed. This reaction was, therefore, attempted using fewer equivalents of TREAT-HF. At 40 $^{o}$C with just 0.2 equivalents of TREAT-HF (entry 12), a 68% conversion to the monofluorinated product **172** and a 6% conversion to the difluorinated product **173** was achieved. The same reaction over 48 hours (entry 13) gave an 82% conversion to the monofluorinated product **172** which was isolated in a 50% yield. The difluorinated product **173** was also observed with an 18% conversion and was isolated in a 9% yield.

The fluorination of ethyl 3-oxo-3-phenylpropanoate **171** was also attempted without using anhydrous or inert conditions (entry 14, Table 10). When the reaction was carried out in air using bench solvents, only very slightly lower conversions and isolated yields were achieved. The stability of the fluoroiodane **154** was tested by leaving it open to the air at room temperature for 7 weeks. After this time, a standard fluorination reaction at 40 $^{o}$C for 24 hours using 2.7 equivalents of TREAT-HF was carried out (entry 15). This gave an almost identical result to the previous reaction using fluoroiodane **154** which had been stored in the freezer (entry 2).

**Table 10** *Further optimisation in the fluorination of ethyl 3-oxo-3-phenylpropanoate*




**171** **172** **173**

| Entry | Temp (°C) | Time (h) | TREAT-HF (eq.) | Solvent | Conversion to **172**[a,b] (%) | Conversion to **173**[a,b] (%) |
|---|---|---|---|---|---|---|
| 1 | 60 | 24 | 2.7 | $CH_2Cl_2$ | 67 (49) | 25 (13) |
| 2 | 40 | 24 | 2.7 | $CH_2Cl_2$ | 89 (63) | 6 |
| 3 | 40 | 48 | 2.7 | $CH_2Cl_2$ | 83 | 11 |
| 4 | 40 | 16 | 2.7 | $CH_2Cl_2$ | 90 | 3 |
| 5 | 40 | 10 | 2.7 | $CH_2Cl_2$ | 78 | 1 |
| 6 | 40 | 24 | 1.0 | $CH_2Cl_2$ | 80 | 6 |
| 7 | 40 | 24 | 0.2 | $CH_2Cl_2$ | 53 | 4 |
| 8 | 40 | 24 | 0 | $CH_2Cl_2$ | 20 (10) | 0 |
| 9 | 60 | 24 | 2.7 | Toluene | 67 | 28 |
| 10 | 60 | 24 | 2.7 | THF | 70 | 22 |
| 11 | 60 | 24 | 2.7 | $CH_3CN$ | 51 | 43 |
| 12 | 40 | 24 | 0.2 | $CH_3CN$ | 68 | 6 |
| 13 | 40 | 48 | 0.2 | $CH_3CN$ | 82 (50) | 18 (9) |
| 14[c] | 40 | 24 | 2.7 | $CH_2Cl_2$ | 86 (53) | 3 |
| 15[d] | 40 | 24 | 2.7 | $CH_2Cl_2$ | 85 | 3 |

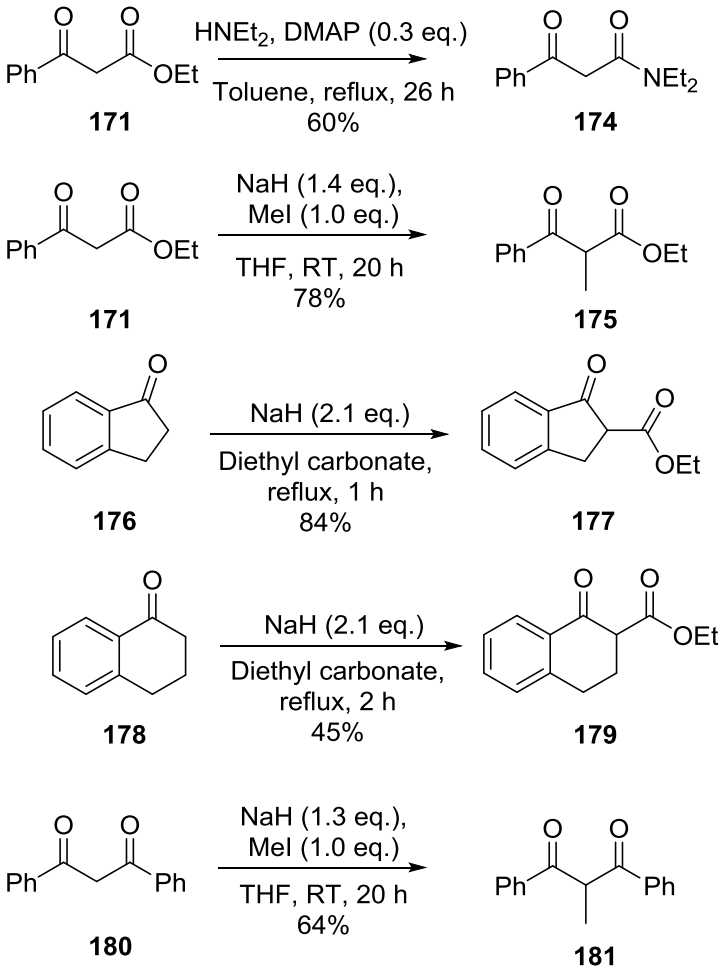
[a] Determined by $^{1}H$ and $^{19}F$ NMR spectroscopy; [b] Isolated yields in parenthesis; [c] Reaction under air using bench solvents; [d] Fluoroiodane **154** stored at room temperature for 7 weeks before use.

Following these optimisation reactions it was decided that the optimum conditions which would be used for further reactions would be 40 °C for 24 hours using 2.7 equivalents of TREAT-HF (entry 2, Table 10). This was because under these conditions a fair compromise between good conversion, high selectivity for the monofluorinated product **172** and a reasonable reaction time was obtainable.

### 2.4.2 Reaction of the Fluoroiodane with other 1,3-Dicarbonyl Compounds

Having established the optimum conditions for the fluorination of ethyl 3-oxo-3-phenylpropanoate **171**, the scope of the reaction was tested with a range of dicarbonyl compounds including other 1,3-ketoesters, 1,3-diketones and 1,3-ketoamides. The fluorination of 2-substituted 1,3-dicarbonyl compounds was also investigated.

Some of the 1,3-dicarbonyl compounds were commercially available, however, *N*,*N*-diethyl-3-oxo-3-phenylpropanamide **174**, ethyl 2-methyl-3-oxo-3-phenylpropanoate **175**, ethyl 1-indanone-2-carboxylate **177**, ethyl-1-tetralone-2-carboxylate **179** and 2-methyl-1,3-diphenylpropane-1,3-dione **181** were prepared according to literature methods (Scheme 17).[31-33]




**Scheme 17** *Preparation of the starting materials for the fluorination reactions*

The relative reactivity of 1,3-dicarbonyl compounds in electrophilic fluorination reactions has been attributed to their enol content.[29, 34] When ethyl 3-(4-methoxyphenyl)-3-oxopropanoate **182** was reacted under the optimum reaction

conditions from Table 10 (entry 2), a 95% conversion to the monofluorinated product was observed and it was isolated in a 67% yield (entry 2, Table 11). The ketoamide *N*,*N*-diethyl-3-oxo-3-phenylpropanamide **174** under the same conditions gave the monofluorinated product in an 88% isolated yield (entry 3).

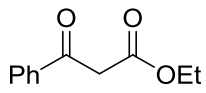
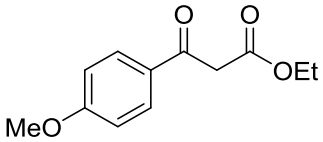
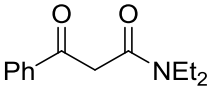
The 1,3-diketone, 1,3-diphenylpropane-1,3-dione **180**, has a much higher enol content than the previous substrates (100% enol in $CDCl_3$ by $^1H$ NMR spectroscopy) and was, therefore, expected to be considerably more reactive. Under the optimum reaction conditions, a mixture of monofluorinated (30%) and difluorinated (55%) products was obtained (entry 4). Extending the reaction time to 48 hours gave a 63% conversion to the difluorinated product, however, there was still some monofluorinated product (25%) and starting material (12%) remaining. The temperature of the reaction was increased to 60 $^oC$ and, again, the conversion to the difluorinated product increased although there was still a small amount of the monofluorinated product and starting material remaining. Finally, the amount of fluoroiodane **154** was increased to 3 equivalents and after 24 hours at 60 $^oC$ a 100% conversion to the difluorinated product was observed (entry 4). 2,2-Difluoro-1,3-diphenylpropane-1,3-dione was isolated in a 71% yield. Another diketone, 1-phenylbutane-1,3-dione **183**, was also reacted under the same conditions (entry 5) and the difluorinated product was isolated in a 45% yield.

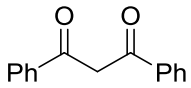
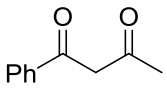
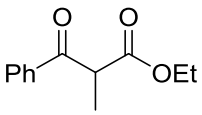
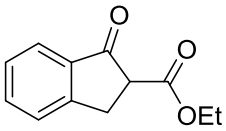
The monosubstituted 1,3-ketoester, ethyl 2-methyl-3-oxo-3-phenylpropanoate **175** had a very low enol content (100% ketone in $CDCl_3$ by $^1H$ NMR spectroscopy) and so was not expected to be very reactive. For this reason, the reaction temperature was increased to 60 $^oC$. When the reaction was carried out in dichloromethane, only a 5% conversion to the fluorinated product was observed after 24 hours. This had increased to 28% after 7 days but did not increase any further than this with additional time. In order to increase the conversion, the reaction was carried out without solvent. A reaction monitored by $^1H$ NMR spectroscopy showed a 30% conversion to the fluorinated product after 24 hours which had increased to 58% after 72 hours. The reaction was repeated without solvent at 60 $^oC$ for 7 days resulting in a 62% conversion to the fluorinated product. Ethyl 2-fluoro-2-methyl-3-oxo-3-phenylpropanoate was isolated in a 55% yield (entry 6). The reaction was repeated at 80 $^oC$ without solvent for 48 hours. Although this resulted in a 100% conversion, the isolated yield of the fluorinated product was lower at 37%. When the same reaction was carried out over 24 hours, a

100% conversion was also observed but the isolated yield of the fluorinated product was lower at 40% (entry 6).

The fluorination of ethyl 1-indanone-2-carboxylate **177** was expected to be more efficient than that of ethyl 2-methyl-3-oxo-3-phenylpropanoate **175** due to its higher enol content (17% enol in $CDCl_3$ by $^1H$ NMR spectroscopy). After 72 hours at 60 $^oC$ without solvent, 100% conversion of the starting material was observed. Disappointingly however, the product was only isolated in a 27% yield. It was thought that the product may have been forming and then decomposing over the long reaction time at high concentration. When the reaction was carried out over 48 hours, 100% conversion of the starting material was also achieved and, in this case, the product was isolated in a 55% yield (entry 7, Table 11).

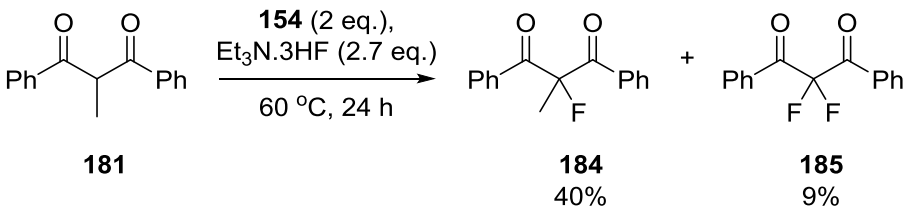
**Table 11** *Fluorination of other dicarbonyl compounds using the fluoroiodane* [a]

| Entry | Substrate | Temp ($^oC$) | Time (h) | Conversion to monofluoro product[b,c] (%) | Conversion to difluoro product[b,c] (%) |
|---|---|---|---|---|---|
| 1 |  **171** | 40 | 24 | 89 (63) | 6 |
| 2 |  **182** | 40 | 24 | 95 (67) | 5 |
| 3 |  **174** | 40 | 24 | 96 (88) | 4 |

| | | | | | |
|---|---|---|---|---|---|
| 4 |  **180** | 40 | 24 | 30 | 55 |
| | | 40 | 48 | 25 | 63 |
| | | 60 | 24 | 11 | 76 |
| | | 60[d] | 24 | 0 | 100 (71) |
| 5 |  **183** | 60[d] | 24 | 0 | 100 (45) |
| 6 |  **175** | 60 | 168 | 28 | NA |
| | | 60[e] | 168 | 62 (55) | NA |
| | | 80[e] | 48 | 100 (37) | NA |
| | | 80[e] | 24 | 100 (40) | NA |
| 7 |  **177** | 60[e] | 72 | 100 (27) | NA |
| | | 60[e] | 48 | 100 (55) | NA |

[a] Reaction conditions: substrate (0.72 mmol), fluoroiodane **154** (1.44 mmol), $Et_3N.3HF$ (1.94 mmol) and dry DCM (1.2 mL); [b] Determined by $^1H$ and $^{19}F$ NMR spectroscopy; [c] Isolated yields in parenthesis; [d] Fluoroiodane **154** (3 eq.); [e] No solvent.

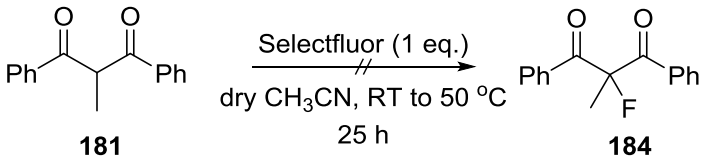
The substituted diketone, 2-methyl-1,3-diphenylpropane-1,3-dione **181** was reacted under similar conditions to the other substituted dicarbonyl compounds. After 24 hours at 60 $^oC$ without solvent 100% conversion of the starting material was observed (Scheme 18). Purification by column chromatography gave the desired fluorinated product **184** (40%) as a mixture with the difluorinated diketone **185** (9%) which suggested that a demethylation reaction had occurred. The reaction was repeated under milder reaction conditions (40 $^oC$ in dichloromethane for 24 hours) but this gave only a 9% conversion to the desired fluorinated product **184** together with a trace of **185**.




**181** **184** 40% **185** 9%

**Scheme 18** *Fluorination of 2-methyl-1,3-diphenylpropane-1,3-dione*

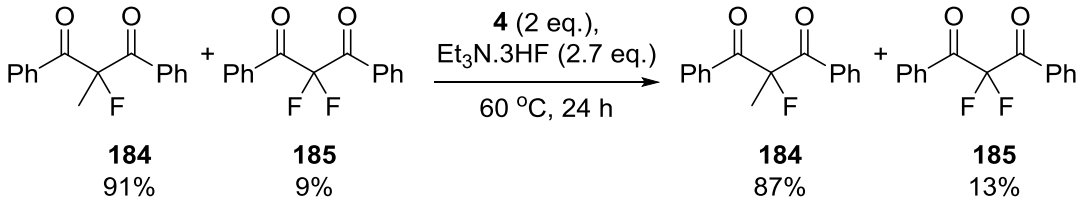
In order to see if this was a general problem in the fluorination of this substrate, it was reacted with Selectfluor (Scheme 19). After 20 hours at room temperature, however, no reaction was observed and this did not change after a further 5 hours at 50 $^{o}$C.




**181** **184**

**Scheme 19** *Test reaction using Selectfluor*

Finally, the mixture of **184** and **185** was reacted again with the fluoroiodane **154** to see if the ratio of the two components changed (Scheme 20) in order to determine whether the difluorinated product **185** was formed from **184** or from the starting material **181**. Although the ratio did change slightly in this experiment, the variation was only very small and was likely to be within experimental error. It is, therefore, still unclear how the difluorinated product **185** was formed.




**184** 91% **185** 9% **184** 87% **185** 13%

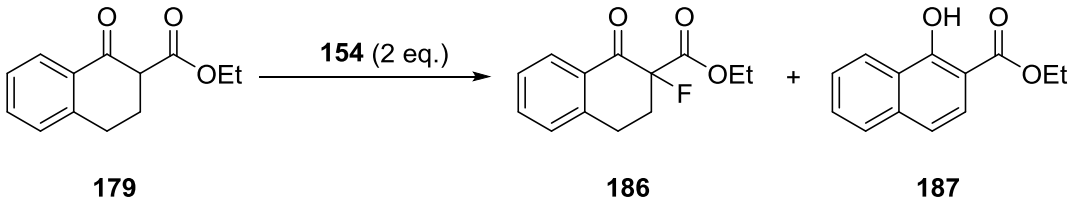
**Scheme 20** *Test reaction in the fluorination of 2-methyl-1,3-diphenylpropane-1,3-dione*

### 2.4.3 Reactivity of the Fluoroiodane as an Oxidising Agent

The fluorination of the tetralone ester **179** (entry 1, Table 12) was attempted under similar conditions to those used for the indanone ester **177** (entry 7, Table 11). After 48 hours at 60 $^{o}$C without solvent, all of the starting material had been consumed and a peak was observed in the $^{19}$F NMR spectrum of the crude product at -164 ppm corresponding to the fluorinated product **186**. The $^{1}$H NMR spectrum of the crude product, however, showed a complicated mixture of products and, therefore, purification was not attempted. The reaction was repeated for 24 hours at a lower temperature in the hope that this would result in a cleaner crude reaction mixture (entry 2). In this case, both starting material **179** and fluorinated product **186** were observed in the $^{1}$H and $^{19}$F NMR spectra of the crude product. Since the $^{1}$H NMR spectra of the starting material **179** and fluorinated product **186** are quite complicated and also

because additional, unidentified products were present, it was not possible to calculate the conversion for the reaction. Purification by column chromatography gave the fluorinated product **186** in just a 4% yield. A further product was isolated in a 45% yield which was identified by $^{1}H$ and $^{13}C$ NMR spectroscopy and ASAP mass spectrometry as the oxidised by-product **187**. The reaction between the tetralone ester **179** and the fluoroiodane **154** was also repeated under more dilute conditions at 40 $^{o}C$ for 24 hours (entry 3). In this case the starting material **179** was recovered in a 57% yield by column chromatography along with the oxidised product **187** in a 26% yield and a trace of the fluorinated product **186**.

**Table 12** *Fluorination of tetralone ester*

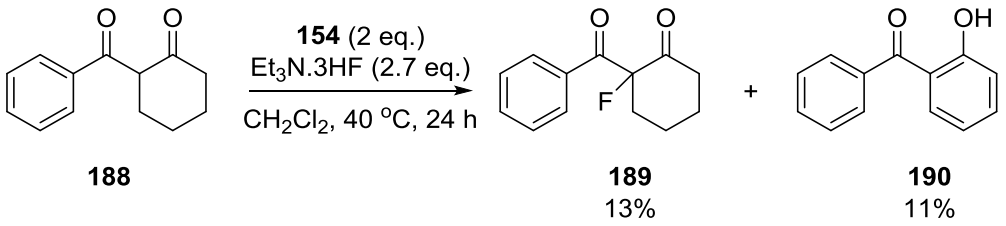



**179** **186** **187**

| Entry | $Et_3N.3HF$ (eq.) | Solvent | Temp ($^{o}C$) | Time (h) | Yield of 186[a] (%) | Yield of 187[a] (%) |
|---|---|---|---|---|---|---|
| 1 | 2.7 | - | 60 | 48 | - | - |
| 2 | 2.7 | - | 40 | 24 | 4 | 45 |
| 3 | 2.7 | $CH_2Cl_2$ | 40 | 24 | 8 | 26 |

[a] Isolated yield.

When 2-benzyloxycyclohexanone **188** was reacted with the fluoroiodane **154** in $CH_2Cl_2$ for 24 hours at 40 $^{o}C$, 100% conversion of the starting material **188** was observed (Scheme 21). The $^{1}H$ NMR spectrum and TLC of the crude reaction mixture were very complicated and only the fluorinated product **189** and the oxidised product **190** were isolated by column chromatography in 13% and 11% yields respectively.

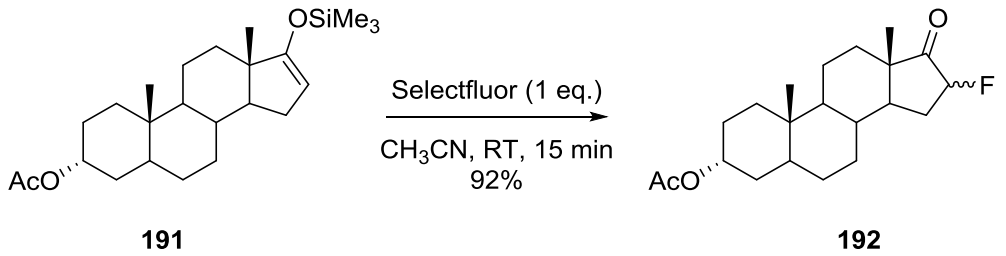



**Scheme 21** *Fluorination of 2-Benzoylcyclohexanone*

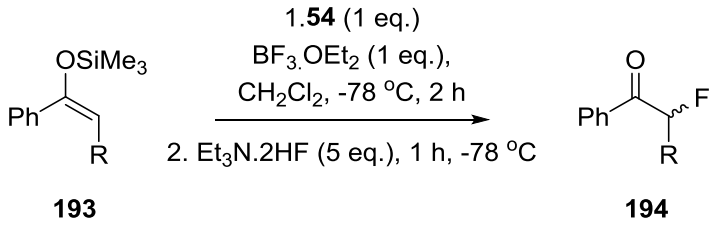
## 2.5 Reactivity of the Fluoroiodane with Other Substrates

### 2.5.1 Reactivity of the Fluoroiodane with Silyl Enol Ethers

α-Fluoro-carbonyl moieties are important synthons in the preparation of biologically active compounds. They can be prepared in a variety of ways[35] including the reaction of silyl enol ethers with either Selectfluor (Scheme 22)[36] or difluoroiodotoluene **54** (Scheme 23).[37]



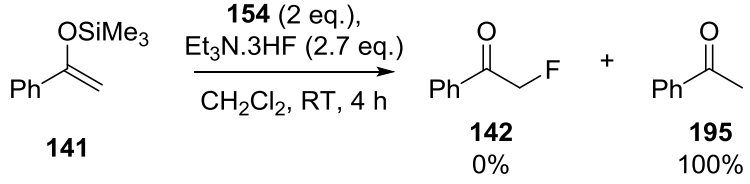

**Scheme 22** *Fluorination of a silyl enol ether using Selectfluor*




**Scheme 23** *Fluorination of a silyl enol ether using difluoroiodotoluene*

We were interested to see if α-fluoro ketones could be prepared using the fluoroiodane **154**. The simple silyl enol ether **141** was chosen as the model substrate for these reactions. It was hoped that the reactions would occur under similar conditions to those used for the fluorination of 1,3-dicarbonyl compounds. Since the silyl enol ethers have

been shown to be more reactive than 1,3-dicarbonyl compounds, however, the reactions were carried out at room temperature instead of at 40 $^{o}$C (Scheme 24).[37]




**Scheme 24** *Attempted fluorination of a silyl enol ether using the fluoroiodane*

Unfortunately, analysis of the $^{1}$H NMR spectrum of the crude product of this reaction showed a 100% conversion to acetophenone **195** with no formation of the desired fluorinated product **142** (Scheme 24). It was also noted that the fluoroiodane **154** remained intact and no conversion to the iodoalcohol by-product **64** was observed. Since the silyl enol ether **141** was shown not to decompose as a result of aqueous work-up or in $CDCl_3$, this suggests that the conversion to acetophenone occurred during the reaction.

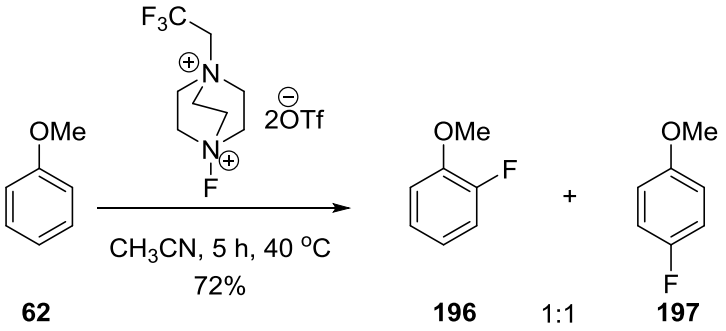
A variety of conditions were tested in order to promote fluorination of the silyl enol ether **141**. TREAT-HF was used in excess and in catalytic amounts, and added either at the beginning or towards the end of the reaction time. The reaction was attempted using a non-protic fluoride source, TBAF, instead of TREAT-HF, and also with no fluoride additive. Again, this was in varying amounts and with addition at different stages of reaction. In all cases, however, the desired fluorinated product **142** was not observed. Finally, the reaction was attempted using $BF_3.OEt_2$ as an additive in combination with TREAT-HF since this had been shown to activate difluoriodotoluene **54** in its reactions with silyl enol ethers (Scheme 11).[37] This, however, resulted in the formation of a complex mixture of products and again, the desired fluorinated product **142** was not observed.

Previous reactions with the fluoroiodane **154** had shown that an additional fluoride source was required in order to obtain good conversions to fluorinated products (section 2.4.1). In the case of silyl enol ethers, the addition of a source of fluoride appeared to cause the reaction of the substrate to form a ketone, which is less reactive. In future, if time allowed, these reactions would be repeated using other additives that could activate

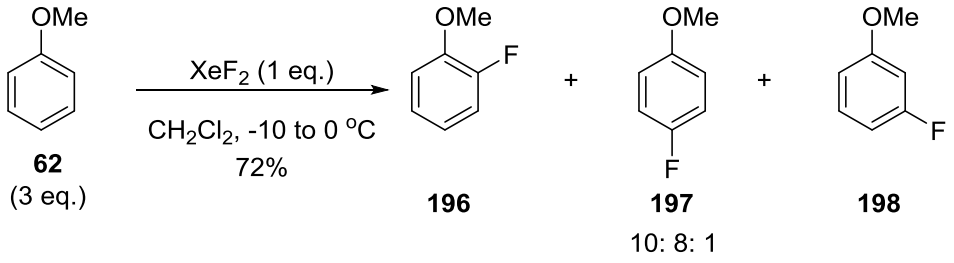
the fluoroiodane **154** without reacting with the substrate, for example, Lewis acid catalysts.

### 2.5.2 Reactivity of the Fluoroiodane with Activated Aromatics

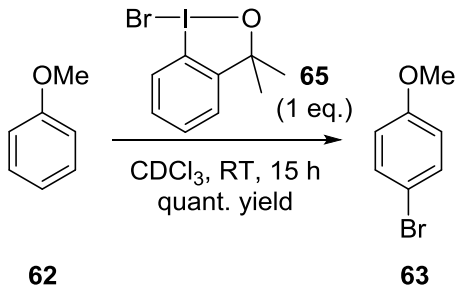
Fluorinated aromatic compounds are extremely important in both the pharmaceutical and agrochemical industries.[38, 39] They can be prepared using a variety of methods [40] including the reaction of activated aromatic compounds such as anisole **62** with a fluoraza reagent (Scheme 25).[41] The fluorination of anisole **62** can also be achieved using xenon difluoride (Scheme 26). The bromination of anisole has been achieved using Braddock's bromoiodane **65** under mild conditions and in quantitative yield (Scheme 27).[5]




**Scheme 25** *Fluorination of anisole using a fluoraza reagent*

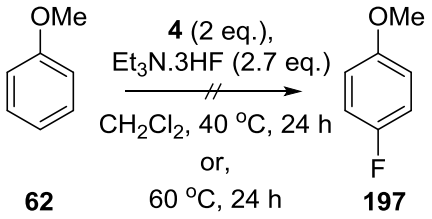



**Scheme 26** *Fluorination of anisole using xenon difluoride*




**Scheme 27** *Bromination of anisole with the bromoiodane*

When the reaction between anisole **62** and the fluoroiodane **154** was attempted in dichloromethane at 40 $^{o}$C in the presence of 2.7 equivalents of TREAT-HF, no reaction was observed and the starting materials were recovered (Scheme 28). The reaction was then attempted without solvent at 60 $^{o}$C, however, this reaction was also unsuccessful and the starting materials were recovered at the end of the reaction. These results are in agreement with Legault's findings that the fluoroiodane **154** does not react with anisole **62**.[21]

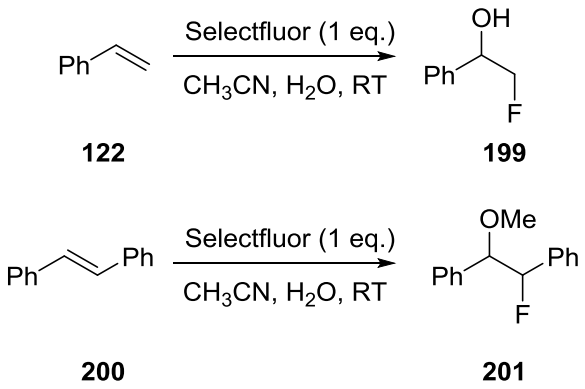



**Scheme 28** *Attempted fluorination of anisole using the fluoroiodane*

Braddock's bromoiodane **65** reacted with anisole at room temperature, without an additive. The fluoroiodane **154** did not fluorinate anisole even at high temperature and concentration and with $Et_3N.3HF$ as an additive. This suggested that either i) the fluoroiodane **154** is considerably less reactive than the bromoiodane **65** or ii) the bromoiodane is reacting *via* a different mechanism to the fluoroiodane **154**.

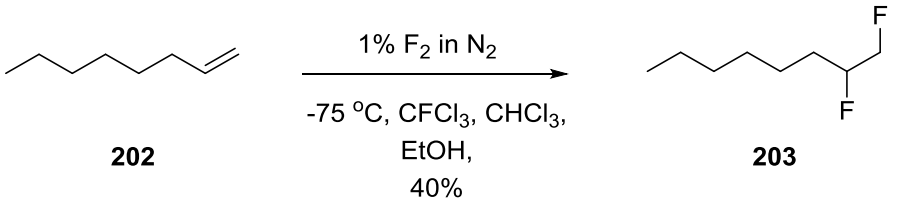
### 2.5.3 Reactivity of the Fluoroiodane with Alkenes

The fluorination of alkenes can be achieved by several different methods, however, the products formed depend on the type of fluorinating reagent used. Selectfluor can be used, in conjunction with a suitable nucleophile, to fluorinate alkenes such as styrene **122** and *trans*-stilbene **200** (Scheme 29).

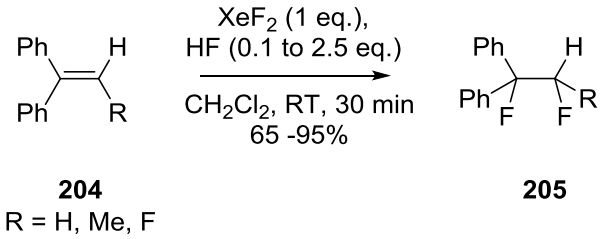



**Scheme 29** *Fluorination of alkenes using Selectfluor*

When elemental fluorine is used as the fluorinating reagent, addition products are seen, such as in the fluorination of octene **202** to 1,2-difluorooctane **203** (Scheme 30).[42] The use of fluorine gas is generally not preferred due to the difficulty in controlling reactions and therefore the requirement to use very low temperatures. Xenon difluoride is a more favourable option for the fluorination of alkenes since the reactions are easier to control although it is very expensive.[43] Xenon difluoride reacts with alkenes **204** in the presence of HF to give addition products (Scheme 31).

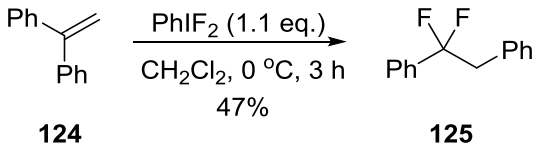



**Scheme 30** *Fluorination of octene using elemental fluorine*

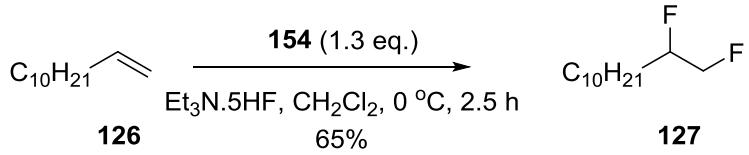



**Scheme 31** *Fluorination of alkenes using xenon difluoride*

The fluorination of alkenes has also been achieved using difluoroiodoarenes. In general, with aryl alkenes, the fluorination reaction is accompanied by a rearrangement (Scheme 32).[4, 44] The fluorination of terminal aliphatic alkenes with aryliododifluorides in the presence of $Et_3N.5HF$, however, results in a 1,2 addition reaction (Scheme 33).[45]

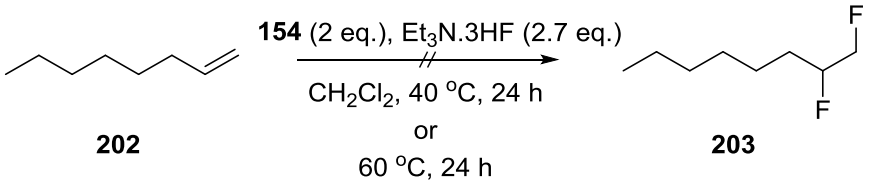



**Scheme 32** *Fluorination of 1,1-diphenylethylene using difluoroiodoarenes*



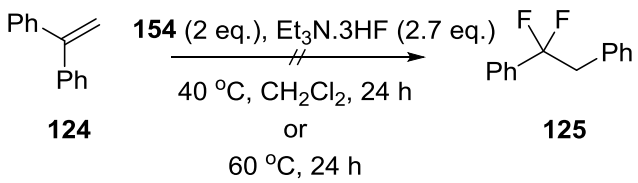

**Scheme 33** *Fluorination of terminal alkenes using difluoroiodoarenes*

The reactivity of the fluoroiodane **154** with alkenes was first attempted using oct-1-ene **202**. The reaction was attempted in the presence of 2.7 equivalents of TREAT-HF for 24 hours in dichloromethane at 40 °C. At the end of the reaction only the starting materials were recovered and no conversion of the fluoroiodane **154** was observed (Scheme 34). The reaction was also repeated without solvent at 60 °C, however, the same result was obtained.




**Scheme 34** *Attempted fluorination of octene using the fluoroiodane*

The reaction between the fluoroiodane **154** and 1,1-diphenylethylene **124** was attempted both at 40 °C in dichloromethane and at 60 °C without solvent. Again, however, only starting materials were recovered at the end of the reaction (Scheme 35). The reaction between the fluoroiodane **154** and allyl phenyl ether **206** and allyl benzyl ether **207** (Figure 9) were also unsuccessful.

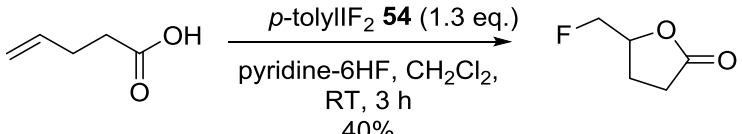



**Scheme 35** *Attempted fluorination of 1,1-diphenylethylene using the fluoroiodane*


**206** **207**

**Figure 9** *Allyl phenyl ether and allyl benzyl ether*

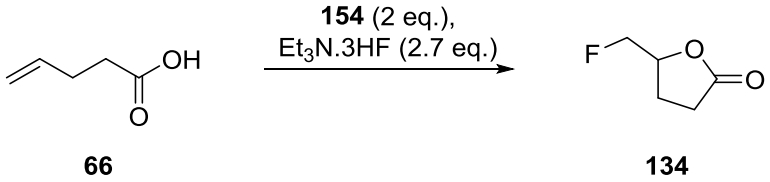
Difluoroiodotoluene **54** is known to react with unsaturated carboxylic acids to give fluorocyclised products (Scheme 36).[46] The reaction between 4-pentenoic acid **66** was attempted using 2 equivalents of the fluoroiodane **154** in the presence of 2.7 equivalents of TREAT-HF (Table 13) After 24 hours at 60 $^{o}$C without solvent, an 84% conversion of the starting material **66** was obtained (entry 1, Table 13). A 48% conversion to the fluorinated product **134** was achieved and this was isolated in 37% yield. In addition to this, several unidentified products were also formed, accounting for 36% of the original starting material. In order to achieve 100% conversion of the starting material, the reaction time was extended to 48 hours. Although a greater conversion of the starting material was achieved in this reaction, the yield of the fluorinated product **134** actually decreased to 26% (entry 2). The increased reaction time led instead to a greater conversion to the by-products of the reaction. In order to reduce the formation of by-products, the reaction was carried at room temperature for 24 hours (entry 3, Table 13). In this case, however, no conversion to the desired products was observed and the starting material was recovered. A control reaction showed that no reaction occurred in the absence of the fluoroiodane **154** (entry 4).




**66** **134**

**Scheme 36** *Reaction of 4-pentenoic acid with difluoroiodotoluene*

**Table 13** *Reaction of 4-pentenoic Acid with the fluoroiodane*

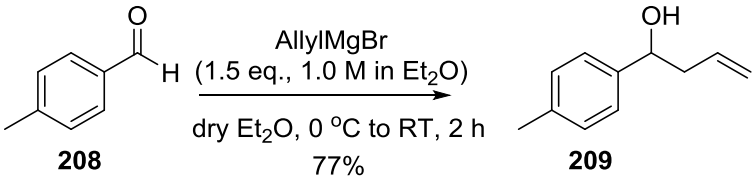



**66** **134**

| Entry | Solvent | Temp (°) | Time (h) | Yield of 66[a, b] (%) | Yield of 134[a, b] (%) | Yield of Other Products[a, c] (%) |
|---|---|---|---|---|---|---|
| 1 | - | 60 | 24 | 16 (16) | 48 (37) | 36 |
| 2 | - | 60 | 48 | 7 | 36 (26) | 57 |
| 3 | $CH_2Cl_2$ | RT | 24 | 100 | 0 | 0 |
| 4[e] | - | 60 | 24 | 100 | 0 | 0 |

[a] Calculated by $^1H$ and $^{19}F$ NMR spectroscopy; [b] Isolated Yield in parenthesis; [c] Based on unaccounted for starting material – these products have not been characterised; [d] No TREAT-HF; [e] Control reaction without fluoroiodane **154**.

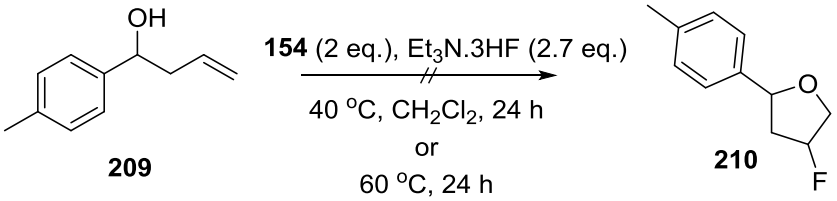
Since the hydroxyl group of a carboxylic acid is not very nucleophilic, an analogous alcohol was prepared. It was hoped that this would undergo cyclisation more quickly, due to the increased nucleophilicity of the hydroxyl group. To this end, 1-(*p*-tolyl)but-3-ene-1-ol **209** was prepared by the reaction of tolualdehyde **208** with allyl magnesium bromide (Scheme 37).




**208** **209**

**Scheme 37** *Preparation of 1-(p-tolyl)but-3-ene-1-ol*

The reaction between **209** and the fluoroiodane **154** was carried out in dichloromethane at 40 °C and at 60 °C without solvent (Scheme 38). In both cases however, the crude $^1H$ NMR spectra were dominated by the starting material and there was no evidence of the formation of any fluorinated products.




**Scheme 38**

*Attempted reaction of 1-(p-tolyl)but-3-ene-1-ol with the fluoroiodane*

The fluoroiodane **154** did not react with simple alkenes, however, a reaction was observed with substrates containing both alkene and carboxylic acid functional groups. In substrates containing alkene and alcohol functional groups, there was also no reaction. This suggests that the acidity of the substrate is the important factor. It could be that the alkenoic acid substrate **66** was activating the fluoroiodane **154** in a similar fashion to the activation of Togni's reagent by sulphonic acid substrates.[47]

In order to increase the reactivity of the fluoroiodane **154** with simple alkenes, additional activation of the fluoroiodane may be required. If time allowed, these reactions would be repeated using pyridine-HF as the fluoride source, which is a more acidic source of HF. This may help to promote the reaction to the desired product and therefore prevent some of the unwanted side reactions from occurring. Activation of the fluoroiodane **154** could also be attempted using a Lewis acid catalyst.

## 2.6 Conclusions

A novel hypervalent iodine derived electrophilic fluorinating reagent **154** has been prepared by four different routes. It can be prepared using an electrophilic source of fluorine, Selectfluor, as well as nucleophilic sources of fluorine such as TREAT-HF and TBAF. The best route for the preparation of the fluoroiodane **154** on a large scale was the nucleophilic route using TREAT-HF. Using this procedure 6-10 g of the fluoroiodane **154** could be prepared in just three steps from the iodoalcohol **5**. This procedure was convenient since all of the reactions were carried out at room temperature without the need for dry solvents or inert conditions. The products could be purified easily by recrystallization. The identity of the fluoroiodane **154** was confirmed by NMR spectroscopy, X-ray crystallography, mass spectrometry and elemental analysis.

Initial testing of the fluoroiodane **154** as an electrophilic fluorinating reagent was promising and good to excellent yields were obtained for the fluorination of 1,3-dicarbonyl compounds. The reactions could be carried out in a variety of solvents such as dichloromethane, acetonitrile, THF and toluene. This is in contrast to Selectfluor, which is only soluble in polar solvents such as acetonitrile and methanol. The new fluoroiodane **154** showed a comparable reactivity to Selectfluor for the fluorination of 1,3-dicarbonyl compounds (Table 5 vs. Table 10). The fluoroiodane **154** also performed similarly to the difluoroiodoarenes for the fluorination of 1,3-dicarbonyl compounds (Table 6 vs. Table 10). An advantage of the fluoroiodane **154** over the difluoroiodoarenes is that aqueous HF is not required and the safer alternative TREAT-HF can be used as the additive.

Disappointingly, attempts to broaden the scope of the reactivity of the fluoroiodane **154** met with limited success. The fluoroiodane **154** did not react with anisole, silyl enol ethers or simple alkenes. Some interesting reactivity was observed, however, in the fluorination of 4-pentenoic acid **66** to give a fluorocyclised product **134**.

The conclusion from the reactions of alkenes with the fluoroiodane **154** was that acid mediated activation of the fluoroiodane **154** may have been an important factor. This will be considered in future reactions with the fluoroiodane **154**.

## 2.7 References for Chapter 2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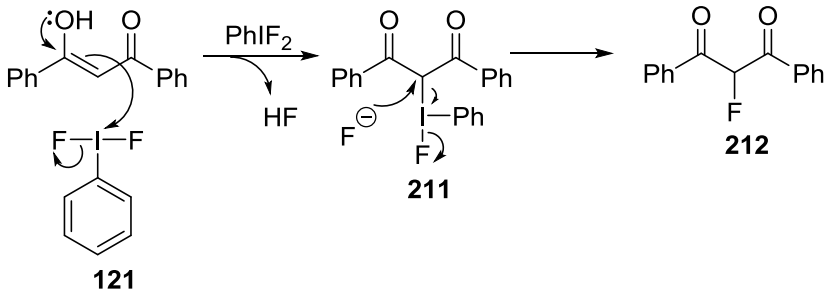
# Chapter 3

# Studies into the Mechanism of the Fluorination of 1,3-Dicarbonyl Compounds using the Fluoroiodane.

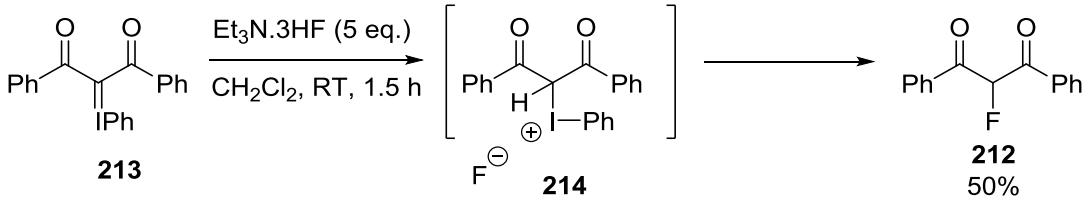
### 3.1 Introduction

Difluoroiodoarenes have been used for the apparent electrophilic fluorination of 1,3-dicarboyl compounds and ketones. The mechanism, however, has been postulated to proceed *via* addition of the iodane species followed by a nucleophilic attack by fluoride (Scheme 1).[1-4] In the proposed mechanism, the enol form of the dicarbonyl compound attacks at the iodine atom of the difluoroiodoarene **121** releasing fluoride to give a 2-iodanyl-1,3-dicarbonyl compound **211**. Subsequent nucleophilic attack by the fluoride anion gives the fluorinated product **212**. The loss of the iodine(III) group and concomitant reduction to normal valency, iodine(I), is a highly energetically favourable process.[5]




**Scheme 1** *Proposed mechanism for the fluorination of 1,3-dicarbonyls with difluoroiodoarenes*

In order to provide supporting evidence for the proposed mechanism of the fluorination reaction, Kitamura prepared a series of iodonium ylides. Iodonium ylides are interchangeably represented as neutral or zwitterionic resonance structures (Figure 1). When the iodonium ylides were reacted with a protic source of fluoride, TREAT-HF, a fluorinated product was obtained **212** (Scheme 2).[6] It was proposed that the iodonium ylide **213** was protonated to form the iodonium intermediate **214** followed by nucleophilic attack by fluoride to give the fluorinated product **212** (Scheme 2).[6]




**Scheme 2** *Fluorination of iodonium ylides using TREAT-HF*

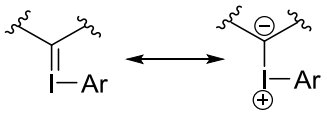



**Figure 1** *Resonance structures of an iodonium ylide*

The non-functionalised, acyclic iodonium ylides prepared by Kitamura, and others, have a low thermal stability and, therefore, are usually made and used *in situ*.[7-9] However, cyclic iodonium ylides **215** and *ortho*-alkoxy functionalised iodonium ylides **216** (Figure 2) are more stable and this improved stability is thought to be due to secondary iodine-oxygen bonding.[10-12]

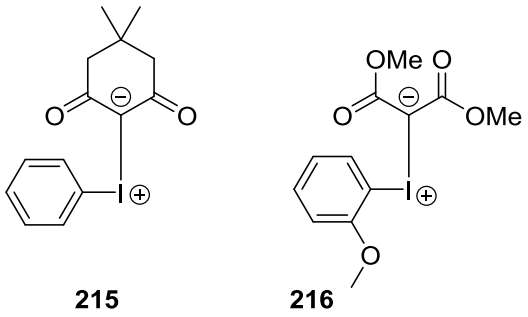
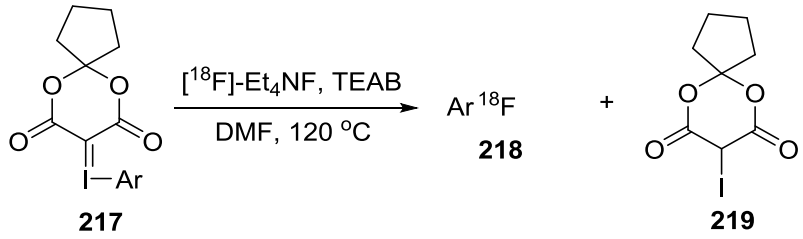


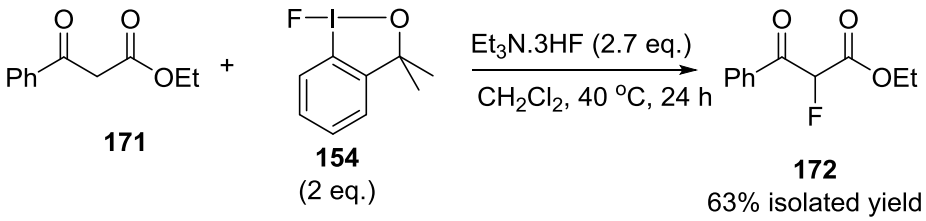

**Figure 2** *Examples of stable iodonium ylides*

Recently, iodonium ylides have been used as alternatives to diaryliodonium salts for the direct preparation of electron-rich and non-activated [$^{18}$F]-fluoroaromatics.[13-15] For example, Liang and co-workers have shown that the spirocyclic iodonium ylide **217** could be used for the radiofluorination of arenes (Scheme 3).[15]




**Scheme 3** *Radiofluorination of arenes using spirocyclic iodonium ylides*

In Chapter 2, the fluoroiodane **154** was used for the electrophilic fluorination of 1,3-dicarbonyl compounds (Scheme 4).[16] The aim of this chapter was to provide insight into the fluorination mechanism by varying the additive used and by varying the iodane species itself.




**Scheme 4** *Fluorination of a 1,3-dicarbonyl compound using the fluoroiodane*

A secondary aim of this chapter subsequently became the preparation of a series of new, stable iodonium ylides. The reactivity of these iodonium ylides with a range of fluoride sources and other protic acids was then investigated and the results provided additional support for the proposed fluorination mechanism.[17]

This chapter will be divided into six key areas:

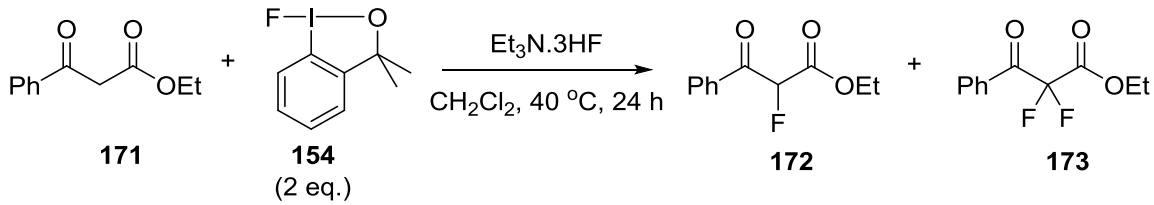
1. The effect of the additive on the fluorination of 1,3-dicarbonyl compounds using the fluoroiodane.
2. The effect of the iodane on the fluorination of 1,3-dicarbonyl compounds in the presence of TREAT-HF.
3. The proposed mechanism for the fluorination reaction using the fluoroiodane.
4. Fluorination of α-substituted 1,3-dicarbonyl compounds and the implications for the proposed mechanism
5. Preparation of new, stable iodonium ylides.
6. Reactivity of the iodonium ylides with protic acids.

## 3.2 The Effect of the Additive on the Fluorination of 1,3-Dicarbonyl Compounds

### 3.2.1 Reactivity of Ethyl 3-oxo-3-phenylpropanoate in the Presence of TREAT-HF

The optimum conditions for the fluorination of ethyl 3-oxo-3-phenylpropanoate **171** using the fluoroiodane **154** were discussed in the previous chapter and are shown in Table 1 (entry 1).[16] The addition of TREAT-HF, a protic source of fluoride, was essential for obtaining good conversions to the fluorinated products. When the amount of TREAT-HF was decreased, the conversion to the monofluorinated product **172** also decreased (entries 2 and 3). When no TREAT-HF was added, only a 20% conversion to the monofluorinated product **172** was observed which was isolated in a 10% yield (entry 4).

**Table 1** *Effect of TREAT-HF on the fluorination of 1,3-dicarbonyls with the fluoroiodane.*




**171** **154** (2 eq.) **172** **173**

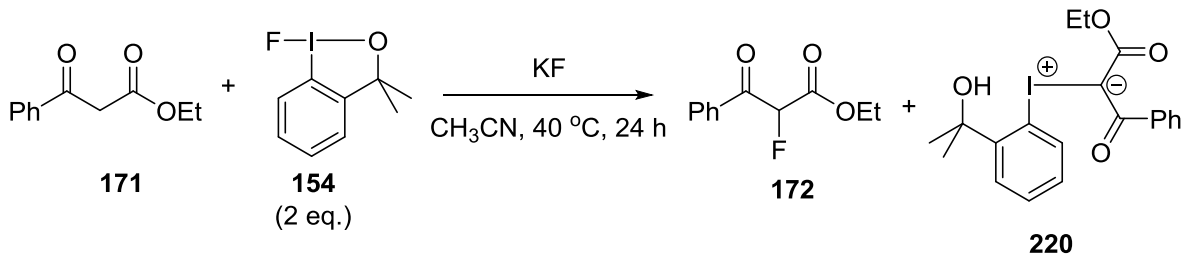
| Entry | $Et_3N.3HF$ (eq.) | 171 [a, b] (%) | 172 [a, b] (%) | 173 [a, b] (%) |
|---|---|---|---|---|
| 1 | 2.7 | 5 | 89 (63) | 6 |
| 2 | 1.0 | 14 | 80 | 6 |
| 3 | 0.2 | 43 | 53 | 4 |
| 4 | 0 | 80 (10) | 20 (10) | 0 |

[a] Conversion determined by $^{1}H$ and $^{19}F$ NMR spectroscopy; [b] Isolated yield in parenthesis.

### 3.2.2 Reactivity of Ethyl 3-oxo-3-phenylpropanoate in the Presence of KF

In order to determine whether it was important for the additive to be an acid or a source of fluoride, the reaction was attempted using a basic source of fluoride, KF. When the fluorination reaction was carried out using the fluoroiodane **154** in the presence of 1.2 equivalents of KF in acetonitrile at 40 $^{o}$C for 24 hours, only an 18% conversion to the monofluorinated product **172** was obtained (entry 1, Table 2). A by-product **220** was also observed which had not been seen before in the fluorination reactions. When the amount of KF was increased, the conversion to the monofluorinated product **172** decreased and the conversion to the by-product **220** increased (entries 2 and 3). With 5.6 equivalents of KF there was a 100% conversion to **220** and no fluorinated products were observed (entry 3). After the by-product **220** had been isolated by column chromatography, it was identified as a new iodonium ylide by $^{1}H$ and $^{13}C$ NMR spectroscopy, electrospray mass spectrometry, X-ray crystallography and elemental analysis.

**Table 2** *Effect of KF on the fluorination of 1,3-dicarbonyls with the fluoroiodane.*




| Entry | KF (eq.) | 171[a, b] (%) | 172[a, b] (%) | 220[a, b] (%) |
|---|---|---|---|---|
| 1 | 1.2 | 34 | 18 | 48 |
| 2 | 2.2 | 8 | 4 | 88 |
| 3[c] | 5.6 | 0 | 0 | 100 (42) |

[a] Conversion determined by $^{1}H$ and $^{19}F$ NMR spectroscopy; [b] Isolated yield in parenthesis; [c] Reaction at 60 °C.

One of the key methods for identifying an iodine(III) species is $^{13}C$ NMR spectroscopy since the chemical shift of the carbon atom next to the iodine atom varies with the oxidation state of the iodine. An aromatic carbon attached to an iodine(I) atom usually resonates at approximately 92 ppm. On oxidation to iodine(III) the attached carbon undergoes a downfield shift of approximately 10 ppm, as observed in the $^{13}C$ NMR spectra of the fluoroiodane **154** and the bromoiodane **65** (Figure 3).[16] In the $^{13}C$ NMR spectrum of the iodonium ylide **220** there were two signals corresponding to the carbons attached to iodine(III). The chemical shift of the aromatic *C*-I(III) was at 109.8 ppm which was characteristic of an aromatic carbon attached to iodine(III) (Figure 3). The chemical shift of the aliphatic *C*-I(III) was 78.5 ppm. This is approximately 30 ppm further downfield than for the α-carbon of the keto form of ethyl 3-oxo-3-phenylpropanoate **171** (45.9 ppm) and, again, this suggested that it was attached to an iodine(III) atom.

In the $^{1}H$ NMR spectrum of **220** the signal corresponding to the hydroxyl hydrogen had shifted significantly from 2.63 ppm in the iodoalcohol **64** to 6.57 ppm in **220**. This was thought to be as a result of intermolecular hydrogen bonding and this hypothesis was confirmed by X-ray crystallography.

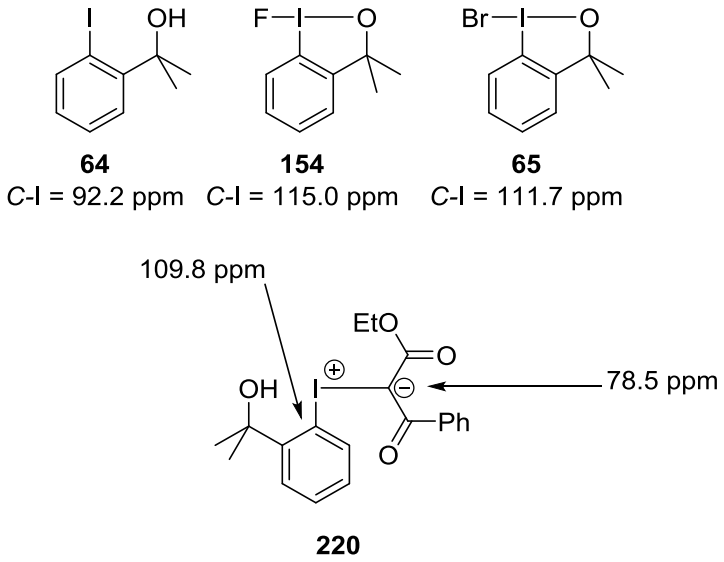



**Figure 3** *$^{13}$C NMR chemical shifts for the iodonium ylide* ***9***

Single crystals of **220** suitable for structure determination by X-ray crystallography were grown by slow evaporation of a diethyl ether solution containing the ylide. As expected for an iodonium ylide, the solid state structure of **220** (Figure 4) showed that the C(10)-I(1) bond length (2.068(5) Å) was slightly shorter than the C(1)-I(1) bond length (2.132(6) Å) (Table 3). Both of these bond lengths are similar to those observed in other iodonium ylides.[10-12] The negative charge of the iodonium ylide was delocalised across the carbonyl group, resulting in a slightly shorter than normal C(10)-C(11) bond length of 1.406(8) Å and a slightly longer than normal C(11)-O(2) bond length of 1.254 Å.[18, 19] The C(10)-I(1)-C(1) bond angle was 98.7(2) $^{o}$, which was within the normal range for an iodonium ylide of approximately 97 – 99 $^{o}$.[10-12] There was a strong intramolecular interaction between I(1) and O(1) (2.729(3) Å) and two weak intramolecular interactions between I(1)and O(2) and I(1) and O(4) (3.028(5) Å and 2.953(5) Å respectively). All of these intramolecular interactions were shorter than the sum of the van der Waals radii (3.5 Å)[20] and contributed to the unusual stability of the iodonium ylide **220**. Furthermore, the C(10)-I(1)···O(1) bond angle of 167.82(18) $^{o}$ was very similar to that found in the fluoroiodane **10**.[21]

The extended structure of the iodonium ylide **220** showed the formation of dimers in the solid state through intermolecular hydrogen bonding between O(1) and O(2)' (2.654(5) Å) (Figure 5). There were also intermolecular interactions between I(1) and O(3)'', resulting in the formation of long chains of dimers in the solid state (Figure 6).

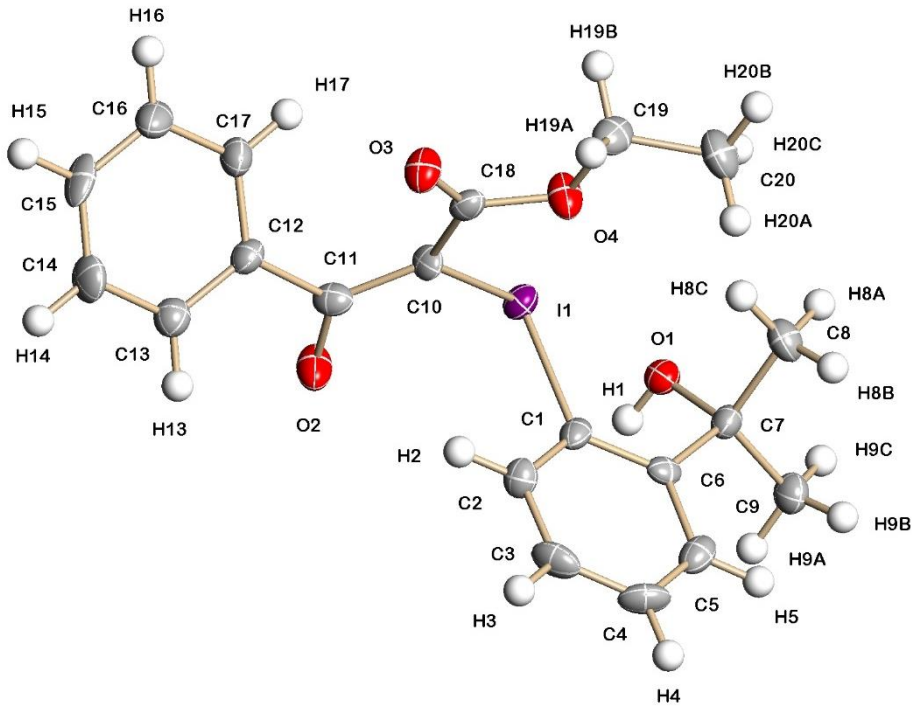



**Figure 4** *Solid state structure of the iodonium ylide* ***220***

**Table 3** *Key bond lengths (Å) and angles (°) for* ***14***

| | **220** | | **220** |
|---|---|---|---|
| C(10)-I(1) | 2.068(5) | I(1)···O(1) | 2.729(3) |
| C(1)-I(1) | 2.132(6) | I(1)···O(2) | 3.028(5) |
| C(11)-C(10) | 1.406(8) | I(1)···O(4) | 2.953(5) |
| C(10)-C(18) | 1.445(7) | I(1)···O(3)'' | 2.975(4) |
| C(11)-O(2) | 1.254(6) | O(1)···O(2)' | 2.654(5) |
| C(18)-O(3) | 1.210(6) | C(10)-I(1)-C(1) | 98.7(2) |
| | | C(10)-I(1)···O(1) | 167.82(18) |

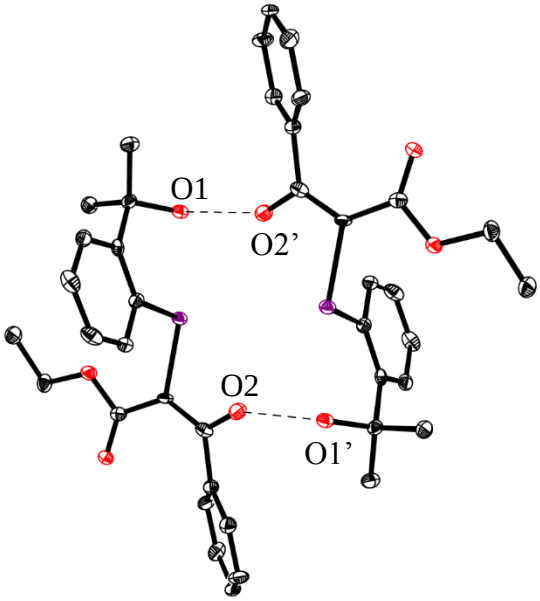



**Figure 5** *Solid state structure of the iodonium ylide showing intermolecular hydrogen bonding between O(1) and O(2)' (2.654(5) Å). The hydrogen atoms have been omitted for clarity.*

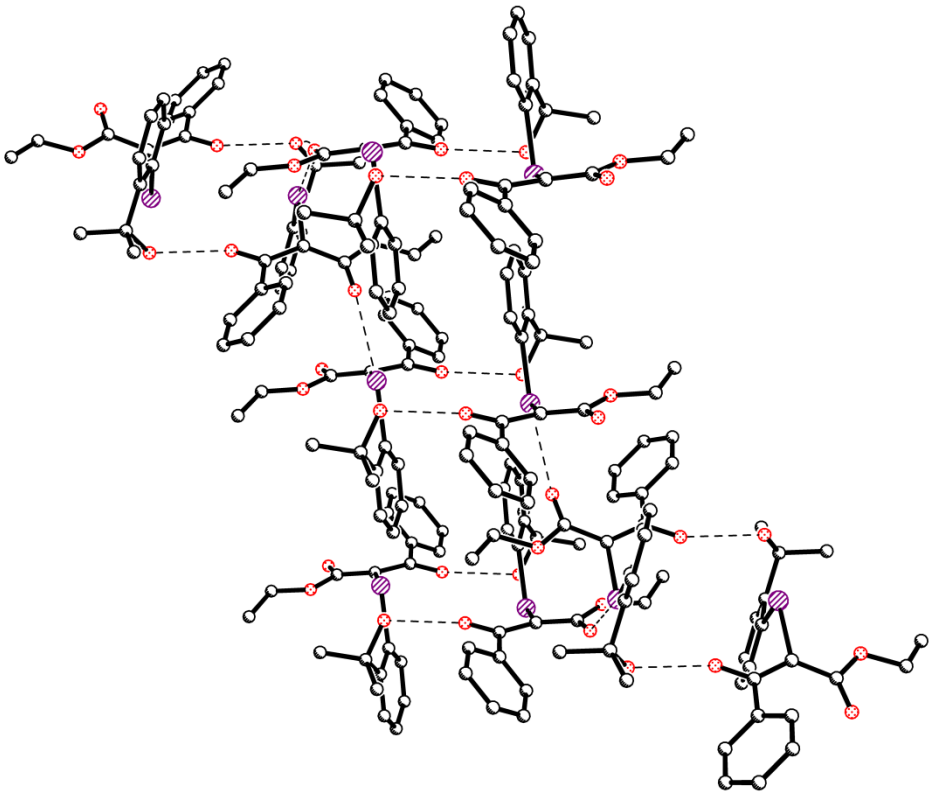
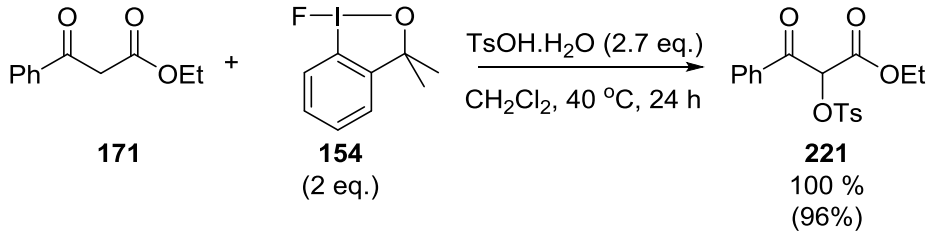


**Figure 6** *Solid-state packing diagram of iodonium ylide showing intermolecular hydrogen bonding for O(1)-O(2)' (2.654(5) Å) and I(1)-O(3)'' (2.975(4) Å)*

These reactions showed that a basic source of fluoride, KF, was not a suitable additive to promote the fluorination reaction as the iodonium ylide **220** was formed instead of the fluorinated product **172**. These results, however, provided a useful insight into the mechanism of the fluorination reaction, suggesting that it proceeds *via* an iodonium intermediate.

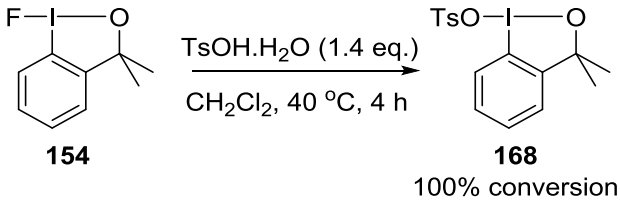
### 3.2.3 Reactivity of Ethyl 3-oxo-3-phenylpropanoate in the Presence of Protic Acids

The fluorination reaction was attempted using $TsOH.H_2O$ in order to determine if a Brønsted acid was a suitable additive. When the 1,3-dicarbonyl compound **171** was reacted with the fluoroiodane **154** in the presence of 2.7 equivalents of $TsOH.H_2O$ only the monotosylated product **221** was observed and it was isolated in a 96% yield (Scheme 5). This reaction showed that the tosylate anion is a much better nucleophile than the fluoride anion.



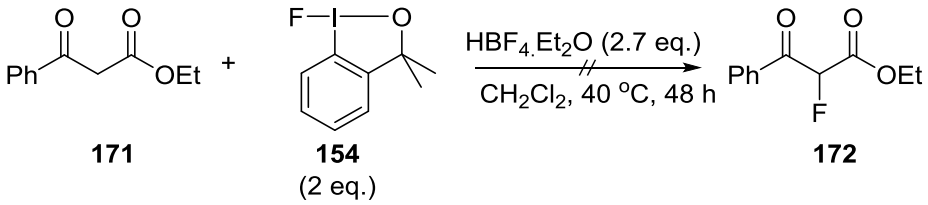

**Scheme 5** *Effect of $TsOH.H_2O$ on the fluorination of 1,3-dicarbonyls with the fluoroiodane.*

The fluoroiodane **154** was reacted with $TsOH.H_2O$ to give complete conversion to the tosyliodane **168** after just 4 hours at 40 $^oC$ (Scheme 6). When the isolation of the tosyliodane was attempted, however, complete conversion back to the fluoroiodane **154** occurred. The tosyliodane **168** is also known to react with **171** to give tosylated products (Section 3.3.2). These results suggested that a simple acid, such as $TsOH.H_2O$ was not a suitable additive to promote the fluorination reaction because of the reaction between the fluoroiodane **154** and $TsOH.H_2O$.




**Scheme 6** *Reaction of the fluoroiodane with TsOH.$H_2O$*

The fluorination of ethyl 3-oxo-3-phenylpropanoate was also attempted in the presence of $HBF_4$, since this could act as an acid but did not have a nucleophilic counter-ion which could compete with fluoride (Scheme 7). In this case, however, a complex mixture of products was obtained, from which purification was not attempted. It appeared that the $HBF_4$ was decomposing the fluoroiodane **154** as the clear, colourless solution turned black immediately on the addition of $HBF_4$.




**Scheme 7** *Effect of $HBF_4$ on the fluorination of 1,3-dicarbonyls with the fluoroiodane.*

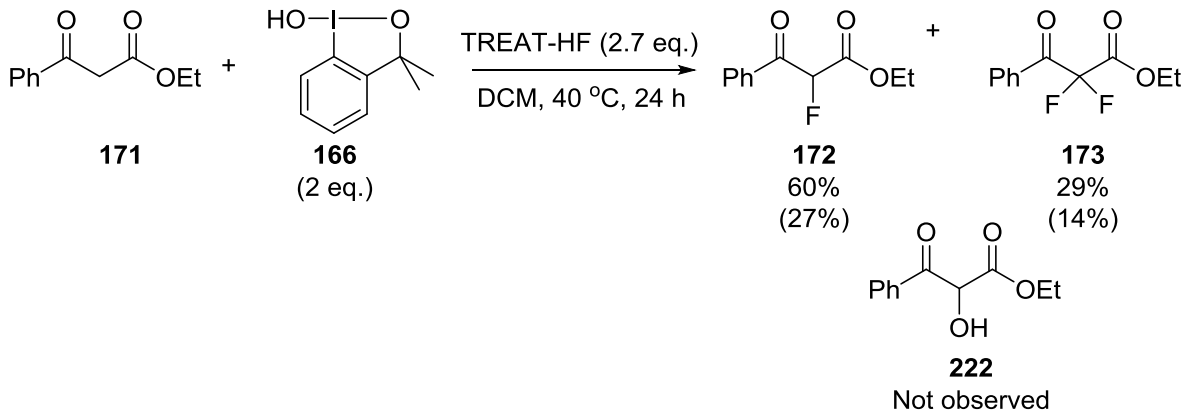
### 3.2.4 Summary of the Reactivity of Ethyl 3-oxo-3-phenylpropanoate in the Presence of Different Additives

The fluorination of ethyl 3-oxo-3-phenylpropanoate **171** worked best using the fluoroiodane **154** and TREAT-HF as the additive. Only a trace of the fluorinated product **172** was obtained in the absence of TREAT-HF. When the reaction was carried out using the fluoroiodane **154** and a basic source of fluoride, KF, the conversion to the fluorinated product **172** was low and instead an iodonium ylide **220** was formed. When the fluorination was carried out using TsOH.$H_2O$, a tosylated product **221** was formed. In the presence of $HBF_4$, the fluoroiodane **154** decomposed. These results suggested that a protic source of fluoride was the best additive in order to promote the fluorination reaction.

## 3.3 The Effect of the Iodane on the Fluorination of 1,3-Dicarbonyl Compounds

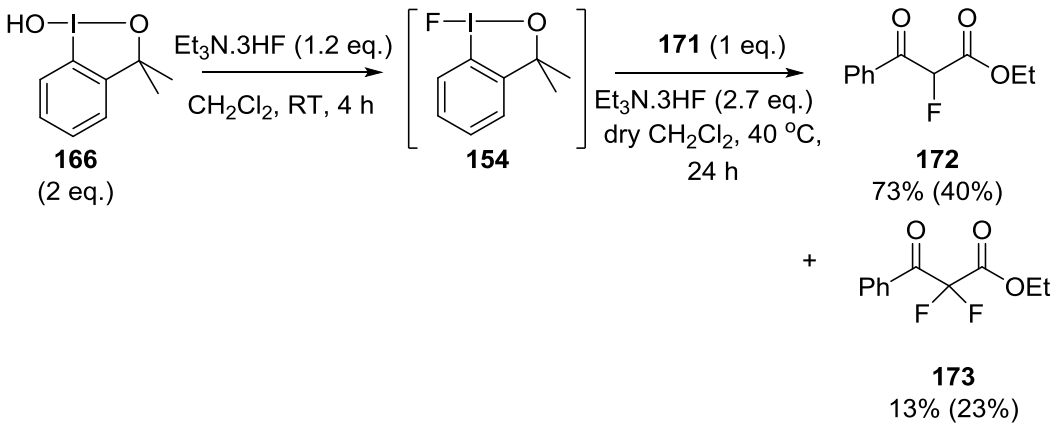
### 3.3.1 Fluorination Reactions using the Hydroxyiodane

Since the addition of a protic source of fluoride, such as TREAT-HF, was required for the fluorinations, it was postulated that the identity of the iodane species may not be important and that fluorinated products could be obtained using any iodane in the presence of a fluoride source. In Chapter 2, it was shown that the hydroxyiodane **166** could be reacted with TREAT-HF to form the fluoroiodane **154** in four hours at room temperature. For this reason the hydroxyiodane **166** was chosen as a suitable iodane, in the presence of TREAT-HF, to promote the fluorination reaction. When the hydroxyiodane **166** was reacted with **171** in the presence of TREAT-HF, the monofluorinated product **172** was isolated in a 27% yield and the difluorinated product in a 14% yield (Scheme 8). There was no evidence of the formation of a hydroxylated product **222**.



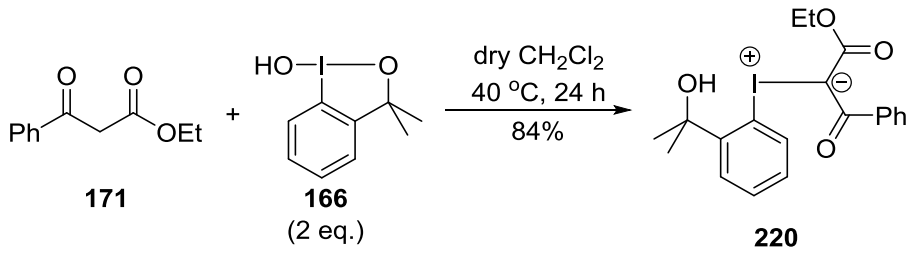

**Scheme 8** *Reaction of the hydroxyiodane and ethyl 3-oxo-3-phenylpropanoate in the presence of TREAT-HF*

The reaction was repeated but this time the hydroxyiodane **166** was stirred with TREAT-HF for four hours at room temperature in order to form the fluoroiodane **154** *in situ* before the addition of **171** (Scheme 9). This resulted in an improved isolated yield of both the mono and difluorinated products **172** and **173** when compared to those described above (Scheme 8). The discrepancy between the conversion and isolated yields arose from overlapping peaks in the $^{1}$H NMR spectrum of the crude product.




**Scheme 9** *Step-wise reaction of the hydroxyiodane and ethyl 3-oxo-3-phenylpropanoate in the presence of TREAT-HF*

Finally, the reaction of the hydroxyiodane **166** with the dicarbonyl substrate **171** was attempted in the absence of an additive (Scheme 10). This reaction resulted in a 100% conversion to the iodonium ylide **220** suggesting that the hydroxyl group of the iodane was acting as a base. This was isolated by column chromatography and recrystallization from diethyl ether in an 84% yield.



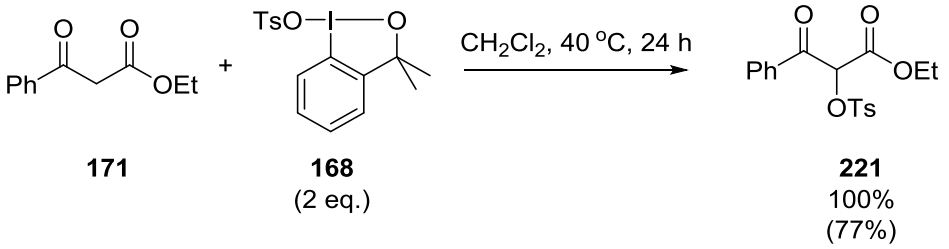

**Scheme 10** *Reaction of the hydroxyiodane with ethyl 3-oxo-3-phenylpropanoate*

The results in this section showed that it was possible to prepare the fluoroiodane **154** *in situ*, however, better conversions were obtained when this was done in a step-wise manner with initial preparation of the fluoroiodane **154** followed by addition of the substrate (Scheme 9). These results have also shown that, in the absence of a protic fluoride source, such as TREAT-HF, the hydroxyiodane **166** reacted to form the iodonium ylide **220** without the need for any additional base.

### 3.3.2 Fluorination Reactions using the Tosyliodane

In contrast to the reactivity of the hydroxyiodane **166**, the tosyliodane **168** did not react with TREAT-HF to form the fluoroiodane **154** (Chapter 2). When the tosyliodane **168**

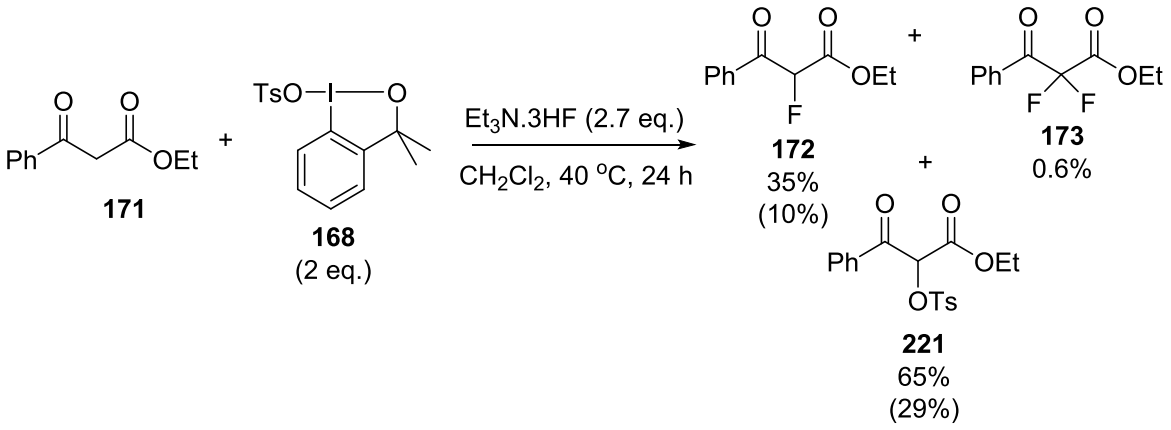
was reacted with **171**, 100% conversion to the monotosylated product **221** was observed and it was isolated in a 77% yield (Scheme 11).




**171** **168** (2 eq.) **221** 100% (77%)

**Scheme 11** *Reaction of the tosyliodane with ethyl 3-oxo-3-phenylpropanoate*

When the tosyliodane **168** was reacted with **171** in the presence of TREAT-HF, the monofluorinated product **172** was formed with a 35% conversion and a trace of the difluorinated product **173** was observed (Scheme 12). The major product was the monotosylated product **221** which was formed with a 65% conversion. These results proved that the tosylate anion was a better nucleophile than fluoride.

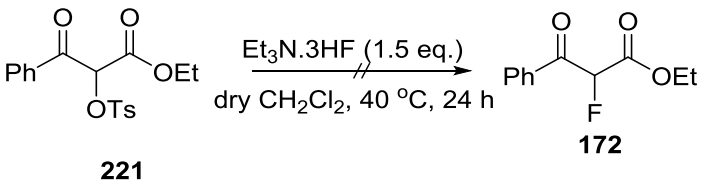



**171** **168** (2 eq.) **172** 35% (10%) **173** 0.6% **221** 65% (29%)

**Scheme 12** *Reaction of the tosyliodane and ethyl 3-oxo-3-phenylpropanoate in the presence of TREAT-HF*

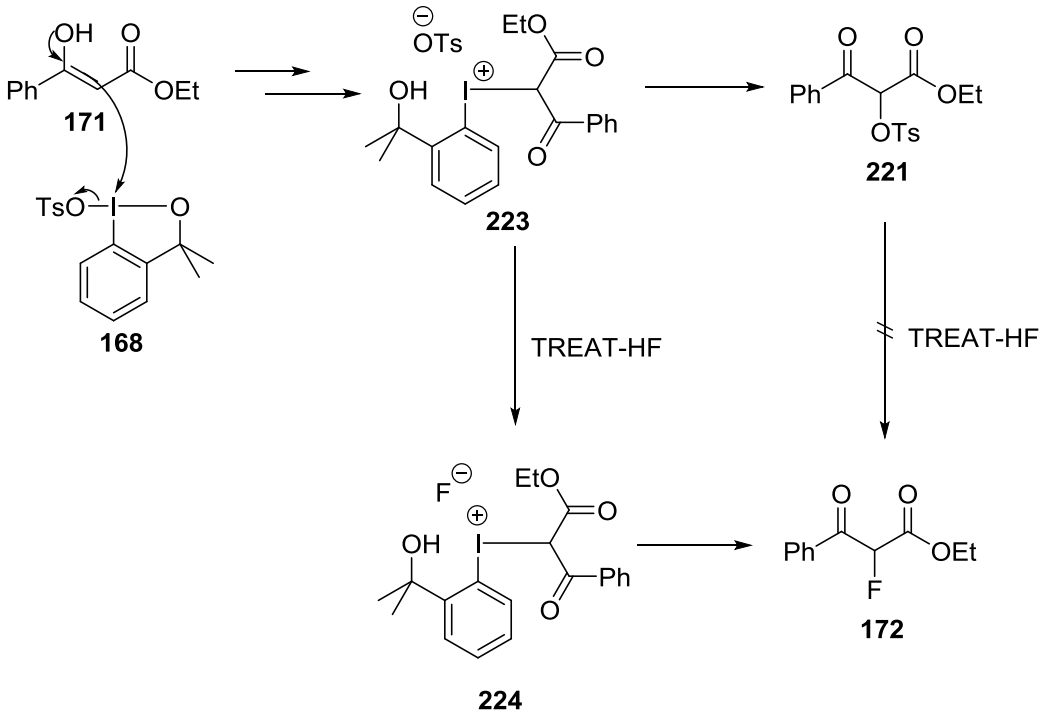
In order to determine if the fluorinated product **172** was formed by nucleophilic substitution of the monotosylated product **221** by fluoride, the monotosylated product **221** was treated with TREAT-HF. No fluorinated products were observed, however, and only the starting material was recovered at the end of the reaction (Scheme 13). This suggested that the formation of the fluorinated products must proceed *via* the formation of an iodonium intermediate **223** followed by either nucleophilic attack by fluoride or a reductive elimination. The tosylated product **221** was most likely formed in the same

way, with nucleophilic attack by the tosylate anion or a reductive elimination (Scheme 14). The higher conversion to the tosylated product **221** in preference to the fluorinated product **172** in the reaction in Scheme 12 was a result of the increased nucleophilicity of the tosylate anion in comparison to the fluoride anion.




**221** **172**

**Scheme 13** *Reaction of the monotosylated product with TREAT-HF*

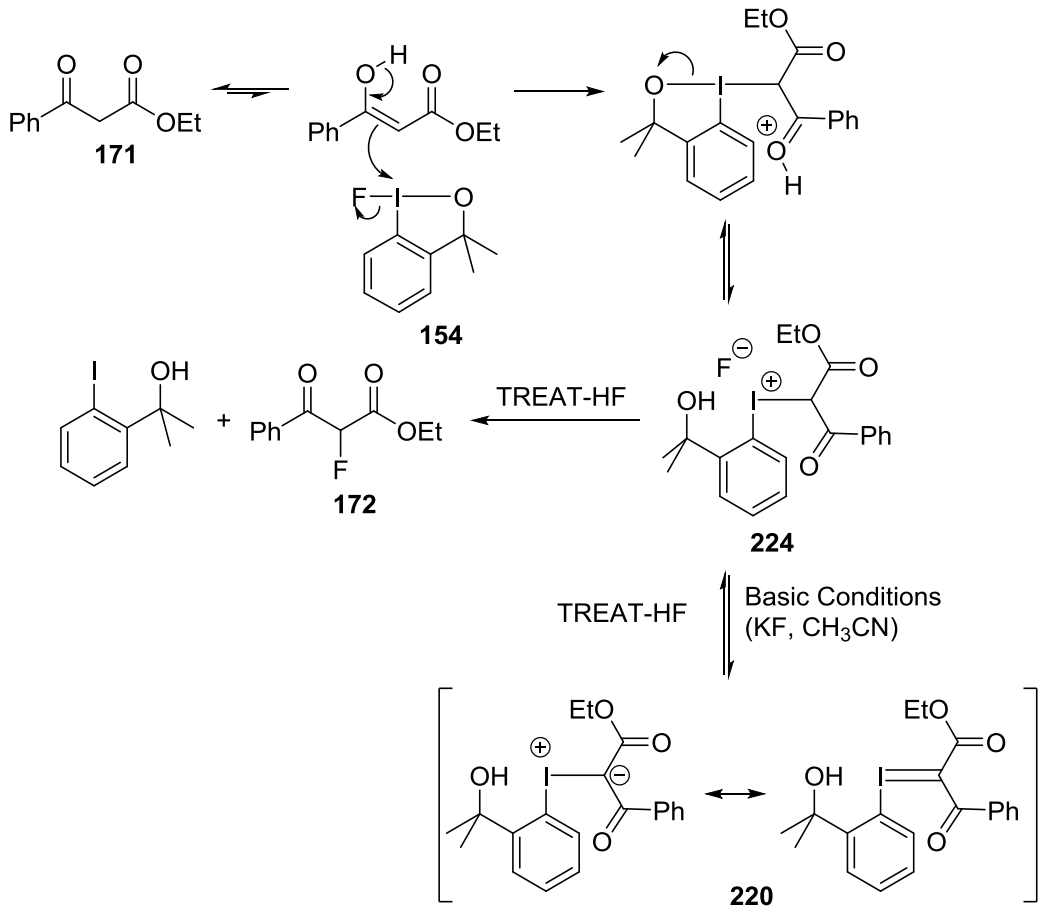



**Scheme 14** *Proposed mechanism for the formation of products in the reaction between the tosyliodane ethyl 3-oxo-3-phenylpropanoate and TREAT-HF*

### 3.4 Proposed Mechanism of the Fluorination Reaction

The reaction of the fluoroiodane **154** with **171** in the presence of KF and the reaction of the hydroxyiodane **166** with **171** resulted in the formation of an iodonium ylide **220**, which strongly suggested that these reactions proceeded *via* an iodonium intermediate. The fluorination of 1,3-dicarbonyl compounds with the tosyliodane **168** were also shown to be highly likely to proceed *via* an iodonium intermediate. Using this evidence,

a mechanism for the fluorination of 1,3-dicarbonyl compounds using the fluoroiodane **154** was proposed (Scheme 15). In the first step of the mechanism the enol form of the 1,3-dicarbonyl compound attacks the fluoroiodane **154** at the iodine atom, releasing fluoride. Following ring opening of the chelate sidearm and proton transfer to the alkoxide, the iodonium intermediate **224** was formed. In the presence of base (KF), the iodonium intermediate **224** was deprotonated to give the resonance stabilised iodonium ylide **220**. In the presence of a protic source of fluoride (TREAT-HF), the iodonium intermediate **224** remained protonated and the fluorinated product **172** was formed by either a nucleophilic substitution or a reductive elimination.[17] This suggests that the fluoroiodane **154** simulates an electrophilic fluorination with 1,3-dicarbonyl compounds *via* an addition-substitution mechanism. Similar mechanisms could be proposed for the reactions of 1,3-dicarbonyls compounds with the hydroxyiodane **166** and the tosyliodane **168.**




**Scheme 15** *Proposed mechanism for the fluorination of 1,3-dicarbonyl compounds using the fluoroiodane and the synthesis of the iodonium ylide*

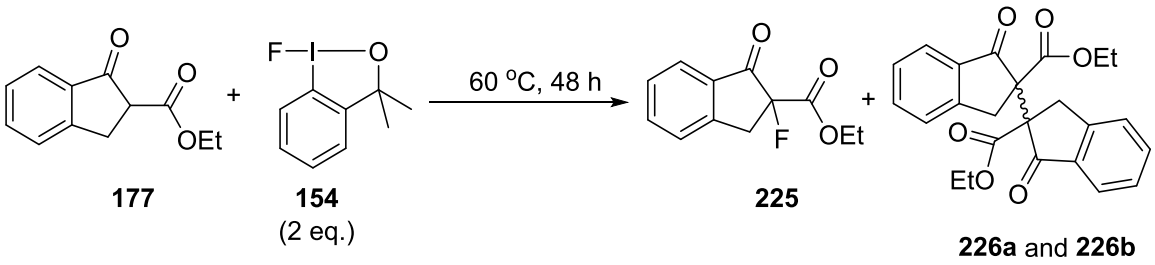
### 3.5 Fluorination of α-Substituted 1,3-Dicarbonyl Compounds and the Implications for the Proposed Mechanism

The proposed mechanism (Scheme 15) showed that the addition of an acidic source of fluoride was essential in order for the iodonium intermediate **224** to remain protonated, facilitating the formation of fluorinated products. For α-substituted 1,3-dicarbonyl compounds, such as ethyl-1-indanone-2-carboxylate **177**, there is no proton in the α-position and, therefore, deprotonation to form an iodonium ylide is not possible. It was postulated, therefore, that for these substrates, fluorinated products could be formed, either without any additive or in the presence of a basic source of fluoride such as KF.

The optimum conditions for the fluorination of ethyl-1-indanone-2-carboxylate **177** were given in chapter 2 and are shown in Table 4 (entry 1). When the reaction was carried out without TREAT-HF (entry 2), the isolated yield decreased from 55% to 38%, which was expected since there was less free fluoride in the reaction mixture. When the same reaction was carried out in acetonitrile, the fluorinated product was isolated with a higher isolated yield of 46%. The formation of dimers **226a** and **226b** was observed for the first time in these reactions. The identity of these new compounds was confirmed by $^{1}H$ and $^{13}C$ NMR spectroscopy in addition to ASAP mass spectrometry. Single crystals of **226** suitable for structure determination by X-ray crystallography were grown by slow evaporation of a dichloromethane solution containing the dimer (Figure 7). A proposed mechanism for the formation of the dimers is given in Scheme 16, however, the formation of these dimers was surprising since the likelihood of nucleophilic attack at such a sterically hindered centre seems low.

The reaction was also attempted in the presence of a basic source of fluoride, KF. Disappointingly, the addition of KF appeared to promote the formation of the dimers **226a** and **226b** and no fluorinated products were obtained (entry 4 and 5, Table 4). The reasons for this were not clear and, due to time constraints, these reactions were not investigated further.

**Table 4** *Fluorination of ethyl-1-indanone-2-carboxylate*




| Entry[a] | Additive (2.7 eq.) | Solvent | 225 [b, c] (%) | 226a [b, c] (%) | 226b [b, c] (%) |
|---|---|---|---|---|---|
| 1 | $Et_3N.3HF$ | - | 100 (55) | 0 | 0 |
| 2 | - | $CH_2Cl_2$ | 65 (38) | 20 | 15 |
| 3 | - | $CH_3CN$ | 72 (46) | 17 | 10 |
| 4 | KF | $CH_2Cl_2$ | 0 | 71 (10) | 29 (5) |
| 5 | KF | $CH_3CN$ | 0 | 64 (3) | 36 (5) |

[a] Concentration was kept constant in all reactions; [b] Conversion determined by $^1H$ and $^{19}F$ NMR spectroscopy; [c] Isolated yield in parenthesis.

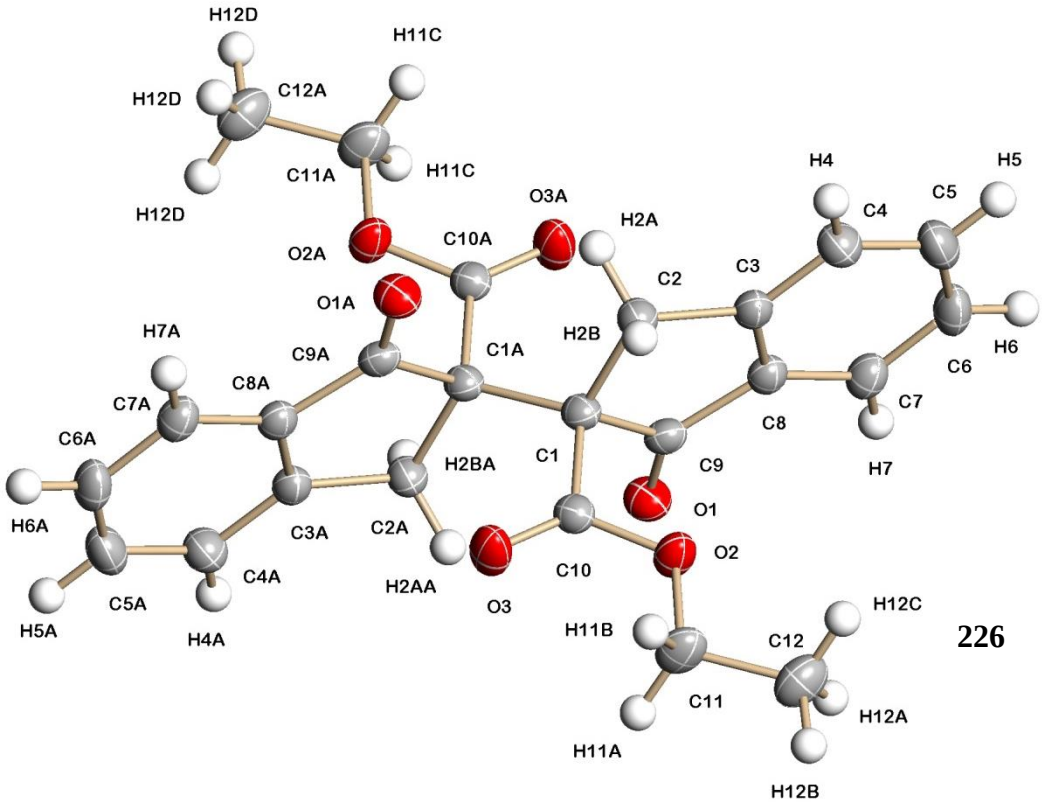
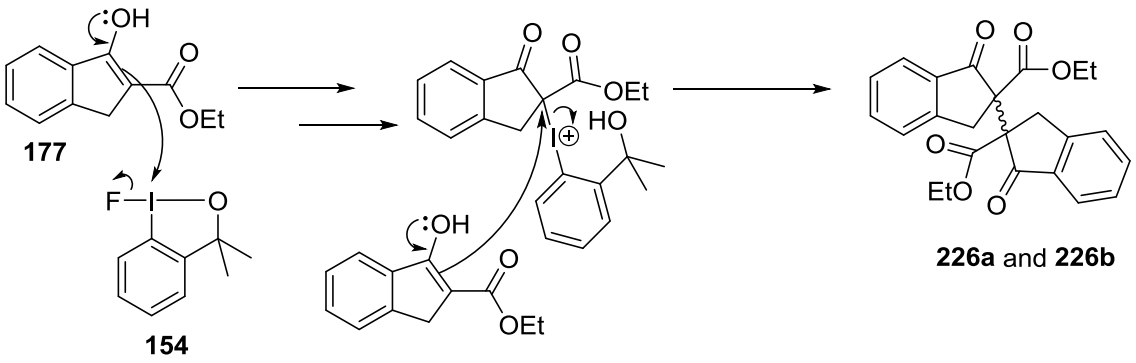


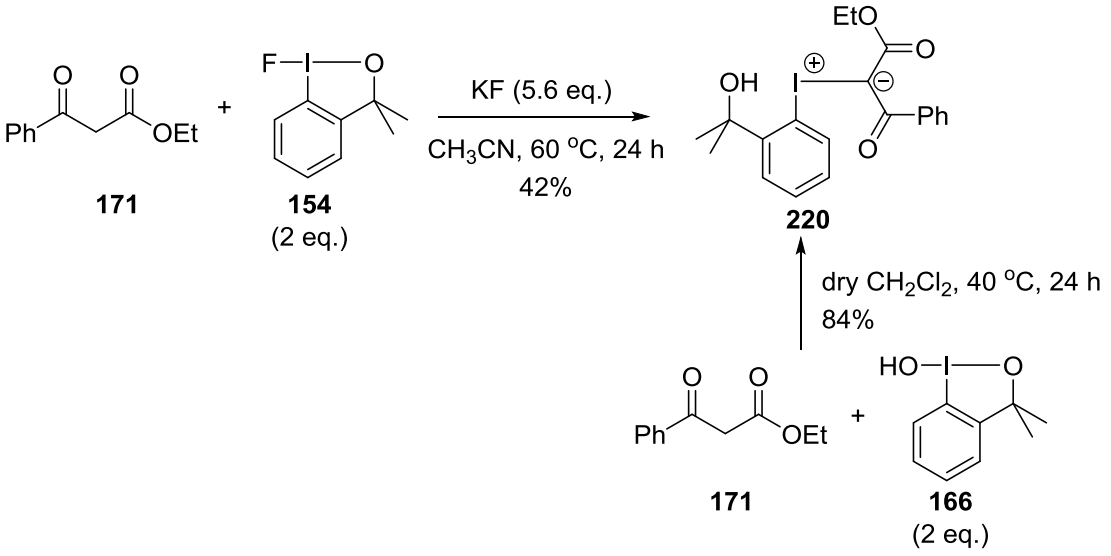

**Figure 7** *Solid-state structure for the dimer*




**Scheme 16** *Proposed mechanism for the formation of dimers 22a and 22b*

### 3.6 Preparation of Iodonium Ylides

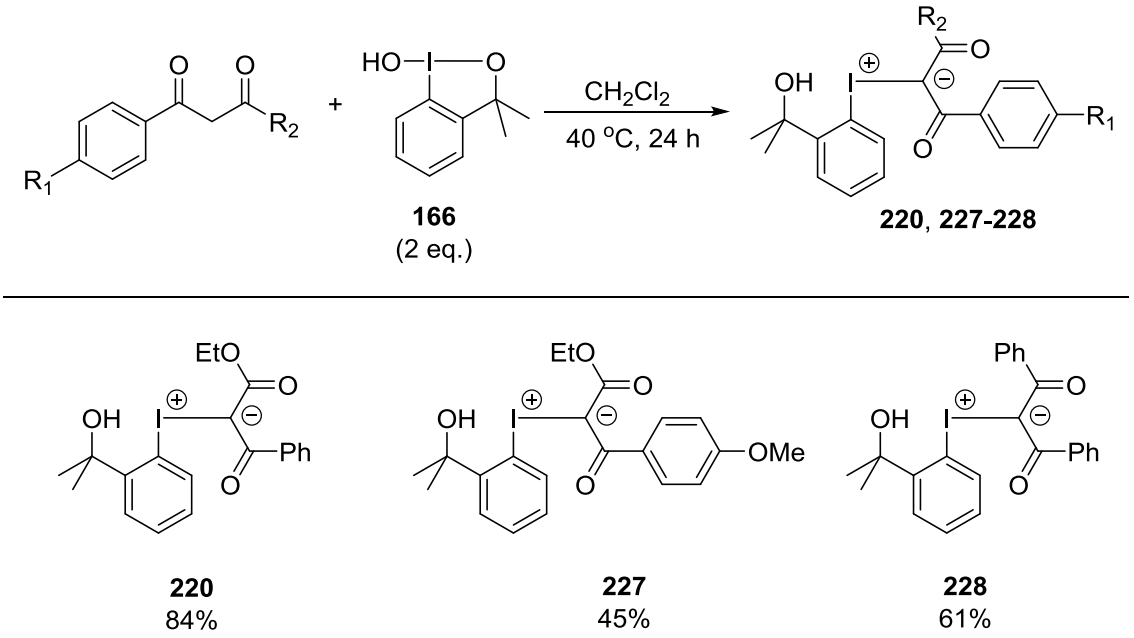
The iodonium ylide **220**, described in the earlier part of this chapter, possessed an unusual stability for an acyclic iodonium ylide and this was due to the presence of three different intramolecular interactions between iodine and oxygen. The ylide was stable at room temperature and could be purified by column chromatography on silica gel. The iodonium ylide **220** was prepared using two different routes (Scheme 17). Of these two routes the one using the hydroxyiodane **166** gave the better yield and, therefore, this route was chosen for the preparation of two further, new iodonium ylides.




**Scheme 17** *Summary of the preparation of the iodonium ylide*

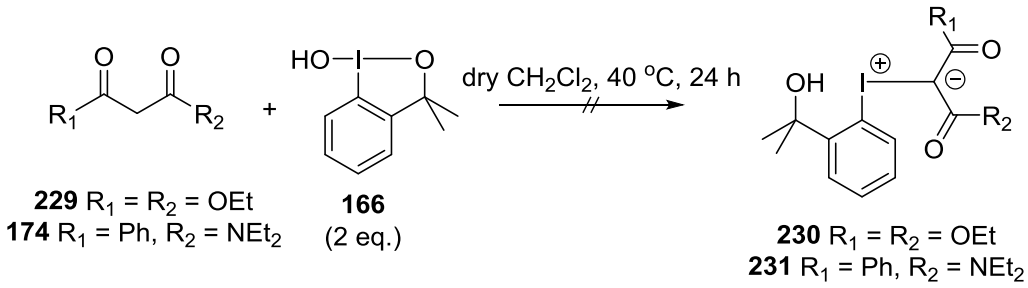
The methoxy-substituted ylide **227** and 1,3-diketone derived ylide **228** were prepared in reasonable yields of 45% and 61% respectively (Scheme 18), and were characterised by

$^{1}H$ and $^{13}C$ NMR spectroscopy, electrospray mass spectrometry and elemental analysis. The data was comparable to that found for iodonium ylide **220** but it was not possible to grow crystals suitable for X-ray diffraction.




**Scheme 18** *Preparation of iodonium ylides from the hydroxyiodane*

The preparation of an iodonium ylide derived from diethyl malonate **229** was also attempted under the same reaction conditions. Disappointingly, however, no reaction was observed and this was attributed to the fact that diethyl malonate exists only in the keto form (Scheme 19). In order to promote enolisation, the reaction was repeated twice in the presence of 2 equivalents of KOH at room temperature and at 40 °C for 4 hours. Again, none of the desired product was formed and the starting materials were recovered.



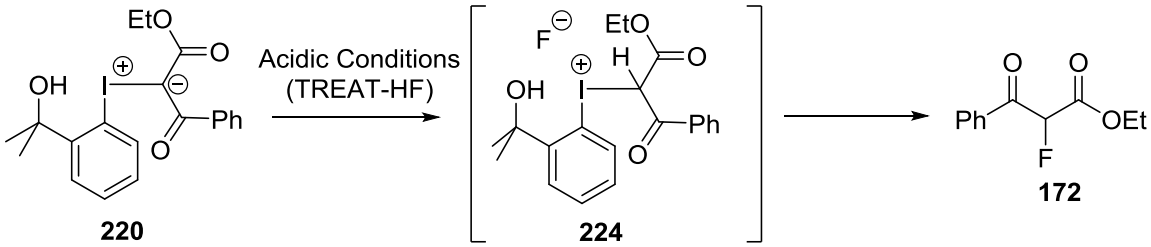

**Scheme 19** *Failed attempts to prepare iodonium ylides*

The preparation of an iodonium ylide derived from *N*,*N*-diethyl-3-oxo-3-phenylpropanamide **174** was also attempted, however, no reaction was observed and the starting materials were recovered at the end of the reaction (Scheme 19). The reasons for this were not clear since the ketoamide has a high enol content (52% by $^{1}$H NMR spectroscopy).

## 3.7 Reactivity of the Iodonium Ylides

### 3.7.1 Reactivity with Protic Fluoride Sources

In order to provide further evidence for the proposed mechanism given in Scheme 15, the iodonium ylides **220**, **227** and **228** were used as alternative starting materials for the fluorination reaction. It was envisaged that, when reacted with a protic fluoride source, protonation of the iodonium ylide **220** would occur to give the iodonium intermediate **224**. Subsequent nucleophilic attack or reductive elimination would give the fluorinated product **172** (Scheme 20).



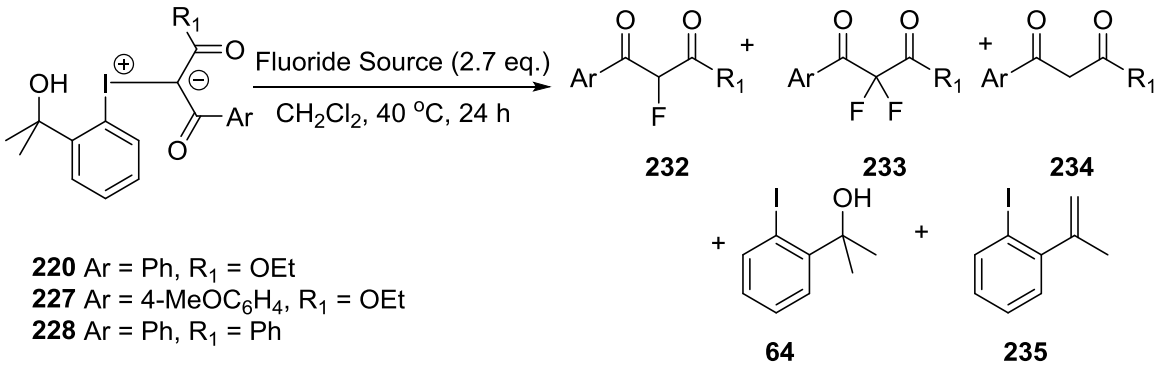

**Scheme 20** *Reaction of iodonium ylides with protic sources of fluoride*

When the iodonium ylide **220** was reacted with 2.7 equivalents of TREAT-HF the monofluorinated product **232** was isolated in a 36% yield (entry 1, Table 5) which is lower than the yield of the monofluorinated product in a normal fluorination reaction (entry 1, Table 1). This may be due to the fact that the pH of $Et_3N.3HF$ is close to neutral[22] and, therefore, is possibly not acidic enough to fully protonate the ylide. The iodoalcohol **64** was also isolated in a 54% yield. A similar result was obtained when the methoxy-substituted iodonium ylide **227** was reacted with TREAT-HF (entry 3, Table 5).

When the iodonium ylide **220** was reacted with the more strongly acidic pyridine-HF, the monofluorinated product **232** was isolated with an increased yield of 40% (entry 2,

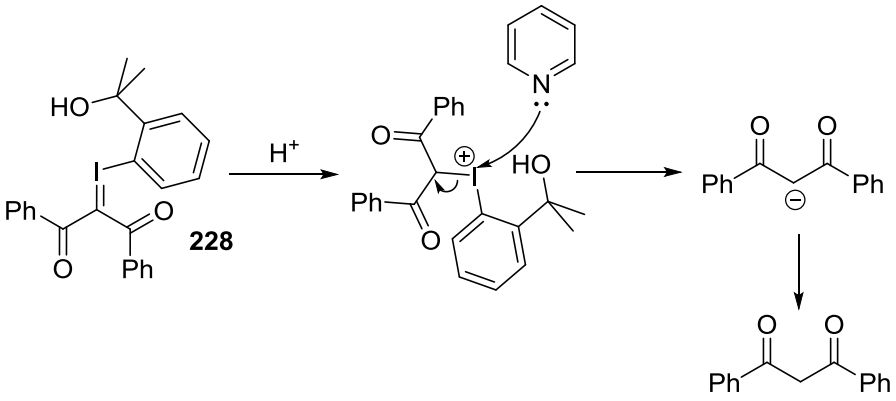
Table 5). The dicarbonyl product **234** was also isolated in a 28% yield. The formation of the dicarbonyl product **234** could be as a result of nucleophilic attack by pyridine on the protonated form of the iodonium ylide (Scheme 21). Due to the increased size of pyridine in comparison to the fluoride anion, nucleophilic attack occurred at iodine rather than at the α-carbon of the dicarbonyl. The affinity of pyridine for iodine(III) is well known, for example in the iodonium salt bis(pyridine)iodonium tetrafluoroborate.[23] Due to the increased acidity of pyridine-HF when compared to that of TREAT-HF some of the iodoalcohol by-product **64** underwent acid catalysed elimination to give the iodoalkene **235** which was isolated in a 64% yield as a by-product from the reaction. The characterisation data for this compound was in agreement with that in the literature.[24]

**Table 5** *Reaction of iodonium ylides with protic fluoride sources*



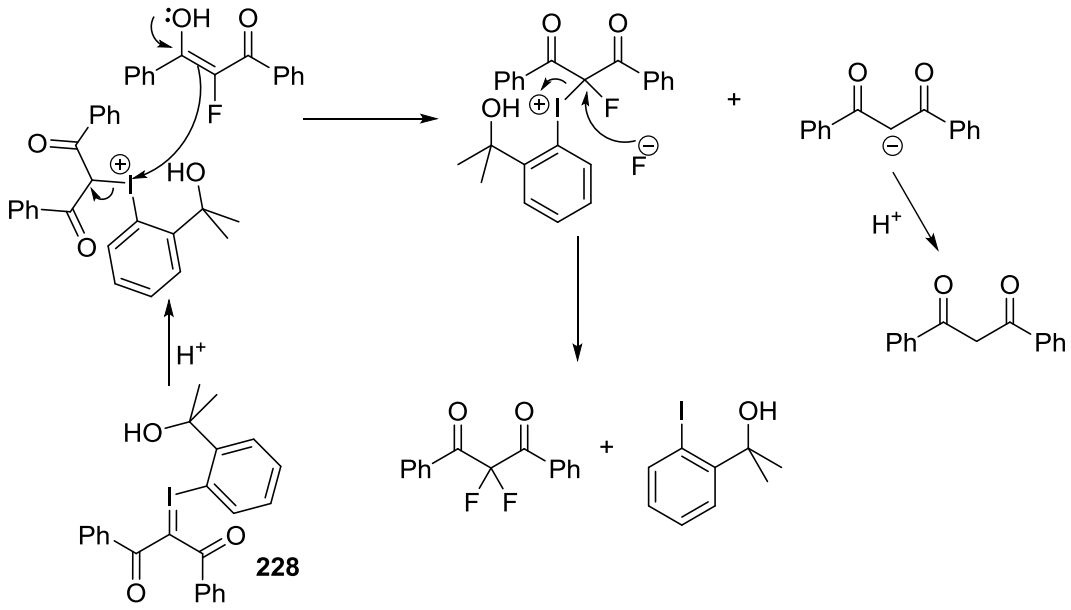

| Entry | Ylide | Fluoride Source (2.7 eq.) | 232[a, b] (%) | 233[a, b] (%) | 234[a, b] (%) | 64[a, b] (%) | 235[a, b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **220** | $Et_3N.3HF$ | 100 (36) | trace | trace | 100 (54) | 0 |
| 2 | **220** | Pyridine-HF | 51 (40) | trace | 49 (28) | 34 | 66 (64) |
| 3 | **227** | $Et_3N.3HF$ | 100 (28) | 0 | 0 | 100 (92) | 0 |
| 4 | **228** | $Et_3N.3HF$ | 79 (64) | 11 (9) | 10 (15) | 100 (67) | 0 |
| 5 | **228** | Pyridine-HF | 55 (20) | 3 | 42 (26) | 0 | 100 (53) |

[a] Conversion determined by $^1H$ and $^{19}F$ NMR spectroscopy; [b] Isolated yield in parenthesis.




**Scheme 21** *Proposed mechanism for the formation of the dicarbonyl product in the presence of pyridine-HF*

When the 1,3-diketone derived iodonium ylide **228** was reacted with TREAT-HF, the monofluorinated **232** product was isolated in a 64% yield (entry 4, Table 5). The monofluorinated product **232** exists as both keto and enol tautomers which meant that it could react with the ylide again to form both the difluorinated **233** and carbonyl **234** products in 9% and 15% yields respectively (Scheme 22). In this case, this seems the more likely route to the formation of the difluorinated **233** and dicarbonyl **234** products since they were both formed in almost equal quantities. Disappointingly, however, when **228** was reacted with the more acidic pyridine HF, the monofluorinated product **232** was only isolated in a 20% yield in addition to the dicarbonyl product **234** in a 26% yield.

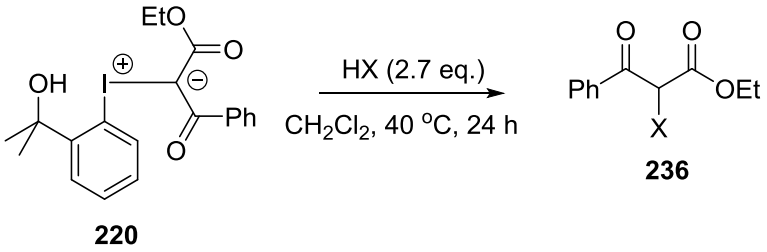



**Scheme 22** *Proposed mechanism for the formation of difluorinated and dicarbonyl products*

### 3.7.2 Reactivity with Other Acids

The reactivity of the iodonium ylide **220** was also investigated with other protic acids. When the iodonium ylide **220** was reacted with hydrochloric acid, the monochlorinated product **236a** was isolated in an excellent yield of 83% (entry 1, Table 6). The reaction of the iodonium ylide with acetic acid gave the monoacetylated product in a 93% yield (entry 2) whilst the reaction with TsOH.$H_2O$ gave the monotosylated product in a 72% yield (entry 3).

**Table 6** *Reaction of the iodonium ylide with protic acids*



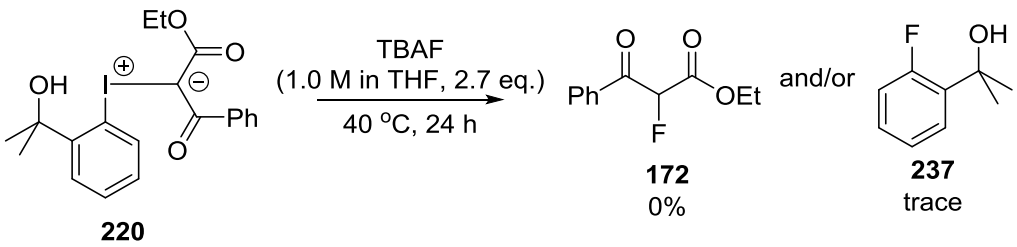

**220** **236**

| Entry | X | Product[a, b] |
|---|---|---|
| 1 | Cl | **236a** |
| | | 100 (83) |
| 2 | OAc | **236b** |
| | | 100 (93) |
| 3 | OTs | **221** |
| | | 100 (72) |

[a] Conversion determined by $^{1}H$ and $^{19}F$ NMR spectroscopy; [b] Isolated yield in parenthesis.

### 3.7.3 Reactivity with Aprotic Fluoride Sources

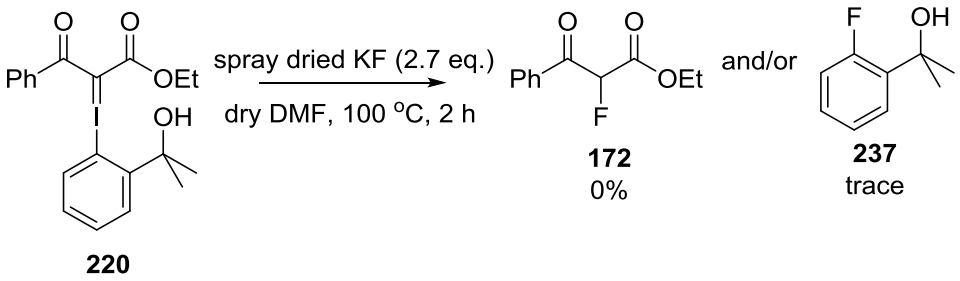
According to the proposed mechanism (Scheme 15) the reaction of the iodonium ylide with an aprotic source of fluoride should not result in the formation of a fluorinated 1,3-dicarbonyl product. When the iodonium ylide **220** was reacted with an aprotic fluoride source, TBAF, 100% conversion of the starting material was observed, however, the fluorinated dicarbonyl **172** was not observed (Scheme 23). A weak peak at -119 ppm in the $^{19}F$ NMR spectrum of the crude product suggested the formation of an aryl fluoride **237**. The reaction of iodonium ylides with a basic source of fluoride, KF, has been shown to give aryl fluoride products.[13-15]




**220** **172** 0% **237** trace

**Scheme 23** *Reaction of the iodonium ylide with TBAF*

A similar reaction was attempted using the same conditions as those used by Liang et al. for the fluorination of iodonium ylides using KF (Scheme 24).[15] Again, none of the fluorinated dicarbonyl product **172** was observed although a peak at -119 ppm in the $^{19}F$ NMR spectrum of the crude product suggested the formation of an aryl fluoride **237** but it could not be isolated by column chromatography.




**220** **172** 0% **237** trace

**Scheme 24** *Reaction of the iodonium ylide with KF*

### 3.8 Conclusions

The reactions in the first part of this chapter showed that the addition of a protic source of fluoride, TREAT-HF, was essential for obtaining good conversions to the fluorinated products in the reactions of the fluoroiodane **154** with 1,3-dicarbonyl compounds. The reactions in the second section showed that the fluoroiodane **154** could be prepared *in situ* from the hydroxyiodane **166**. The use of other iodane species, such as the tosyliodane **168** was not suitable for the preparation of fluorinated products because the additional nucleophile, the tosylate anion, competed with fluoride to give a tosylated product **221**.

From these results, it was proposed that the fluoroiodane **154** simulated an electrophilic fluorination with 1,3-dicarbonyl compounds *via* an addition-substitution reaction (Scheme 15). The isolation of an iodonium ylide from the reaction of the fluoroiodane **154** with ethyl 3-oxo-3-phenylpropanoate **171** in the presence of KF gave strong evidence that an addition reaction occurred between **171** and the fluoroiodane **154** to give an iodonium fluoride **224**. Under basic conditions, deprotonation of the iodonium intermediate occurred to give an iodonium ylide. Under acidic conditions, substitution by fluoride or reductive elimination gave the fluorinated product **172**.

A series of unusually stable iodonium ylides have also been prepared. The inclusion of an *ortho*-propan-2-ol group increased the stability of these iodonium ylides through

inter- and intramolecular iodine-oxygen interactions. When the iodonium ylide was reacted with a series of protic acids (TREAT-HF, HCl, AcOH and $TsOH.H_2O$), the 2-fluoro, 2-chloro, 2-acetyl and 2-tosyl-1,3-ketoesters were formed giving further evidence to support the proposed mechanism. When the iodonium ylide **220** was reacted with aprotic fluoride sources, such as TBAF and KF, the fluorinated 1,3-dicarbonyl product **172** was not formed, as expected from the proposed mechanism.

### 3.9 References for Chapter 3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# Chapter 4

# Intramolecular Fluorocyclisations of Unsaturated Carboxylic Acids using the Fluoroiodane

## 4.1 Introduction

The intramolecular fluorocyclisation of alkenes is a powerful technique for the construction of multiple bonds in a single step and provides easy access to fluorinated heterocycles.[1-3] These are highly-sought after building blocks for the pharmaceutical and agrochemical industries.[4-6] Isobenzofuranones **238** and **239** (Figure 1), which contain a γ-lactone fused to an aromatic ring, appear in a number of natural products and have been shown to possess anti-fungal, anti-bacterial and anti-tumour activity.[7-11] Benzyl substituted γ-lactones **240** have been shown to have anti-cancer and anti-inflammatory properties.[12] Whilst new strategies have been developed for the synthesis of benzyl-substituted γ-lactones,[12-16] fluorinated analogues have not yet been reported.

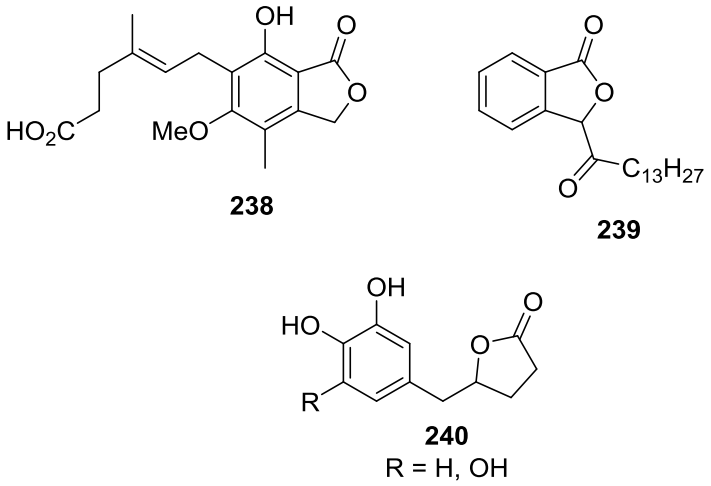


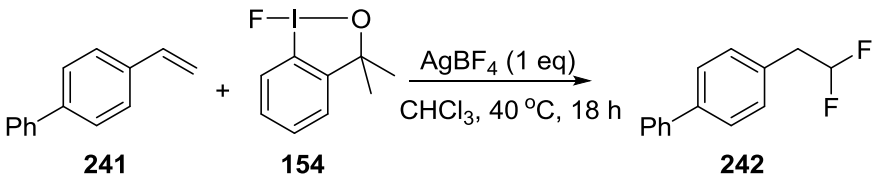

**Figure 1** *Examples of γ-lactones*

Fluoraza reagents such as *N*-fluoropyridinium salts and Selectfluor have been used, in combination with a base, for a variety of fluorolactonisation reactions.[17-20] For example, *N*-fluoro-2,6-dichloropyridinium triflate and Selectfluor have been used to prepare γ-lactones.[17, 18] The fluoraza reagents have also been used in fluoroetherification reactions to provide tetrahydrofurans, tetrahydropyrans and isobenzofurans[21-23] and in aminofluorinations to give fluoropyrrolidines and fluoropyrroloindoles.[23-25] The disadvantage of the fluoraza reagents, however, is that they are prohibitively expensive for large scale applications because they are normally made from elemental fluorine.

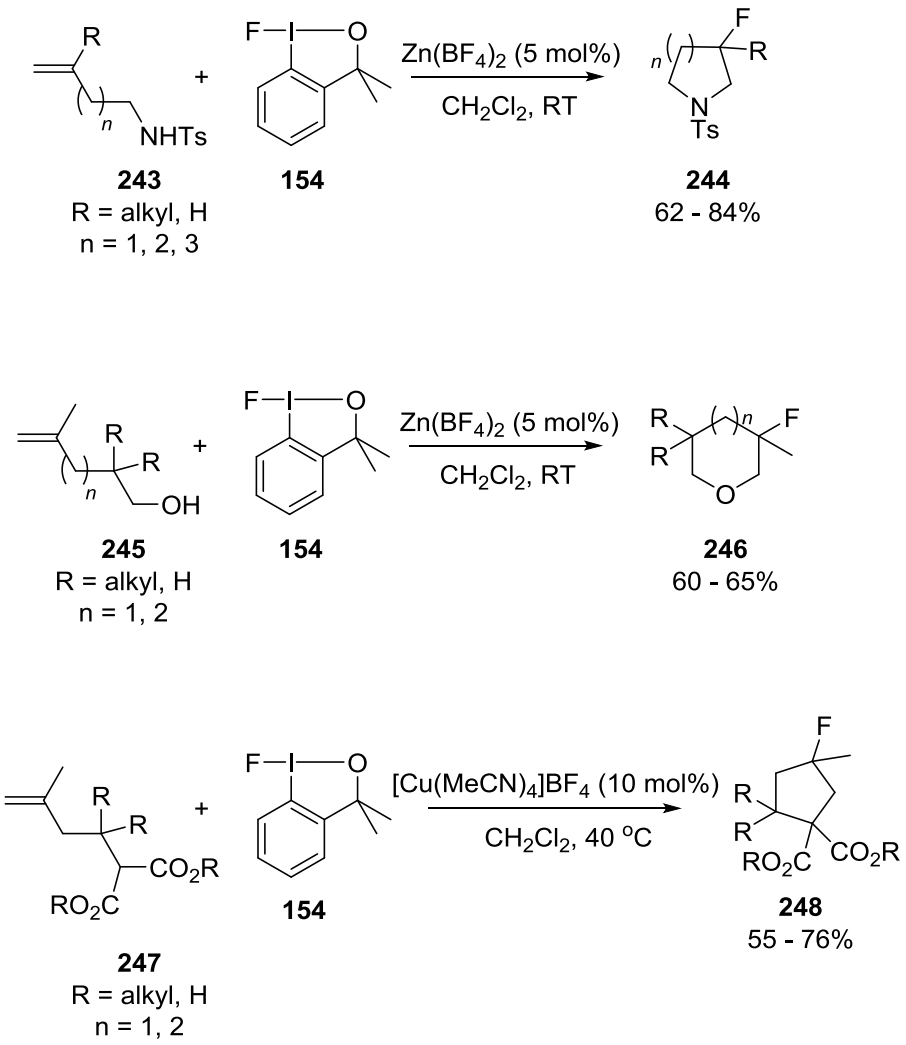
Nucleophilic fluoride sources are more attractive since they are usually cheaper and more readily available. In addition, they provide higher specific radiochemical activities

than electrophilic fluorine sources for the preparation of [$^{18}$F]-labelled radiotracers for positron emission tomography (PET). Difluoroiodoarenes are usually prepared from sources of the fluoride anion and act as electrophilic fluorinating reagents. They have been used in aminofluorination reactions to prepare 3-fluoropyrrolidines, 3-fluoropiperidines and 3-fluoroazepanes.[26-29] In contrast, there is only one example of the use of difluoroiodotoluene, in the presence of pyridine-6HF, to give fluorinated γ-lactones.[30] A disadvantage of many of these procedures is that they require the use of pyridine-HF which is highly corrosive and cannot be used in normal glassware.

The fluoroiodane **154** can be prepared from cheap and readily available sources of fluoride [31, 32] and can be used for the formation of C-F bonds under mild conditions. For example, in this thesis, it has been shown that the fluoroiodane **154** reacts with 1,3-dicarbonyl compounds in the presence of TREAT HF.[31, 33] This is a safer alternative to pyridine-HF and can be used in normal glassware.[34] Szabó has shown that the fluoroiodane **154** can be used for the difluorination of alkenes in the presence of $AgBF_4$ (Scheme 1).[35] In these reactions, a phenyl migration was observed to give 2,2-difluorinated products **242**. More recently, Szabó has shown that the fluoroiodane **154** can also be used for fluorocyclisation reactions of unsaturated amines, alcohols and malonates using catalytic amounts of either $Zn(BF_4)_2.xH_2O$ or $[Cu(MeCN)_4]BF_4$ (Scheme 2).[36]

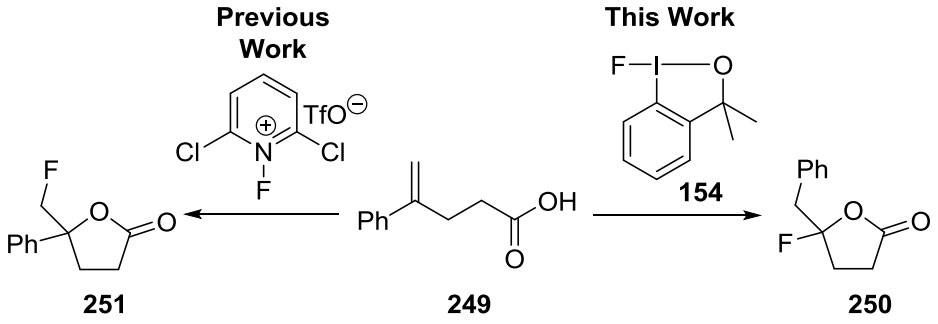



**Scheme 1** *Fluorination of alkenes using the fluoroiodane*




**Scheme 2** Fluorocyclisations using the fluoroiodane

In an extension to Szabó's work, this chapter will discuss the fluorocyclisation of phenyl-substituted unsaturated carboxylic acids. These unusual reactions combine an intramolecular fluorocyclisation with a phenyl migration to deliver novel lactones containing a tertiary alkyl fluoride **250**. In contrast, when the fluoraza reagents are reacted with phenyl-substituted unsaturated alkenes, γ-lactones containing a primary alkyl fluoride **251** are produced (Scheme 3).[17, 18]




**Scheme 3** *Reactivity of the fluoraza reagents compared to the fluoroiodane*

In this chapter the reactivity of the fluoroiodane **154** with 4-phenyl-4-pentenoic acid **249** will be discussed. The optimisation of the reaction in the presence of different additives and the substrate scope with different unsaturated carboxylic acids will also be presented.[37]

A secondary aim of this chapter was to investigate the potential application of the fluorocyclisation reaction to [$^{18}$F]-PET chemistry. Since **154** is easily prepared from simple anionic fluoride salts, it could be viewed as an attractive reagent for preparing [$^{18}$F]-labelled radiotracers for PET imaging. To explore its potential application for synthesising [$^{18}$F]-labelled lactones, the fluorocyclisation of **249** in the absence of any fluoride additives was investigated. This would ensure that the fluoride could only be provided by **154** and was not coming from any additives.[37]

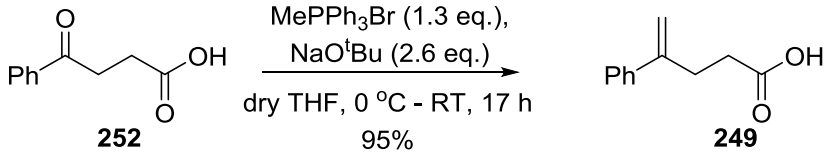
Finally, the reactivity of a bromoiodane **65** in a cyclisation reaction was investigated, in order to determine if the selectivity of the reaction was the same as that observed with the fluoroiodane **154**.

The chapter will be divided into five sections:

1. Initial reactions between the fluoroiodane and 4-phenyl-4-pentenoic acid.
2. Optimisation of the reaction between the fluoroiodane and 4-phenyl-4-pentenoic acid.
3. Substrate scope of the fluorocyclisation reaction.
4. Additive-free fluorocyclisation reactions.
5. Bromocyclisation reactions.

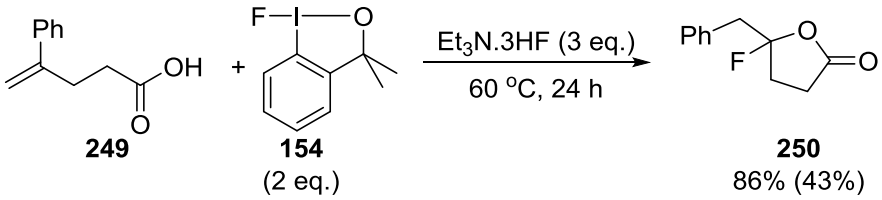
## 4.2 Initial Reactions between the Fluoroiodane and 4-Phenyl-4-pentenoic Acid

In order to probe the feasibility of an intramolecular fluorocyclisation reaction using the fluoroiodane **154**, 4-phenyl-4-pentenoic acid **249** was chosen as a model substrate. 4-Phenyl-4-pentenoic acid **249** was prepared from 4-oxo-4-phenylbutanoic acid **252** in an excellent yield of 95% following the literature procedure (Scheme 4).[38] The characterisation data for **249** was in agreement with the literature.[39]




**Scheme 4** *Preparation of 4-phenyl-4-pentenoic acid*

The model substrate **249** was initially reacted under similar conditions to those used for the fluorination of 1,3-dicarbonyl compounds (Chapter 2). When 4-phenyl-4-pentenoic acid **249** was reacted with 2 equivalents of the fluoroiodane **154** in the presence of 3 equivalents of TREAT-HF a novel product was formed which contained a tertiary alkyl fluoride **250** (Scheme 5). This was isolated in a 43% yield by column chromatography.

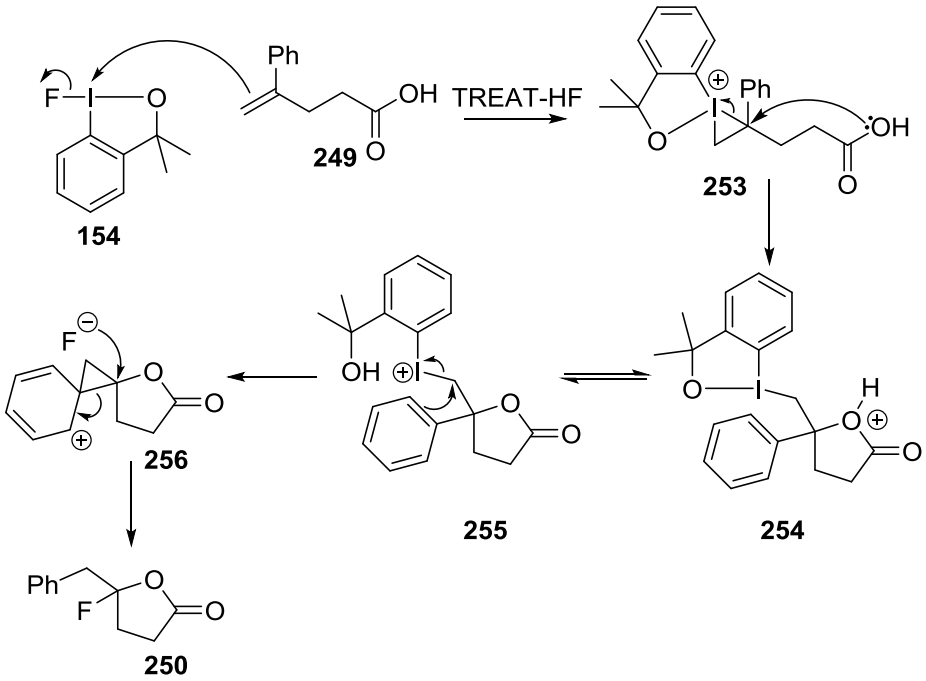



**Scheme 5** *Fluorocyclisation of 4-phenyl-4-pentenoic acid with the fluoroiodane*

The identity of **250** was confirmed by $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectroscopy and ASAP mass spectrometry. In the $^{13}C$ NMR spectrum a doublet corresponding to a quaternary carbon with a coupling constant of 230.7 Hz was observed at 119.2 ppm. This large C-F coupling constant, suggested that the fluorine atom was directly attached to a quaternary carbon. In the $^{1}H$ NMR spectrum a 2H doublet was observed at 3.29 ppm with a coupling constant of 14.7 Hz. This was consistent with $^{3}J_{HF}$ coupling and suggested the presence of a C$H_2$CF moiety. Unusually, both of the protons of the $CH_2$ group appear equivalent. This must have been due to the fact that their chemical shifts are very similar. In the $^{19}F$ NMR spectrum of **250** a peak was observed at -97.0 ppm, which was in stark contrast to the $^{19}F$ NMR signal of γ-lactones containing a primary alkyl fluoride.

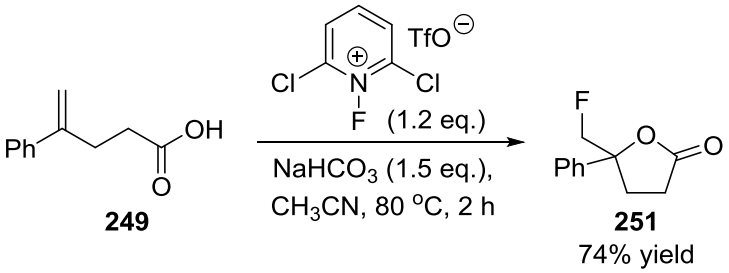
For example, the $^{19}F$ NMR signal of 5-(fluoromethyl)dihydrofuran-2(3H)-one **134** (Chapter 2) was observed at -232.5 ppm.

A proposed mechanism for the cyclisation, phenyl migration and fluorination reaction is given in Scheme 6. In the first step the fluoroiodane **154** undergoes an electrophilic addition to the alkene **249** to give the cyclic iodonium intermediate **253**. An intramolecular nucleophilic attack of the hydroxyl group occurs at the more substituted carbon because it is better able to stabilise a partial positive charge and is therefore more electrophilic. The π donation of the aromatic ring is promoted by the excellent leaving group ability of the iodoaryl group. Finally, regioselective ring opening of the cyclopropane ring of **256** gives the fluorinated product **250**. A similar aryl migration has also been reported by Szabó in the difluorination of styrenes using fluoroiodane **154** and by Wirth in the intramolecular lactonisation of **249** with (diacetoxyiodo)benzene.[35, 40]




**Scheme 6** *Proposed mechanism for the fluorocyclisation reaction*

In contrast to the reaction of **249** with the fluoroiodane **154**, it has been reported that when **249** is reacted with the fluoraza reagent, *N*-fluoro-2,6-dichloropyridinium triflate, a γ-lactone containing a primary alkyl fluoride **251** was formed (Scheme 7).[17] This shows that the fluoroiodane **154** provides a unique opportunity to prepare new fluorinated lactones, which are inaccessible *via* current methods.




**Scheme 7** *Fluorocyclisation of 4-phenyl-4-pentenoic acid with a fluoraza reagent*

## 4.3 Optimisation of the Reaction between the Fluoroiodane and 4-Phenyl-4-pentenoic Acid

### 4.3.1 Optimisation with TREAT-HF

Encouraged by the initial results, the reaction conditions were optimised. In the reaction shown in the previous section (Scheme 5), the conversion was calculated from the amount of fluorinated product **250** observed relative to the amount of starting material **249** remaining. In order to improve the accuracy of the conversion calculation, an internal standard was introduced. One equivalent of naphthalene was added at the end of the reaction, before any work-up had taken place and conversions were calculated by $^{1}$H NMR spectroscopy. In order to facilitate a large number of optimisation reactions, the scale was reduced to just 0.54 mmol (0.15 g) of the fluoroiodane **154** compared to the 2.9 mmol (0.8 g) of the fluoroiodane **154** discussed above.

The reaction between the fluoroiodane **154** and 4-phenyl-4-pentenoic acid **249** in the presence of 3 equivalents of TREAT-HF at 60 $^{o}$C for 24 hours resulted in a 35% conversion to the desired fluorinated product **250** (entry 1, Table 1). When the amount of TREAT-HF was doubled, the conversion to **250** increased slightly to 40% (entry 2) but the addition of more TREAT-HF did not improve the conversion (entry 3). Interestingly, there was more starting material remaining in the reactions when more TREAT-HF was used (entries 2 and 3), suggesting that the reaction was cleaner and that fewer by-products were formed. When the fluorination reaction was carried out in the absence of TREAT-HF, all of the starting material was consumed but the desired product **250** was not observed (entry 4). It was not possible to identify any individual

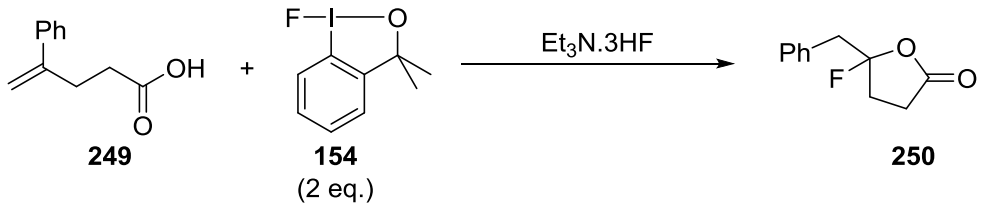
compounds from this complex mixture. A similar result was obtained when the more acidic, pyridine-HF, was used instead of TREAT-HF(entry 5).

When the temperature of the fluorination reaction was decreased to 40 $^{o}$C, the yield of the fluorinated product decreased to 24% but the reaction was much cleaner, as demonstrated by the significant amount of starting material remaining (entry 6). The duration of this reaction was extended to 48 hours but this only resulted in a very slight increase in conversion to the desired product **250** (entry 7). When the reaction was carried out at 80 $^{o}$C, almost all of the starting material was consumed but the conversion to **250** was low (entry 8).

Various changes were made to the duration of the reaction and this showed that the conversion to the product did not increase significantly after 16 hours. The starting material continued to be consumed, however, suggesting that side reactions were occurring (entries 1, 9, 10 and 11).

Polar aprotic solvents are known to increase the nucleophilicity of the fluoride anion.[41] For this reason the reaction was attempted in acetonitrile and the conversion to **250** increased slightly to 43% (entry 12). The reaction in DMF, however, was much slower and only an 8% conversion to **250** was observed after 24 hours at 60 $^{o}$C (entry 13). No reaction occurred in the absence of the fluoroiodane **154**, demonstrating that it is essential for the reaction to proceed (entry 14).

**Table 1** Optimisation of the reaction between 4-phenyl-4-pentenoic acid and the fluoroiodane using TREAT-HF as an additive




| Entry | $Et_3N.3HF$ (eq.) | Solvent | Time (h) | Temp. ($^oC$) | NMR yield[a] (%) | |
|---|---|---|---|---|---|---|
| | | | | | 249 | 250 |
| 1 | 3 | - | 24 | 60 | 19 | 35 |
| 2 | 6 | - | 24 | 60 | 45 | 40 |
| 3 | 9 | - | 24 | 60 | 43 | 37 |
| 4 | 0 | $CH_2Cl_2$ | 24 | 60 | 0 | 0 |
| 5 | 3[b] | - | 24 | 60 | 0 | 0 |
| 6 | 3 | - | 24 | 40 | 71 | 24 |
| 7 | 3 | - | 48 | 40 | 49 | 31 |
| 8 | 3 | - | 24 | 80 | 3 | 19 |
| 9 | 3 | - | 16 | 60 | 40 | 30 |
| 10 | 3 | - | 48 | 60 | 12 | 34 |
| 11 | 3 | - | 72 | 60 | 8 | 39 |
| 12 | 3 | $CH_3CN$ | 24 | 60 | 18 | 43 |
| 13 | 3 | DMF | 24 | 60 | 65 | 8 |
| 14[c] | 3 | - | 24 | 60 | 84 | 0 |

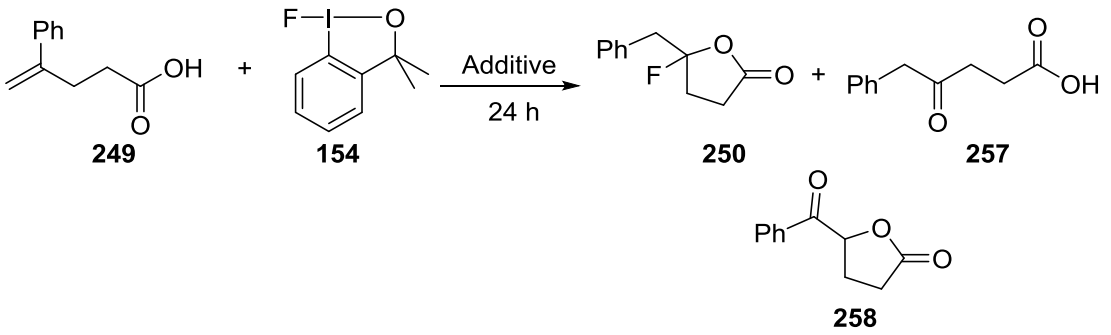
[a] Conversion calculated by $^1H$ NMR spectroscopy using naphthalene as an internal standard; [b] Pyridine-HF used instead of TREAT-HF; [c] Control reaction without fluoroiodane **154**.

### 4.3.2 Optimisation with Other Additives

Despite numerous changes to the reaction conditions using TREAT-HF as an additive, the fluorinated product **250** could only be obtained in a maximum of 43% conversion (entry 12, Table 1). For this reason, the effect of other additives to the reaction was investigated. When a basic source of fluoride, KF, was used as an additive for the fluorination reaction, the reaction was completely inhibited (entries 1 and 2, Table 2).

Lewis acidic copper(I) catalysts have been widely used for the activation of Togni's trifluoromethyliodane.[42] When the reaction was attempted in the presence of 0.3 equivalents of $[Cu(MeCN)_4]PF_6$ 100% of the starting material was consumed but none of the desired product **250** was observed (entry 3). Instead, an open-chain product **257** and a ketolactone **258** were observed with 21% and 17% conversions respectively. An almost identical result was obtained in the presence of 0.3 equivalents of $AgBF_4$ (entry 4). Under Szabó's conditions for the difluorination of alkenes[35] the conversion to the ring opened product **257** increased significantly to 75% (entry 5).

**Table 2** Optimisation of the reaction between 4-phenyl-4-pentenoic acid and the fluoroiodane using other additives




| Entry | IF (eq.) | Additive | Solvent | Temp ($^oC$) | NMR Yield [a] (%) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 249 | 250 | 257 | 258 |
| 1 | 2 | KF (3 eq.) | $CH_3CN$ | 60 | 94 | 0 | 0 | 0 |
| 2 | 2 | KF (3 eq.) | DMF | 60 | 81 | 0 | 0 | 0 |
| 3 | 2 | $[Cu(MeCN)_4]PF_6$ (0.3 eq.) | $CH_3CN$ | 60 | 0 | 0 | 21 | 17 |
| 4 | 2 | $AgBF_4$ (0.3 eq.) | $CH_2Cl_2$ | 60 | 0 | 0 | 23 | 12 |
| 5[b] | 1 | $AgBF_4$ (1 eq.) | $CH_2Cl_2$ | 40 | 4 | 0 | 75 | 0 |
| 6[b] | 1 | $AgBF_4$ (1 eq.), mol sieves | $CH_2Cl_2$ | 40 | 0 | 76 | 0 | 0 |

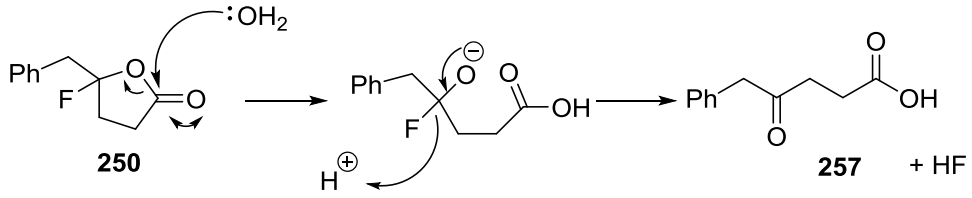
[a] Conversion calculated by $^1H$ NMR spectroscopy using naphthalene as an internal standard; [b] Reaction time reduced to 18 h.

The ring opened product **257** could have been formed by acid catalysed ring-opening of the fluorinated product **250** (Scheme 8). The fluorinated product **250** was found to decompose to the ring-opened product **257**, however, this only occurred after

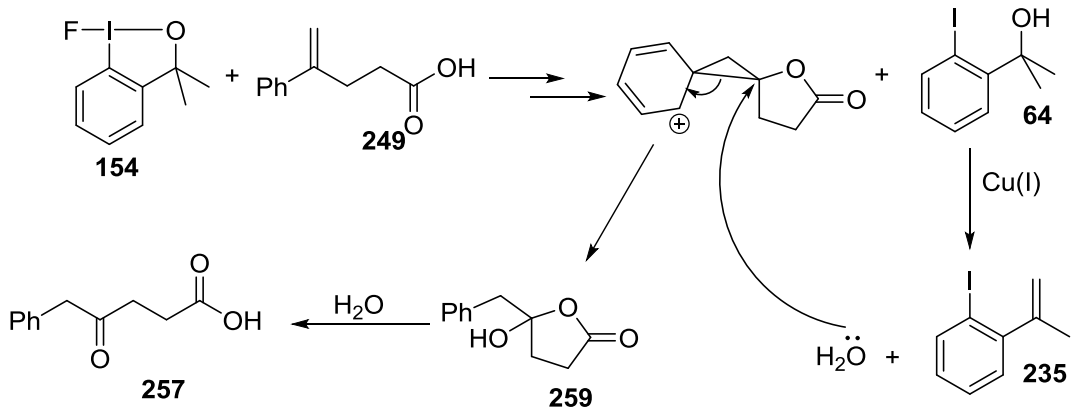
approximately 2-3 days in air at room temperature. The product **250** was stable during column chromatography showing that it is not highly sensitive to acid hydrolysis. It was, therefore, not thought that this was the route to the formation of **257** in the reaction.

The iodoalkene **235** was observed as a by-product in both the $[Cu(MeCN)_4]PF_6$ and $AgBF_4$ catalysed reactions (entries 3-5). This was presumably formed by the Lewis acid catalysed dehydration of the iodoalcohol by-product **64**. An alternative theory for the formation of the ring-opened by-product **257**, therefore, was that water was acting as a competing nucleophile to form the hydroxy-substituted lactone **259** which gave **257** following hydrolysis (Scheme 9).

In order to test the theory that water was acting as a competing nucleophile the reaction was repeated in the presence of 4Å molecular sieves. This resulted in a striking change in the reaction and a 76% conversion to the fluorinated product **250** was observed (entry 6, Table 2). Interestingly, rather than absorbing any water formed by the Lewis acid catalysed dehydration of the iodoalcohol **235**, the addition of molecular sieves actually stopped the dehydration reaction occurring. It is not clear why molecular sieves would act in this way.



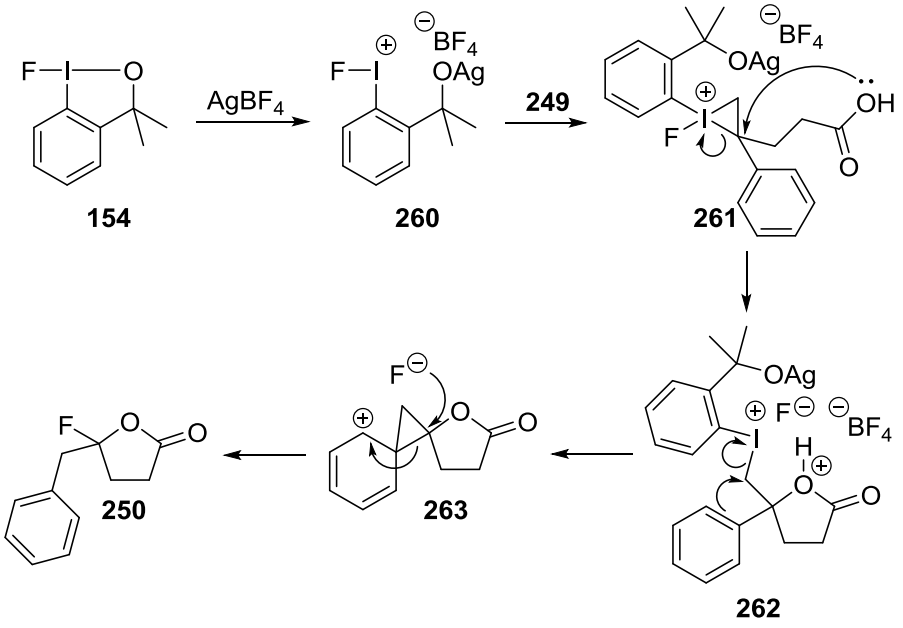

**Scheme 8** *Proposed mechanism for the formation of the ring opened by-product*




**Scheme 9** *Alternative proposed mechanism for the formation of the ring opened by-product*

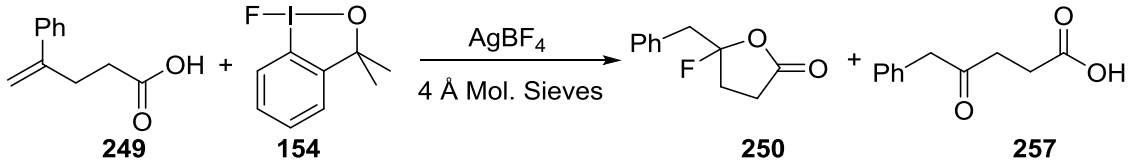
### 4.3.3 Optimisation with $AgBF_4$

The role of the $AgBF_4$ additive in the previous reactions (Table 2) was most likely to activate the fluoroiodane **154** as proposed by Szabó.[35] The proposed mechanism for the fluorination reaction in the presence of $AgBF_4$ is similar to that given in Scheme 6 (page 6) except for the activation of the fluoroiodane **154** to give intermediate **260** (Scheme 10).




**Scheme 10** *Proposed mechanism for the $AgBF_4$ catalysed fluorocyclisation reaction*

**Table 3** *Optimisation of the reaction between 4-phenyl-4-pentenoic acid and the fluoroiodane using $AgBF_4$ as an additive*




249 154 250 257

| Entry | IF (eq.) | $AgBF_4$ (eq.) | Temp. ($^oC$) | Time (h) | Solvent | NMR Yield[a, b] (%) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | 249 | 250 | 257 |
| **1** | 1 | 1 | 40 | 18 | $CH_2Cl_2$ | 11 | 76 | 2 |
| **2** | 1.5 | 1 | 40 | 18 | $CH_2Cl_2$ | 1 | 93 | 6 |
| **3** | 1.5 | 1 | 40 | 18 | $CH_3CN$ | 6 | 83 | 5 |
| **4** | 1.5 | 1 | RT | 18 | $CH_2Cl_2$ | 4 | 93 | 2 |
| **5** | 1.5 | 1 | RT | 8 | $CH_2Cl_2$ | 2 | 57 | 1 |
| **6** | 1.5 | 1 | 40 | 8 | $CH_2Cl_2$ | 0 | 92 | 2 |
| **7** | 1.5 | 1 | 40 | 4 | $CH_2Cl_2$ | 3 | 87 | 2 |
| **8** | 1.5 | 1 | 40 | 1 | $CH_2Cl_2$ | trace | 88 (81) | 3 |
| **9** | 1.5 | 0.6 | 40 | 18 | $CH_2Cl_2$ | trace | 89 | 4 |
| **10** | 1.5 | 0.4 | 40 | 18 | $CH_2Cl_2$ | 5 | 86 | 3 |
| **11** | 1.5 | 0 | 40 | 18 | $CH_2Cl_2$ | 0 | 63 (52) | 4 |
| **12** | 0 | 1 | 40 | 18 | $CH_2Cl_2$ | 92 | 0 | 0 |

[a] Conversion calculated by $^1$H NMR spectroscopy using naphthalene as an internal standard; [b] Isolated yields in parenthesis.

When the reaction between 4-phenyl-4-pentenoic acid **249** and 1 equivalent of the fluoroiodane **154** was carried out using 1 equivalent of $AgBF_4$ and molecular sieves at 40 $^o$C for 18 hours, a 76% conversion to the fluorinated product was observed (entry 1, Table 3). When the amount of the fluoroiodane **154** was increased to 1.5 equivalents, all of the starting material was consumed and the conversion to **250** increased to 93% (entry 2). No increase in conversion was observed when the reaction was carried out in acetonitrile (entry 3). High conversions were obtained at room temperature (entry 4), however the conversion fell to 57% when the duration of the room temperature reaction was decreased to 8 hours (entry 5). In contrast, at 40 $^o$C, the duration of the reaction could be reduced to just one hour with no significant decrease in the conversion to the fluorinated product **250** (entry 8). When the reaction was carried out at 40 $^o$C for 18

hours, the amount of $AgBF_4$ could be reduced to 0.4 equivalents and the conversion to **250** remained high at 86%. When no $AgBF_4$ was added a 63% conversion to the fluorinated product was obtained with the molecular sieves as the only additive (entry 11). The product from this reaction was isolated in a 52% yield. Finally, a test reaction showed that the addition of the fluoroiodane **154** was essential for the reaction to proceed (entry 12).

Following these optimisation reactions it was decided that the optimum conditions which would be used for further reactions would be 40 $^{o}$C for 1 hour using 1 equivalent of $AgBF_4$ in the presence of 4 Å molecular sieves (entry 8, Table 3). This was because under these conditions a fair compromise between high conversion and a short reaction time was obtained.

### 4.4 Substrate Scope of the Fluorocyclisation Reaction

All of the substrates used in this section were prepared in a Wittig reaction according to the literature procedure (see Chapter 6).[38] The substrates **265**-**268** and **270**-**273** were obtained in good to excellent yields (57-100%) after purification by column chromatography and/or recrystallization (Figure 2). 4-(4-Methoxyphenyl)pent-4-enoic acid **264**, 2-(1-phenylvinyl)benzoic acid **269** and 2-(prop-1-en-2-yl)benzoic acid **274** were quite insoluble in organic solvents and were therefore obtained in lower yields after purification (22-35%).

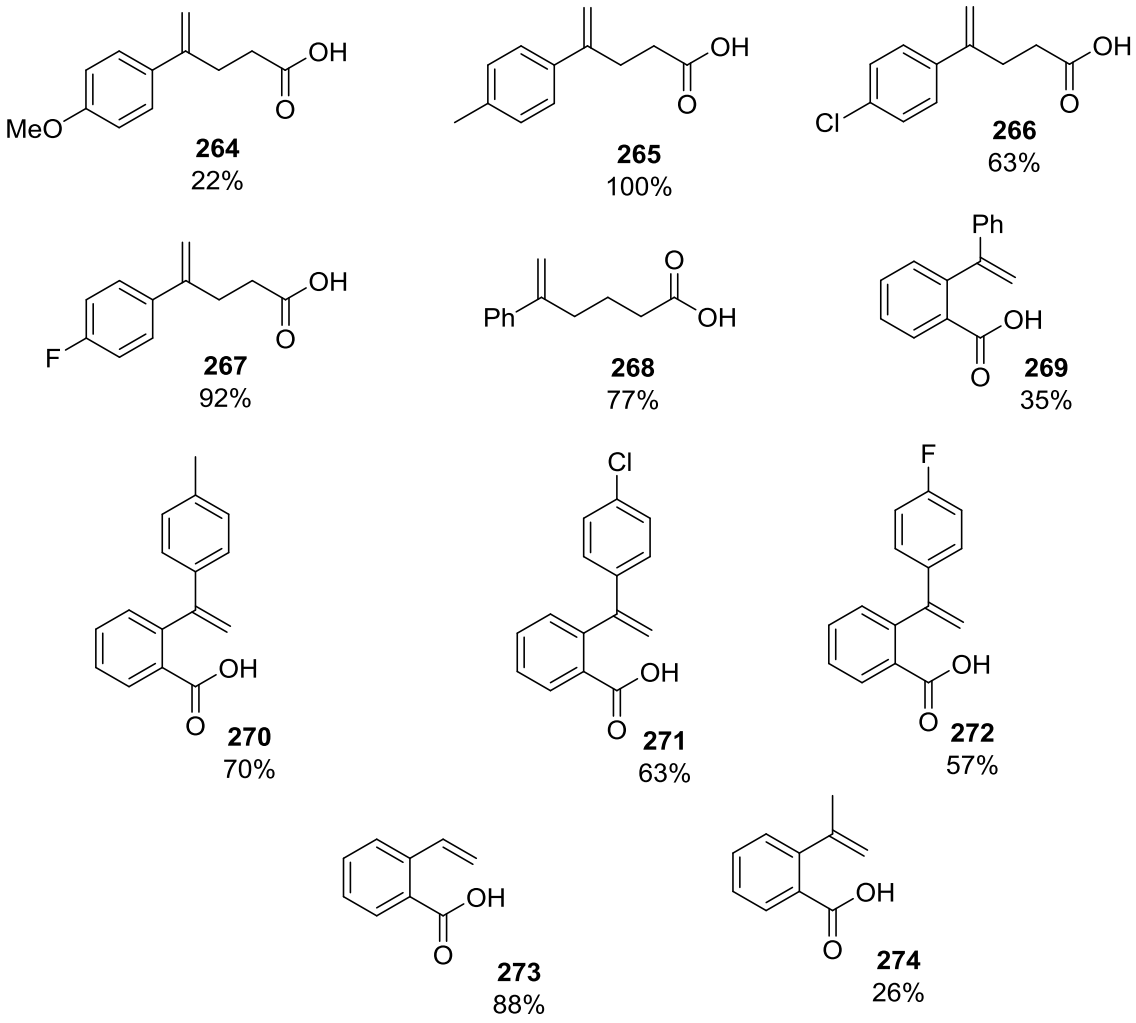
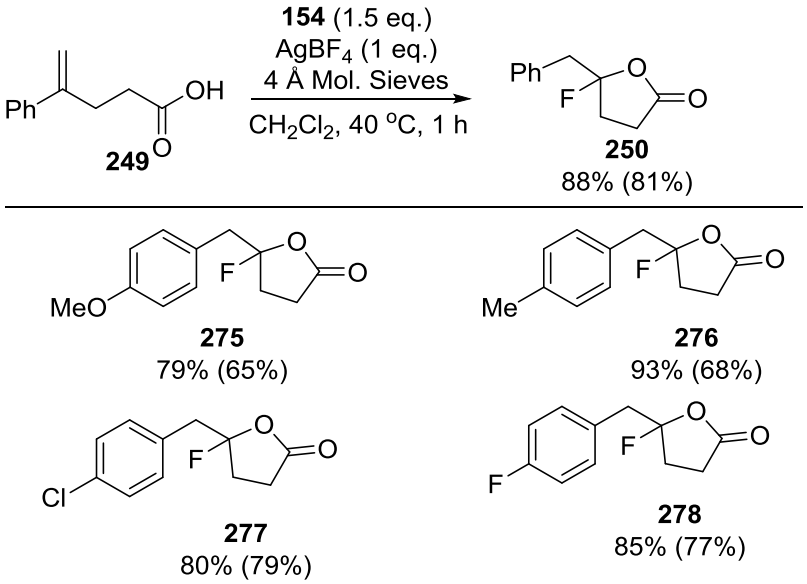



**Figure 2** *Substrates for the fluorocyclisation reactions*

### 4.4.1 Preparation of Benzyl-Substituted γ-Lactones

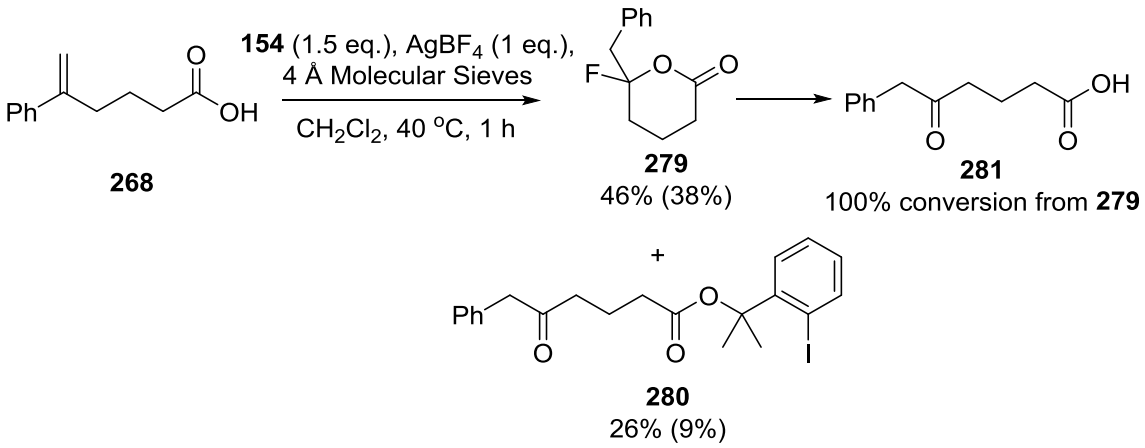
The scope of the fluorocyclisation reaction was probed with a series of unsaturated carboxylic acids (Scheme 11). The mild reaction conditions were compatible with a number of functional groups on the aromatic ring including alkoxy, alkyl, and halide substituents. The fluorinated γ-lactones were each isolated in high yields (65-81%) showing that the reaction was unaffected by the introduction of either electron-donating or electron-withdrawing substituents onto the aromatic ring. The novel γ-lactones **275-278** were characterised by $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectroscopy and ASAP mass spectrometry and the data was similar to that found for **250**.



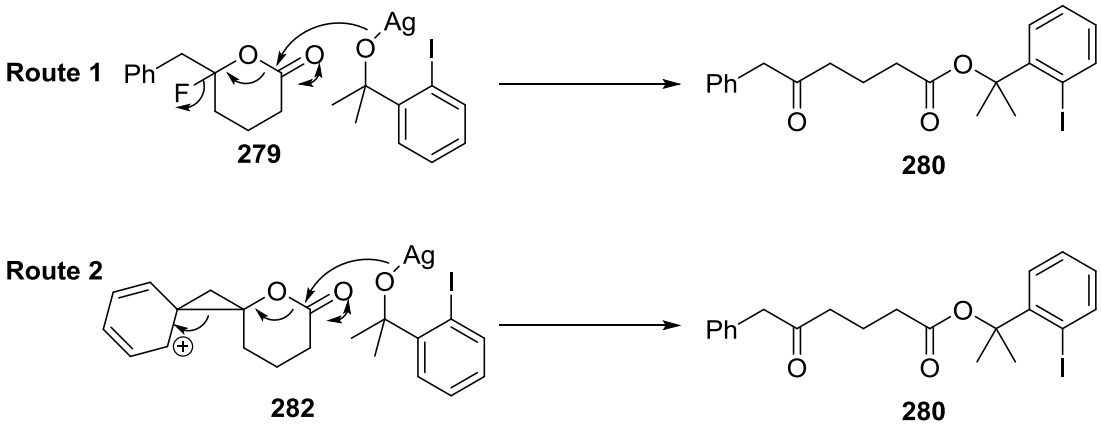

**Scheme 11** *Preparation of γ-lactones*

### 4.4.2 Preparation of a Benzyl-Substituted δ-Lactone

The fluorocyclisation of 5-phenyl-5-hexenoic acid **268** was studied to investigate if δ-lactones could be accessed using this methodology, but the desired product **279** was isolated in only a moderate yield of 38% (Scheme 12). The identity of **279** was confirmed by $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectroscopy and ASAP mass spectrometry and the data was similar to those found for **250**. The δ-lactone **279** was very unstable and decomposed to the ring opened by-product **281** over 2-3 hours in $CDCl_3$ and as an oil at room temperature over approximately 6 hours. Another ring-opened by-product **280** was isolated from this reaction; this new compound was characterised by the usual spectroscopic methods and the data was as expected. The formation of **280** could have been as a result of nucleophilic attack by the alkoxide of the iodoalcohol **64** on either the fluorinated product (route 1, Scheme 13) or the carbocation intermediate **282** (route 2, Scheme 13).



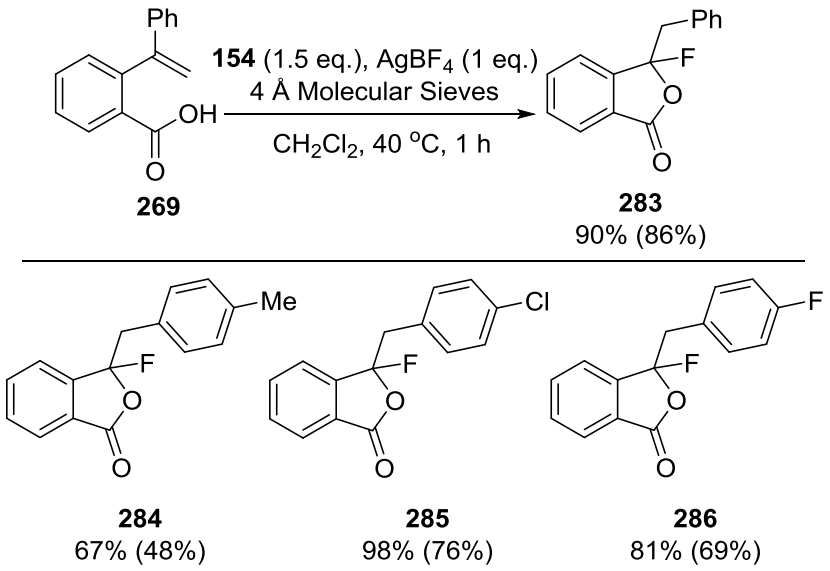

**Scheme 12** *Preparation of δ-lactones*




**Scheme 13** *Proposed mechanisms for the formation of* ***36***

### 4.4.3 Preparation of Fluorinated Isobenzofuranones

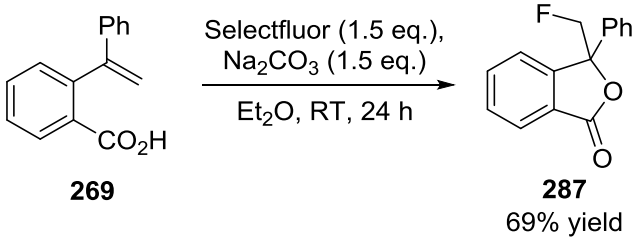
Isobenzofuranones are privileged structures that appear in numerous natural products and can have useful biological properties.[43] When 2-(1-phenylvinyl)-benzoic acid **269** was reacted under the standard reaction conditions the fluorinated isobenzofuranone **283** was obtained in an excellent yield of 86% (Scheme 14). The more electron rich terminal phenyl group underwent the phenyl migration rather than the aromatic backbone. Substitution at the 4-position of the terminal aromatic ring was tolerated well with halides giving high yields (69-76%), but a slightly lower yield of 48% was obtained with the methyl substituent.




**Scheme 14** *Preparation of fluorinated isobenzofuranones*

The identities of the new fluorinated isobenzofuranones **283-286** were confirmed by $^{1}H$, $^{19}F$ and $^{13}C$ NMR spectroscopy and ASAP mass spectrometry. This data was comparable with those found for **250**. In the $^{1}H$ NMR spectra of the fluorinated isobenzofuranones, however, the C$H_A$C$H_B$ protons were seen as two individual doublets of doublets rather than a singlet doublet which was observed for the simple γ-lactones shown in Scheme 11.

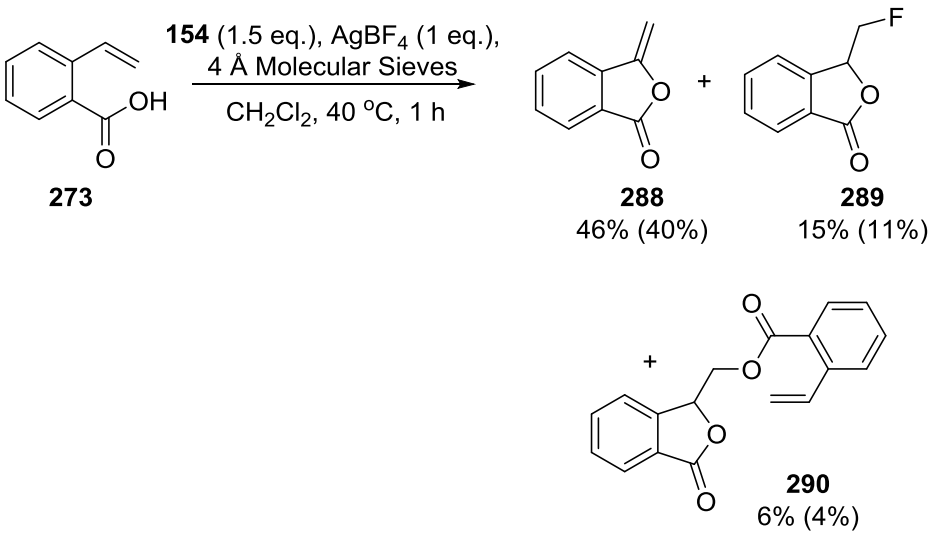
In contrast to the reaction with the fluoroiodane **154**, it has been reported that when **269** was reacted with a fluoraza reagent, Selectfluor, an isobenzofuranone containing a primary alkyl fluoride **287** was obtained (Scheme 15).[18] As with 4-phenyl-4-pentenoic acid, this shows that the fluoroiodane **154** gives the opportunity to prepare new compounds which are not accessible *via* current methods.




**Scheme 15** *Fluorocyclisation of 2-(1-phenylvinyl)-benzoic acid with Selectfluor*

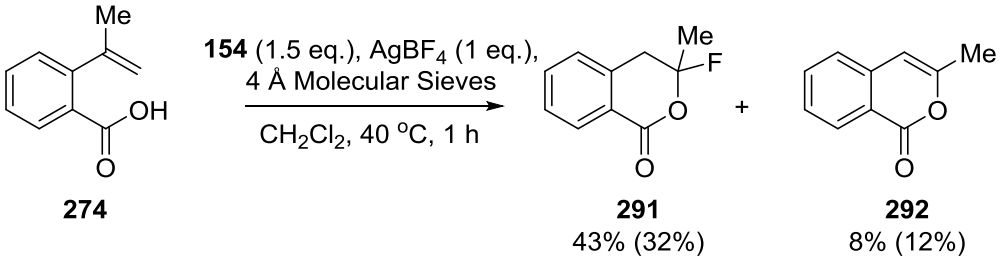
When the fluorination of 3-methyleneisobenzofuran-1-one **273** was attempted the major product, was an alkene **288** which was formed by an elimination reaction (Scheme 16).

The characterisation data for **288** was in agreement with that in the literature.[44] The anticipated new fluorinated product **289** was isolated in an 11% yield and characterised by $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectroscopy and ASAP mass spectrometry. In the $^{19}F$ NMR spectrum of **47** a signal was observed at -228.9 ppm. This was substantially different to the $^{19}F$ signal observed for **250** and **283** and was as expected for a primary alkyl fluoride (the $^{19}$NMR peak of 5-(fluoromethyl)dihydrofuran-2(3H)-one **134** (Chapter 2) was observed at -232.5 ppm). In the $^{1}H$ NMR spectrum, two 1H doublets of doublets of doublets were observed at 4.73 and 4.80 ppm, corresponding to the C$H_A$C$H_B$F protons. In the $^{13}C$ NMR spectrum a signal corresponding to a $CH_2$ group with a $^{1}J_{CF}$ coupling constant of 178.3 Hz was observed at 82.3 ppm. The adduct **290**, which was also isolated from this reaction, must have been formed as a result of the deprotonated starting material **273** acting as a competing nucleophile. **290** was only partially characterised by $^{1}H$ and $^{13}C$ NMR spectroscopy as it was only isolated in a very small amount, as a mixture with the fluorinated product.




**Scheme 16** *Fluorocyclisation of 3-methyleneisobenzofuran-1-one*

In order to prevent an elimination pathway occurring, the fluorination reaction was carried out using the methyl-substituted alkene **274**. In this case, the aromatic backbone underwent the phenyl migration resulting in a δ-lactone fused to an aromatic ring **291** in a 32% yield (Scheme 17). The alkene **292** was also formed in a 12% yield. The new fluorinated product **291** was characterised by $^{1}H$, $^{19}F$ and $^{13}C$ NMR spectroscopy and the data were similar to those for the other fluorinated isobenzofuranones (Scheme 14). The characterisation data for **292** was in agreement with that in the literature.[45]



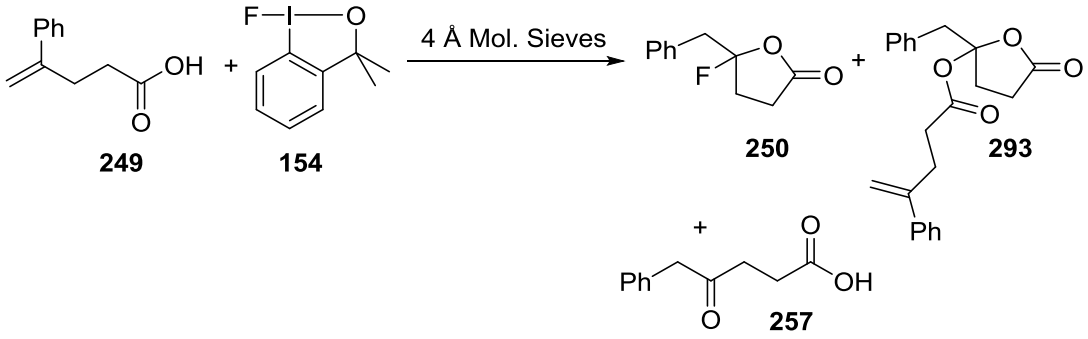

**Scheme 17** *Fluorocyclisation of 2-(prop-1-en-2-yl)benzoic acid*

### 4.5 Additive-Free Fluorocyclisation Reactions

In order to explore the potential of the fluoroiodane **154** for synthesizing $^{18}$F-labelled lactones, the fluorocyclisation of **249** was further investigated using molecular sieves as the only additive. This would ensure that any fluoride incorporated into the product could only be provided by **154** and was not coming from the tetrafluoroborate anion of the silver catalyst as reported by Szabó in the difluorination of styrenes with **154**.[35] Under the standard reaction conditions without any metal catalyst a 63% conversion to **250** was obtained (entry 1, Table 4). A simple pH test revealed that the 4 Å molecular sieves are basic (pH = 10) and, so, it was postulated that the molecular sieves were deprotonating the carboxylic acid to form the more nucleophilic carboxylate which facilitated the intramolecular cyclization. Further evidence to support this theory was the observation of an adduct **293** with an 11% conversion. Presumably, the carboxylate anion of **249** was acting as a competing nucleophile to fluoride in the formation of **293**.

A short reaction time for the fluorination is desirable in view of the short half-life of $^{18}$F (110 min), and so the duration of the reaction was reduced from 18 h to 1 h. This resulted in a decrease in the conversion to **250** to 46% (entry 2). There was no significant change in the conversion to **250** when 2 equivalents of the fluoroiodane **154** were used or at 60 $^{o}$C (entries 3 and 4). In acetonitrile, however, the conversion increased to 58% and **154** was isolated in a 54% yield after a reaction time of just one hour (entry 6).

**Table 4** *Optimization of fluorocyclizations with molecular sieves*

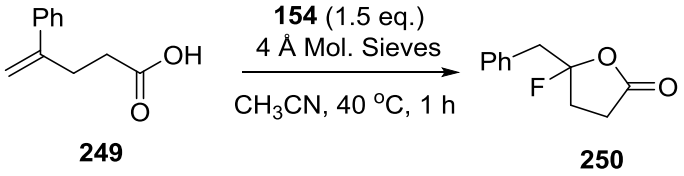



| Entry | IF (eq.) | Temp. ($^{o}$C) | Time (h) | Solvent | NMR Yield[a, b] (%) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | **249** | **250** | **257** | **293** |
| **1** | 1.5 | 40 | 18 | $CH_2Cl_2$ | 0 | 63 (52) | 4 | 11 |
| **2** | 1.5 | 40 | 1 | $CH_2Cl_2$ | 14 | 46 | 2 | 9 |
| **3** | 2 | 40 | 1 | $CH_2Cl_2$ | 18 | 50 (41) | 2 | 9 |
| **4** | 1.5 | 60 | 1 | $CH_2Cl_2$ | 12 | 48 | 3 | 12 |
| **5** | 1.5 | 40 | 1 | $CH_3CN$ | 6 | 58 (54) | 1 | 14 (7) |
| **6** | 2 | 40 | 1 | $CH_3CN$ | 10 | 64 | 2 | 10 |

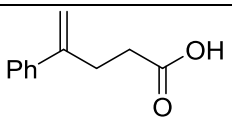
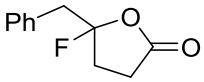
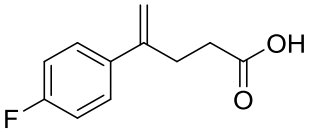
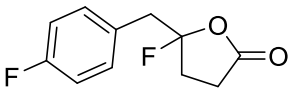
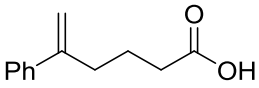
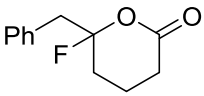
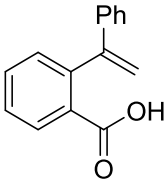
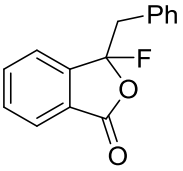
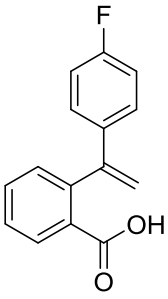
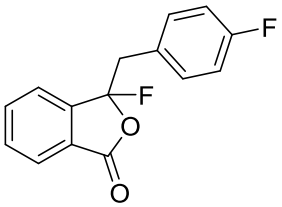
[a] Conversion calculated by $^{1}$H NMR spectroscopy using naphthalene as an internal standard; [b] Isolated yields in parenthesis.

The new fluorination protocol was applied to a small series of unsaturated carboxylic acids (Table 5) and moderate yields were obtained in the formation of the two simple benzyl-substituted γ-lactones **250** and **278** (entries 1 and 2). The formation of the 6-membered ring **279** was much slower, as demonstrated by 23% of the unreacted starting material **268** being recovered (entry 3). Adducts **294** (Figure 3), resulting from the nucleophilic addition of the deprotonated starting material, were isolated from all three of these reactions in low yields (<10%). Since these by-products were only isolated in small amounts, as mixtures with either the respective fluorinated product or the respective starting material, only partial characterisation was possible.

**Table 5** *Substrate scope with molecular sieves*




**249** **250**

| Entry | Starting Material | Product | NMR Yield[a, b] (%) Starting Material | Product |
|---|---|---|---|---|
| 1 |  **249** |  **250** | 6 | 58 (54) |
| 2 |  **267** |  **278** | 10 | 55 (50) |
| 3 |  **268** |  **279** | 30 (23) | 19 (22) |
| 4 |  **269** |  **283** | 8 | 61 (50) |
| 5 |  **278** |  **286** | 3 | 60 (33) |

[a] Conversion calculated by $^{1}$H NMR spectroscopy using naphthalene as an internal standard; [b] Isolated yields in parenthesis.

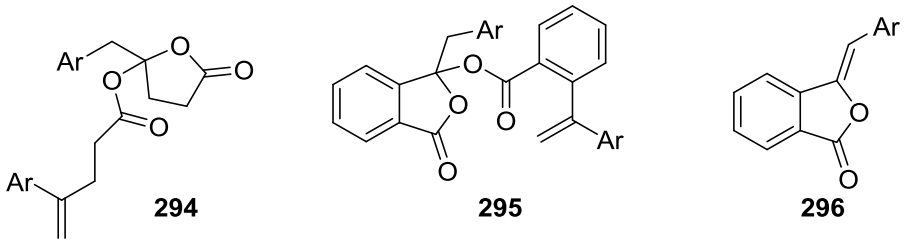


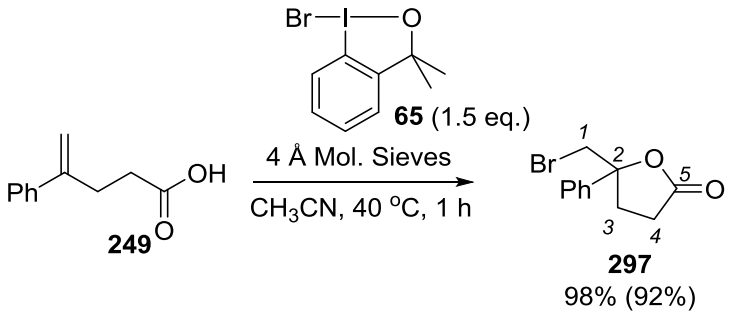

**Figure 3** *By-products of the reactions with molecular sieves*

It was also possible to obtain fluorinated isobenzofuranones **283** and **286** in moderate yields using the new procedure (entries 4 and 5, Table 5). The yield of the *p*-fluoro-substituted product **286** was slightly low because purification by both column chromatography and recrystallization were necessary to obtain a pure material. Again, the related adducts **295** (Figure 3) resulting from nucleophilic addition of the deprotonated starting material, were isolated in small amounts from these reactions (5% in entry 4 and 12% in entry 5). Elimination products **296** (Figure 3) were also isolated in small amounts (<10%) in both entries 4 and 5.

These promising results suggest that the fluoroiodane reagent **154** holds great potential for preparing novel $^{18}$F-labelled heterocycles and developing new PET tracers that are currently inaccessible with conventional nucleophilic fluorination chemistry.

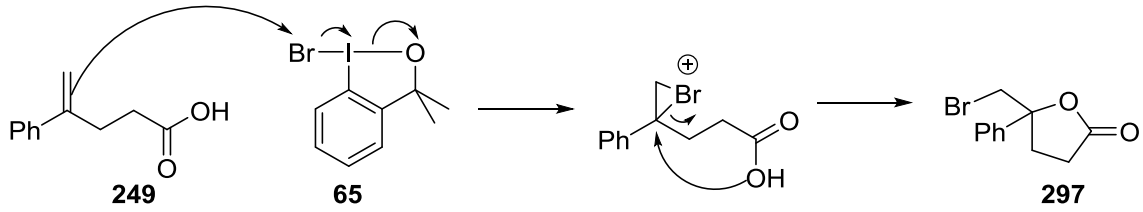
### 4.6 Bromination Reactions

In order to determine if other iodane species could promote analogous cyclisation/ aryl migration pathways with 4-phenyl-4-pentenoic acid **249**, the reaction with the bromoiodane **65** was attempted. In the presence of 4 Å molecular sieves at 40 $^{o}$C for one hour, a 98% conversion to the non-phenyl-migrated primary alkyl brominated lactone **297** was observed (Scheme 18). This was isolated in a 92% yield after column chromatography. The identity of **297** was confirmed by comparison of the spectroscopic data with those in the literature.[39] In order to further confirm that a phenyl migration had not taken place, an HMBC spectrum of the product was recorded. In the HMBC spectrum, the H1 and H1' protons correlated to C2, C3 and the aromatic ring quaternary carbon. There was no correlation between H1/H1' and the *ortho* aromatic proton.




**Scheme 18** *Bromination of 4-phenyl-4-pentenoic acid*

There are two possible explanations for this result. The first is that, due to the increased nucleophilicity of the bromide anion compared to the fluoride anion, nucleophilic attack or reductive elimination occurred too fast for a phenyl migration to take place. It cannot be ruled out, however, that the bromination reaction takes place *via* a completely different mechanism to the fluorination reaction, involving a direct electrophilic bromination (Scheme 19) as reported elsewhere for brominations using **65**.[46]




**Scheme 19** *Possible mechanism for the bromination reaction*

## 4.7 Conclusions

In this chapter, it has been demonstrated that the fluoroiodane **154** can be used for the fluorocyclisation of phenyl-substituted unsaturated carboxylic acids under mild conditions using $AgBF_4$ and molecular sieves. The reaction combines an intramolecular fluorocyclization and an aryl migration to deliver novel lactones which contain a tertiary alkyl fluoride.[37] In contrast, the same reactions with fluoraza reagents give different selectivity and provide lactones containing a primary alkyl fluoride.

It was also shown that the fluorination can proceed in the presence of 4 Å molecular sieves at 40 $^{o}$C in 1 h without a metal catalyst. This demonstrates clearly that the fluoroiodane reagent **154** is suitable for the production of new $^{18}$F-labelled radiotracers for PET imaging.[37]

Finally, it has been shown that when the bromoiodane **65** is used, instead of the fluoroiodane **154**, the selectivity of the reaction changes. A phenyl migration was not observed with the bromoiodane **65** and a γ-lactone containing a primary alkyl bromide **297** was obtained.

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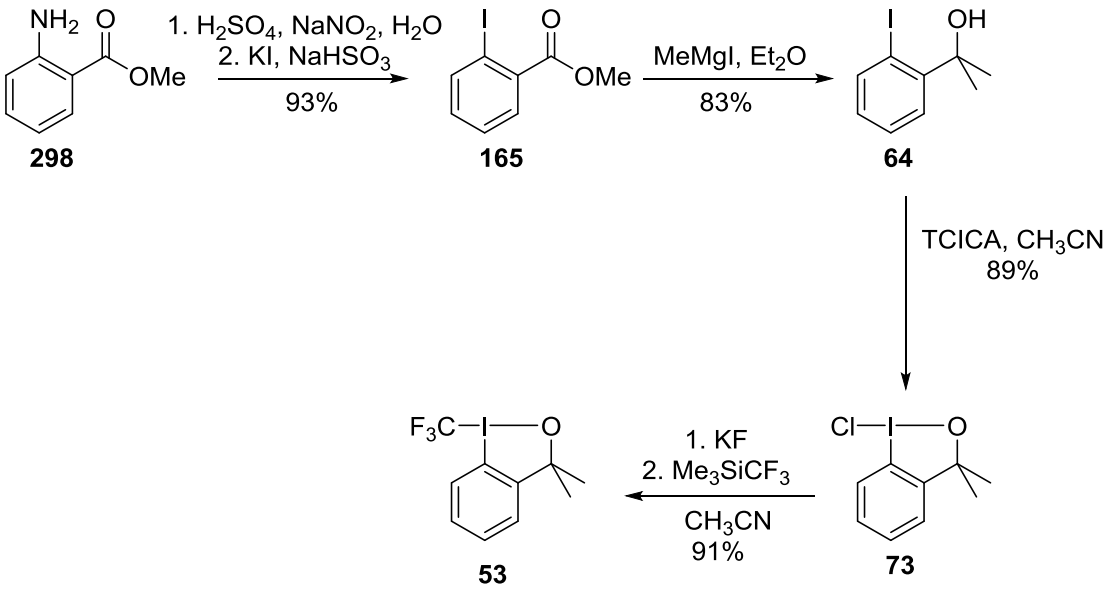
# Chapter 5

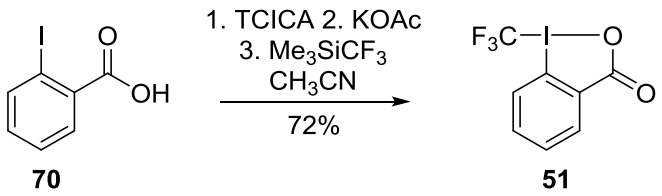
# Synthesis of a Novel Fluoroiodoxolone and Initial Testing as an Electrophilic Fluorinating Reagent.

## 5.1 Introduction

The use of hypervalent iodine compounds as oxidative atom transfer reagents has been well documented in recent years.[1] In particular, Togni's reagents have become extremely popular as electrophilic trifluoromethylating reagents. Togni's alcohol reagent **53** can be prepared in four steps from the commercially available methyl anthranilate **298** (Scheme 1).[2] In contrast, Togni's acid reagent **51** can be prepared in just one pot from 2-iodobenzoic acid **70** (Scheme 2).[3] A wide variety of electrophilic trifluoromethylation reactions have been carried out using these reagents, but due to the range of proposed mechanisms for these reactions, a general comparison of reactivity is not possible.[2] For example, in the trifluoromethylation of *N*-phenylpyrrole, the alcohol reagent **53** gave good yields, whereas the acid reagent **51** gave only trace amounts of the product under the same conditions.[4] In a copper catalysed allylic trifluoromethylation reaction, however, the acid reagent **51** gave excellent yields while the alcohol reagent **53** gave only a trace of the desired product.[5] Despite the lack of a comparative study into the relative reactivity of Togni's two reagents, the acidic reagent **51** is by far the more popular. This is most likely to be attributable to the ease of its synthesis when compared to that for the alcohol reagent **53**.[2]

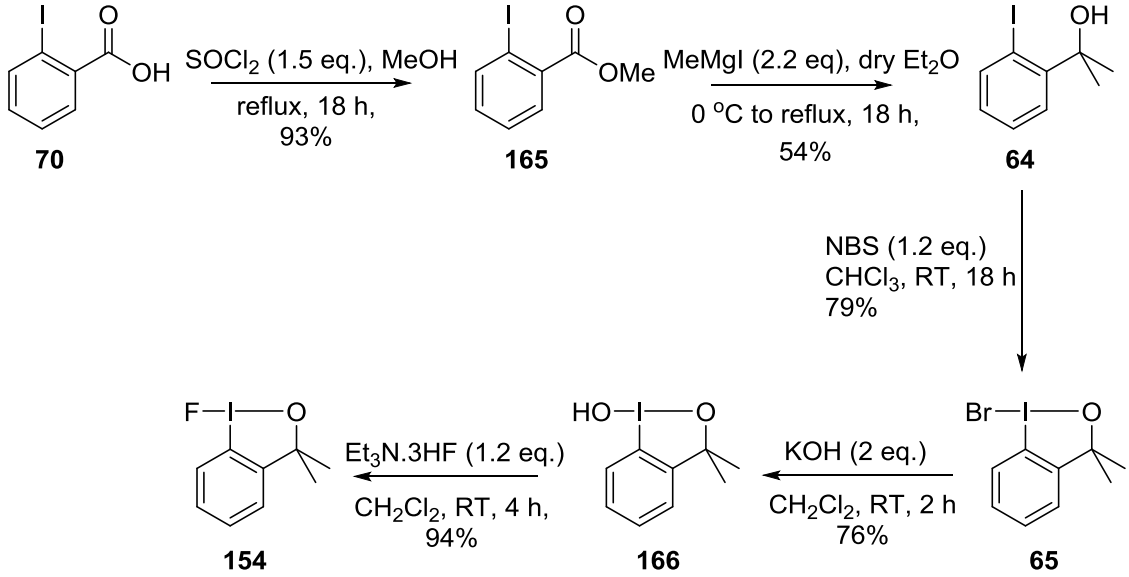



**Scheme 1** *Preparation of Togni's Alcohol Reagent*



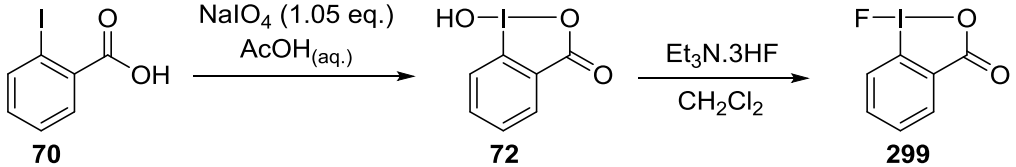

**Scheme 2** *Preparation of Togni's Acid Reagent*

The synthesis of the alcohol derived fluoroiodane **154** via four different routes was discussed in chapter 2. The most viable of these routes for the preparation of the fluoroiodane **154** on a large scale used TREAT-HF as a cheap and readily available source of fluoride (Scheme 3). This process gave the fluoroiodane **154** in five steps from the commercially available 2-iodobenzoic acid **70**.[6]




**Scheme 3** *Preparation of the Fluoroiodane*

The aim of the work in this chapter was to prepare an acid derived fluoroiodoxolone **299** in 2 steps from 2-iodobenzoic acid *via* the hydroxyiodoxolone **72** which is a known compound (Scheme 4).[7, 8] This much shorter synthesis would be a significant advantage over the fluoroiodane **154**.




**Scheme 4** *Proposed Route to the Fluoroiodoxolone*

Another aim of this chapter was to investigate the relative reactivity of the fluoroiodoxolone **299** and the fluoroiodane **154** using 1,3-dicarbonyl compounds as model substrates.

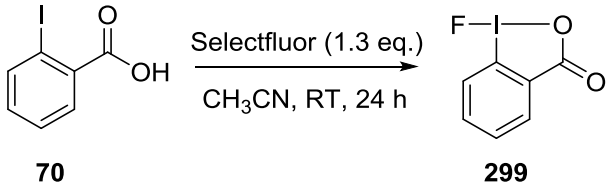
In this chapter, three key areas will be discussed:

1. The synthesis of a novel fluoroiodoxolone species **299** using both electrophilic and nucleophilic sources of fluoride.
2. Testing of the fluoroiodoxolone **299** as a fluorinating reagent with 1,3-dicarbonyl compounds.
3. Comparison of the reactivity of the fluoroiodane **154** with the fluoroiodoxolone **299**.

## 5.2 Preparation of the Fluoroiodoxolone

### 5.2.1 Preparation of the Fluoroiodoxolone using Selectfluor

In the first instance, the synthesis of the fluoroiodoxolone **299** was attempted in just one step from 2-iodobenzoic acid **70** and an electrophilic source of fluorine, Selectfluor. This would allow the fluoroiodoxolone **299** to be prepared quickly and its properties established. This method had also been used for the preparation of the fluoroiodane **154** in one step from the iodoalcohol **64** (Chapter 2). When a solution of 2-iodobenzoic acid **70** and Selectfluor was stirred at room temperature for 24 hours (Scheme 5) an insoluble white solid was obtained. ASAP Mass spectrometry of the solid showed a very small molecular ion peak ($MH^+$) at 266.9307 corresponding to the desired fluoroiodoxolone **299**. Further peaks were also observed in the ASAP mass spectrum corresponding to 2-iodobenzoic acid **70** and 2-iodobenzoic acid with the loss of a hydroxyl group. These peaks could have arisen from the loss of fluorine from the fluoroiodoxolone **299** or they could be due to residual starting material present in the sample. Due to the insolubility of the product of this reaction, further analysis was not possible and, therefore, the product could not be unequivocally assigned as the fluoroiodoxolone **299**.

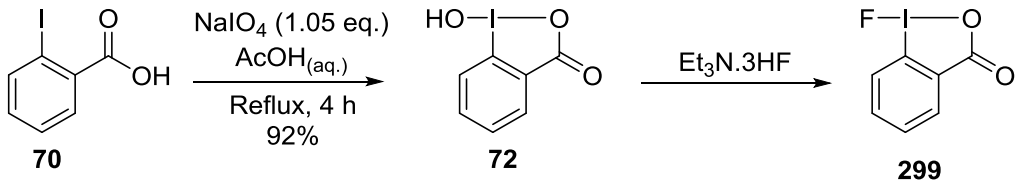



**70** **299**

**Scheme 5** *Preparation of the Fluoroiodoxolone using Selectfluor*

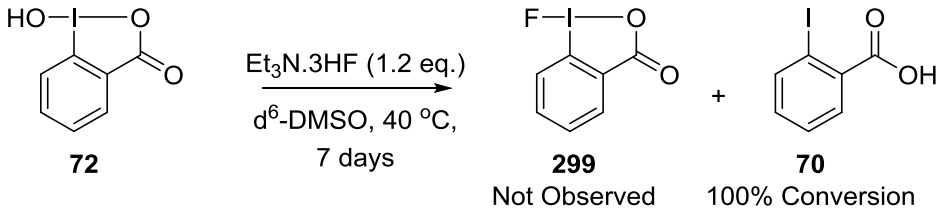
### 5.2.2 Preparation of the Fluoroiodoxolone using TREAT-HF

The preparation of the fluoroiodoxolone **299** was then attempted in two steps using a nucleophilic source of fluoride. In the first step, the hydroxyiodoxolone **72** was prepared from 2-iodobenzoic acid **70** following the literature procedure (Scheme 6).[7] The product was obtained in an excellent yield of 92% and the characterisation data was in agreement with that in the literature.[8] Unfortunately, the hydroxyiodoxolone **72** was only sparingly soluble in DMSO and completely insoluble in other organic solvents such as $CH_3CN$, dichloromethane and toluene. This insolubility, coupled with its high melting point (239-241 $^oC$), meant that subsequent reactions to prepare the fluoroiodoxolone **299** were difficult. Several reactions were carried out in a range of solvents using TREAT-HF as the source of the fluoride anion but in all cases, the starting material was recovered at the end of the reaction.




**Scheme 6** *Attempted Preparation of the Fluoroiodoxolone*

Since the hydroxyiodoxolone **72** was soluble in DMSO, an NMR scale reaction between **72** and TREAT-HF was carried out in $d^6$-DMSO (Scheme 7). After four hours at room temperature, no reaction had occurred and only the starting material was observed by $^1H$ NMR spectroscopy. The reaction mixture was then heated to 40 $^oC$ for 19 hours, upon which, a 26% conversion to 2-iodobenzoic acid **70** was observed in addition to a peak in the $^{19}F$ NMR spectrum at -125.5 ppm. After 7 days at 40 $^oC$, 100% conversion to 2-iodobenzoic acid **70** was observed in the $^1H$ NMR spectrum (Figure 1) and the signal in the $^{19}F$ NMR spectrum also became stronger over this time. It is known that DMSO can be fluorinated by $IF_5$ to give several products.[9] One of these products, thought to be $FCH_2SCHO$, is reported to have a peak in its $^{19}F$ NMR spectrum at -124.8 ppm. This suggests that the fluoroiodoxolone **299** may have formed at the higher temperature but immediately reacted with DMSO to form a product, possibly $FCH_2SCHO$, with a peak in the $^{19}F$ NMR spectrum at -125.5 ppm.




**Scheme 7** *Reaction between the Hydroxyiodoxolone and TREAT-HF in DMSO*

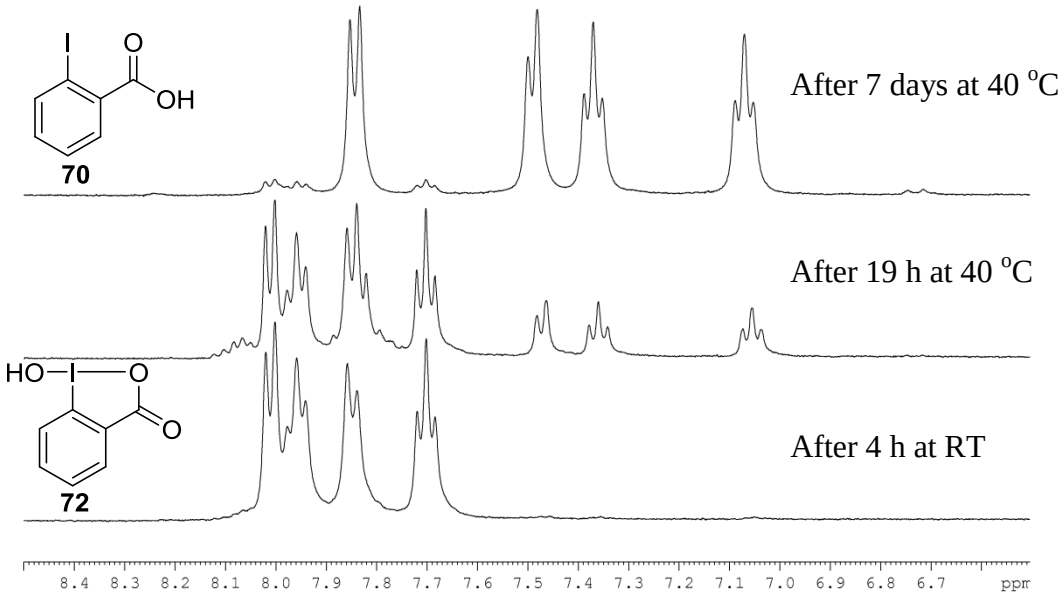
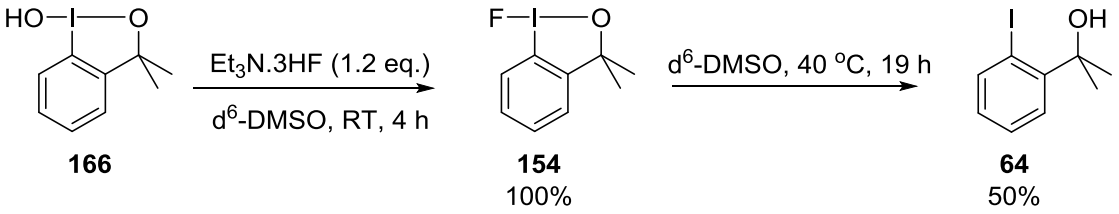



**Figure 1** *Reaction between the Hydroxyiodoxolone and TREAT-HF in DMSO*

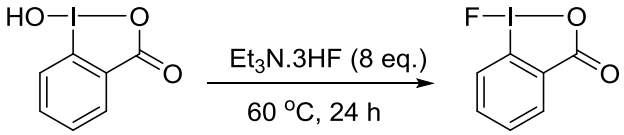
A similar reaction between the hydroxyiodane **166** and TREAT-HF in $d^6$-DMSO was performed in order to establish that DMSO was a suitable solvent for substitution of hydroxide for fluoride using TREAT-HF (Scheme 8). In this case, 100% conversion to the fluoroiodane **154** was observed after 4 hours at room temperature. After this time, the solution was heated to 40 °C and, after 19 hours at this temperature, a 50% conversion to the iodoalcohol **64** was observed, in addition to the appearance of a signal in the $^{19}F$ NMR spectrum at -125.5 ppm. This suggests that the fluoroiodane **154** was formed and at higher temperatures it reacted in a similar way with the solvent.




**166** **154** 100% **64** 50%

**Scheme 8** *Reaction between the Hydroxyiodane and TREAT-HF in DMSO*

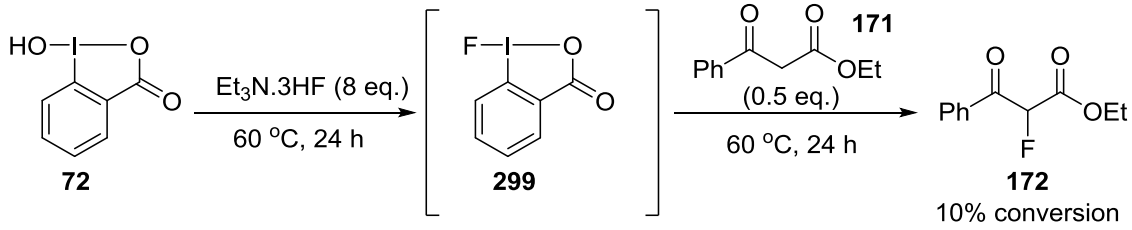
Since the product from the reaction of the hydroxyiodoxolone **72** with TREAT-HF in $d^6$-DMSO may have reacted with the solvent, the reaction was repeated without a solvent and with an increased amount of TREAT-HF. The hydroxyiodoxolone **72** was reacted with 8 equivalents of TREAT-HF without solvent at 60 °C for 24 hours (Scheme 9). The resultant insoluble white solid was analysed by ASAP mass spectrometry, however, a peak for the expected fluoroiodoxolone **299** was not observed. A peak corresponding to 2-iodobenzoic acid **70** was observed, however, which was not seen in the ASAP mass spectrum of the starting material. This suggests that either i) the fluoroiodoxolone **299** fragmented to give 2-iodobenzoic acid **6** during analysis or ii) the fluoroiodoxolone **299** may have formed in the reaction but reacted immediately to form 2-iodobenzoic acid **70.**




**72** **299**

**Scheme 9** *Reaction between the Hydroxyiodoxolone and TREAT-HF*

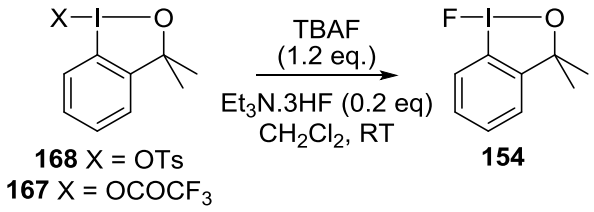
The same reaction was repeated and, after stirring of the hydroxyiodoxolone **72** for 24 hours at 60 °C with 8 equivalents of TREAT-HF, the 1,3-dicarbonyl substrate, ethyl 3-oxo-3-phenylpropanoate **171** was added (Scheme 10). This resulted in a 10% conversion of the starting material to the monofluorinated product **172**. Since it was found in Chapter 2 that ethyl 3-oxo-3-phenylpropanoate **171** does not react with TREAT-HF to form fluorinated products, this result suggested that the fluoroiodoxolone **299** was being formed *in situ*. It cannot be established from this result, however, whether the low conversion to the fluorinated product was because i) only a small amount of the fluoroiodoxolone **299** was present in the reaction mixture, ii) the fluoroiodoxolone **299** is less reactive than the fluoroiodane **154** or iii) the fluoroiodoxolone **299** is insoluble in the reaction mixture.



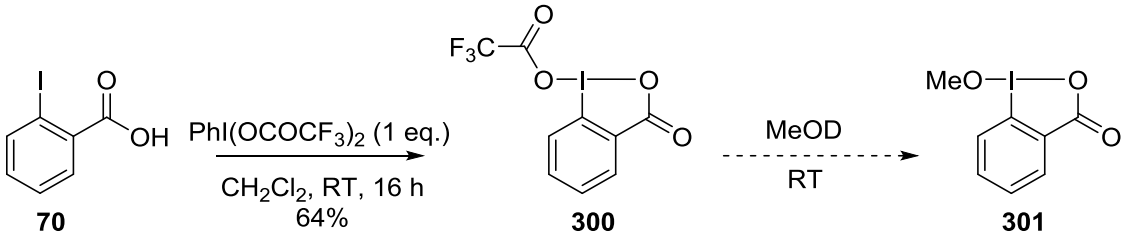

**Scheme 10** *In situ Fluorination using the Fluoroiodoxolone*

### 5.2.3 Preparation of the Fluoroiodoxolone using TBAF

The preparation of the fluoroiodoxolone **299** was also attempted using TBAF as the source of the fluoride anion. This method had also been used for the preparation of fluoroiodane **154** (Scheme 11).[6] The starting material required for this reaction, the trifluoroacetoxyiodoxolone **300**, was prepared from 2-iodobenzoic acid **70** and [bis(trifluoroacetoxy)iodo]benzene in a 64% yield (Scheme 12). A $^{1}$H NMR spectrum of the product was obtained in d$^{4}$-methanol however the data did not match with that expected from the literature.[10] It was not possible to obtain a $^{13}$C NMR spectrum due to the low solubility of the compound. After several days at room temperature in d$^{4}$-methanol, crystals formed in the solution which were identified as the methoxyiodoxolone **301** by X-ray crystallography (Figure 2). ASAP Mass spectrometry, however, did confirm the formation of the trifluoroacetoxyiodoxolone **300**.




**Scheme 11** *Preparation of the Fluoroiodane using TBAF*




**Scheme 12** *Preparation of the Trifluoroacetoxyiodoxolone*

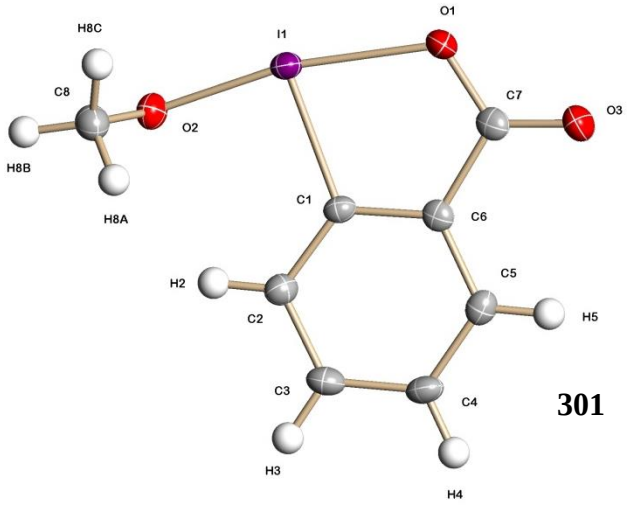
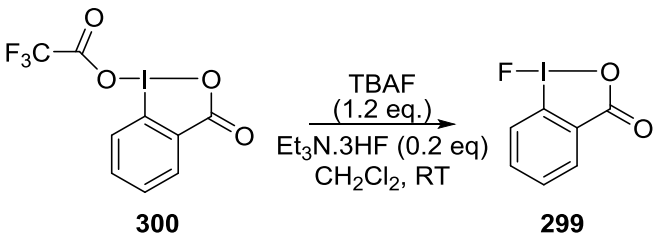


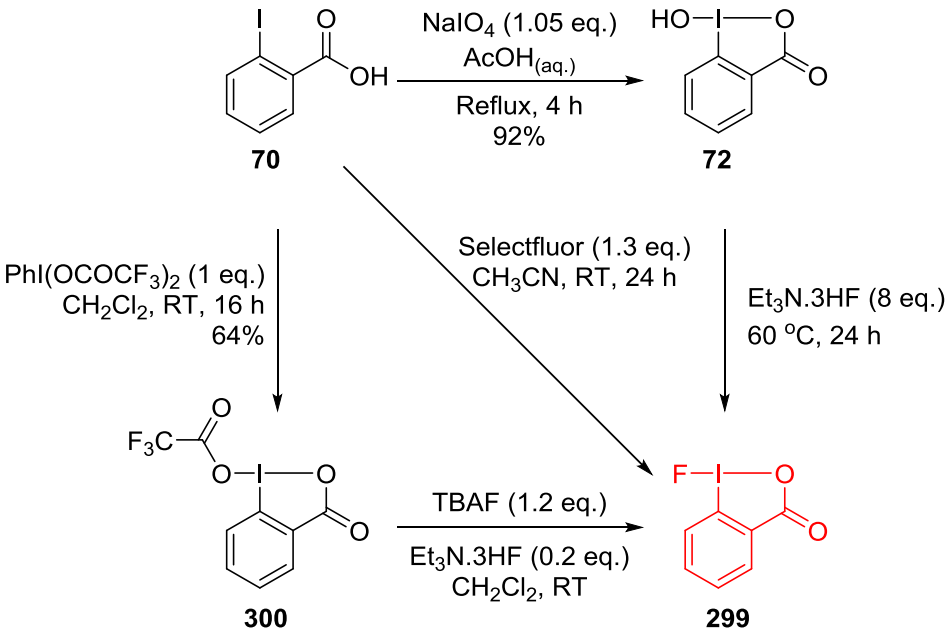

**Figure 2** *Solid-state structure for the methoxyiodoxolone*

In the reaction between the trifluoroacetoxyiodane **167** and TBAF, the formation of the hydroxyiodane **166** had been a significant side reaction. This problem was found to be eliminated by the addition of a small amount of TREAT-HF to the reaction mixture (Scheme 11). The same approach, therefore, was used for the preparation of the fluoroiodoxolone **299** from the trifluoroacetoxyiodoxolone **300**. In order to remove any residual tetrabutylammonium hydroxide from the TBAF solution, it was stirred for one hour at room temperature with 0.2 equivalents of TREAT-HF before the addition of **300** (Scheme 13). At the end of the reaction, the solvent was removed to give a white solid which was partially soluble in DMSO. $^{1}$H NMR Spectroscopy showed a complex mixture of products whilst the $^{19}$F NMR spectrum showed peaks at -73.4 ppm ($OCOCF_3^-$), -125.9 ppm (possibly $FCH_2SCHO$) and a very broad peak at -161.5 ppm (product). ASAP Mass spectrometry of the solid revealed a strong molecular ion peak ($MH^+$) at 266.9327 for the desired fluoroiodoxolone **299** as well as a large number of unidentified peaks.




**Scheme 13** *Preparation of the Fluoroiodoxolone from TBAF*

### 5.2.4 Summary of the Preparation of the Fluoroiodoxolone




**Scheme 14** *Attempted Preparation of the Fluoroiodoxolone*

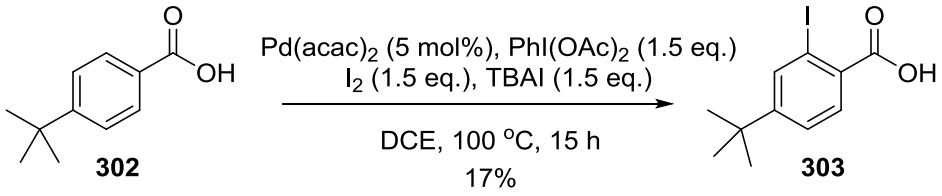
The reactions carried out in this section are summarised in Scheme 14 and provided strong evidence that the fluoroiodoxolone **299** was being formed. The preparation of the fluoroiodoxolone **299** from 2-iodobenzoic acid **70** and Selectfluor was carried out at room temperature, as was the reaction between the trifluoroacetoxyiodoxolone **300** and TBAF. These reactions appeared more successful and the desired product was observed by ASAP mass spectrometry. In order to prepare the fluoroiodoxolone **299** from the hydroxyiodoxolone **72** and TREAT HF, elevated temperatures were required (40 - 60 $^{o}$C). At these higher temperatures, the fluoroiodoxolone reacted with the solvent. The insolubility of the fluoroiodoxolone **299** made definitive characterisation challenging. The synthetic utility of the reagent would also be severely limited if it was insoluble in all commonly used organic solvents.

## 5.3 Preparation of 6-(*tert*-butyl)-1-Fluoro-1$\lambda^3$-benzo[d][1,2]iodaoxol-3(1*H*)-one

### 5.3.1 Preparation of 4-(*tert*-butyl)-2-Iodobenzoic Acid

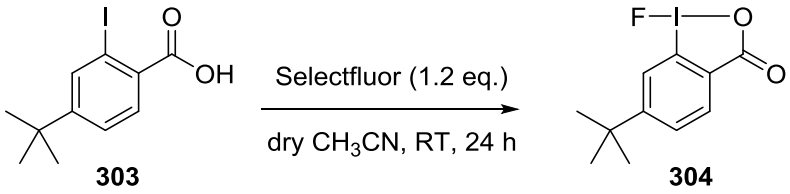
In order to increase the solubility of the fluoroiodoxolone **299** in organic solvents, the inclusion of a *tertiary*-butyl group onto the aromatic ring was investigated. In a literature procedure iodination *ortho* to a carboxylic acid on an aromatic ring *via* a palladium catalysed iodination reaction had been reported.[11] This approach was attempted using the commercially available 4-(*tert*-butyl)benzoic acid **302** (Scheme 15).

Unfortunately, despite numerous modifications to the procedure, consistently low conversions to the iodinated product **303** were obtained. Both the product **303** and the starting material **302** had very similar $R_F$ values and, therefore, purification by column chromatography was difficult. Esterification of the mixture of starting material and product did not make the separation easier. This meant that the iodinated product **303** could only be isolated in a 17% yield. Analysis of the final product by $^{1}H$ and $^{13}C$ NMR spectroscopy as well as ASAP mass spectrometry confirmed the identity of this new compound.




**Scheme 15** *Preparation of 4-(tert-butyl)-2-iodobenzoic acid*

### 5.3.2 Preparation of 6-(*tert*-butyl)-1-Fluoro-1$\lambda^3$-benzo[d][1,2]iodaoxol-3(1*H*)-one using Selectfluor




**Scheme 16** *Preparation of 6-(tert-butyl)-1-fluoro-1$\lambda^3$-benzo[d][1,2]iodaoxol-3(1H)-one using Selectfluor*

The reaction between 4-(*tert*-butyl)-2-iodobenzoic acid **303** and Selectfluor was attempted under the same conditions as had been used previously (Scheme 16). This time, the crude product from the reaction was soluble in $CDCl_3$, showing that the addition of the *tertiary*-butyl group had increased the solubility. $^{1}H$ NMR Spectroscopy of the crude product showed a 100% conversion of the starting material and two major products. The $^{1}H$ NMR signal for the proton *para* to the iodine atom shifted downfield from 7.45 ppm in 4-(*tert*-butyl)-2-iodobenzoic acid **303** to 7.74 ppm in the product suggesting the formation of an iodine(III) species (Figure 3). The $^{1}H$ NMR signal for the proton *ortho* to the carboxylic acid also shifted from 7.98 ppm in the starting material to 8.21 ppm in the product, again suggesting the formation of an iodine(III) species. A weak peak in the $^{19}F$ NMR spectrum was also observed at -166.6 ppm. This

was at a similar chemical shift to that observed in the $^{19}F$ NMR spectrum in the reaction between the trifluoroacetoxyiodoxolone **300** and TBAF (-161.5 ppm). A strong peak was observed by ASAP mass spectrometry at 322.9935 corresponding to the molecular ion of the expected product **304** ($MH^+$). The product was stable in $CDCl_3$ and only minimal decomposition occurred after more than 24 hours. Unfortunately, however, due to the small scale of the reaction, purification was not attempted.

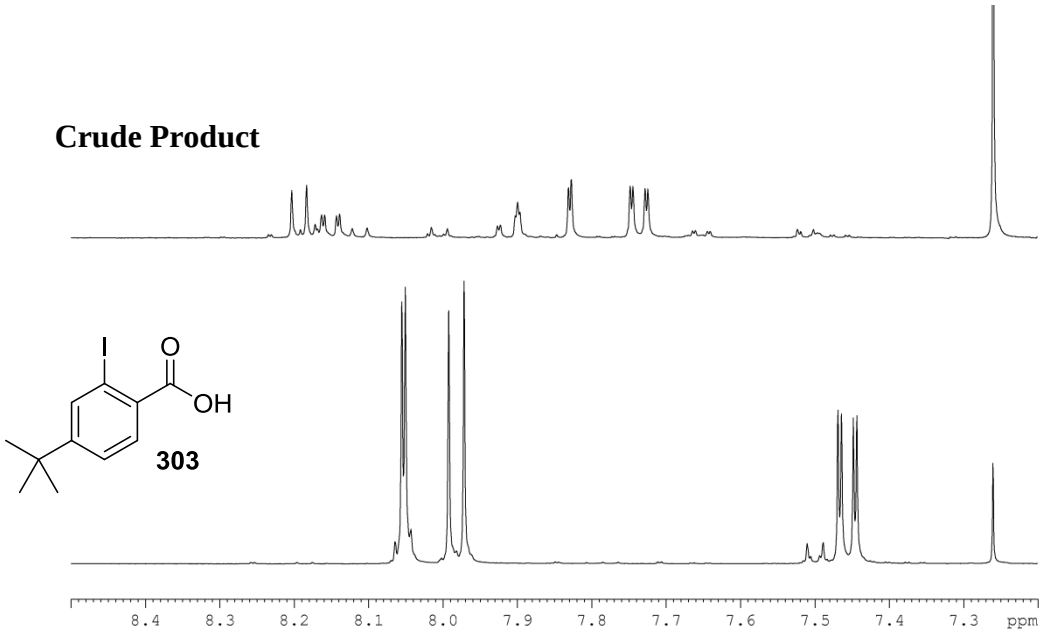
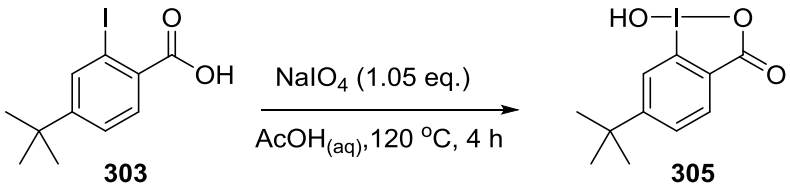



**Figure 3** *Comparison of the $^1H$ NMR spectra of the starting material and product*

### 5.3.3 Preparation of 6-(*tert*-butyl)-1-Hydroxy-1λ$^3$-benzo[d][1,2]iodaoxol-3(1*H*)-one

The preparation of 6-(*tert*-butyl)-1-hydroxy-1λ$^3$-benzo[d][1,2]iodaoxol-3(1*H*)-one **305** was attempted under the same conditions as those used to prepare the hydroxyiodoxolone **166** (Scheme 17) but the product of this reaction was only soluble in DMSO. $^1H$ NMR Spectroscopy showed an 81% conversion of the starting material. The $^1H$ NMR signal for the proton *para* to the iodine atom shifted downfield from 7.45 ppm in the starting material to 7.74 ppm in the product suggesting the formation of an iodine(III) species (Figure 4). ASAP Mass spectrometry did not show a molecular ion peak for **305**. Peaks corresponding to the loss of a hydroxyl group **306** and the formation of a dimer **307** and trimer **308** were observed (Figure 5). Again, however, due to the small size of the sample, purification was not attempted.




**Scheme 17** *Preparation of 6-(tert-butyl)-1-hydroxy-1λ³-benzo[d][1,2]iodaoxol-3(1H)-one*

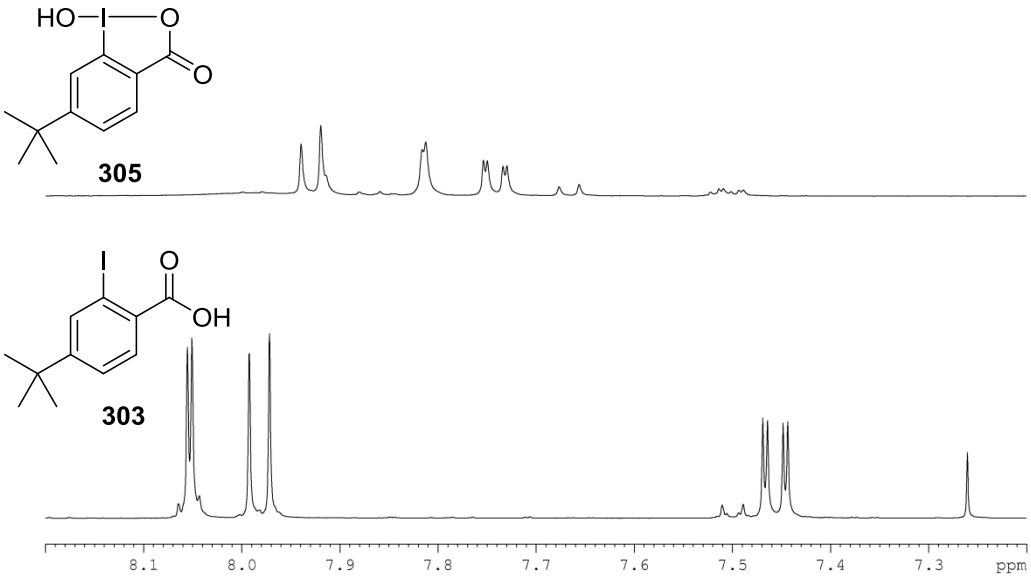



**Figure 4** *Comparison of the $^{1}H$ NMR spectra of the starting material and product.*

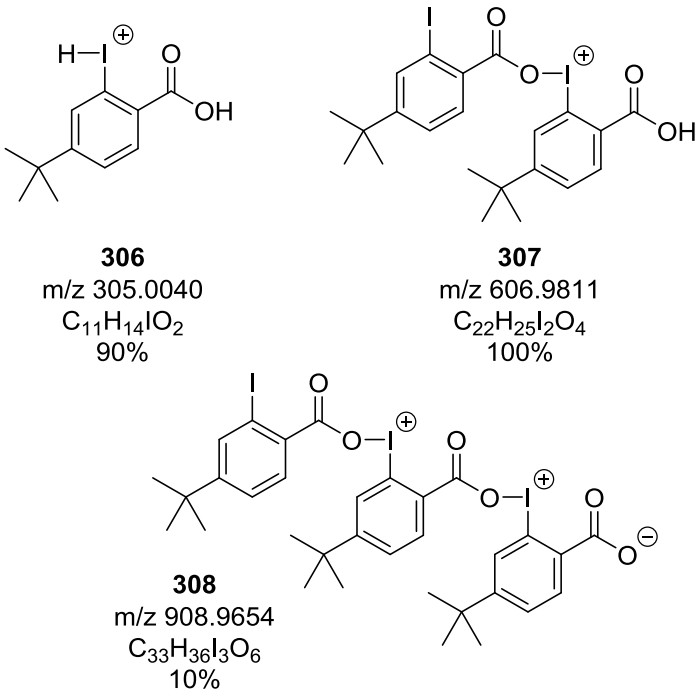
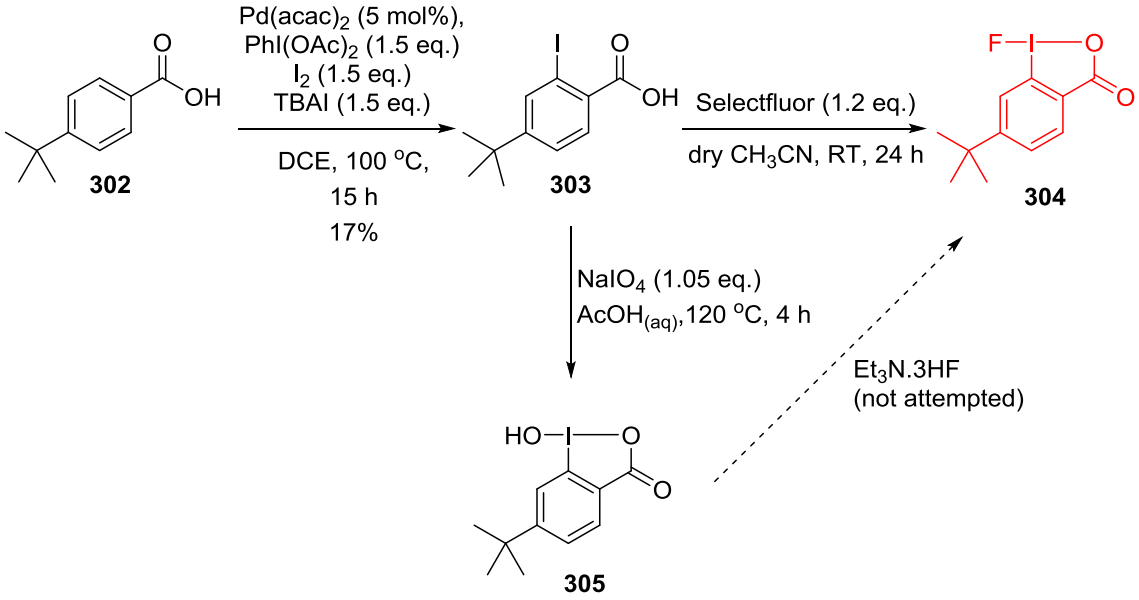



**Figure 5** *Suggested fragmentation in ASAP mass spectrometry*

### 5.3.4 Summary of the Preparation of 6-(*tert*-butyl)-1-Fluoro-1λ$^3$-benzo[d][1,2]iodaoxol-3(1*H*)-one




**Scheme 18** *Summary of the preparation of 6-(tert-butyl)-1-fluoro-1λ$^3$-benzo[d][1,2]iodaoxol-3(1H)-one*

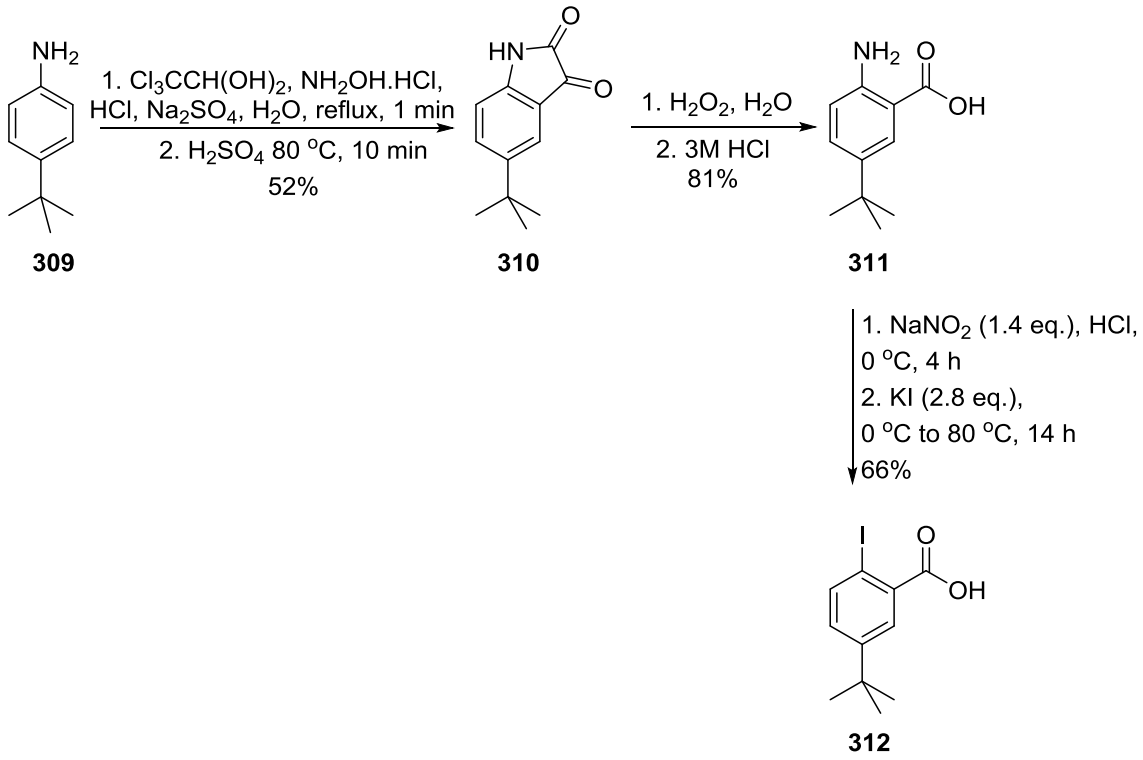
The *tertiary*-butyl group on the aromatic ring had the desired effect of making the resultant fluoroiodoxolone **304** more soluble. The reaction between 4-(*tert*-butyl)-2-iodobenzoic acid **303** and Selectfluor appeared to result in the formation of **304** although the crude product contained more than one compound. The preparation of **305** was successful, although the reaction did not go to completion. If this were to be repeated, the duration of the reaction would be increased in order to increase the conversion. Unfortunately, it was only possible to prepare approximately 200 mg of 4-(*tert*-butyl)-2-iodobenzoic acid **303** in each reaction using the palladium catalysed iodination reaction. This was not sufficient to investigate these reactions further. For this reason, an alternative procedure for the preparation of a *tert*-butyl substituted 2-iodobenzoic acid was investigated.

## 5.4 Preparation of 5-(*tert*-butyl)-1-Fluoro-1λ$^3$-benzo[d][1,2]iodaoxol-3(1*H*)-one

### 5.4.1 Preparation of 5-(*tert*-butyl)-2-Iodobenzoic acid

Due to the difficulties involved in the preparation of 4-(*tert*-butyl)-2-iodobenzoic acid **303**, an alternative procedure was sought for the preparation of a *tert*-butyl substituted 2-iodobenzoic acid. A three step procedure for the preparation of 5-(*tert*-butyl)-2-

iodobenzoic acid **312** from the commercially available 4-(*tert*-butyl)aniline **309** was proposed (Scheme 19). In the first step of this synthesis, 4-(*tert*-butyl)aniline **309** was converted to the isatin, 5-(*tert*-butyl)indoline-2,3-dione **310** according to a literature procedure.[12] Analysis of the $^{1}$H NMR spectrum of the crude product showed that the reaction had gone to completion and the product was isolated in a 52% yield by column chromatography. The characterisation data for this known compound was in agreement with the literature.[13]




**Scheme 19** *Preparation of 5-(tert-butyl)-2-iodobenzoic acid*

2-Amino-5-(*tert*-butyl)benzoic acid **311** was prepared *via* a Baeyer-Villiger oxidation according to a literature procedure (Scheme 19).[14] The product was obtained in an excellent yield of 81% without the need for any purification. The identity of the product was confirmed by $^{1}$H and $^{13}$C NMR spectroscopy as well as electrospray mass spectrometry. The melting point of 146 – 148 $^{o}$C was in agreement with the literature value of 153-154 $^{o}$C.[15]

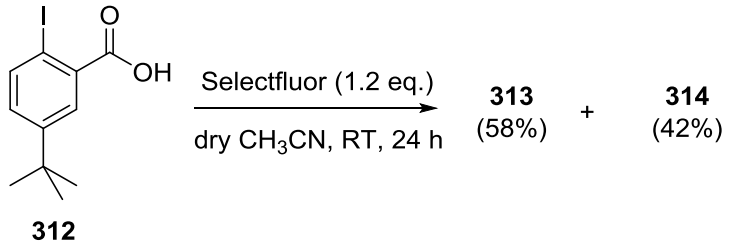
In the final step of the synthesis, 2-amino-5-(*tert*-butyl)benzoic acid **311** was converted to 5-(*tert*-butyl)-2-iodobenzoic acid **312** using a diazotisation followed by iodination. This reaction proceeded with good conversion and no purification was required. The

identity of the new product **312** was confirmed by $^{1}H$ and $^{13}C$ NMR spectroscopy as well as ASAP mass spectrometry.

Although the synthetic route to 5-(*tert*-butyl)-2-iodobenzoic acid **312** involved three steps whereas the route to 4-(*tert*-butyl)-2-iodobenzoic acid **303** was just one step, this route was more efficient. Each of the steps could be carried out on a large scale and only one purification by column chromatography was required. This meant that 3-4 g of 5-(*tert*-butyl)-2-iodobenzoic acid **312** could be prepared at a time.

### 5.4.2 Preparation of 5-(*tert*-butyl)-1-Fluoro-1$\lambda^3$-benzo[d][1,2]iodaoxol-3(1*H*)-one using Selectfluor

The reaction between 5-(*tert*-butyl)-2-iodobenzoic acid **312** and Selectfluor was first carried out at room temperature for 24 hours (Scheme 20). Following extraction into chloroform, $^{1}H$ NMR spectroscopy of the crude product showed 100% conversion of the starting material. Two major products **313** and **314** were observed in a 58:42 ratio respectively. One moderately intense peak was also observed in the $^{19}F$ NMR spectrum at -166.8 ppm, which was in a similar position to that observed in previous attempts to prepare the fluoroiodoxolone (see section 4.2.3 and 4.3.2). After a few hours in $CDCl_3$, the conversion to **314** increased, suggesting that it was a decomposition product of **313**. The use of dry, distilled $CDCl_3$ as the NMR solvent did not prevent this decomposition, nor did the use of other NMR solvents such as $CD_2Cl_2$, toluene or $CD_3CN$.

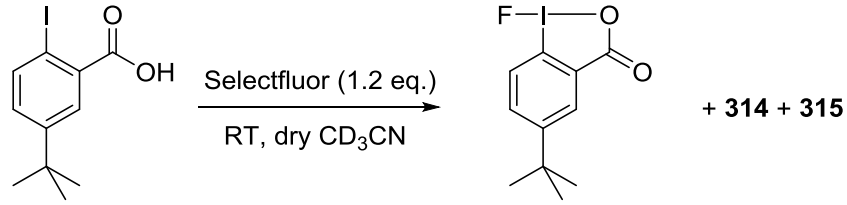



**Scheme 20** *Reaction between 5-(tert-butyl)-2-iodobenzoic acid and Selectfluor*

In order to gain a greater insight into how the different products of the reaction formed, a reaction was monitored by $^{1}H$ NMR spectroscopy (Table 1). This showed that the conversion to product **313** increased gradually throughout the course of the reaction. Since this coincided with a strengthening of the peak observed in the $^{19}F$ NMR spectrum at -166.8 ppm, it was determined that this was the desired product of the reaction. The by-product **314** was formed within two hours and did not change significantly during the initial 6 hours. After work up however, conversion to **314**

increased. A third by-product **315** was also observed which formed quickly but started to decrease as the reaction progressed, suggesting that it may have been an intermediate. The identities of by-products **314** and **315** could not be determined but since there were no additional peaks in the $^{19}F$ NMR spectrum, it was established that they did not contain fluorine.

**Table 1** *Reaction between 5-(tert-butyl)-2-iodobenzoic acid and Selectfluor monitored by $^{1}H$ NMR spectroscopy*




**312** **313**

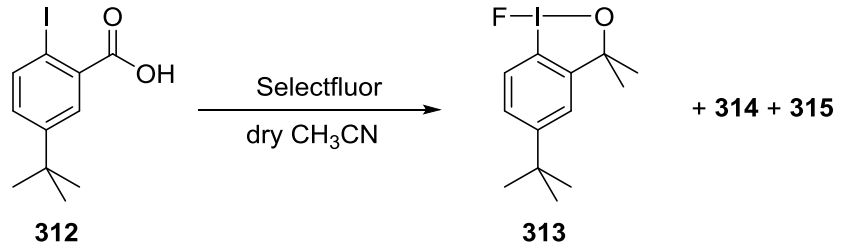
| Entry | Time (h) | 312[a] (%) | 313[a] (%) | 314[a] (%) | 315[a] (%) |
|---|---|---|---|---|---|
| 1 | 2 | 19 | 43 | 19 | 19 |
| 2 | 5 | 0 | 70 | 15 | 15 |
| 3 | 6 | 0 | 73 | 16 | 11 |

[a] Conversion calculated by $^{1}H$ NMR spectroscopy.

The results of the reaction monitored by $^{1}H$ NMR spectroscopy showed that complete consumption of the starting material had occurred within 5 hours. For this reason, the reaction was repeated for 4 hours at room temperature. After work-up, however, the conversion to the product **313** was just 39%, with 22% of the starting material remaining (entry 2, Table 2). By-products **314** and **315** were also observed with 18% and 21% conversions respectively. When the reaction was carried out at 0 $^{o}C$, the conversion to the decomposition product **314** decreased but the reaction was much slower (entry 3) with more of the intermediate **315** formed (44%) and none of the desired product **313** was observed. Increasing the temperature to 40 $^{o}C$ resulted in a 79% conversion to the desired product **313** (entry 4) and a 21% conversion to the decomposition product **314**. A similar result was obtained when 2 equivalents of Selectfluor were used (entry 5). In order to try and decrease the formation of **314** the reaction was carried out for just one hour (entry 6). This helped to decrease the conversion to **314**, however the reaction was not complete and the intermediate **315** was still observed. This was rectified by increasing the temperature of the reaction to 60 $^{o}C$

(entry 7). At this temperature, an acceptable conversion to the product **313** was observed, with only a minimal amount of the decomposition product **314** and none of the intermediate **315**.

**Table 2** *The Optimisation of the Reaction between 5-(tert-butyl)-2-iodobenzoic acid and Selectfluor*




**312** **313**

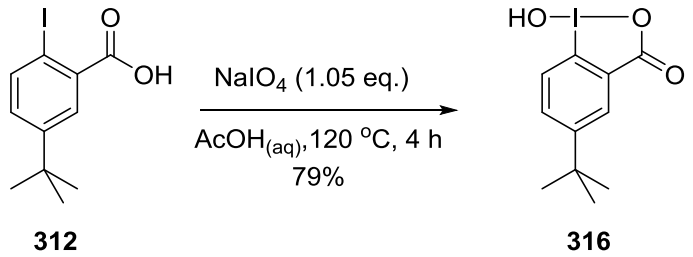
| Entry | Selectfluor (eq.) | Temp. ($^{o}$C) | Time (h) | 312[a] (%) | 313[a] (%) | 314[a] (%) | 315[a] (%) |
|---|---|---|---|---|---|---|---|
| 1 | 1.2 | RT | 24 | 0 | 58 | 42 | 0 |
| 2 | 1.2 | RT | 4 | 22 | 39 | 18 | 21 |
| 3 | 1.2 | 0 | 6 | 47 | 0 | 9 | 44 |
| 4 | 1.2 | 40 | 6 | 0 | 79 | 21 | 0 |
| 5 | 2.0 | 40 | 6 | 0 | 81 | 19 | 0 |
| 6 | 1.2 | 40 | 1 | 14 | 58 | 13 | 15 |
| 7 | 1.2 | 60 | 1 | 0 | 85 | 15 | 0 |

[a] Conversion calculated by $^{1}$H NMR spectroscopy.

These reactions showed that the formation of **313** required short reaction times at high temperatures. Due to the instability of the product it was not possible to isolate it pure. The solid decomposed rapidly to by-product **314** at room temperature and some decomposition even occurred under nitrogen in the freezer.

### 5.4.3 Preparation of 5-(*tert*-butyl)-1-Fluoro-1λ$^{3}$-benzo[d][1,2]iodaoxol-3(1*H*)-one using TREAT-HF

A nucleophilic pathway for the preparation of **313** was also investigated. In the first step, 5-(*tert*-butyl)-1-hydroxy-1λ$^{3}$-benzo[d][1,2]iodaoxol-3(1H)-one **316** was prepared from 5-(*tert*-butyl)-2-iodobenzoic acid **312** (Scheme 21).




**Scheme 21** *Preparation of 5-(tert-butyl)-1-hydroxy-1λ³-benzo[d][1,2]iodaoxol-3(1H)-one*

In the $^{1}$H NMR spectrum of the product a downfield shift of the $^{1}$H NMR signal corresponding to the proton *para* to the carboxylic acid shifted from 7.24 ppm in the starting material to 7.92 ppm in the product suggesting the formation of an iodine (III) species (Figure 6). The reaction was worked up according to the literature procedure for the preparation of the hydroxyiodoxolone **72** by washing with water and acetone. In this case, however, the presence of the *tert*-butyl group meant that the product **316** was partially soluble in acetone. For this reason the yield of the reaction was low at just 13%. When the reaction was repeated and the acetone washing step omitted, the yield increased significantly to 79%. The product of this reaction was highly unstable and decomposition in $CDCl_3$ occurred within a few hours (Figure 6).

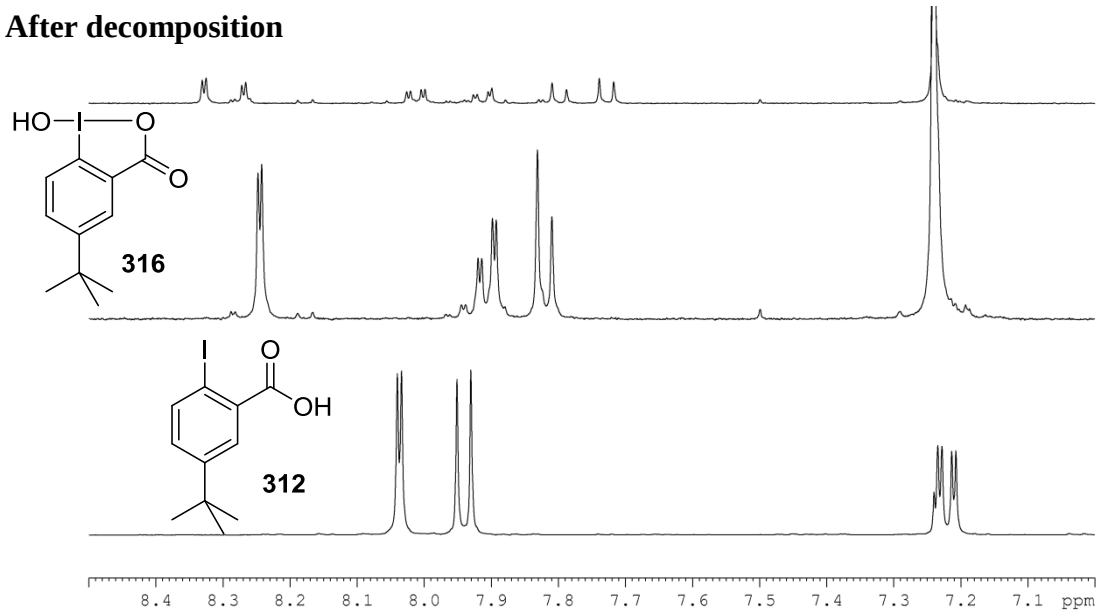
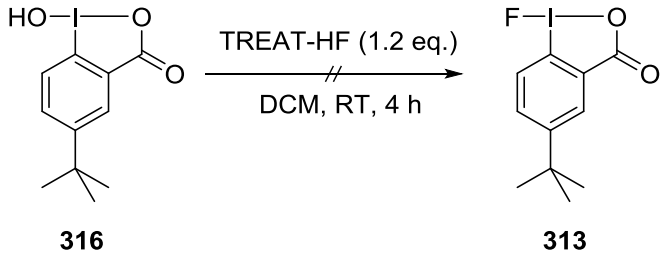



**Figure 6** *Comparison of the starting material and product*

Due to the instability of **316** in $CDCl_3$, it was not possible to obtain a $^{13}$C NMR spectrum. The solid was also unstable and decomposed quickly even when stored in the

freezer. It was not possible to confirm the identity of the decomposition product, although the peaks were in very similar places to those of the desired product, suggesting that it was an iodine(III) species (Figure 6).

The freshly prepared hydroxyiodoxolone **316** was reacted with 1.2 equivalents of TREAT-HF for 4 hours at room temperature (Scheme 22). After removal of the solvent, a weak signal was observed in the $^{19}$F NMR spectrum at -166.8 ppm consistent with the formation of the desired product **313**. Disappointingly, however, **313** was only a minor component in the $^{1}$H NMR spectrum of the crude product. The major product was in fact the same as that which was observed after the decomposition of **316**. This reaction was also repeated for just 10 minutes at 40 $^{o}$C, since the Selectfluor reaction required short times at high temperatures. Unfortunately, however, no improvement was seen in this reaction and a similar result was obtained.

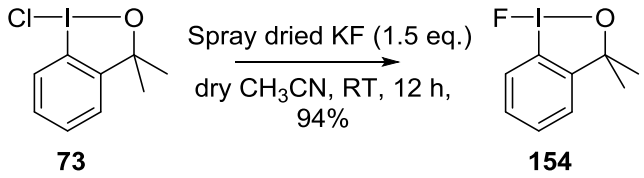



**316** **313**

**Scheme 22** *Preparation of* 5-(*tert*-butyl)-1-fluoro-1λ$^{3}$-benzo[d][1,2]iodaoxol-3(1*H*)-one *using TREAT-HF*

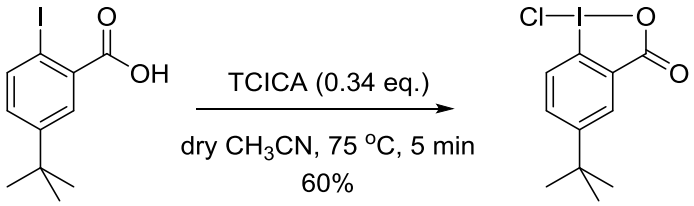
### 5.4.4 Preparation of 5-(*tert*-butyl)-1-fluoro-1λ$^{3}$-benzo[d][1,2]iodaoxol-3(1*H*)-one using KF

The fluoroiodane **154** has been prepared by Togni from the chloroiodane **73** and spray-dried KF (Scheme 23).[3] For this reason, the preparation of **313** was attempted using a similar procedure. In the first step of the synthesis, 5-(*tert*-butyl)-1-chloro-1λ$^{3}$-benzo[d][1,2]iodaoxol-3(1*H*)-one **317** was prepared in one step from 5-(*tert*-butyl)-2-iodobenzoic acid **29** using Togni's procedure for the preparation of the chloroiodoxolone (Scheme 24).[3] This step was straightforward and proceeded with a 60% yield. The product was characterised by $^{1}$H and $^{13}$C NMR spectroscopy as well as ASAP mass spectrometry. The characterisation data for this new compound was as expected for an iodine(III) species. The product of this reaction was very stable and no decomposition was seen even after 2 days in $CDCl_3$.




**73** **154**

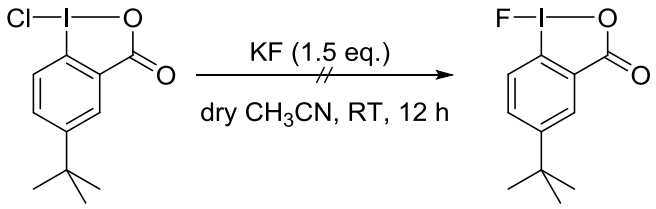
**Scheme 23** *Preparation of the fluoroiodane from the chloroiodane*




**312** **317**

**Scheme 24** *Preparation of 5-(tert-butyl)-1-chloro-1$\lambda^3$-benzo[d][1,2]iodaoxol-3(1H)-one*

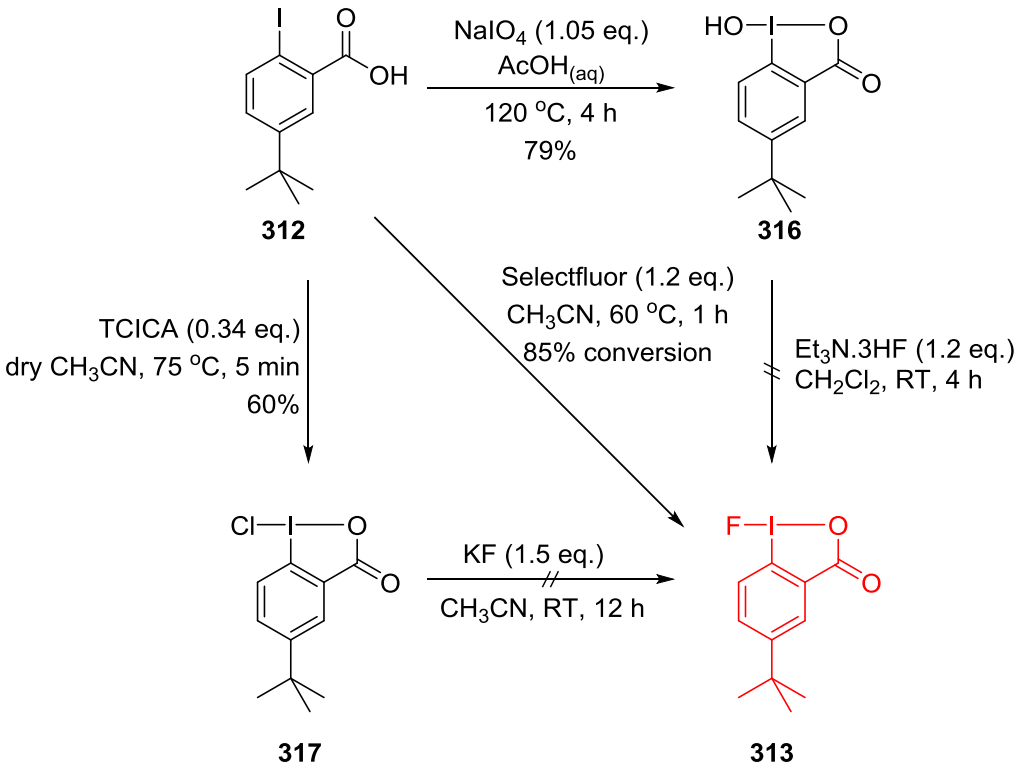
Having prepared **317**, it was then reacted with spray-dried KF in dry acetonitrile (Scheme 25). After 12 hours at room temperature, however, only the starting material was recovered and no peaks corresponding to a fluorinated product were observed in the $^{19}$F NMR spectrum. The reaction was repeated using 3 equivalents of spray-dried KF for 4 hours at 75 $^{o}$C. This resulted in complete consumption of the starting material and the $^{1}$H NMR spectrum showed a complex mixture of products. No peaks corresponding to a fluorinated product were observed in the $^{19}$F NMR spectrum.




**317** **313**

**Scheme 25** *Preparation of 5-(tert-butyl)-fluoroiodoxolone from 5-(tert-butyl)-chloroiodoxolone*

### 5.4.5 Summary of the Preparation of 5-(*tert*-butyl)-1-Fluoro-3,3-dimethyl-1,3-dihydro-1λ$^3$-benzo[d][1,2]iodaoxole



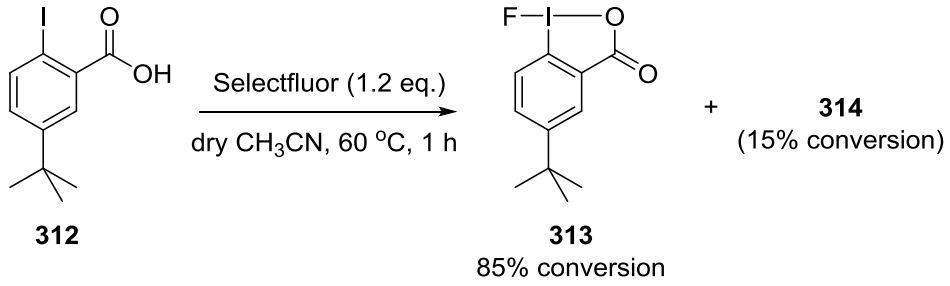

**Scheme 26** *Summary of the preparation of 5-(tert-butyl)-1-fluoro-3,3-dimethyl-1,3-dihydro-1λ$^3$-benzo[d][1,2]iodaoxole*

The attempted preparation of 5-(*tert*-butyl)-1-fluoro-1λ$^3$-benzo[d][1,2]iodaoxol-3(1*H*)-one **313** is summarised in Scheme 26. The reaction between 5-(*tert*-butyl)-2-iodobenzoic acid **312** and Selectfluor was successful when the reaction was carried out at high temperature (60 °C) for a short amount of time (1 h). Unfortunately, the product was not stable and decomposed even as a solid in the freezer. 5-(*tert*-Butyl)-1-hydroxy-1λ$^3$-benzo[d][1,2]iodaoxol-3(1*H*)-one **316** was prepared from 5-(*tert*-butyl)-2-iodobenzoic acid **312** and $NaIO_4$. When **316** was reacted with TREAT-HF, only a trace of the desired product was formed along with decomposition products. An attempt to prepare 5-(*tert*-butyl)fluoroiodoxolone **313** by nucleophilic fluorination of 5-(*tert*-butyl)-1-chloro-1λ$^3$-benzo[d][1,2]iodaoxol-3(1*H*)-one **317** using spray-dried KF was also unsuccessful.

## 5.5 Testing of 5-(*tert*-butyl)-1-Fluoro-1λ$^3$-benzo[d][1,2]iodaoxol-3(1*H*)-one as a Fluorinating Reagent with a 1,3-Dicarbonyl Compound

The ability of 5-(*tert*-butyl)-1-fluoro-1λ$^3$-benzo[d][1,2]iodaoxol-3(1*H*)-one **313** to act as an electrophilic fluorinating reagent was tested using the 1,3-dicarbonyl compound,

ethyl 3-oxo-3-phenylpropanoate **171**, as a model substrate. Since the most successful route for the preparation of **313** was the direct reaction between 5-(*tert*-butyl)-2-iodobenzoic acid **312** and Selectfluor this method was used for the preparation of the fluorinating reagent (Scheme 27).

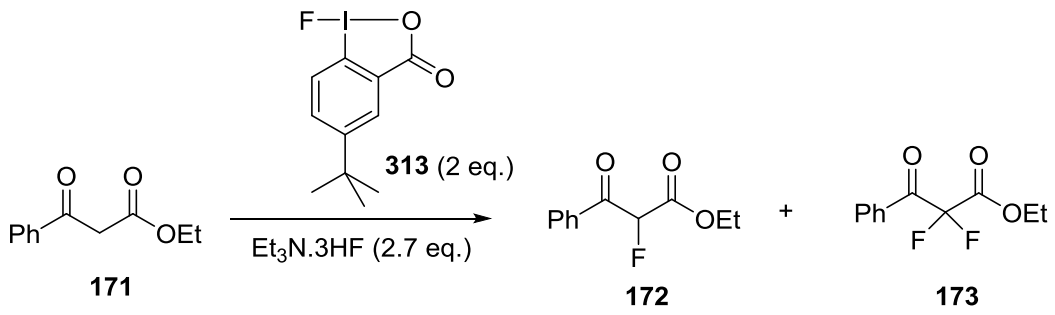



**Scheme 27** *Preparation of the fluorinating reagent*

The preparation of the fluorinating reagent also resulted in the formation of a by-product **314**. The instability of the fluorinating reagent meant that purification was not possible and the fluorinating reagent needed to be prepared and used straight away. It was necessary, however, to extract the fluorinating reagent into chloroform prior to using it in the fluorination reaction. This ensured that no residual Selectfluor was carried through to the fluorination reaction which could also have reacted with the substrate. The removal of any residual Selectfluor was confirmed by $^{1}H$ and $^{19}F$ NMR spectroscopy.

In the first instance, the fluorination reaction was carried out using the same conditions that had been used for the fluorination of ethyl 3-oxo-3-phenylpropanoate **171** using the fluoroiodane **154**. This gave only a very low conversion to the monofluorinated product **172** of just 4% (entry 1, Table 3). In order to increase the concentration of the reaction, it was also carried out without solvent at 40 $^{o}C$ for 24 hours. This increased the conversion to the monofluorinated product **172** to 19% and a trace of the difluorinated product **173** was also observed (entry 2).

**Table 3** *Reaction between 5-(tert-butyl)-1-fluoro-3,3-dimethyl-1,3-dihydro-1λ³-benzo[d][1,2]iodaoxole and ethyl 3-oxo-3-phenylpropanoate*



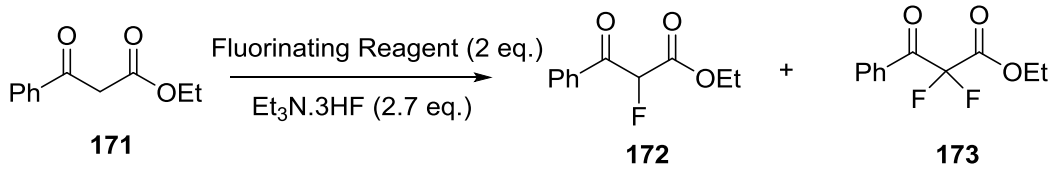

| Entry | Solvent | Time (h) | Temp. ($^{o}$C) | 171[a] (%) | 172[a] (%) | 173[a] (%) |
|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 24 | 40 | 96 | 4 | 0 |
| 2 | - | 24 | 40 | 80 | 19 | 1 |

[a] Conversion calculated by $^{1}H$ and $^{19}F$ NMR spectroscopy.

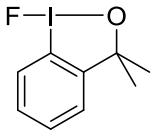
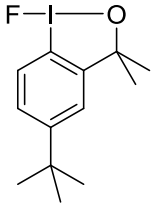
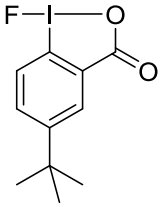
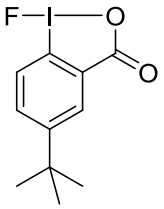
### 5.6 Comparison of the Reactivity of the Fluoroiodane with the Fluoroiodoxolone

The fluorination of ethyl 3-oxo-3-phenylpropanoate **171** using the fluoroiodane **154** was carried out in dichloromethane at 40 $^{o}$C for 24 hours. This resulted in an 89% conversion to the monofluorinated product **172** (entry 1, Table 4). Addition of a *tert*-butyl group at the *para* position of the fluoroiodane **318** resulted in a similar conversion however the isolated yield of this reaction was slightly lower (entry 2).[16] This showed that the installation of a *tert*-butyl group had only a minor effect on the reactivity of the fluoroiodane. Under the same conditions, the fluoroiodoxolone reagent **313** gave a considerably lower conversion to the monofluorinated product **171** of just 4% (entry 3). Even when the reaction was carried out without solvent, in order to increase the concentration, the conversion to the monofluorinated product **171** was still very low at just 19% (entry 4).

**Table 4** *Comparison of the reactivity of the fluoroiodane with the fluoroiodoxolone*




171 172 173

| Entry | Fluorinating Reagent | 171[a] (%) | 172[a, b] (%) | 173[a] (%) |
|---|---|---|---|---|
| 1 |  **154** | 5 | 89 (63) | 6 |
| 2 |  **318** | 5 | 92 (54) | 3 |
| 3 |  **313** | 96 | 4 | 0 |
| 4 |  **313** | 80 | 19 | 1 |

[a] Conversion calculated by $^{1}H$ and $^{19}F$ NMR spectroscopy; [b] Isolated yield in parenthesis.

These results showed that the acid derived 5-(*tert*-butyl)-fluoroiodoxolone **313** was considerably less reactive than the alcohol derived fluoroiodane **154** for this fluorination reaction. In both reactions of the fluoroiodoxolone **313** (entries 3 and 4), it was found that the majority of the fluorinating agent was still intact at the end of the reaction (less than 20% consumed in both cases). This is in contrast to the observation that the fluoroiodoxolone **313** decomposes as a solid even at low temperature and suggested that

the presence of TREAT-HF in the reaction mixture helped to stabilise the fluoroiodoxolone **313**. A similar observation was made by Shreeve in the preparation of difluoroiodoarenes.[17] Since the unreacted fluoroiodoxolone reagent **313** was recovered at the end of the reaction this showed that it was less reactive than the fluoroiodane **154** and not that it was too unstable and therefore decomposed before it was able to react with the substrate.

The addition of the *tert*-butyl group to the fluoroiodane **318** had only a minor effect on the reactivity of the fluorinating reagent (entry 1 vs. entry 2) and, therefore, it was concluded that the addition of a *tert*-butyl group to the fluoroiodoxolone **313** was not the cause of the decrease in reactivity.

Togni has carried out numerous studies aimed at relating the structure of trifluoromethylating reagents **51** and **53** to their reactivity.[2] One study attempted to relate I-O and I-$CF_3$ bond lengths to reactivity in trifluoromethylation reactions. Although weak correlations were found between a lengthening of the I-O bond and an increased reactivity, these were not conclusive results.[2] It was also noted that X-ray crystallography of solid samples is not an ideal tool for predicting solution phase behaviour. Another study in which a nitro group was installed on the aromatic ring of the trifluoromethyliodoxolone **51** was carried out in order to test the theory that an electron withdrawing group increased the propensity of the iodine(III) atom towards reduction to iodine(I). Again, these studies were inconclusive.[18]

In order to accurately predict which fluorinating reagent would be more reactive in a particular reaction, the precise mechanism and kinetics of the reaction would need to be known. Without this, the reactivity of the reagent can only be proposed. It should also be noted that a lack of reactivity in the fluorination of 1,3-dicarbonyl compounds does not necessarily mean a lack of reactivity with other substrates, since different mechanisms will be occurring in each case.

### 5.7 Conclusions and Future Work

The aim of this chapter was to prepare an acid derived fluoroiodoxolone species so that the preparation, properties and reactivity could be compared with that of the alcohol derived fluoroiodane **154**. It was proposed that the acid derived species should be considerably simpler to prepare and it was hoped that it would be more reactive.

Initial work to prepare a fluoroiodoxolone **299** had some success, for example, molecular ion peaks for the desired products were observed by ASAP mass spectrometry. This work was limited, however, by the poor solubility of the reagent in all organic solvents.

In order to increase the solubility of the fluoroiodoxolone, a *tertiary* butyl group was installed. Initially, 4-(*tert*-butyl)-2-iodobenzoic acid **303** was prepared *via* the palladium catalysed iodination of 4-(*tert*-butyl)benzoic acid **302**. Unfortunately, due to the difficulty in preparing large amounts, it was not possible to fully investigate the preparation of 6-(*tert*-butyl)-1-fluoro-1$\lambda^3$-benzo[d][1,2]iodaoxol-3(1H)-one **304** using this approach.

An alternative procedure enabled the preparation of a 5-(*tert*-butyl)-2-iodobenzoic acid **312** in sufficient quantities to investigate the preparation of the *tert*-butyl substituted fluoroiodoxolone **313**. In this case, the most successful procedure for the preparation of the fluoroiodoxolone was the reaction between the acid **312** and Selectfluor. Disappointingly, however, the fluoroiodoxolone **313** was found to be unstable and, therefore, it was not possible to isolate a pure sample.

Studies into the fluorination of a 1,3-dicarbonyl compound using the fluoroiodoxolone **313** showed that it was considerably less reactive than the fluoroiodane **154**. The reasons for this are not clear and are difficult to explain without a clear understanding of the mechanism and kinetics of the fluorination reaction.

Since the fluoroiodoxolone reagent **313** was in fact more difficult to prepare than the fluoroiodane **154**, due to the additional need to install a tertiary butyl group, it can be concluded that the fluoroiodane **154** is a superior reagent. In terms of reactivity towards 1,3-dicarbonyl compounds and stability, the fluoroiodane **154** is also a superior reagent. One of the key aims of this thesis was to prepare an electrophilic fluorinating reagent from a cheap and readily available source of the fluoride anion. In the case of the fluoroiodoxolone **313**, it was only possible to prepare the reagent from Selectfluor, an expensive, electrophilic source of fluorine. In this regard also, the fluoroiodane **154** was the superior reagent, since this can be prepared from several different sources of the fluoride anion.[3, 6]

The lack of reactivity of the fluoroiodoxolone **313** towards 1,3-dicarbonyl compounds does not, however, mean that the same would be true for other substrates. If time

allowed, the fluoroiodoxolone **313** would be tested as an electrophilic fluorinating reagent with other substrates, for example, those with which the fluoroiodane **154** was not found to be a good fluorinating reagent. It may also be interesting to test the reactivity of the fluoroiodoxolone **313** in the presence of Lewis acidic copper(I) catalysts since these have been shown to activate Togni's trifluoromethyliodoxolone reagent.[2]

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# Chapter 6

# Conclusions

The aim of the work in this thesis was primarily to create a new, electrophilic fluorinating reagent **154** which could be prepared from cheap and readily available sources of the fluoride anion. This would be beneficial since most of the currently available electrophilic fluorinating reagents are expensive, since they must be prepared from elemental fluorine.[1]

Selectfluor is one of the most popular reagents for electrophilic fluorination and it reacts with substrates such as 1,3-dicarbonyl compounds, activated aromatics and alkenes.[2] It was hoped that the new hypervalent iodine derived fluoroiodane **154** would participate in similar reactions. It was also desirable that the new fluoroiodane **154** would participate in reactions in which Selectfluor was not a suitable reagent, to give new products which are not accessible using existing methodologies.

In Chapter 2 of this thesis, the new air and moisture stable fluoroiodane reagent **154** was prepared from both electrophilic and nucleophilic sources of fluoride. The fluoroiodane could be prepared in 5 steps from the commercially available 2-iodobenzoic acid and TREAT-HF, which is a cheap and moderately safe source of the fluoride anion. This route allowed 6-10 g of the fluoroiodane **154** to be prepared and four out of the five steps did not require dry or inert conditions.[3]

An alternative route to the fluoroiodane **154** used TBAF as the source of the fluoride anion since this is a commonly used source of [$^{18}$F]-fluoride for the preparation of radiotracers for positron emission tomography. The fluoroiodane **154** could be prepared in just four steps, from 2-iodobenzoic acid **70**, *via* either the trifluoroacetoxyiodane **167** or the tosyliodane **168**. This route was more suitable for the small scale synthesis of the fluoroiodane **154** and could potentially provide a route to the preparation of an [$^{18}$F]-analogue of the fluoroiodane.[3]

Whilst the work in Chapter 2 was being carried out, other groups reported the synthesis of the fluoroiodane **154**, showing that it is a relevant and interesting new reagent. Legault *et al* reported the synthesis of the fluoroiodane **154** *via* an electrophilic route using Selectfluor.[4] Togni and co-workers showed that the fluoroiodane **154** could be prepared *via* a nucleophilic route using KF as the source of the fluoride anion.[5]

Preliminary reactivity studies showed that the fluoroiodane **154** could be used to fluorinate 1,3-ketoesters and 1,3-diketones in good to excellent yields (45-88%) in both

polar and non-polar solvents. This is in contrast to Selectfluor, which is only soluble in polar solvents such as acetonitrile and methanol. The reactivity of the fluoroiodane **154** was comparable to both Selectfluor and the difluoroiodoarenes (Chapter 2).

The addition of TREAT-HF was essential in order to obtain good yields in the fluorination of 1,3-dicarbonyl compounds. It was found that the addition of a basic source of fluoride, KF, resulted in the formation of an iodonium ylide **220**. This, and other results in Chapter 3, led to the conclusion that the fluoroiodane **154** actually simulates an electrophilic fluorination with 1,3-dicarbonyls *via* an addition-elimination mechanism.[6]

Attempts to fluorinate other substrates using the fluoroiodane **154** initially met with disappointment. It was found that aromatic compounds, such as anisole, silyl enol ethers and simple alkenes were all unreactive towards the fluoroiodane **154** (Chapter 2). Some success was found in the fluorination of unsaturated carboxylic acids **66**, suggesting that acidic activation of the fluoroiodane **154** may be important, as seen with Togni's trifluoromethyliodane **53**.[7]

During the course of this work, a report by Szabó showed that Lewis acidic activation of the fluoroiodane **154** using $AgBF_4$ was possible and good yields were obtained in the *geminal*-difluorination of styrenes.[8] Inspired by this, we investigated the fluorocylisation of alkenes (Chapter 4) in the presence of a range of additives, and $AgBF_4$ was found to be the most effective. The addition of 4Å molecular sieves in these reactions was crucial in order to prevent the formation of hydrolysed by-products. Using these reaction conditions, a range of fluorinated γ-lactones and isobenzofuranones were prepared in good to excellent yields (48-86%).[9] These reactions combined a fluorocyclisation with a phenyl migration to give interesting novel products which contained a tertiary alkyl fluoride. When fluoraza reagents such as Selectfluor were reacted with similar substrates, products containing a primary alkyl fluoride were obtained.[10, 11] This showed that the fluoroiodane **154** represented a unique opportunity to prepare new compounds which are not accessible *via* current methods.

It was also found that the fluoroiodane **154** could be reacted with phenyl-substituted unsaturated carboxylic acids in the absence of a metal catalyst (Chapter 4). Moderate yields of fluorinated γ-lactones and isobenzofuranones (50-54%) were obtained using 4Å molecular sieves as the only additive.[9] This ensured that the fluoride was only

provided by the fluoroiodane **154** and was not coming from the tetrafluoroborate anion of the silver catalyst as reported by Szabó in the difluorination of styrenes.[8] This clearly showed that the fluoroiodane reagent **154** was suitable for the production of new $^{18}F$-labelled radiotracers for PET imaging.

At a similar time, Szabo reported a similar reaction for the fluorocyclisation of unsaturated amines, alcohols and malonates using catalytic amounts of either $Zn(BF_4)_2.xH_2O$ or $[Cu(MeCN)_4]BF_4$.[12] Heterocycles containing a tertiary alkyl fluoride were formed.

Finally, the synthesis of an acid derived fluoroiodoxolone **299** was attempted as it was proposed that this would be easier to prepare than the fluoroiodane **154**. A synthetic route was proposed to the fluoroiodoxolone **299** in just two steps from 2-iodobenzoic acid **70**. In fact, the addition of a *tert*-butyl group onto the aromatic ring was required in order to increase the solubility of the fluoroiodoxolone **313** in organic solvents. This meant that the number of steps in the synthetic route to the fluoroiodoxolone **313** increased. Whilst the aim of this project was to prepare electrophilic fluorinating reagents from the fluoride anion, it was not possible to prepare the fluoroiodoxolone **313** *via* a nucleophilic route. The most successful route to prepare the fluoroiodoxolone **313** used the electrophilic fluorinating reagent, Selectfluor, as the source of fluoride. When the new fluoroiodoxolone reagent was tested as an electrophilic fluorinating reagent for the fluorination of 1,3-dicarbonyl compounds, it was found to be significantly less reactive than the fluoroiodane **154**. Since the fluoroiodoxolone **313** was more difficult to prepare than the fluoroiodane **154**, less stable and less reactive with 1,3-dicarbonyl compounds, it was established that the fluoroiodane **154** was the superior reagent.

When this project started, the fluoroiodane **154** was a novel compound which had not been reported in the literature. Over the course of the last four years, its popularity has grown as demonstrated by fact that two groups, in additions to ours, have reported its synthesis.[4, 5] This thesis has demonstrated that the fluoroiodane **154** is a suitable reagent for the fluorination of 1,3-dicarbonyl compounds and the fluorocyclisation of alkenes.[3, 6, 9] Szabó has also shown that the fluoroiodane **154** can be used, in the presence of a metal catalyst, or the difluorination of styrenes and in fluorocyclisation reactions.[8, 12]

With the knowledge of how the fluoroiodane **154** reacts with 1,3-dicarbonyl compounds (Chapters 2 and 3) and how the fluoroiodane **154** can be activated in order to increase its reactivity (Chapter 4) further reactions of the fluoroiodane **154** can be explored. For example, the fluorination of aromatic compounds under mild conditions is a key challenge in fluorine chemistry and the fluoroiodane **154** could be useful in this area.

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# Chapter 7

# Experimental

## 7.1 General Information

Proton, $^{19}F$ and $^{13}C$ NMR spectra were recorded on Bruker AV 500, Bruker DRX 400, Bruker AM 300 spectrometers at ambient temperatures. They were referenced to external $SiMe_4$ ($^{1}H$), external $CFCl_3$ ($^{19}F$) and to external $SiMe_4$ ($^{13}C$) using the high frequency positive convention. All chemical shifts are quoted in δ (ppm) and coupling constants in Hertz. The specified deuterated solvent was used. The following spectrometer frequencies were used:

Bruker AM 300 spectrometer: $^{1}H$ at 300.13 MHz

$^{19}F\{^{1}H\}$ at 283.57 MHz

$^{13}C\{^{1}H\}$ at 75.47 MHz

Bruker DRX 400 spectrometer: $^{1}H$ at 400.13 MHz

$^{19}F\{^{1}H\}$ at 376.46 MHz

$^{13}C\{^{1}H\}$ at 100.62 MHz

Bruker AV 500 spectrometer: $^{1}H$ at 500.13 MHz

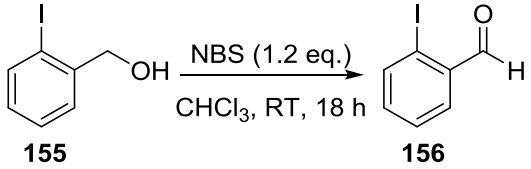
$^{13}C\{^{1}H\}$ at 125.76 MHz

Elemental analyses were performed by the Elemental Analysis Service at the University of North London. Electron impact (EI) mass spectra were recorded on a Kratos concept 1 H, double focussing, forward geometry mass spectrometer, Atmospheric Solids Analysis Probe (ASAP) mass spectra were recorded on a Xevo QTof mass spectrometer (Waters) and Electrospray (ES) mass spectra were obtained by LC-MS using a Xevo QTof mass spectrometer (Waters) coupled to an Acquity LC system (Waters) with an Acquity UPLC BEH C18 column (2.1 x 50 mm). X-ray crystallography data were collected on a Bruker Apex SMART 2000 diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). DSC data was obtained using a Mettler Toledo DSC1 STAR system and the data was analysed using STARe software (version 12.1).

Dry solvents were obtained dry from a distillation machine model Puresolve$^{TM}$, and were stored in sealed ampoules over 4Å molecular sieves under an atmosphere of dry nitrogen. Where a reaction was carried out at an elevated temperature, the temperature stated is the oil bath temperature. Starting materials were used as received from Sigma-Aldrich, Apollo Scientific, Alfa Aesar, Fluorochem, Acros Organics and Manchester Organics. PMA and $KMnO_4$ stains were used for visualising TLC plates.

## 7.2 Experimental for Chapter 2

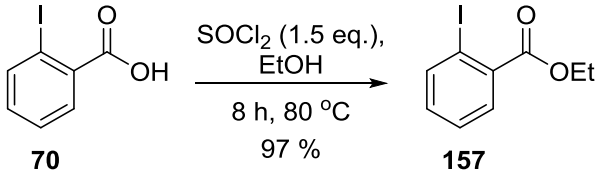
### 7.2.1 Reaction between 2-iodobenzyl alcohol and NBS




**155** **156**

NBS (0.457 g, 2.57 mmol) was added to a solution of 2-iodobenzyl alcohol **155** (0.500 g, 2.14 mmol) in $CHCl_3$ (8.6 mL) and the suspension stirred at room temperature for 18 hours. After this time, $^1$H NMR spectroscopy showed 2-iodobenzaldehyde **156** as the major product. Further purification was not attempted.

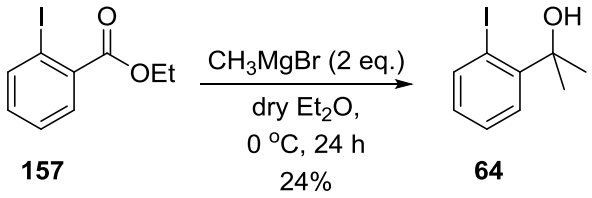
### 7.2.2 Preparation of ethyl-2-iodobenzoate[1]




**70** **157**

A solution of 2-iodobenzoic acid **70** (20.00 g, 80.6 mmol) in ethanol (121 mL) was cooled to 0 $^o$C before thionyl chloride (8.8 mL, 120.9 mmol) was added dropwise over 10 minutes. The resulting solution was heated to reflux at 80 $^o$C for 8 hours. After this time, the disappearance of the starting material was observed by TLC (33% EtOAc in hexane). The reaction mixture was concentrated on a rotary evaporator to give ethyl-2-iodobenzoate **157** as a yellow oil (21.5 g, 97 %). The product was shown to be pure by $^1$H NMR spectroscopy and therefore, no further purification was required. The characterisation data was in agreement with the literature.[2] $\delta_H$ ($CDCl_3$, 400 MHz) 1.32 (3H, t, $^3J_{HH}$ = 7.7 Hz, $CH_3$), 4.31 (2H, q, $^3J_{HH}$ = 7.7 Hz, $OCH_2$), 7.04 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6 Hz, ArH), 7.30 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.2 Hz, ArH), 7.71 (1H, dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6 Hz, ArH), 7.91 (1H, dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.2 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 14.2 ($CH_3$), 61.6 ($CH_2$), 94.0 (C), 127.8 (CH), 130.8 (CH), 132.4 (CH), 135.6 (C), 141.2 (CH), 166.6 (CO). m/z (EI) 276.9732 ($MH^+$, $C_9H_{10}O_2I$ requires 276.9726, 98 %).

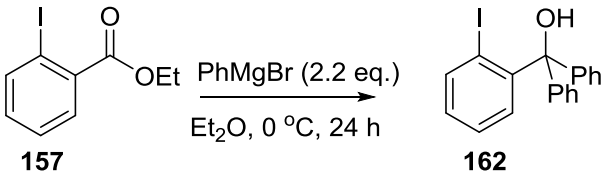
### 7.2.3 Preparation of 2-(2-iodophenyl)propan-2-ol from ethyl-2-iodobenzoate[3]




**157** **64**

A dry, 3 necked flask was equipped with a dropping funnel, septum and nitrogen supply. Methylmagnesium bromide (36.2 mL, 36.2 mmol, 1.0 M solution in diethyl ether) was charged to the dropping funnel. A solution of ethyl-2-iodobenzoate **157** (5.00 g, 18.1 mmol) in dry diethyl ether (18 mL) was added to the reaction flask and cooled to 0 $^{o}$C. The Grignard reagent was then added to the reaction flask dropwise, over half an hour and the reaction was stirred at 0 $^{o}$C, in the dark, for 24 hours. After this time, the excess Grignard reagent was destroyed with a saturated solution of ammonium chloride (30 mL) and the product was extracted into diethyl ether (3 x 20 mL). The organic layers were combined, washed with 1% HCl (20 mL) and water (2 x 20 mL), dried ($MgSO_4$) and concentrated on a rotary evaporator. Purification by column chromatography (9% ethyl acetate in hexane) gave 2-(2-iodophenyl)propan-2-ol **64** as a yellow oil (1.13 g, 24%). The characterisation data was in agreement with the literature.[4] $\delta_H$ ($CDCl_3$, 400 MHz) 1.64 (6H, s, 2 x $CH_3$), 2.63 (1H, br s, OH), 6.77 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 2.0 Hz, ArH), 7.20 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.4 Hz, ArH), 7.51 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 2.0 Hz, ArH), 7.83 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.4 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 28.5 ($CH_3$), 72.5 (C), 92.1 (CI), 125.6 (CH), 127.0 (CH), 127.5 (CH), 141.6 (CH), 147.5 (C). m/z (EI) 261.98491 ($M^+$, $C_9H_{11}IO$ requires 261.98519, 30 %), 247 ($(M - CH_3)^+$, 100%).

### 7.2.4 Reaction between ethyl-2-iodobenzoate and phenyl magnesium bromide

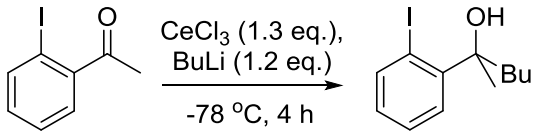



**157** **162**

A dry, 3 necked flask was equipped with a dropping funnel, septum and nitrogen supply. Phenylmagnesium bromide (15.9 mL, 15.9 mmol, 1.0 M solution in diethyl ether) was charged to the dropping funnel. A solution of ethyl-2-iodobenzoate **157** (2.00 g, 7.24 mmol) in dry diethyl ether (18 mL) was added to the reaction flask and cooled to

0 $^{o}$C. The Grignard reagent was then added to the reaction flask dropwise, over half an hour and the resultant solution was stirred at 0 $^{o}$C, in the dark, for 4 hours. After this time, the excess Grignard reagent was destroyed with a saturated solution of ammonium chloride (10 mL) and the organic layer washed with 2% HCl (20 mL) and water (2 x 20 mL). The product was extracted into diethyl ether (3 x 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated on a rotary evaporator to give a yellow oil. $^{1}$H NMR spectroscopy of the crude product showed a complex mixture of products and purification was not attempted.

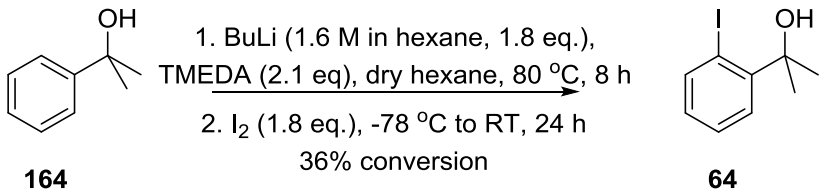
### 7.2.5 Reaction between ethyl-2-iodobenzoate and $BuCeCl_2$[5]




**158** **163**

A suspension of anhydrous $CeCl_3$ (1.04 g, 4.22 mmol) in dry THF (13 mL) was prepared under nitrogen and stirred for two hours at room temperature. After this time, the suspension was cooled to -78 $^{o}$C and BuLi (2.4 mL, 3.90 mmol, 1.6 M in hexanes) was added dropwise. This was stirred at -78 $^{o}$C for 30 minutes, resulting in the solution changing from white to dark green in colour. After this time, a solution of 1-(2-iodophenyl)ethanone **158** (0.46 mL, 3.25 mmol) in dry THF (6.5 mL) was added, resulting in the solution turning pale brown. This solution was then left to stir at -78 $^{o}$C for four hours. The reaction mixture was then warmed to room temperature and a saturated solution of $NH_4Cl$ (15 mL) was added. The mixture was filtered through celite and the product was extracted into EtOAc (3 x 10 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated on a rotary evaporator. $^{1}$H NMR spectroscopy showed a complex mixture of products and purification was not attempted.

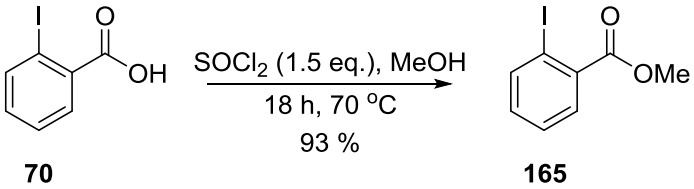
### 7.2.6 Preparation of 2-(2-iodophenyl)propan-2-ol by *ortho*-lithiation and iodination of 2-phenylpropan-2-ol[6]




**164** **64**

A solution of 2-phenylpropan-2-ol **164** (1.00 g, 7.35 mmol) and TMEDA (2.3 mL, 15.4 mmol) in dry hexane (15 mL) was prepared under nitrogen and stirred overnight with molecular sieves. The molecular sieves were then removed and BuLi (8.3 mL, 13.2 mmol, 1.6 M in hexanes) was added dropwise over ten minutes. The reaction mixture was then heated to reflux and stirred at this temperature for 11 hours. After this time, the reaction mixture was cooled to room temperature and stirred for a further 15 hours. The solution was then cooled to 0 $^{o}$C and a solution of iodine (3.35 g, 13.2 mmol) in dry diethyl ether (62 mL) was added dropwise over half an hour. The reaction mixture was stirred at 0 $^{o}$C for 4 hours and a further 24 hours at room temperature. After this time a saturated solution of $NH_4Cl$ (20 mL) was added and the product was extracted into diethyl ether (3 x 20 mL). The organic layers were washed with $NH_4Cl$ (2 x 10 mL) and a 10% solution of $Na_2S_2O_3$ (2 x 20 mL). They were then combined, dried ($MgSO_4$) and concentrated on a rotary evaporator to give a yellow oil (1.33 g). The $^{1}$H NMR spectrum of the crude product showed a 36% conversion to the desired product **64**. Purification could not be achieved, either by column chromatography or distillation.

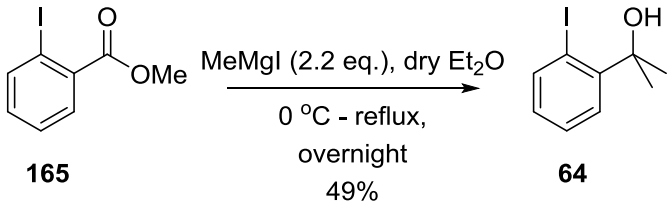
### 7.2.7 Preparation of methyl-2-iodobenzoate[1]




**70** **165**

A solution of 2-iodobenzoic acid **70** (25.00 g, 100.8 mmol) in methanol (151 mL) was cooled to 0 °C before thionyl chloride (11.0 mL, 151.2 mmol) was added dropwise over 30 minutes. The resulting solution was heated to reflux 70 °C for 18 hours. After concentrating the reaction mixture on a rotary evaporator to give a yellow oil it was dissolved in ethyl acetate (50 mL) and washed with brine until the aqueous layer was no longer acidic (3 x 50 mL). The organic layer was then dried ($MgSO_4$) and concentrated on a rotary evaporator to give methyl-2-iodobenzoate **165** as a yellow oil (24.5 g, 93 %). The characterisation data was in agreement with the literature.[7] $\delta_H$ ($CDCl_3$, 400 MHz) 3.94 (3H, s, $CH_3$), 7.16 (1H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.41 (1H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.80 (1H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 8.00 (1H, d, $^3J_{HH}$ = 7.5 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 52.6 ($CH_3$), 94.2 (CI), 127.9 (CH), 130.9 (CH), 132.6 (CH), 135.0 (C), 141.3 (CH), 166.8 (CO). m/z (ASAP) 262.9566 ($MH^+$, $C_8H_8IO_2$ requires 262.9569, 100 %), 230.9317 ($(M - OCH_3)^+$, 99%).

### 7.2.8 Preparation of 2-(2-iodophenyl)propan-2-ol from methyl-2-iodobenzoate[4]



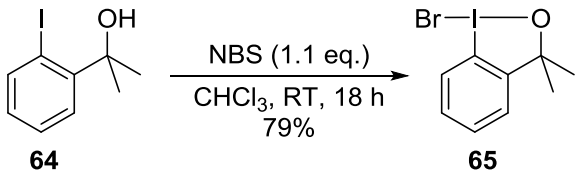

**165** **64**

A dry, 3 necked 250 mL round bottomed flask equipped with a reflux condenser, dropping funnel and nitrogen supply was charged with magnesium turnings (4.72 g, 197 mmol). Dry diethyl ether (12.5 mL) was added to the flask whilst a solution of methyl iodide (8.7 mL, 139 mmol) in dry diethyl ether (12.5 mL) was charged to the dropping funnel. The solution in the dropping funnel was then added to the flask dropwise. Initiation of the reaction was observed after the addition of approximately 2 mL of the methyl iodide. At this point the flask was diluted with more dry diethyl ether (17.5 mL). Addition of the methyl iodide solution was then continued at a rate of approximately 1

mL/min so as to maintain a gentle reflux. After all of the methyl iodide solution had been added, the contents of the flask were cooled to room temperature and allowed to settle. A new, dry 3 necked 250 mL round bottomed flask was set up equipped with a dropping funnel, reflux condenser and nitrogen supply. The methylmagnesium iodide solution was then transferred to the new flask via a cannula. The excess magnesium turnings were rinsed with more dry diethyl ether (12.5 mL) and this was also transferred to the new flask. The methylmagnesium iodide solution was cooled to 0 $^{o}$C and a solution of methyl-2-iodobenzoate (16.5 g, 63 mmol) in dry diethyl ether (10 mL) was added to the dropping funnel. The methyl-2-iodobenzoate **165** solution was then added to the methyl magnesium iodide solution dropwise over 10 minutes. The dropping funnel was rinsed with more dry diethyl ether (6.5 mL). The solution was then left to warm slowly to room temperature, with stirring, for 16 hours.

After this time, the reaction mixture was refluxed for 1.5 h. TLC analysis (20% ethyl acetate in hexane) of the crude reaction mixture revealed complete consumption of the starting material. The mixture was then poured into an ice cold saturated solution of ammonium chloride (75 mL) cautiously. Water (150 mL) was added and the mixture was stirred for half an hour until most of the solids had dissolved. After filtration through celite the organic layer was separated and the aqueous layer was extracted with more diethyl ether (4 x 100 mL). The organic layers were combined, dried ($K_2CO_3$) and concentrated on a rotary evaporator to give a brown oil (12.4 g). Purification by column chromatography gave 2-(2-iodophenyl)propan-2-ol **64** as a yellow oil (9.15 g, 56%).

### 7.2.9 Preparation of 1-bromo-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole[8]

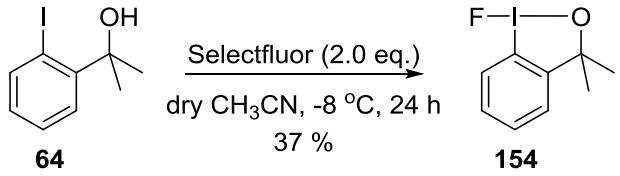



**64** **65**

A solution of 2-(2-iodophenyl)propan-2-ol **64** (10.0 g, 38.2 mmol) in $CHCl_3$ (100 mL) was prepared in a round bottomed flask. To this was added NBS (8.15 g, 45.8 mmol) in three portions. The suspension was stirred at room temperature overnight. After this time, the clear yellow solution was transferred to a separating funnel and the organic layer was washed with water (2 x 50 mL) and brine (50 mL). The organic layer was then dried ($MgSO_4$) and concentrated on a rotary evaporator to give a yellow solid

which was recrystallized from ethyl acetate to give 1-bromo-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **65** as bright yellow crystals (10.2 g, 79%). The characterisation data was in agreement with the literature.[8] mp 127 – 129 $^{o}$C (lit.,[8] 126 – 128 $^{o}$C) $\delta_H$ ($CDCl_3$, 400 MHz) 1.49 (6H, s, 2 x $CH_3$), 7.06-7.08 (1H, m, ArH), 7.44-7.50 (2H, m, ArH), 7.91-7.93 (1H, m, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 29.4 ($CH_3$), 84.0 (C), 111.7 (CI), 126.2 (CH), 129.4 (CH), 130.4 (CH), 131.2 (CH), 149.8 (C). m/z (EI) 327/325 ($(M - CH_3)^+$, 50 %), 261 ($(M – Br)^+$, 38 %).

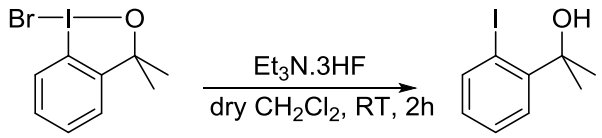
### 7.2.10 Preparation of 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole using Selectfluor




**64** **154**

A solution of 2-(2-iodophenyl)propan-2-ol **64** (1.04 g, 3.97 mmol) in dry acetonitrile (80 mL) was prepared under nitrogen and cooled to -8 $^{o}$C. To this was added Selectfluor (2.81 g, 7.94 mmol) and the reaction mixture was stirred at -8 $^{o}$C for 24 hours. After this time the reaction mixture was concentrated to give a white solid which was extracted with chloroform (3 x 10 mL). The chloroform solution was concentrated on a rotary evaporator and dried under high vacuum to give a yellow oil. The product was then extracted with hexane (3 x 15 mL) and recrystallised from hexane to give 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** as a white solid (0.42 g, 37 %). Crystals suitable for X-ray crystallography were grown by slow evaporation of a hexane solution containing 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154**. The characterisation data was in agreement with the literature.[9] mp 82 – 84 $^{o}$C. (Found: C, 38.52, H, 3.43. Calc. for $C_9H_{10}FIO$: C, 38.58, H, 3.57%). $\delta_H$ ($CDCl_3$, 400 MHz) 1.45 (6H, s, 2 x $CH_3$), 7.09 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.2 Hz, ArH), 7.39 (1H, td, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 0.8 Hz, ArH), 7.47 (1H, td, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.2 Hz, ArH), 7.71 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 0.8 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -142.4 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 28.0 ($CH_3$), 84.1 (C), 115.0 (CI), 124.9 (CH), 127.5 (CH), 129.1 (CH), 129.5 (CH), 147.5 (C). m/z (ASAP) 280.9855 ($MH^+$, $C_9H_{11}FIO$ requires 280.9839, 5%), 260.9798 ($(M – F)^+$, 100 %), 244.9834 ($(M– F – CH_3)^+$, 50 %).

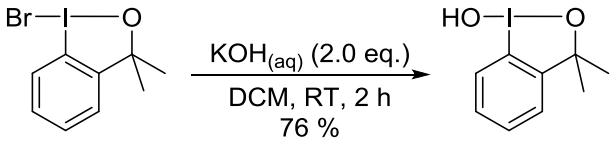
### 7.2.11 Reaction of 1-bromo-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole with $Et_3N.3HF$




**65** **64**

A solution of 1-bromo-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole **65** (0.10 g, 0.29 mmol) in dry dichloromethane (2 mL) was prepared under nitrogen. To this was added $Et_3N.3HF$ (0.06 mL, 0.35 mmol) and the reaction mixture was stirred at room temperature for 2 hours, during which, the colour of the reaction mixture turned from yellow to colourless. After this time, the reaction mixture was concentrated on the Schlenk line and $^1$H NMR spectroscopy of the crude product showed complete conversion to 2-(2-iodophenyl)propan-2-ol **64**.

### 7.2.12 Preparation of 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole[10]

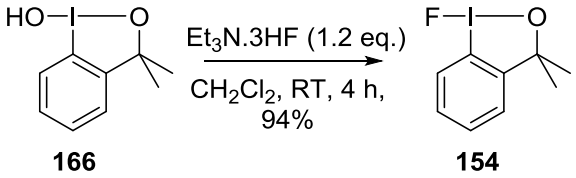



**65** **166**

A solution of 1-bromo-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole **65** (10.2 g, 29.9 mmol) in dichloromethane (120 mL) was prepared in a round bottomed flask. To this was added a solution of KOH (3.35 g, 59.8 mmol) in water (120 mL). The mixture was then stirred vigorously for 2 hours. After this time, the organic layer was separated and the aqueous layer was extracted with more dichloromethane (3 x 50 mL). The organic layers were then combined, dried ($MgSO_4$) and concentrated on a rotary evaporator to give 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole **166** as a pale yellow solid (6.34 g, 76%). The characterisation data was in agreement with the literature.[10] mp. 140 - 142 $^o$C (from diethyl ether and hexane) (lit.,[10] 126-128 $^o$C). (Found C, 39.00, H, 3.84. Calc. for $C_9H_{11}IO_2$: C, 38.87, H, 3.99%). $\delta_H$ ($CDCl_3$, 400 MHz) 1.42 (6H, s, 2 x $CH_3$), 7.15 (1H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.38 (1H, dd, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 7.0 Hz, ArH), 7.44 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 7.0 Hz, ArH), 7.73 (1H, d, $^3J_{HH}$ = 8.0 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 30.2 ($CH_3$), 80.3 (C), 115.4 (CI), 126.3

(CH), 126.8 (CH), 129.3 (CH), 130.0 (CH), 149.6 (C). m/z (ES) 278.9887 ($MH^+$, $C_9H_{12}IO_2$ requires 278.9882, 100%), 260.9787 ($(M\text{-}OH)^+$, 38%).

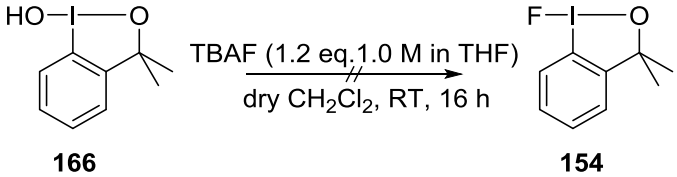
### 7.2.13 Preparation of 1-fluoro-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole using TREAT-HF




**166** **154**

$Et_3N.3HF$ (3.2 mL, 19.4 mmol) was added to a solution of 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole **166** (4.50 g, 16.2 mmol) in dichloromethane (230 mL) and the reaction mixture was stirred at room temperature for 4 hours. After this time, water (200 mL) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 200 mL). The organic layers were then combined and concentrated on a rotary evaporator to give a white solid. Residual water was removed by coevaporation with toluene (3 x 50 mL). Recrystallisation from hexane gave 1-fluoro-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole **154** as a white crystalline solid (4.24 g, 94%).

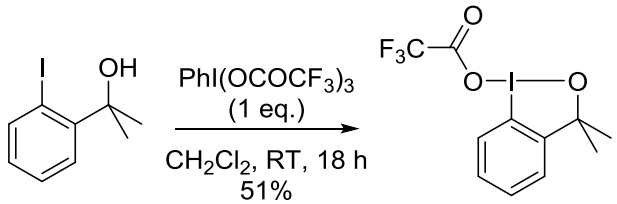
### 7.2.14 Reaction between 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole and TBAF




**166** **154**

TBAF (0.86 mL, 0.86 mmol, 1.0M solution in THF) was added to a solution of 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole **166** (0.200 g, 0.72 mmol) in dry dichloromethane (10 mL). The solution was stirred at room temperature under nitrogen for 4 hours. After this time, the reaction mixture was concentrated on a rotary evaporator to give a brown oil. Analysis by $^1$H NMR spectroscopy showed that the desired product **154** had not formed.

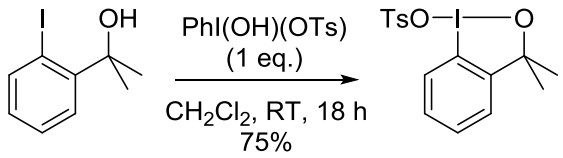
### 7.2.15 Preparation of 1-trifluoroacetoxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole[11]




**64** **167**

[Bis(trifluoroacetoxy)iodo]benzene (1.64 g, 3.82 mmol) was added to a solution of 2-(2-iodophenyl)propan-2-ol **64** (1.00 g, 3.82 mmol) in dry dichloromethane (19 mL) stirring at room temperature under nitrogen. After stirring the reaction mixture overnight, it was concentrated on a rotary evaporator to give an oily orange solid which was washed with cold pentane (4 x 10 mL) to give 1-trifluoroacetoxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole **167** (0.73 g, 51%) as a pale yellow solid. Crystals suitable for X-ray crystallography were grown by slow evaporation of a diethyl ether/hexane solution containing 1-trifluoroacetoxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]-iodoxole **167**. mp 124 – 126 $^{o}$C. (Found: C, 35.2; H, 2.7. Calc. for $C_{11}H_{10}F_3IO_3$: C, 35.3; H, 2.7%). $\delta_H$ ($CDCl_3$, 400 MHz) 1.54 (6H, s, 2 x $CH_3$), 7.12 (1H, dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.50 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.0 Hz, ArH), 7.52 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.66 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.0 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -74.4 (s, $CF_3$). $\delta_C$ ($CDCl_3$, 100 MHz) 28.7 ($CH_3$), 87.7 (C), 114.1 (q, $^1J_{CF}$ = 289.9 Hz, $CF_3$), 115.6 (CI), 126.5 (CH), 129.5 (CH), 130.9 (CH), 131.1 (CH), 149.0 (C), 162.0 (q, $^2J_{CF}$ = 38.2 Hz, CO). m/z (ES$^+$) 260.9791 ((M-$OCOCF_3$)$^+$, $C_9H_{10}IO$ requires 260.9776, 100%).

### 7.2.16 Preparation of 1-tosyloxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole[11]

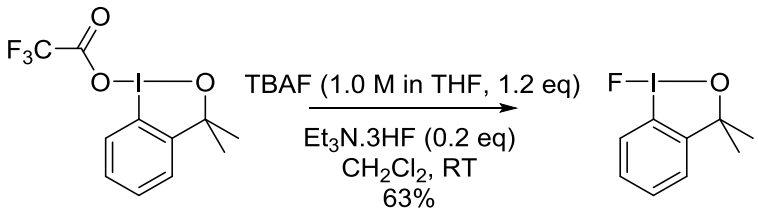



**64** **168**

A solution of 2-(2-iodophenyl)propan-2-ol **64** (0.984 g, 3.76 mmol) in dry dichloromethane (19 mL) was prepared under nitrogen. To this was added

[hydroxy(tosyloxy)iodo]benzene (1.47 g, 3.76 mmol) and the suspension was stirred at room temperature overnight. After this time, the clear, yellow solution was concentrated on a rotary evaporator to give a yellow solid which was washed with hexane (3 x 10 mL) to give 1-tosyloxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **168** as a pale yellow solid (1.22 g, 75%). Crystals suitable for X-ray crystallography were grown by slow evaporation of an ethyl acetate/hexane solution containing 1-tosyloxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **168**. mp 80 - 86 $^{o}$C. (Found: C, 44.5; H, 4.0. Calc. for $C_{16}H_{17}ISO_4$: C, 44.5; H, 4.0%). $\delta_H$ ($CDCl_3$, 400 MHz) 1.50 (6H, s, 2 x $CH_3$), 2.33 (3H, s, $CH_3$), 7.06 (1H, dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.19 (2H, d, $^3J_{HH}$ = 8.0 Hz, ArH), 7.42 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.0 Hz, ArH), 7.48 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.75 (2H, d, $^3J_{HH}$ = 8.0 Hz, ArH), 7.76 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.0 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 21.9 ($CH_3$), 28.5 ($CH_3$), 89.7 (C), 116.6 (CI), 126.3 (CH), 126.4 (CH), 129.3 (CH), 129.7 (CH), 131.2 (CH), 131.3 (CH), 138.6 (C), 142.2 (C), 148.8 (C). m/z ($ES^+$) 260.9759 ($(M\text{-}OTs)^+$, $C_9H_{10}IO$ requires 260.9776, 35%).

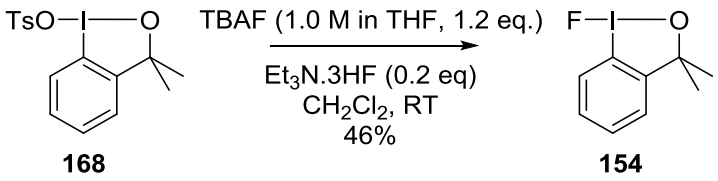
### 7.2.17 Preparation of 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole using TBAF




**167** **154**

A solution of 1-trifluoroacetoxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **167** (1.00 g, 2.67 mmol) in dry dichloromethane (36.5 mL) was prepared under nitrogen. To this was added $Et_3N.3HF$ (0.87 mL, 0.53 mmol, 0.61 M in dichloromethane) followed by TBAF (3.21 mL, 3.21 mmol, 1.0 M in THF). On addition of the TBAF solution white fumes were observed. The flask was sealed and stirred at room temperature for 4 hours. After this time the reaction mixture was concentrated on a rotary evaporator to give a pale yellow oil (2.11 g) which was extracted into warm hexane (40 $^{o}$C, 3 x 30 mL, each batch stirred for half an hour) to give a white solid (0.741 g). The solid was recrystallized from hexane to give 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** as a white solid (0.47g, 63%).

### 7.2.18 Preparation of 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole using TBAF




**168** **154**

A solution of 1-tosyloxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **168** (0.200 g, 0.46 mmol) in dry dichloromethane (6.3 mL) was prepared under nitrogen. To this was added $Et_3N.3HF$ (0.14 mL, 0.092 mmol, 0.64 M in dichloromethane) followed by TBAF (0.56 mL, 0.56 mmol, 1.0 M in THF). On addition of the TBAF solution white fumes were observed. The flask was sealed and stirred at room temperature for 4 hours. After this time the reaction mixture was concentrated on a rotary evaporator to give a pale yellow oil (0.386 g) which was extracted into warm hexane (40 $^oC$, 3 x 30 mL, each batch stirred for half an hour) to give a white solid (0.116 g). Recrystallisation from hexane gave 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** as a white crystalline solid (0.060 g, 46%).

### 7.2.19 Procedure for the fluorinations in Table 7

Ethyl-3-oxo-3-phenylpropanoate **171** (0.062 mL, 0.357 mmol) was added to a solution of 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.200 g, 0.715 mmol) in the required amount of $Et_3N.3HF$ (0.71 M solution in dichloromethane). The flask was then sealed and heated to the required temperature for 24 hours. After this time, the reaction mixture was cooled to room temperature and a saturated solution of $NaHCO_3$ (4 mL) was added. The organic layer was separated and the aqueous layer was extracted with more dichloromethane (3 x 5 mL). The organic layers were then combined, dried ($MgSO_4$) and concentrated on a rotary evaporator to give a yellow oil which was analysed by $^1H$ and $^{19}F$ NMR spectroscopy.

### 7.2.20 Procedure for fluorinations in Table 8

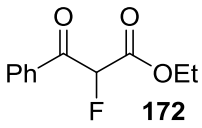
Ethyl-3-oxo-3-phenylpropanoate **171** (0.062 mL, 0.357 mmol) was added to a solution of 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.200 g, 0.715 mmol) and $Et_3N.3HF$ (0.16 mL, 0.96 mmol) in the required amount of dichloromethane. The flask was then sealed and heated to the required temperature for

24 hours. After this time, the reaction mixture was cooled to room temperature and a saturated solution of $NaHCO_3$ (4 mL) was added. The organic layer was separated and the aqueous layer was extracted with more dichloromethane (3 x 5 mL). The organic layers were then combined, dried ($MgSO_4$) and concentrated on a rotary evaporator to give a yellow oil which was analysed by $^1H$ and $^{19}F$ NMR spectroscopy.

### 7.2.21 Procedure for fluorinations in Table 9

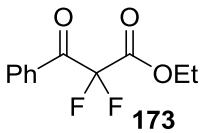
A solution of 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.44 mmol) in the dry solvent (1.2 mL) was prepared under nitrogen. To this was added the required amount of $Et_3N.3HF$ followed by ethyl-3-oxo-3-phenylpropanoate **171** (0.12 mL, 0.72 mmol). The flask was then sealed and heated to either 40 or 60 $^oC$ for the required amount of time. After this time, the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give a yellow oil which was analysed by $^1H$ and $^{19}F$ NMR spectroscopy.

### 7.2.22 Characterisation data for the products from Table 9



**172**

The crude product from entry 2 (Table 9) was purified by column chromatography (5% ethyl acetate in hexane) to give ethyl 2-fluoro-3-oxo-3-phenylpropanoate **172** as a yellow oil (0.106 g, 63%). The characterisation data was in agreement with the literature.[12] $\delta_H$ ($CDCl_3$, 400 MHz) 1.17 (3H, t, $^3J_{HH}$ = 7.0 Hz, $CH_3$), 4.21 (2H, $m_{AB}$, dq, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 7.0 Hz, $OCH_AH_B$), 5.80 (1H, d, $^2J_{HF}$ = 50.0 Hz, CHF), 7.42 (2H, t, $^3J_{HH}$ = 8.0 Hz, ArH), 7.55 (1H, t, $^3J_{HH}$ = 8.0 Hz, ArH), 7.95 (2H, d, $^3J_{HH}$ = 8.0 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -190.4 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 14.5 ($CH_3$), 62.9 ($CH_2$), 90.0 (d, $^1J_{CF}$ = 197.2 Hz, CH), 128.8 (CH), 129.5 (CH), 133.4 (C), 134.5 (CH), 164.9 (d, $^2J_{CF}$ = 24.1 Hz, CO), 189.5 (d, $^2J_{CF}$ = 20.1 Hz, CO). m/z (ASAP) 211.0760 ($MH^+$, $C_{11}H_{12}FO_3$ requires 211.0770, 100 %).

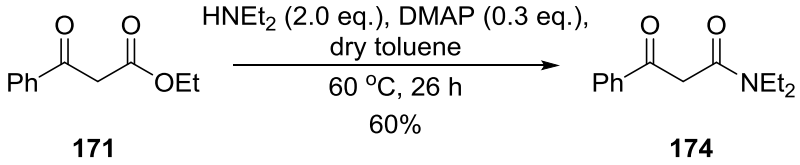


**173**

The crude product from entry 1 (Table 9) was purified by column chromatography (5% ethyl acetate in hexane) to give ethyl 2-fluoro-3-oxo-3-phenylpropanoate **172** (0.074 g, 49%) and ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate **173** as a colourless oil (0.021 g, 13%). The characterisation data for ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate **173** was in agreement with the literature.[13] $\delta_H$ ($CDCl_3$, 400 MHz) 1.24 (3H, t, $^3J_{HH}$ = 7.2 Hz, $CH_3$), 4.31 (2H, q, $^3J_{HH}$ =

7.2 Hz, $OCH_2$), 7.45 (2H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.60 (1H, tt, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, ArH), 8.00 (2H, dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.1 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -107.6 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 12.8 ($CH_3$), 62.7 ($CH_2$), 108.8 (t, $^1J_{CF}$ = 264.7 Hz, $CF_2$), 128.0 (CH), 128.9 (CH), 130.1 (C), 134.1 (CH), 160.8 (t, $^2J_{CF}$ = 30.3 Hz, CO), 184.5 (t, $^2J_{CF}$ = 27.4 Hz, CO). m/z (ASAP) 229.0677 ($MH^+$, $C_{11}H_{11}F_2O_3$ requires 229.0676, 20 %), 201.0259 (75), 105.0234 (100).

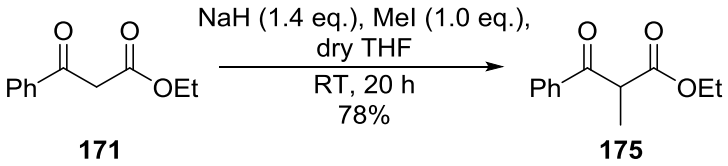
### 7.2.23 Preparation of *N,N*-diethyl-3-oxo-3-phenylpropanamide[14]




**171** **174**

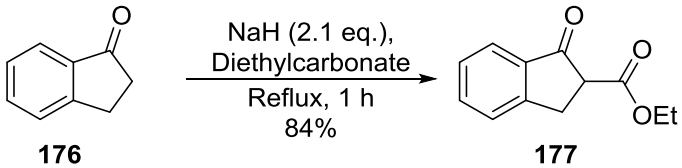
A solution of DMAP (1.91 g, 15.6 mmol), $HNEt_2$ (10.7 mL, 104.2 mmol) and ethyl 3-oxo-3-phenylpropanoate **171** (9.0 mL, 52.1 mmol) in dry toluene (73 mL) was prepared under nitrogen and stirred at 60 °C for 26 hours. After this time the solution was cooled to room temperature and concentrated on a rotary evaporator to give a yellow oil (15.03 g) which was purified by column chromatography (5% EtOAc in petroleum ether 40-60 to 100% EtOAc) to give *N,N*-diethyl-3-oxo-3-phenylpropanamide **174** as a colourless oil (6.85 g, 60%, 52% enol: 48% keto). The characterisation data does not entirely agree with the literature (full characterisation for keto and enol forms not given),[14] however it is believed that the characterisation data presented here is correct. $\delta_H$ ($CDCl_3$, 400 MHz) 1.03 (6H, t, $^3J_{HH}$ = 7.1 Hz, keto $CH_3$), 1.07 (6H, t, $^3J_{HH}$ = 7.3 Hz, enol $CH_3$), 3.23 (4H, q, $^3J_{HH}$ = 7.1 Hz, keto $CH_2$), 3.29 (4H, q, $^3J_{HH}$ = 7.3 Hz, enol $CH_2$), 3.94 (2H, s, keto $CH_2$), 5.64 (1H, s, enol CH), 7.26 – 7.31 (3H, m, enol ArH), 7.34 (2H, t, $^3J_{HH}$ = 7.4 Hz, keto ArH), 7.45 (1H, t, $^3J_{HH}$ = 7.4 Hz, keto ArH), 7.66 – 7.68 (2H, m, enol ArH), 7.90 (2H, d, $^3J_{HH}$ = 7.4 Hz, keto ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 12.8 ($CH_3$), 14.2 ($CH_3$), 40.2 ($CH_2$), 42.7 ($CH_2$), 45.6 ($CH_2$), 84.9 (CH), 125.9 (CH), 128.4 (CH), 128.7 (2 x CH), 130.5 (CH), 133.5 (CH), 135.2 (C), 136.4 (C), 166.2 (C), 171.3 (CO), 171.4 (CO), 194.2 (CO). m/z (ES) 242.1182 ($MNa^+$, 10%), 220.1340 ($MH^+$, $C_{13}H_{18}NO_2$ requires 220.1338, 100%).

### 7.2.24 Preparation of ethyl 2-methyl-3-oxo-3-phenylpropanoate[15]




A solution of ethyl 3-oxo-3-phenylpropanoate **171** (1.7 mL, 10.0 mmol) in dry THF (15 mL) was prepared under nitrogen. To this was added NaH (0.54 g, 13.5 mmol, 60% dispersion in mineral oil), in small portions over half an hour. MeI (0.62 mL, 10.0 mmol) was then added dropwise over ten minutes. The flask was sealed and stirred at room temperature for 20 hours. After this time, a saturated solution of $NH_4Cl$ (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated on a rotary evaporator to give a yellow oil (2.35 g) which was purified by column chromatography (5% EtOAc in hexane) to give ethyl 2-methyl-3-oxo-3-phenylpropanoate **175** as a colourless oil (1.60 g, 78%). The characterisation data was in agreement with the literature.[15] $\delta_H$ ($CDCl_3$, 400 MHz) 1.01 (3H, t, $^3J_{HH}$ = 7.1 Hz, $CH_3$), 1.35 (3H, d, $^3J_{HH}$ = 7.1 Hz, $CH_3$), 3.99 (2H, q, $^3J_{HH}$ = 7.1 Hz, $OCH_2$), 4.28 (1H, q, $^3J_{HH}$ = 7.1 Hz, CH), 7.32 (2H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.42 (1H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.85 (2H,d, $^3J_{HH}$ = 7.7 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 12.6 ($CH_3$), 12.8 ($CH_3$), 47.2 (CH), 60.2 ($CH_2$), 127.5 (CH), 127.7 (CH), 132.4 (CH), 134.9 (C), 169.7 (CO), 194.8 (CO). m/z (ASAP) 207.1022 ($MH^+$, $C_{12}H_{15}O_3$ requires 207.1021, 12%), 105.0299 ($PhCO^+$. 100%).

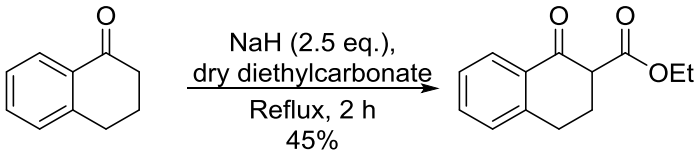
### 7.2.25 Preparation of ethyl-1-indanone-2-carboxylate




A solution of indanone **176** (2.01 g, 15.2 mmol) in dry diethyl carbonate (55 mL) was added to a suspension of NaH (1.28 g, 31.9 mmol, 60% dispersion in mineral oil) in dry diethyl carbonate (55 mL) under nitrogen. This was refluxed at 150 $^oC$ for one hour before cooling to room temperature. HCl (2 M, 100 mL) was added and the product was extracted into ethyl acetate (4 x 100 mL). The organic layers were combined, dried

($MgSO_4$) and concentrated on a rotary evaporator to give a brown oil. Purification by column chromatography (10% EtOAc in hexane) gave ethyl-1-indanone-2-carboxylate **177** as a yellow oil (2.61 g, 84%, 17 % enol, 83% keto). The product was stored in the freezer to prevent decomposition. The characterisation data was in agreement with the literature.[16] $\delta_H$ ($CDCl_3$, 400 MHz) 1.22 (3H, t, $^3J_{HH}$ = 7.2 Hz, keto ester $CH_3$), 1.28 (3H, t, $^3J_{HH}$ = 7.0 Hz, enol ester $CH_3$), 3.28 (1H, dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 8.6 Hz, keto ring $CH_2$), 3.43 (2H, s, enol ring $CH_2$), 3.47 (1H, dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 4.0 Hz, keto ring $CH_2$), 3.62 (1H, dd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 4.0 Hz, keto ring COCHCO), 4.16 (2H, qd, $^3J_{HH}$ = 7.2 Hz, $^5J_{HH}$ = 1.4 Hz, keto ester $CH_2$), 4.24 (2H, q, $^3J_{HH}$ = 7.0 Hz enol ester $CH_2$), 7.27-7.34 (m, 1H keto + 2H enol ArH), 7.34-7.39 (1H, m, enol ArH), 7.41 (1H, dt, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 0.8 Hz, keto ArH), 7.53 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, keto ArH), 7.55 (1H, m, enol ArH), 7.68 (1H, d, $^3J_{HH}$ = 7.8 Hz, keto ArH), 10.34 (1H, br s, enol OH). $\delta_C$ ($CDCl_3$, 100 MHz) 14.2 ($CH_3$, keto), 14.5 ($CH_3$, enol), 30.3 ($CH_2$, keto), 32.6 ($CH_2$, enol), 53.3 (CH, keto), 60.1 ($CH_2$, enol), 61.7 ($CH_2$, keto), 102.5 (C, enol), 120.7 (CH, enol), 124.6 (CH, keto), 124.7 (CH, enol), 126.5 (CH, keto), 126.8 (CH, enol), 127.8 (CH, keto), 129.3 (CH, enol), 135.3 (C, keto), 135.4 (CH, keto), 136.9 (C, enol), 143.2 (C, enol), 153.6 (C, keto), 169.1 (CO, keto), 169.4 (C, enol), 169.6 (C, enol), 199.5 (CO, keto). Can't distinguish between CO, C and C-OH in $^{13}C$ NMR spectrum. m/z (ES) 227.0688 ($MNa^+$, $C_{12}H_{12}O_3Na$ requires 227.0684, 100%), 205.0867 ($MH^+$, $C_{12}H_{13}O_3$ requires 208.0865, 20%), 177.0556 ($MH^+$-$C_2H_4$, 45%), 159.0483 (M-OEt, 12%), 131.0497 (M-$CO_2$Et, 9%).

### 7.2.26 Preparation of ethyl-1-tetralone-2-carboxylate

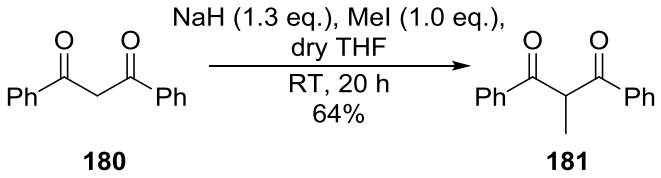



**178** **179**

A solution of 1-tetralone **178** (2 mL, 15.1 mmol) in dry diethyl carbonate (55 mL) was added to a suspension of NaH (1.48 g, 37.0 mmol, 60% dispersion in mineral oil) in dry diethyl carbonate (55 mL) under nitrogen. This was refluxed at 150 $^oC$ for 2 hours before cooling to room temperature. The solid formed was filtered and dissolved in HCl (2 M, 100 mL). The aqueous solution was then extracted with ethyl acetate (4 x 100 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated on a rotary

evaporator to give a dark yellow oil (4.63 g). Purification by column chromatography (8% EtOAc in hexane) gave ethyl-1-tetralone-2-carboxylate **179** as a yellow oil (1.49 g, 45%, 63% enol, 33% keto). The product was stored in the freezer to prevent decomposition. The characterisation data was in agreement with the literature.[17] $\delta_H$ ($CDCl_3$, 400 MHz) 1.19 (3H, t, $^3J_{HH}$ = 7.0 Hz, keto ester $CH_3$), 1.24 (3H, t, $^3J_{HH}$ = 7.1 Hz, enol ester $CH_3$), 2.21-2.28 (1H, m, keto ring $CH_2$), 2.34-2.44 (1H, m, keto ring $CH_2$), 2.45-2.50 (2H, m, enol ring $CH_2$), 2.68-2.73 (2H, m, enol ring $CH_2$), 2.83-3.00 (2H, m, keto ring $CH_2$), 3.48 (1H, dd, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 4.9 Hz, keto ring COCHCO), 4.15 (2H, qd, $^3J_{HH}$ = 7.0 Hz, $^5J_{HH}$ = 3.3 Hz, keto ester $CH_2$), 4.18 (2H, q, $^3J_{HH}$ = 7.1 Hz, enol ester $CH_2$), 7.06 (1H, d, $^3J_{HH}$ = 7.2 Hz, enol ArH), 7.11-7.24 (m, 2H enol + 2H keto ArH), 7.38 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.4 Hz, keto ArH), 7.70 (1H, dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.5 Hz, enol ArH), 7.94 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.3 Hz, keto ArH), 12.43 (1H, br s, enol OH). $\delta_C$ ($CDCl_3$, 100 MHz) 14.2 ($CH_3$, enol), 14.3 ($CH_3$, keto), 20.6 ($CH_2$, enol), 26.4 ($CH_2$, keto), 27.6 ($CH_2$, keto), 27.8 ($CH_2$, enol), 54.6 (CH, keto), 60.5 ($CH_2$, enol), 61.2 ($CH_2$, keto), 97.0 (C, enol), 124.3 (CH, enol), 126.6 (CH, enol), 126.9 (CH, keto), 127.4 (CH, enol), 127.7 (CH, keto), 128.8 (CH, keto), 130.1 (C, enol), 130.5 (CH, enol), 131.8 (C, keto), 133.8 (CH, keto), 139.4 (C, enol), 143.7 (C, keto), 165.0 (C-OH, enol), 170.2 (CO, keto), 172.8 (CO, enol), 193.2 (CO, keto). m/z (ES) 241.0845 ($MNa^+$, $C_{13}H_{14}O_3Na$ requires 241.0841, 90%), 219.1032 ($MH^+$, $C_{13}H_{15}O_3$ requires 219.1021, 50%), 191.0716 ($MH^+$ - $C_2H_4$, 100%), 173.0588 (M-OEt, 10%), 145.0635 (M-$CO_2$Et, 30%).

### 7.2.27 Preparation of 2-methyl-1,3-diphenylpropane-1,3-dione




**180** **181**

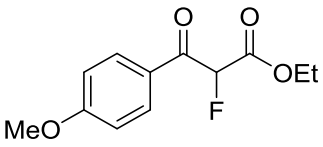
A solution of dibenzoyl methane **180** (2.00 g, 8.93 mmol) in dry THF (13 mL) was prepared under nitrogen. To this was added NaH (0.47 g, 11.9 mmol, 60% dispersion in mineral oil), in small portions over half an hour. MeI (0.56 mL, 8.93 mmol) was then added dropwise over ten minutes. The flask was sealed and stirred at room temperature for 20 hours. After this time, a saturated solution of $NH_4Cl$ (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10

mL). The organic layers were combined, dried ($MgSO_4$) and concentrated on a rotary evaporator to give a brown oily solid (2.34 g) which was purified by column chromatography (5% ethyl acetate in hexane) to give 2-methyl-1,3-diphenylpropane-1,3-dione **181** as a white solid (1.37 g, 64%). The characterisation data was in agreement with the literature.[18] mp 82 -84 $^oC$ (lit.,[19] 83 - 84 $^oC$). $\delta_H$ ($CDCl_3$, 400 MHz) 1.54 (3H, d, $^3J_{HH}$ = 7.0 Hz, $CH_3$), 5.19 (1H, q, $^3J_{HH}$ = 7.0 Hz, CH), 7.38 (4H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.49 (2H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.89 (4H, d, $^3J_{HH}$ = 7.5 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 14.4 ($CH_3$), 51.1 (CH), 128.5 (CH), 128.9 (CH), 133.5 (CH), 135.7 (C), 197.0 (CO). m/z (ES) 261.0900 ($MNa^+$, $C_{16}H_{14}O_2Na$ requires 261.0891, 50%), 239.1073 ($MH^+$, $C_{16}H_{15}O_2$ requires 239.1072, 15%), 105.0324 ($PhCO^+$, 100%).

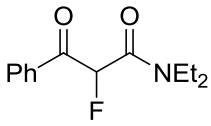
### 7.2.28 Procedure for the fluorinations in Table 10

The flask was charged with 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.44 mmol), either dry dichloromethane (1.2 mL) or no solvent, $Et_3N.3HF$ (0.31 mL, 1.92 mmol) and the substrate (0.72 mmol). The flask was then sealed and heated to either 40 or 60 $^oC$ for the required amount of time. The reaction mixture was then cooled to room temperature and concentrated on a rotary evaporator to give the crude product which was analysed by $^1H$ and $^{19}F$ NMR spectroscopy. The crude product was purified by column chromatography (ethyl acetate/hexane) on silica gel.

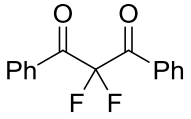
### 7.2.29 Characterisation data for the products from Table 10



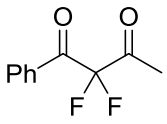

The crude product from entry 2 was purified by column chromatography (14% ethyl acetate in hexane) to give ethyl 2-fluoro-3-(4-methoxyphenyl)-3-oxo-propanoate as a colourless oil (0.116 g, 67%). The characterisation data was in agreement with the literature.[20] $\delta_H$ ($CDCl_3$, 400 MHz) 1.19 (3H, t, $^3J_{HH}$ = 7.5 Hz, $CH_3$), 3.82 (3H, s, OMe), 4.22 (2H, $m_{AB}$, dq, $^2J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 7.5 Hz, $OCH_AH_B$), 5.74 (1H, d, $^2J_{HF}$ = 48.4 Hz, CHF), 6.89 (2H, d, $^3J_{HH}$ = 9.0 Hz, ArH), 7.96 (2H, d, $^3J_{HH}$ = 9.0 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -189.5 (s). $\delta_C$ ($CDCl_3$, 100 MHz): 13.0 ($CH_3$), 54.6 ($CH_3$), 61.6 ($CH_2$), 89.2 (d, $^1J_{CF}$ = 197.6 Hz, CH), 113.1 (CH), 125.3 (C), 131.0 (d, $^4J_{CF}$ = 3.1 Hz, CH), 163.6 (C), 164.2 (d, $^2J_{CF}$ = 24.1 Hz, CO), 186.8 (d, $^2J_{CF}$ = 20.8 Hz, CO). m/z (ES) 241.0880 ($MH^+$, $C_{12}H_{14}FO_4$ requires 241.0876, 60%), 135.0452 (100).



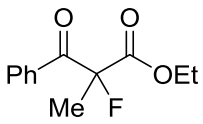
The crude product from entry 3 was purified by column chromatography (10% ethyl acetate in hexane) to give *N*,*N*-diethyl-2-fluoro-3-oxo-3-phenylpropanamide as a yellow oil (0.148 g, 88%). (Found: C, 65.84, H, 6.69, N, 5.78 Calc. for $C_{13}H_{16}FNO_2$: C, 65.82, H, 6.75, N, 5.91%). $\delta_H$ ($CDCl_3$, 400 MHz) 1.02 (3H, t, $^3J_{HH}$ = 7.1 Hz, $CH_3$), 1.11 (3H, t, $^3J_{HH}$ = 7.1 Hz, $CH_3$), 3.30 (2H, q, $^3J_{HH}$ = 7.1 Hz, $CH_2$), 3.41 (2H, m, $CH_2$), 6.04 (1H, d, $^2J_{HF}$ = 49.1 Hz, CHF), 7.40 (2H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.52 (1H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 8.05 (2H, d, $^3J_{HH}$ = 7.7 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -186.6 (s). $\delta_C$ ($CDCl_3$, 100 MHz): 12.4 ($CH_3$), 14.1 ($CH_3$), 40.9 ($CH_2$), 41.6 (d, $^4J_{CF}$ = 4.8 Hz, $CH_2$), 92.5 (d, $^1J_{CF}$ = 197.5 Hz, CHF), 128.6 (CH), 129.6 (d, $^4J_{CF}$ = 2.2 Hz, CH), 133.7 (C), 134.2 (CH), 163.4 (d, $^2J_{CF}$ = 20.6 Hz, CO), 191.9 (d, $^2J_{CF}$ = 20.7 Hz, CO). m/z (ES) 260.1083 ($MNa^+$, $C_{13}H_{16}NO_2FNa$ requires 260.1063, 55%), 238.1245 ($MH^+$, $C_{13}H_{17}NO_2F$ requires 238.1243, 100%), 100.0748 ($CONEt_2^+$, 45%).



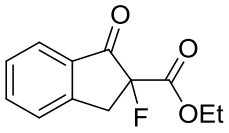
The crude product from entry 4 was purified by column chromatography (5% ethyl acetate in hexane) to give 1,3-diphenyl-2,2-difluoro-1,3-propanedione as a white solid (0.144 g, 71%). The characterisation data was in agreement with the literature.[13] mp 61 - 63 $^oC$ (lit.,[13] 55 - 57 $^oC$). $\delta_H$ ($CDCl_3$, 400 MHz) 7.41 (2H, t, $^3J_{HH}$ = 8.0 Hz, ArH), 7.56 (1H, t, $^3J_{HH}$ = 8.0 Hz, ArH), 8.00 (2H, d, $^3J_{HH}$ = 8.0 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -102.6 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 112.7 (t, $^1J_{CF}$ = 265.1 Hz, $CF_2$), 128.9 (CH), 130.3 (CH), 131.6 (C), 135.0 (CH), 187.4 (t, $^2J_{CF}$ = 27.4 Hz). m/z (EI) 260 ($M^+$, 28%), 105 (100), 77 (88).



The crude product from entry 5 was purified by column chromatography (100% hexane then 5% ethyl acetate in hexane) to give 1-phenyl-2,2-difluoro-1,3-butanedione as a colourless oil (0.064 g, 45%). The characterisation data was in agreement with the literature.[21] $\delta_H$ ($CDCl_3$, 400 MHz) 2.34 (3H, t, $^4J_{HF}$ = 1.7 Hz, $CH_3$), 7.43 (2H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.59 (1H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.97 (2H, d, $^3J_{HH}$ = 7.7 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -108.9 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 25.0 ($CH_3$), 111.3 (t, $^1J_{CF}$ = 265.8 Hz, $CF_2$), 128.9 (CH), 130.1 (t, $^4J_{CF}$ = 2.4 Hz, CH), 131.4 (C), 135.1 (CH), 187.6 (t, $^2J_{CF}$ = 26.9 Hz, CO), 195.9 (t, $^2J_{CF}$ = 28.1 Hz, CO).

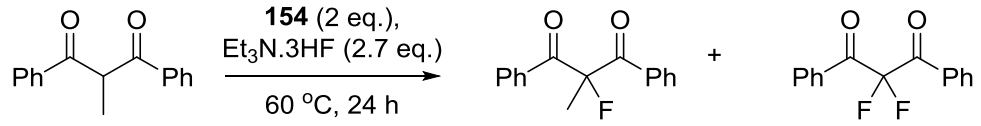


The crude product from entry 6 was purified by column chromatography (5% ethyl acetate in hexane) to give ethyl 2-fluoro-2-methyl-3-oxo-3-phenylpropanoate as a colourless oil (0.088 g, 55%). The characterisation data was in agreement with the literature.[22, 23] $\delta_H$ ($CDCl_3$, 400 MHz) 1.12 (3H, t, $^3J_{HH}$ = 7.1 Hz, $OCH_2CH_3$), 1.80 (3H, d, $^3J_{HF}$ = 23.8 Hz, $CH_3$), 4.17 (2H, $m_{AB}$, dq, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 7.1 Hz, $OCH_AH_B$), 7.38 (2H, t, $^3J_{HH}$ = 8.0 Hz, ArH), 7.51 (1H, t, $^3J_{HH}$ = 8.0 Hz, ArH), 7.97 (2H, d, $^3J_{HH}$ = 8.0 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -151.8 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 13.8 ($CH_3$), 20.9 (d, $^2J_{CF}$ = 23.8 Hz, $CH_3$), 62.5 ($CH_2$), 97.0 (d, $^1J_{CF}$ = 194.9 Hz, C), 128.6 (CH), 129.7 (d, $^4J_{CF}$ = 5.6 Hz, CH), 133.4 (d, $^3J_{CF}$ = 4.8 Hz, C), 133.9 (CH), 168.4 (d, $^2J_{CF}$ = 25.3 Hz, CO), 191.7 (d, $^2J_{CF}$ = 25.6 Hz, CO).



The crude product from entry 7 was purified by column chromatography (5% ethyl acetate in hexane) to give ethyl 1-indanone-2-fluoro-2-carboxylate as a colourless oil (0.090 g, 55%). The characterisation data was in agreement with the literature.[16] $\delta_H$ ($CDCl_3$, 400 MHz) 1.18 (3H, t, $^3J_{HH}$ = 7.2 Hz, $CH_3$), 3.36 (1H, dd, $^3J_{HF}$ = 23.5 Hz, $^2J_{HH}$ = 17.8 Hz, ring $CH_AH_B$), 3.72 (1H, dd, $^2J_{HH}$ = 17.8 Hz, $^3J_{HF}$ = 11.6 Hz, ring $CH_AH_B$), 4.21 (2H, q, $^3J_{HH}$ = 7.2 Hz, $OCH_2$), 7.39 (1H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.43 (1H, d, $^3J_{HH}$ = 7.7 Hz, ArH), 7.63 (1H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.76 (1H, d, $^3J_{HH}$ = 7.7 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -164.4 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 14.0 ($CH_3$), 38.3 (d, $^2J_{CF}$ = 24.0 Hz, $CH_2$), 62.6 ($CH_2$), 94.5 (d, $^1J_{CF}$ = 202.7 Hz, C), 125.6 (CH), 126.6 (CH), 128.6 (CH), 133.3 (C), 136.7 (CH), 150.9 (d, $^3J_{CF}$ = 3.1 Hz, C), 167.3 (d, $^2J_{CF}$ = 27.3 Hz, CO), 195.3 (d, $^2J_{CF}$ = 18.4 Hz, CO). m/z (ES) 245.0583 ($MNa^+$, $C_{12}H_{11}FO_3Na$ requires 245.0590, 100%), 223.0771 ($MH^+$, $C_{12}H_{12}FO_3$ requires 223.0770, 47%), 195.0455 (38%).

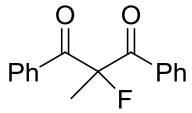
### 7.2.30 Fluorination of 2-methyl-1,3-diphenylpropane-1,3-dione




**181** **184** **185**

1-Fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.44 mmol), $Et_3N.3HF$ (0.31 mL, 1.92 mmol) and 2-methyl-1,3-diphenylpropane-1,3-dione (0.17 g, 0.72 mmol) were charged to a small Schlenk flask under nitrogen. This was then sealed

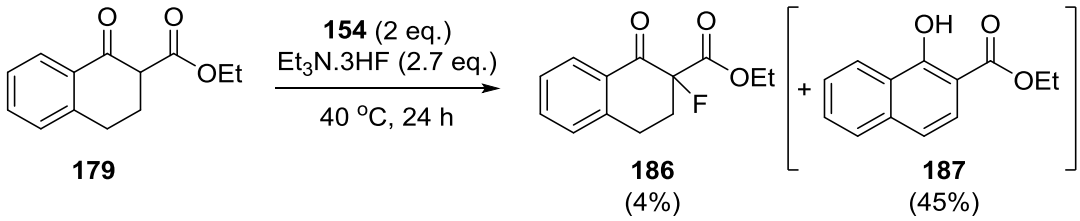
and the contents heated to 60 °C for 24 h. After this time, the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give the crude product. Purification by column chromatography (5% EtOAc in hexane) gave an inseparable mixture of 2-fluoro-2-methyl-1,3-diphenylpropane-1,3-dione **184** (40%) and 2,2-difluoro-1,3-diphenylpropane-1,3-dione **185** (9%).



**184**

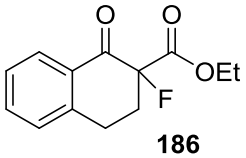
$\delta_H$ ($CDCl_3$, 400 MHz) 1.93 (3H, d, $^3J_{HF}$ = 23.8 Hz, $CH_3$), 7.33 (4H, t, $^3J_{HH}$ = 7.9 Hz, ArH), 7.46 (2H, t, $^3J_{HH}$ = 7.9 Hz, ArH), 7.91 (4H, d, $^3J_{HH}$ = 7.9 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -144.9 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 20.9 ($^2J_{CF}$ = 23.7 Hz, $CH_3$), 101.4 (d, $^1J_{CF}$ = 195.5 Hz, $C(CH_3)F$), 127.7 (CH), 128.9 (d, $^4J_{CF}$ = 5.0 Hz, CH), 132.1 (d, $^3J_{CF}$ = 2.8 Hz, C), 132.9 (CH), 193.0 (d, $^2J_{CF}$ = 24.3 Hz, CO). m/z (ES) 257.0977 ($MH^+$, $C_{16}H_{14}FO_2$ requires 257.0978, 2%), 105.0290 ($PhCO^+$, 100%.).

### 7.2.31 Fluorination of ethyl-1-tetralone-2-carboxylate



**179** **186** (4%) **187** (45%)

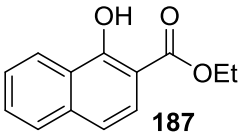
Ethyl-1-tetralone-2-carboxylate **179** (0.154 g, 0.71 mmol), 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.395 g, 1.41 mmol) and $Et_3N.3HF$ (0.31 mL) were charged to a small Schlenk flask under nitrogen. The flask was then sealed and the contents stirred at 40 °C for 24 hours. After this time, the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator. Purification by column chromatography (100% hexane) gave a mixture of ethyl 1-hydroxy-2-naphthoate **187** (45%) and ethyl 1-tetralone-2-fluoro-2-carboxylate **186** (4%).



**186**

The characterisation data for ethyl 1-tetralone-2-fluoro-2-carboxylate **186** was in agreement with the literature.[24] $\delta_H$ ($CDCl_3$, 400 MHz) 1.21 (3H, t, $^3J_{HH}$ = 7.0 Hz, ester $CH_3$), 2.43-2.53 (1H, m, ring $CH_2$), 2.60-2.73 (1H, m, ring $CH_2$), 2.97-3.16 (2H, m, ring $CH_2$), 7.21 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH), 7.30 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.48 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 8.01 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -164.3 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 14.0 ($CH_3$), 24.9 (d, $^3J_{CF}$ = 6.7 Hz, $CH_2$), 31.9 (d, $^2J_{CF}$ = 22.4 Hz,

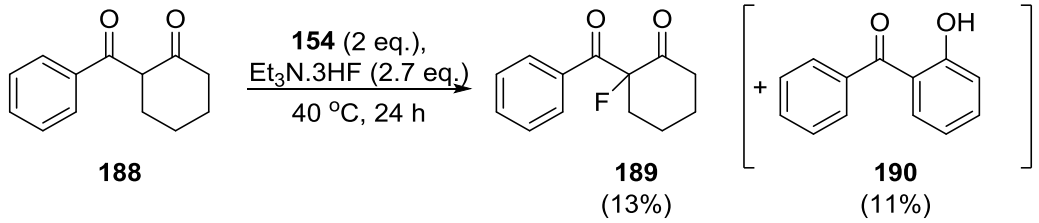
$CH_2$), 62.4 ($OCH_2$), 93.2 (d, $^1J_{CF}$ = 192.1 Hz, CF), 127.3 (CH), 128.5 (CH), 128.7 (CH), 130.7 (C), 134.5 (CH), 143.1 (C). $^{13}$C NMR spectrum was not strong enough to observe CO signals. m/z (ASAP) 237.0921 ($MH^+$, $C_{13}H_{14}FO_3$ requires 237.0927, 100%).



**187**

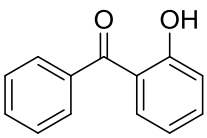
The characterisation data for ethyl 1-hydroxy-2-naphthoate **187** was in agreement with the literature.[25] $\delta_H$ ($CDCl_3$, 400 MHz) 1.33 (3H, t, $^3J_{HH}$ = 7.0 Hz, $CH_3$), 4.34 (2H, q, $^3J_{HH}$ = 7.0 Hz, $OCH_2$), 7.15 (1H, d, $^3J_{HH}$ = 9.0 Hz, ArH), 7.40 (1H, t, $^3J_{HH}$ = 8.0 Hz, ArH), 7.48 (1H, t, $^3J_{HH}$ = 8.0 Hz, ArH), 7.63 (1H, d, $^3J_{HH}$ = 8.0 Hz, ArH), 7.66 (1H, d, $^3J_{HH}$ = 9.0 Hz), 8.31 (1H, d, $^3J_{HH}$ = 8.0 Hz, ArH), 11.97 (1H, s, OH). $\delta_C$ ($CDCl_3$, 100 MHz) 11.8 ($CH_3$), 58.9 ($CH_2$), 103.3 (C), 116.0 (CH), 121.4 (CH), 121.9 (CH), 122.4 (C) 123.2 (CH), 125.0 (CH), 126.8 (CH), 134.9 (C), 158.6 (C), 168.7 (CO). m/z (ASAP) 217.0867 ($MH^+$, $C_{13}H_{13}O_3$ requires 217.0865, 100%).

### 7.2.32 Fluorination of 2-benzoylcyclohexanone



**188** **189** (13%) **190** (11%)

2-Benzoylcyclohexanone **188** (0.145 g, 0.71 mmol), 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.44 mmol) and $Et_3N.3HF$ (0.31 mL, 1.92 mmol) were charged to a small Schlenk flask. This was sealed and the contents stirred at 40 °C for 24 hours. After this time, the reaction mixture was cooled to room temperature and the crude product was purified by column chromatography (5% EtOAc in hexane). 2-Benzoyl-2-fluorocyclohexanone **189** was isolated as a yellow oil (0.020 g, approx. 13%, sample was not pure). Since the fluorinated product was not isolated pure, the characterisation data is not given here. (2-hydroxyphenyl)(phenyl)methanone **190** was also isolated as a yellow oil (0.015 g, 11%).

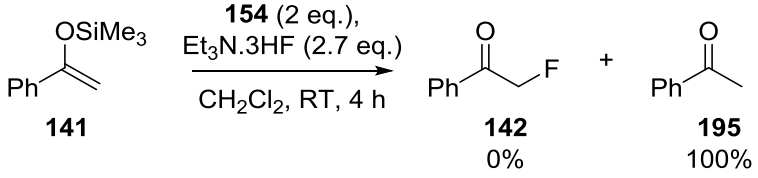


**190**

The characterisation data for (2-hydroxyphenyl)(phenyl)methanone **190** was in agreement with the literature.[26] $\delta_H$ ($CDCl_3$, 400 MHz) 6.80 (1H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.00 (1H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.1 Hz, ArH), 7.43 (3H, m, ArH), 7.52 (2H, m, ArH), 7.60 (2H, m, ArH), 11.99 (1H, s, OH). $\delta_C$ ($CDCl_3$, 100 MHz) 118.4 (CH), 118.7 (CH), 119.2 (C),

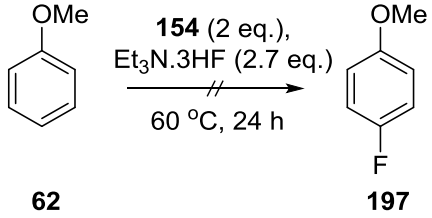
128.4 (CH), 129.2 (CH), 131.9 (CH), 133.6 (CH), 136.3 (CH), 138.0 (C), 163.3 (C), 201.6 (CO). m/z (ES) 199.0753 ($MH^+$, $C_{13}H_{11}O_2$ requires 199.0759), 121.0272 ($(M-Ph)^+$, 30%).

### 7.2.33 Example procedure for the fluorination of silyl enol ethers



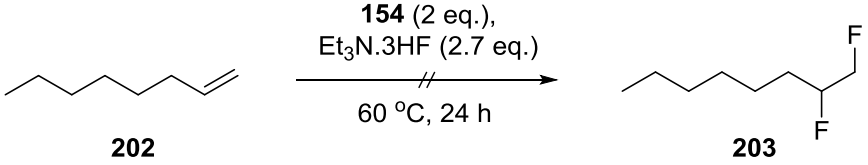

1-Fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.43 mmol) and $Et_3N.3HF$ (0.31 mL, 1.92 mmol) were added to a solution of 1-phenyl-1-trimethylsiloxyethane **141** (0.150 mL, 0.71 mmol) in dry dichloromethane (1.2 mL) in a small Schlenk flask under nitrogen. The flask was sealed and the content stirred for 4 hours at room temperature. After this time, water was added and the mixture stirred for 15 mins. The organic layer was then separated and the aqueous layer extracted with dichloromethane (3 x 2 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated on a rotary evaporator to give a pale yellow oil (0.476 g). $^1$H NMR spectroscopy showed 100% conversion of the starting material to acetophenone **195**. The desired fluorinated product **142** was not observed.

### 7.2.34 Attempted fluorination of anisole



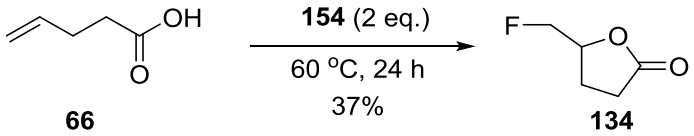

1-Fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.43 mmol), $Et_3N.3HF$ (0.31 mL, 1.92 mmol) and anisole **62** (0.078 mL, 0.71 mmol) were charged to a small Schlenk flask under nitrogen. The flask was sealed and the contents stirred for 24 hours at 60 $^o$C. After this time, $^1$H NMR spectroscopy of the crude product showed that no reaction had occurred. This reaction was also carried out using dichloromethane (1.2 mL) as the solvent for 24 hours at 40 $^o$C.

### 7.2.35 Attempted fluorination of alkenes



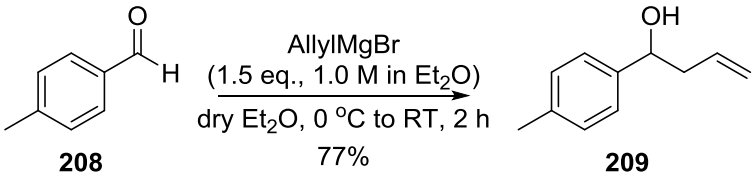

1-Fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.43 mmol), $Et_3N.3HF$ (0.31 mL, 1.92 mmol) and oct-1-ene **202** (0.112 mL, 0.71 mmol) were charged to a small Schlenk flask under nitrogen. The flask was sealed and the contents stirred for 24 hours at 60 °C. After this time, $^1$H NMR spectroscopy of the crude product showed that no reaction had occurred. This reaction was also carried out using dichloromethane (1.2 mL) as the solvent for 24 hours at 40 °C. The reactions of 1,1-diphenylethylene **124**, allyl phenyl ether **206** and allyl benzyl ether **207** under the same conditions were also unsuccessful.

### 7.2.36 Fluorination of 4-pentenoic acid



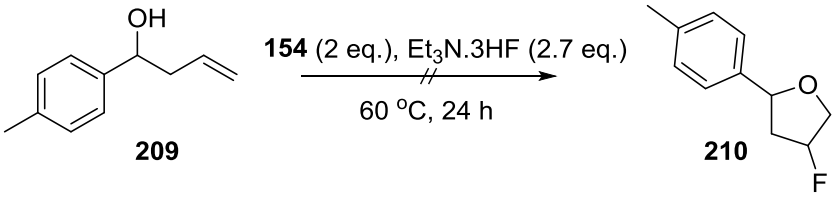

4-Pentenoic acid **66** (0.073 mL, 0.71 mmol), $Et_3N.3HF$ (0.31 mL, 1.92 mmol) and 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.43 mmol) were charged to a small Schlenk flask under nitrogen. The flask was sealed and the contents stirred at 60 °C for 24 hours. After this time the reaction mixture was cooled to room temperature. Purification by column chromatography (10% EtOAc in hexane) removed 2-(2-iodophenyl)propan-2-ol **64** from the crude reaction mixture. Further purification by column chromatography (50% EtOAc in hexane, PMA stain) gave 5-(fluoromethyl)dihydrofuran-2(3*H*)-one **134** as a colourless oil (0.031 g, 37%). The characterisation data was in agreement with the literature.[27] $\delta_H$ ($CDCl_3$, 400 MHz) 2.08 – 2.17 (1H, m, ring $CH_2$), 2.24 – 2.34 (1H, m, ring $CH_2$), 2.43 – 2.61 (2H, m, ring $CH_2$), 4.40 (1H, ddd, $^2J_{HF}$ = 47.9 Hz, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 2.4 Hz, C$H_A$C$H_B$F), 4.58 (1H, ddd, $^2J_{HF}$ = 46.4 Hz, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 3.6 Hz, C$H_A$C$H_B$F), 4.58 – 4.69 (1H, m, OCH). $\delta_F$ ($CDCl_3$, 376 MHz) -232.5 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 22.7 (d, $^3J_{CF}$ = 6.2 Hz, $CH_2$), 28.1 ($CH_2$), 77.8 (d, $^2J_{CF}$ = 20.4 Hz, CH), 83.6 (d, $^1J_{CF}$ = 175.7 Hz, $CH_2F$), 176.7 (CO). m/z (ES) 119.0503 ($MH^+$, $C_5H_8O_2F$ requires 119.0508).

### 7.2.37 Preparation of 1-(p-tolyl)but-3-en-1-ol[28]




A solution of tolualdehyde **208** (2.4 mL, 20 mmol) in dry diethyl ether (20 mL) was prepared under nitrogen and cooled to 0 °C. To this was added allylmagnesium bromide (30 mL, 30 mmol, 1.0 M in diethyl ether) dropwise over 20 minutes. The reaction mixture was then warmed to room temperature and stirred for 2 hours. After this time, the solution was cooled to 0 °C and a saturated solution of $NH_4Cl$ was added (25 mL). The product was extracted into ethyl acetate (3 x 25 mL) and the organic layers were combined and washed with brine (2 x 25 mL). The organic phase was dried ($MgSO_4$) and concentrated on a rotary evaporator to give a colourless oil (4.02 g). Purification by column chromatography (10% EtOAc in hexane) gave 1-(p-tolyl)but-3-en-1-ol **209** as a colourless oil (2.51 g, 77%). The characterisation data was in agreement with the literature.[29] $\delta_H$ ($CDCl_3$, 400 MHz) 2.41 (3H, s, $ArCH_3$), 2.42 (1H, s, OH), 2.54 (2H, t, $^3J_{HH}$ = 6.8 Hz, $CH_2$), 4.71 (1H, t, $^3J_{HH}$ = 6.8 Hz, CH(OH)), 5.15 – 5.22 (2H, m, alkene $CH_2$), 5.85 (1H, ddt, $^3J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 6.8 Hz, alkene CH), 7.21 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 7.28 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 21.1 ($CH_3$), 43.7 ($CH_2$), 73.3 (CH), 118.0 ($CH_2$), 125.9 (CH), 129.1 (CH), 134.7 (CH), 131.1 (C), 141.1 (C). m/z (ES) 145 ($(M\text{-}OH)^+$, 100%).

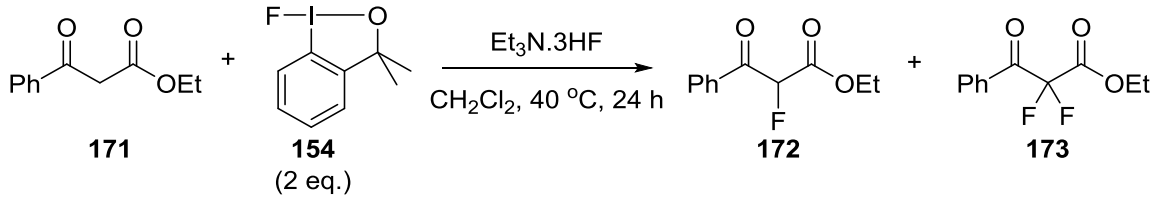
### 7.2.38 Attempted fluorination of 1-(p-tolyl)but-3-en-1-ol




1-Fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.43 mmol), $Et_3N.3HF$ (0.31 mL, 1.92 mmol) and 1-(p-tolyl)but-3-en-1-ol **209** (0.116 g, 0.71 mmol) were charged to a small Schlenk flask under nitrogen. The flask was sealed and the contents stirred for 24 hours at 60 °C. After this time, $^1$H NMR spectroscopy of the crude product showed that no reaction had occurred. This reaction was also carried out using dichloromethane (1.2 mL) as the solvent for 24 hours at 40 °C.

## 7.3 Experimental for Chapter 3

### 7.3.1 Procedure for the fluorinations in Table 1

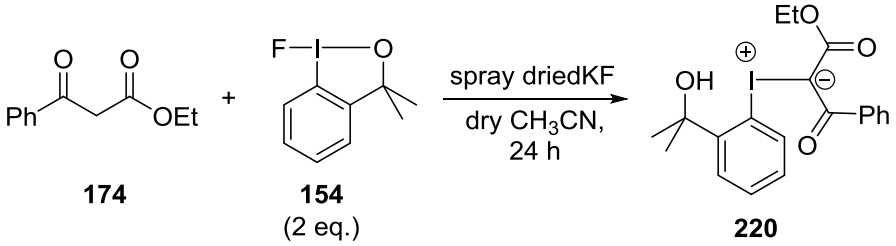



A solution of 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.44 mmol) in dry dichloromethane (1.2 mL) was prepared under nitrogen. To this was added the required amount of $Et_3N.3HF$ and ethyl 3-oxo-3-phenylpropanoate **171** (0.12 mL, 0.72 mmol). The flask was then sealed and the contents stirred at 40 $^oC$ for 24 h. After cooling the reaction mixture to room temperature, it was concentrated on a rotary evaporator to give a yellow oil which was analysed by $^1H$ and $^{19}F$ NMR spectroscopy.

The crude product from entry 1 (Table 1) was purified by column chromatography (5% ethyl acetate in hexane) to give ethyl 2-fluoro-3-oxo-3-phenylpropanoate **172** as a yellow oil (0.106 g, 63%).

The crude product from entry 4 (Table 1) was purified by column chromatography (5% ethyl acetate in hexane) to give ethyl 2-fluoro-3-oxo-3-phenylpropanoate **172** as a yellow oil (0.015 g, 10%) and ethyl 3-oxo-3-phenylpropanoate as a yellow oil (0.014 g, 10%).

### 7.3.2 Procedure for the fluorinations in Table 2

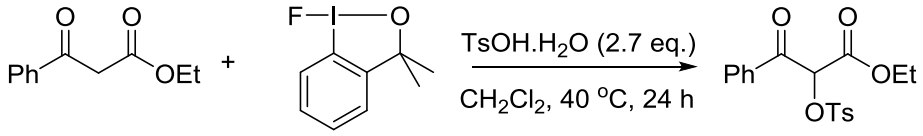



The required amount of KF, 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.44 g, 1.58 mmol), dry acetonitrile (1.3 mL) and ethyl 3-oxo-3-phenylpropanoate **171** (0.14 mL, 0.79 mmol) were charged to a small Schlenk flask under nitrogen. The flask was sealed and the contents stirred at the required temperature for 24 hours. After this time, the reaction mixture was cooled to room

temperature and concentrated on a rotary evaporator to give an orange solid (0.881 g) which was analysed by $^{1}H$ and $^{19}F$ NMR spectroscopy.

The crude product from entry 3 was purified by column chromatography (10% EtOAc in petroleum ether 40-60 then 100% EtOAc) followed by washing with $Et_2O$ gave the ylide **220** as a white solid (0.15 g, 42%). Crystals suitable for X-ray crystallography were grown by slow evaporation of a diethyl ether solution containing the ylide **220**. mp 126-127 $^{o}$C. (Found: C, 53.00, H, 4.69. Calc. for $C_{20}H_{21}IO_4$: C, 53.11, H, 4.68%). $\delta_H$ ($CDCl_3$, 500 MHz) 0.88 (3H, t, $^{3}J_{HH}$ = 7.3 Hz, $CH_3$), 1.48 (6H, s, 2 x $CH_3$), 3.89 (2H, q, $^{3}J_{HH}$ = 7.3 Hz, $OCH_2$), 6.57 (1H, br s, OH), 7.22-7.25 (2H, m, ArH), 7.36 – 7.41 (4H, m, ArH), 7.51-7.55 (3H, m, ArH). $\delta_C$ ($CDCl_3$, 126 MHz) 14.0 ($CH_3$), 29.8 (2 x $CH_3$), 60.3 ($CH_2$), 73.6 ($CMe_2$), 78.5 (C=I), 109.8 (ArCI), 127.3 (CH), 127.3 (CH), 127.4 (CH), 127.9 (CH), 129.2 (CH), 129.5 (CH), 129.7 (CH), 140.7 (C), 146.6 (C), 166.2 (CO), 189.1 (CO). m/z (ES) 475.0376 ($MNa^+$, $C_{20}H_{21}O_4INa$ requires 475.0382, 35 %), 453.0578 ($MH^+$, $C_{20}H_{22}O_4I$ requires 453.0563, 100%), 407.0136 (20%).

### 7.3.3 Reaction between ethyl 3-oxo-3-phenylpropanoate, 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole and TsOH.$H_2O$



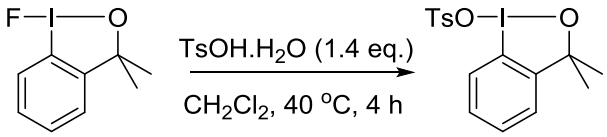

**171** **154** (2 eq.) **221** 100 % (96%)

A solution of 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.44 mmol) in dry dichloromethane (1.2 mL) was prepared under nitrogen. To this was added TsOH.$H_2O$ (0.365 g, 1.92 mmol) and ethyl 3-oxo-3-phenylpropanoate **171** (0.12 mL, 0.72 mmol). The flask was then sealed and the contents stirred at 40 $^{o}$C for 24 h. After cooling the reaction mixture to room temperature, it was concentrated on a rotary evaporator to give a yellow oil (0.833 g). The crude product was purified by column chromatography (14 % EtOAc in hexane) to give ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate **221** as a yellow oil (0.249 g, 96%). The characterisation data was in agreement with the literature.[30] $\delta_H$ ($CDCl_3$, 400 MHz) 1.10 (3H, t, $^{3}J_{HH}$ = 7.1 Hz, $CH_3$), 2.36 (3H, s, $ArCH_3$), 4.10 (2H, $m_{AB}$, dq, $^{2}J_{HH}$ = 10.7 Hz, $^{3}J_{HH}$ = 7.1 Hz,

$OCH_AH_B$), 5.92 (1H, s, CH), 7.22 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.38 (2H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.53 (1H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.71 (2H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.85 (2H, d, $^3J_{HH}$ = 7.7 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 13.8 ($CH_3$), 21.7 ($CH_3$), 62.9 ($CH_2$), 78.1 (CH), 128.4 (CH), 128.8 (CH), 129.4 (CH), 129.9 (CH), 132.5 (C), 133.4 (C), 134.4 (CH), 145.6 (C), 164.2 (CO), 188.3 (CO). m/z (ASAP) 363.0905 ($MH^+$, $C_{18}H_{19}O_6S$ requires 363.0902, 100%), 317.0449 ($(M - OEt)^+$, 38%).

Note: Ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate **221** exists as both keto and enol tautomers (93% keto : 7% enol) in $CDCl_3$. Full characterisation of the enol tautomer by $^1$H NMR spectroscopy was not possible because many of the peaks in the aromatic region are obscured and it was not possible to obtain $^{13}$C NMR data for the enol tautomer since it represents such a low percentage of the total sample. Partial $^1$H NMR data is given: $\delta_H$ ($CDCl_3$, 400 MHz) 1.25 (3H, t, $^3J_{HH}$ = 7.0 Hz, $OCH_2CH_3$), 2.25 (3H, s, $ArCH_3$), 4.23 (2H, q, $^3J_{HH}$ = 7.0 Hz, $OCH_2CH_3$), 6.92 (2H, d, $^3J_{HH}$ = 8.3 Hz, ArH), 7.11 (2H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 11.91 (br s, enol OH).

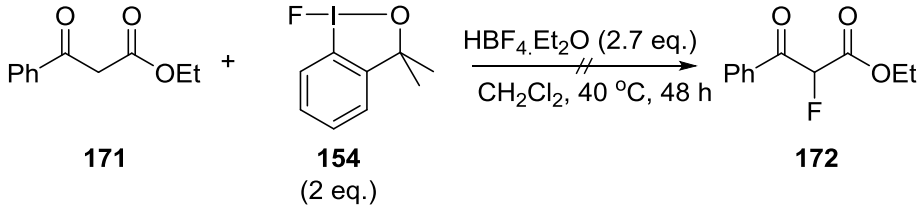
### 7.3.4 Reaction between 1-fluoro-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole and TsOH.$H_2O$




**154** **168**

A solution of 1-fluoro-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.44 mmol) in the dry dichloromethane (1.2 mL) was prepared under nitrogen. To this was added TsOH.$H_2O$ (0.364 g, 1.92 mmol). The flask was then sealed and the contents stirred at 40 °C for 4 hours. After this time, the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give a yellow oil (0.714 g). Analysis of the $^1$H and $^{19}$F NMR spectra of the crude product appeared to show formation of the tosyliodane. The crude product was washed with water in an attempt to remove the residual TsOH.$H_2O$. Analysis of the $^1$H and $^{19}$F NMR spectra of the product after washing with water showed complete conversion back to the fluoroiodane **154**.

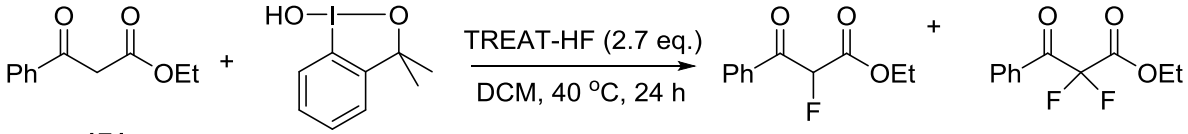
### 7.3.5 Reaction between ethyl 3-oxo-3-phenylpropanoate, 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole and $HBF_4$




**171** **154** (2 eq.) **172**

A solution of 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.44 mmol) in dry dichloromethane (1.2 mL) was prepared under nitrogen. To this was added $HBF_4.Et_2O$ (0.26 mL, 1.94 mmol) and ethyl 3-oxo-3-phenylpropanoate **171** (0.12 mL, 0.72 mmol). The flask was then sealed and the contents stirred at 40 °C for 48 h. After cooling the reaction mixture to room temperature, it was concentrated on a rotary evaporator to give a brown oily solid (0.848 g). Analysis by $^1H$ and $^{19}F$ NMR spectroscopy showed a complex mixture of products and purification was not attempted.

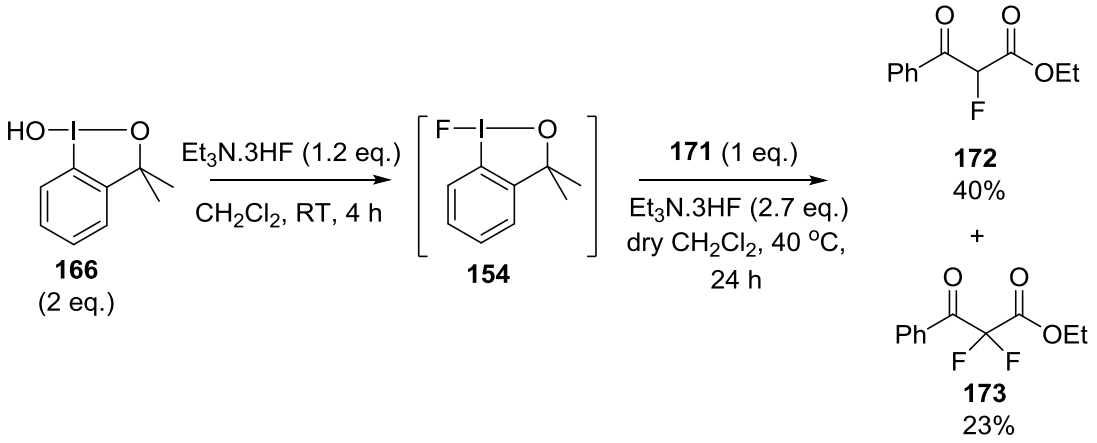
### 7.3.6 Reaction between 1-hydroxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole, ethyl 3-oxo-3-phenylpropanoate and $Et_3N.3HF$




**171** **166** (2 eq.) **172** 60% (27%) **173** 29% (14%)

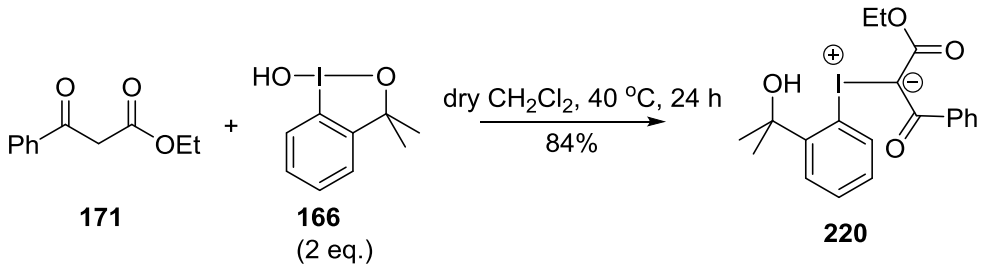
A solution of 1-hydroxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **166** (0.400 g, 1.44 mmol) in dry dichloromethane (1.2 mL) was prepared under nitrogen. To this was added TREAT-HF (0.31 mL, 1.92 mmol) followed by ethyl 3-oxo-3-phenylpropanoate **171** (0.12 mL, 0.72 mmol). The flask was then sealed and the contents stirred at 40 °C for 24 hours. After this time the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give a yellow oil. This was purified by column chromatography (5% EtOAc in hexane) to give ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate **173** (0.023 g, 14%) and ethyl 2-fluoro-3-oxo-3-phenylpropanoate **172** (0.041 g, 27%).

### 7.3.7 Reaction between 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole, $Et_3N.3HF$ and ethyl 3-oxo-3-phenylpropanoate




A solution of 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole **166** (0.400 g, 1.44 mmol) in dry dichloromethane (0.9 mL) was prepared under nitrogen. To this was added TREAT-HF (0.28 mL, 1.73 mmol). The flask was then sealed and the contents stirred at room temperature for 4 hours. After this time, more TREAT-HF was added (0.31 mL, 1.94 mmol) followed by ethyl 3-oxo-3-phenylpropanoate **171** (0.12 mL, 0.72 mmol). The flask was the resealed and the contents stirred at 40 $^oC$ for 24 hours. After this time, the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give a pale yellow oil (1.20 g). This was purified by column chromatography (5% EtOAc in hexane) to give ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate **173** (0.037 g, 23%) and ethyl 2-fluoro-3-oxo-3-phenylpropanoate **172** (0.061 g, 40%).

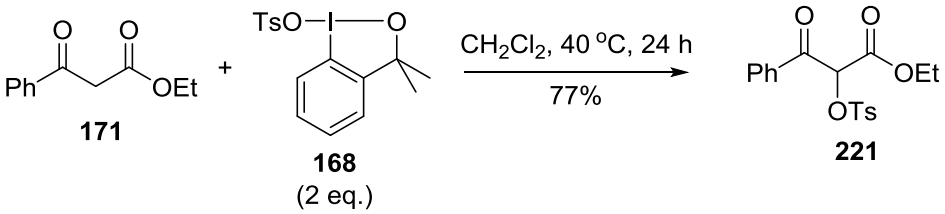
### 7.3.8 Preparation of iodonium ylide 220 from 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole




A solution of 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole **166** (2.00 g, 7.19 mmol) in dry dichloromethane (7.6 mL) was prepared under nitrogen. To this was added ethyl 3-oxo-3-phenylpropanoate **171** (0.62 mL, 3.60 mmol). The flask was

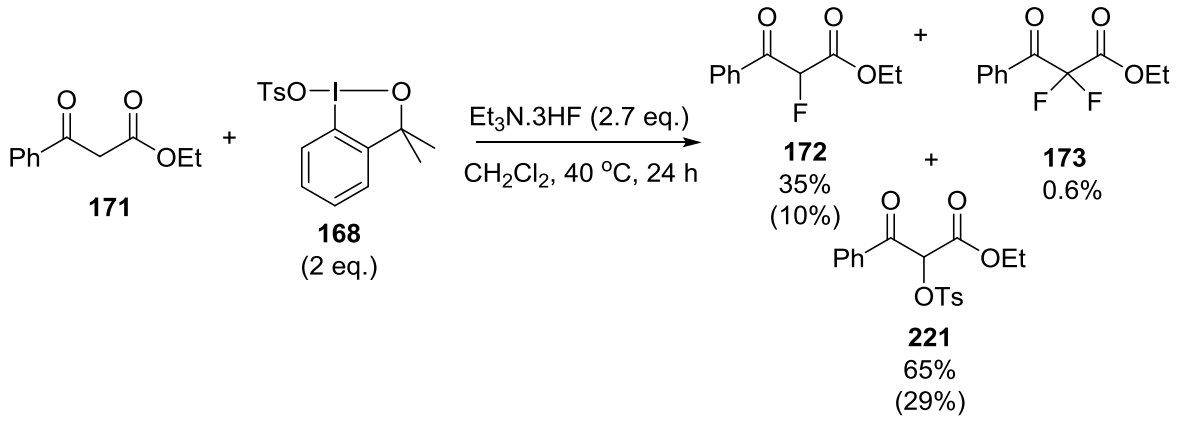
then sealed and the contents stirred at 40 °C for 24 hours. After this time, the reaction mixture was concentrated on a rotary evaporator to give a pale yellow oil (2.82 g). Purification by column chromatography (10% EtOAc in petroleum ether 40-60 then 100% EtOAc) followed by washing with $Et_2O$ gave the iodonium ylide **220** as a white solid (1.37 g, 84%).

### 7.3.9 Preparation of ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate




A solution of 1-tosyloxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **168** (0.400 g, 0.93 mmol) and ethyl 3-oxo-3-phenylpropanoate **171** (0.080 mL, 0.46 mmol) in dry dichloromethane (1.0 mL) was prepared under nitrogen. The flask was then sealed and the contents stirred at 40 °C for 24 hours. After this time, the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give a yellow oily solid (0.474 g). Purification by column chromatography (20% EtOAc in hexane) gave ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate **221** as a yellow oil (0.129 g, 77%).

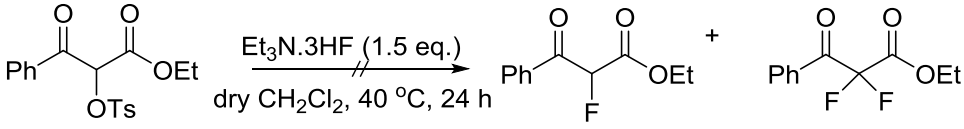
### 7.3.10 Reaction of 1-tosyloxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole, ethyl 3-oxo-3-phenylpropanoate and $Et_3N.3HF$




A solution of 1-tosyloxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **168** (0.400 g, 0.93 mmol) in dry dichloromethane (0.8 mL) was prepared under nitrogen. To this was added $Et_3N.3HF$ (0.2 mL, 1.24 mmol) followed by ethyl 3-oxo-3-phenylpropanoate

**171** (0.08 mL, 0.46 mmol). The flask was then sealed and the contents stirred at room temperature for 24 hours. After this time, the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give a yellow oil (0.663 g). Purification by column chromatography (5% EtOAc in hexane) gave ethyl 2-fluoro-3-oxo-3-phenylpropanoate **172** as a pale yellow oil (0.01 g, 10%) and ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate **221** as a yellow oil (0.048 g, 29%).

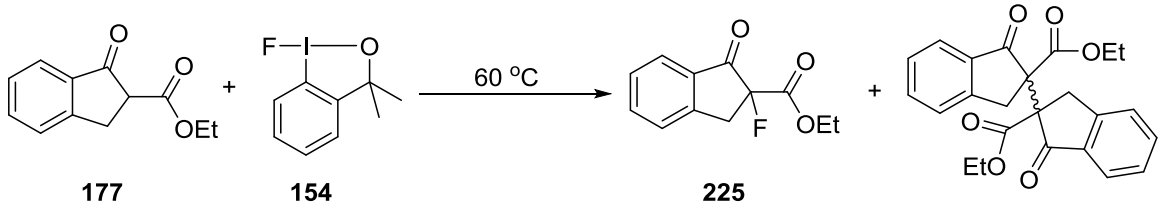
### 7.3.11 Reaction between ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate and TREAT-HF




**221** **172** **173**

A solution of ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate **221** (0.046g, 0.13 mmol) in dry dichloromethane (0.37 mL) was prepared under nitrogen. To this was added $Et_3N.3HF$ (0.03 mL, 0.19 mmol). The flask was then sealed and the contents stirred at 40 $^oC$ for 24 hours. After this time the reaction mixture was cooled to room temperature and concentrated on the rotary evaporator to give a pale yellow oil (0.121 g). Analysis by $^1H$ and $^{19}F$ NMR spectroscopy showed that no conversion of the starting material had occurred.

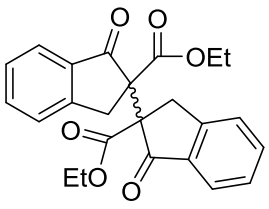
### 7.3.12 Procedure for Table 4




**177** **154** **225** **226a** and **226b**

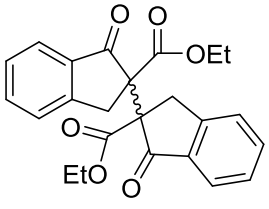
A solution of ethyl-1-indanone-2-carboxylate **177** (0.147 g, 0.72 mmol) and 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.400 g, 1.44 mmol) and any additional additives in the dry solvent/$Et_3N.3HF$ (0.3 mL) was prepared under nitrogen in a small Schlenk flask. The flask was sealed and the contents stirred at 60 $^oC$ for the required amount of time. After this time, the reaction mixture was cooled to room

temperature and concentrated on a rotary evaporator to give a yellow oil. The crude product was purified by column chromatography (5% EtOAc in petroleum ether 40 – 60).



**226a**

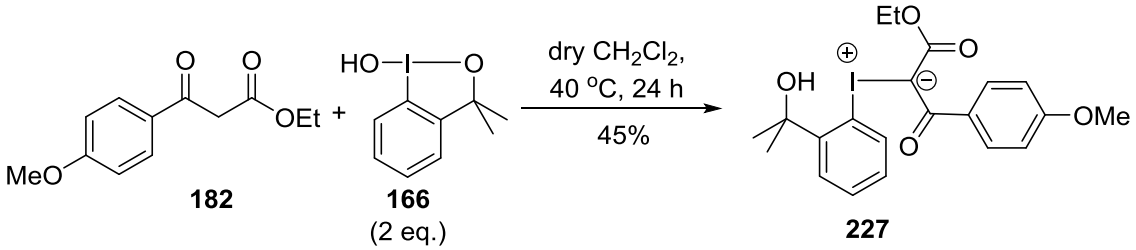
$\delta_H$ ($CDCl_3$, 400 MHz) 1.17 (6H, t, $^3J_{HH}$ = 7.4 Hz, $CH_3$), 3.92 (2H, d, $^2J_{HH}$ = 18.3 Hz, ring $CH_2$), 4.11 – 4.22 (4H, m, $OCH_2$), 4.53 (2H, d, $^2J_{HH}$ = 18.3 Hz, ring $CH_2$), 7.25 (2H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.40 (2H, d, $^3J_{HH}$ = 7.7 Hz, ArH), 7.51 (2H, d, $^3J_{HH}$ = 7.7 Hz, ArH), 7.59 (2H, d, $^3J_{HH}$ = 7.7 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 13.9 ($CH_3$), 37.4 ($CH_2$), 61.9 ($CH_2$), 63.1 (C), 124.3 (CH), 126.1 (CH), 127.3 (CH), 135.2 (C), 135.7 (CH), 154.7 (C), 170.3 (CO), 200.2 (CO). m/z (ASAP) 429.1328 ($MNa^+$, $C_{24}H_{22}O_6Na$ requires 429.1314, 100%), 407.1489 ($MH^+$, $C_{24}H_{23}O_6$ requires 407.1495, 100%), 361.1094 ($(M\text{-}OEt)^+$, 90%).



**226b**

$\delta_H$ ($CDCl_3$, 400 MHz) 0.84 (6H, t, $^3J_{HH}$ = 7.0 Hz, $CH_3$), 3.65 (2H, d, $^2J_{HH}$ = 18.3 Hz, ring $CH_2$), 3.88 (4H, q, $^3J_{HH}$ = 7.0 Hz, $OCH_2$), 4.17 (2H, d, $^2J_{HH}$ = 18.3 Hz, ring $CH_2$), 7.42 (2H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.51 (2H, d, $^3J_{HH}$ = 7.6 Hz, ArH), 7.62 (2H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.85 (2H, d, $^3J_{HH}$ = 7.6 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 13.4 ($CH_3$), 38.1 ($CH_2$), 61.9 ($CH_2$), 62.9 (C), 124.3 (CH), 126.1 (CH), 127.5 (CH), 134.8 (CH), 136.6 (C), 152.7 (C), 170.5 (CO), 201.7 (CO). m/z (ASAP) 429.1328 ($MNa^+$, $C_{24}H_{22}O_6Na$ requires 429.1314, 100%), 407.1489 ($MH^+$, $C_{24}H_{23}O_6$ requires 407.1495, 100%), 361.1094 ($(M\text{-}OEt)^+$, 90%).

### 7.3.13 Preparation of iodonium ylide 227

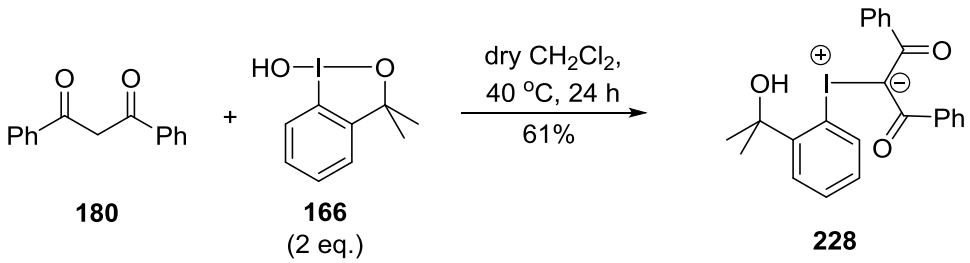



**182** + **166** (2 eq.) → **227**

A solution of 1-hydroxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **166** (1.00 g, 3.60 mmol) in dry dichloromethane (3.8 mL) was prepared under nitrogen. To this was added ethyl 3-(4-methoxyphenyl)-3-oxo-propanoate **182** (0.34 mL, 1.80 mmol).

The flask was then sealed and the contents stirred at 40 °C for 24 hours. After this time, the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give a yellow solid (1.49 g). Purification by column chromatography (10% EtOAc in petroleum ether then 100% EtOAc) followed by trituration with diethyl ether gave the ylide **227** as a pale yellow solid (0.39 g, 45%). mp 128-129 °C. (Found C, 52.37, H, 4.75. Calc. for $C_{21}H_{23}IO_5$: C, 52.30, H, 4.81%). $\delta_H$ ($CDCl_3$, 400 MHz) 0.91 (3H, t, $^3J_{HH}$ = 7.1 Hz, $CH_3$), 1.48 (6H, s, $CH_3$), 3.85 (3H, s, $OCH_3$), 3.90 (2H, q, $^3J_{HH}$ = 7.1 Hz, $OCH_2$), 6.62 (1H, s, OH), 6.88 (2H, d, $^3J_{HH}$ = 8.8 Hz, ArH), 7.17-7.22 (2H, m, ArH), 7.33 (1H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.51 (1H, d, $^3J_{HH}$ = 7.7 Hz, ArH), 7.56 (2H, d, $^3J_{HH}$ = 8.8 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 14.2 ($CH_3$), 29.9 (2 x $CH_3$), 55.3 ($OCH_3$), 60.2 ($CH_2$), 73.5 ($CMe_2$), 77.7 (C=I), 110.0 (CI), 112.6 (CH), 127.2 (CH), 127.5 (CH), 129.5 (CH), 129.7 (CH), 130.4 (CH), 132.5 (C), 146.6 (C), 160.9 (C), 166.3 (CO), 188.3 (CO). m/z (ES) 483.0691 ($MH^+$, $C_{21}H_{24}O_5I$ requires 483.0669, 100%), 437.0263 (M-OEt, 40%), 221.0823 ($C_{12}H_{13}O_4^+$, 60%), 193.0865 ($C_{10}H_9O_4$, 60%).

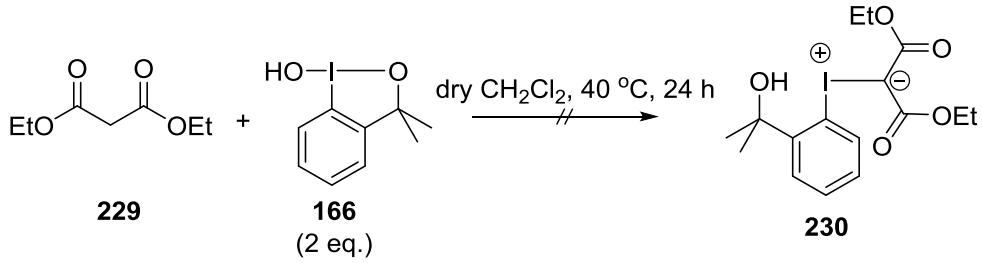
### 7.3.14 Preparation of iodonium ylide 228




A solution of 1,3-diphenylpropane-1,3-dione **180** (0.43 g, 1.93 mmol) and 1-hydroxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **166** (1.07 g, 3.86 mmol) in dry dichloromethane (4.1 mL) was prepared under nitrogen. The flask was sealed and the contents stirred at 40 °C for 24 hours. After this time, the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give a yellow solid (1.53 g). Purification by column chromatography (10% EtOAc in petroleum ether then 100% EtOAc) followed by washing with diethyl ether gave the ylide **228** as a yellow solid (0.57 g, 61%). mp 149-150 °C. (Found: C, 59.45, H, 4.45. Calc. for $C_{24}H_{21}IO_3$: C, 59.52, H, 4.37%). $\delta_H$ ($CDCl_3$, 400 MHz) 1.49 (6H, s, $CH_3$), 6.66 (1H, s, OH), 6.98 (4H, t, $^3J_{HH}$ = 7.7 Hz, ArH), 7.04-7.08 (2H, m, ArH), 7.16-7.21 (2H, m, ArH), 7.29-7.33 (5H, m, ArH), 7.63 (1H, dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.1 Hz ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 29.8 ($CH_3$), 73.6 ($CMe_2$), 98.3 (C=I), 110.0 (CI), 127.2 (CH), 127.4 (2 x CH), 128.0 (CH),

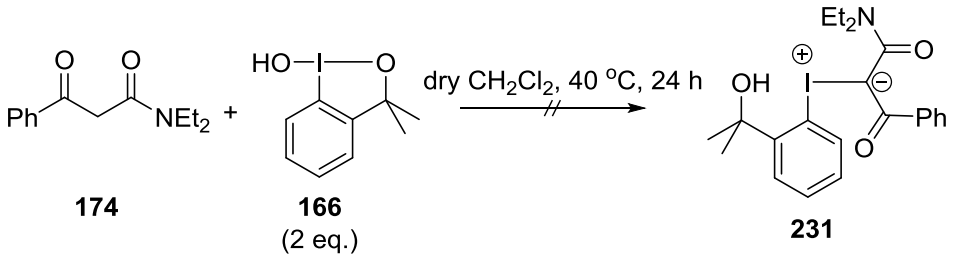
129.3 (CH), 129.7 (CH), 129.8 (CH), 139.6 (C), 146.8 (C), 189.6 (CO). m/z (ES) 485.0610 ($MH^+$, $C_{24}H_{22}O_3I$ requires 485.0614, 100%).

### 7.3.15 Attempted preparation of iodonium ylide 230



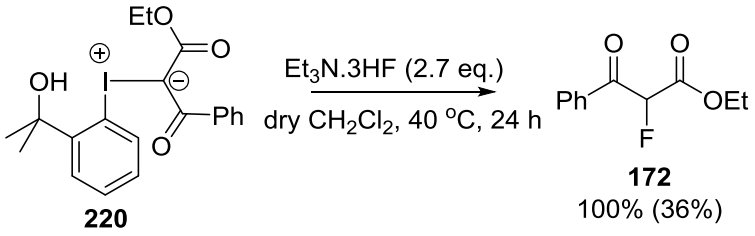

A solution of 1-hydroxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **166** (2.00 g, 7.19 mmol) in dry dichloromethane (7.6 mL) was prepared under nitrogen. To this was added diethyl malonate **229** (0.55 mL, 3.60 mmol). The flask was then sealed and the contents stirred at 40 °C for 24 hours. After this time, the $^1$H NMR spectrum of the crude product showed only starting material.

### 7.3.16 Attempted preparation of iodonium ylide 231



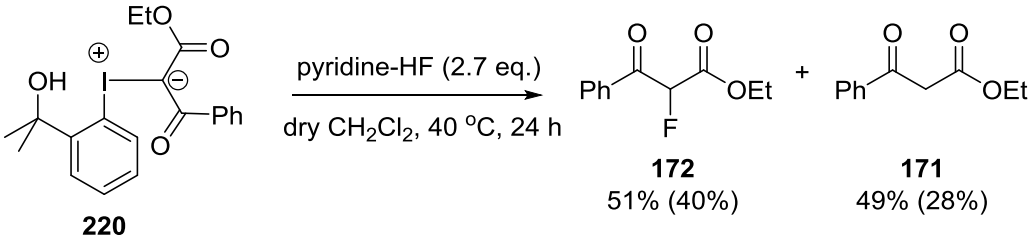

A solution of 1-hydroxy-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **166** (1.00 g, 3.60 mmol) in dry dichloromethane (7.6 mL) was prepared under nitrogen. To this was added *N*,*N*-diethyl-3-oxo-3-phenylpropanamide **174** (0.39 mL, 1.80 mmol). The flask was then sealed and the contents stirred at 40 °C for 24 hours. After this time, the $^1$H NMR spectrum of the crude product showed only starting material.

### 7.3.17 Reaction between iodonium ylide 220 and $Et_3N.3HF$

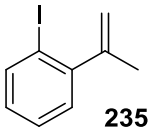



A solution of the ylide **220** (0.200 g, 0.44 mmol) in dry dichloromethane (0.8 mL) was prepared under nitrogen. To this was added $Et_3N.3HF$ (0.19 mL, 1.19 mmol). The flask was then sealed and the contents stirred at 40 $^oC$ for 24 hours. After this time, the reaction mixture was concentrated on a rotary evaporator to give a pale yellow oil (0.402 g). Purification by column chromatography (5% EtOAc in hexane) gave ethyl 2-fluoro-3-oxo-3-phenylpropanoate **171** as a pale yellow oil (0.033 g, 36%) in addition to 2-(2-iodophenyl)propan-2-ol **64** as a pale yellow oil (0.062 g, 54 %).

### 7.3.18 Reaction between iodonium ylide 220 and pyridine-HF



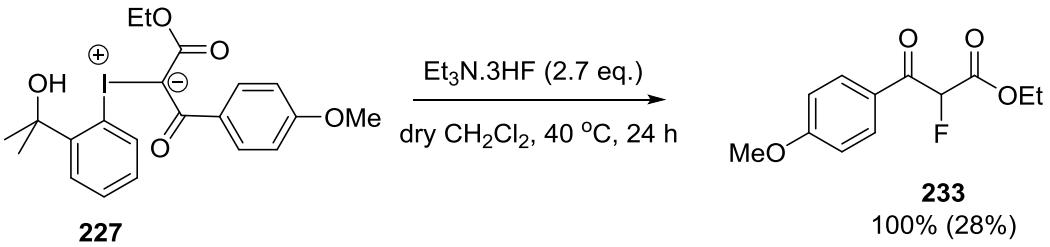

A solution of the ylide **220** (0.200 g, 0.44 mmol) in dry dichloromethane (0.72 mL) was prepared under nitrogen. To this was added pyridine HF (0.28 mL, 1.19 mmol, 70% HF, 30% pyridine). The tube was then sealed and the contents stirred at 40 $^oC$ for 24 hours. After this time, the reaction mixture was cooled to room temperature to give a yellow oil. Water (5 mL) and dichloromethane (5 mL) were added and the aqueous layer extracted with dichloromethane (5 x 5 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated on a rotary evaporator to give a pale yellow oil (0.176 g). Purification by column chromatography (5% EtOAc in petroleum ether 40-60) gave ethyl 3-oxo-3-phenylpropanoate **171** (0.024 g, 28%) and ethyl 2-fluoro-3-oxo-3-phenylpropanoate **172** (0.037 g, 40%). 1-iodo-2-(prop-1-en-2-yl)benzene **235** was also isolated (0.069 g, 64%).



**235**

The characterisation data for 1-iodo-2-(prop-1-en-2-yl)benzene was in agreement with the literature.[31] $\delta_H$ ($CDCl_3$, 400 MHz) 1.98 (3H, dd, $^4J_{HH}$ = 1.1 Hz, $^4J_{HH}$ = 1.4 Hz $CH_3$), 4.79-4.81 (1H, m, alkene CH), 5.12-5.14 (1H, m, alkene CH), 6.83 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.07 (1H, dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.20 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.74 (1H, dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.5 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 23.9 ($CH_3$), 97.0 (CI), 116.1 ($CH_2$), 128.1 (CH), 128.4 (CH), 128.5 (CH), 139.2 (CH), 148.4 (C), 148.9 (C). m/z (ASAP) 244.9816 ($MH^+$, $C_9H_{10}I$ requires 244.9827, 100%).

### 7.3.19 Reaction between iodonium ylide 227 and $Et_3N.3HF$

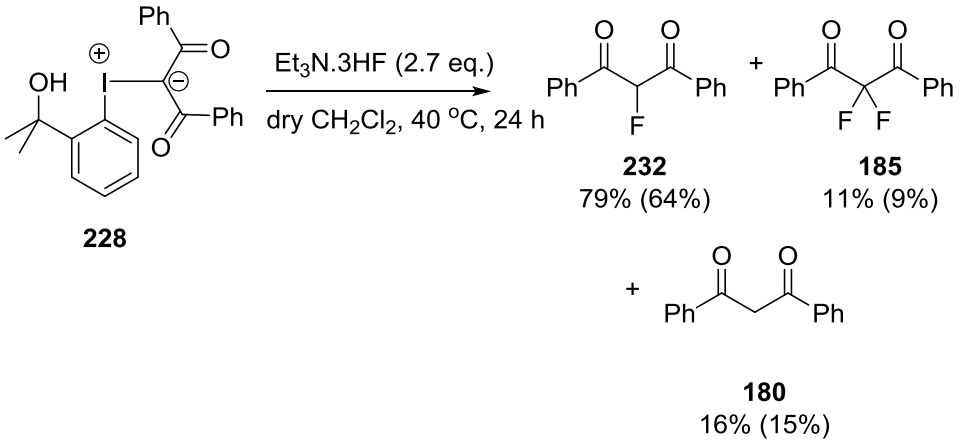



**227**

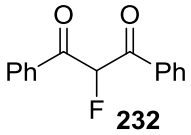
**233**
100% (28%)

A solution of the ylide **227** (0.200 g, 0.41 mmol) in dry dichloromethane (0.75 mL) was prepared under nitrogen. To this was added $Et_3N.3HF$ (0.18 mL, 1.12 mmol). The flask was sealed and the contents stirred at 40 °C for 24 hours. After this time the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give a yellow oil (0.443 g). Purification by column chromatography (17% EtOAc in petroleum ether 40-60) gave 2-(2-iodophenyl)propan-2-ol **64** as a pale yellow oil (0.099 g, 92%) and ethyl 2-fluoro-3-(4-methoxyphenyl)-3-oxopropanoate **233** as a colourless oil (0.027 g, 28%).

### 7.3.20 Reaction between iodonium ylide 228 and $Et_3N.3HF$



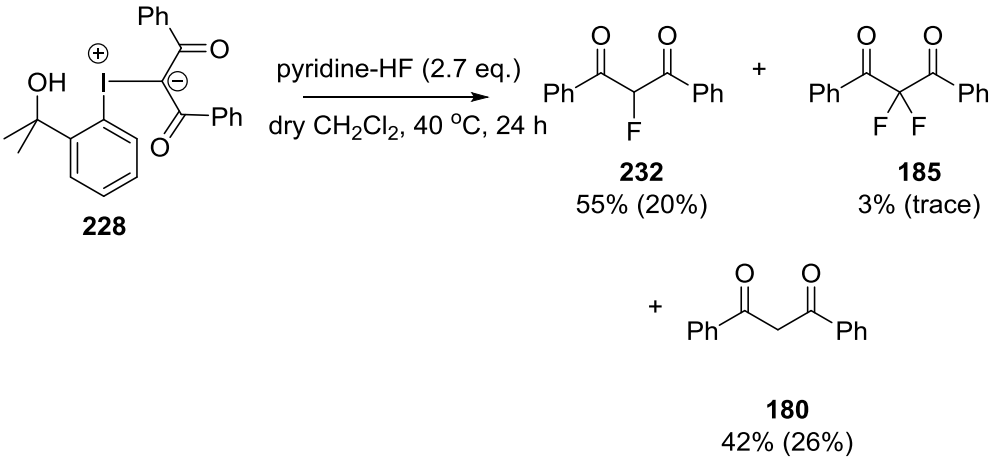

A solution of the ylide 228 (0.200 g, 0.41 mmol) in dry dichloromethane (0.75 mL) was prepared under nitrogen. To this was added Et3N.3HF (0.18 mL, 1.11 mmol). The flask was then sealed and the contents stirred at 40 oC for 24 hours. After this time the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give a yellow oil (0.416 g). Column chromatography (10% EtOAc in petroleum ether 40-60) gave a mixture of 2-fluoro-1,3-diphenylpropane-1,3-dione 232, 2,2-difluoro-1,3-diphenylpropane-1,3-dione 185, 1,3-diphenylpropane-1,3-dione 180 (0.072 g). Further elution gave 2-(2-iodophenyl)propan-2-ol 64 (0.072 g, 67%).



**232**

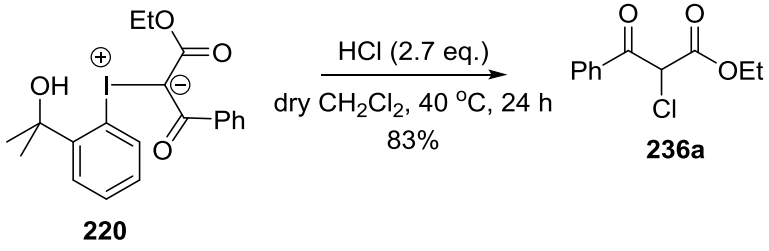
2-Fluoro-1,3-diphenyl-propane-1,3-dione exists as a mixture of tautomers (54% keto: 46% enol) and the characterisation data was in agreement with the literature.[12] $\delta_H$ ($CDCl_3$, 500 MHz) 6.53 (1H, d, $^2J_{HF}$ = 49.1 Hz, keto CHF), 7.46-7.51 (4H keto + 4H enol, m, ArH), 7.54-7.57 (2H, m, enol ArH), 7.60 (2H, t, $^3J_{HH}$ = 7.4 Hz, keto ArH), 8.02 (4H, d, $^3J_{HH}$ = 8.5 Hz, enol ArH), 8.09 (4H, d, $^3J_{HH}$ = 8.3 Hz, keto ArH), 17.74 (1H, d, $^4J_{HF}$ = 3.1 Hz, enol OH). $\delta_F$ ($CDCl_3$, 376 MHz) -168.6 (s, enol), -186.7 (s, keto). $\delta_C$ ($CDCl_3$, 126 MHz) 96.6 (d, $^1J_{CF}$ = 198.9 Hz, keto CH), 128.5 (enol CH), 128.8 (keto CH), 129.1 (d, $^4J_{CF}$ = 8.5 Hz, enol CH), 129.8 (d, $^4J_{CF}$ = 3.3 Hz, keto CH), 132.4 (enol CH), 133.2 (d, $^3J_{CF}$ = 5.1 Hz, enol C), 133.6 (d, $^3J_{CF}$ = 1.9 Hz, keto, C), 134.5 (keto, CH), 144.2 (d, $^1J_{CF}$ = 235.4 Hz, enol CF), 176.0 (d, $^2J_{CF}$ = 21.5 Hz, enol CO), 191.2 (d, $^2J_{CF}$ = 20.1 Hz, keto CO). m/z (ASAP) 243.0824 ($MH^+$, $C_{15}H_{12}O_2F$ requires 243.0821, 100 %).

### 7.3.21 Reaction between iodonium ylide 228 and Pyridine-HF




A solution of the ylide **228** (0.15 g, 0.31 mmol) in dry dichloromethane (0.5 mL) was prepared under nitrogen. To this was added pyridine HF (0.20 mL, 0.84 mmol). The flask was then sealed and the contents stirred at 40 $^{o}$C for 24 hours. After this time, the reaction mixture was cooled to room temperature to give a yellow oil. Water (5 mL) and dichloromethane (5 mL) were added and the organic layer washed with water (3 x 5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The organic layer was dried ($MgSO_4$) and concentrated on a rotary evaporator to give a pale yellow oil (0.140 g). Column chromatography (5% EtOAc in petroleum ether 40-60) gave a mixture of 2-fluoro-1,3-diphenylpropane-1,3-dione **232**, 2,2-difluoro-1,3-diphenylpropane-1,3-dione **185**, 1,3-diphenylpropane-1,3-dione **180** (0.033 g). Further elution gave 1-iodo-2-(prop-1-en-2-yl)benzene **253** (0.040 g, 53%).

### 7.3.22 Reaction between iodonium ylide 220 and HCl

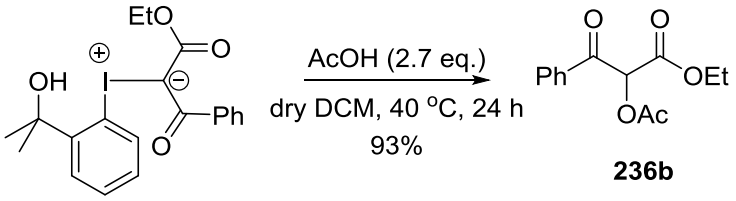



A solution of the ylide **220** (0.200 g, 0.44 mmol) in dry dichloromethane (0.9 mL) was prepared under nitrogen. To this was added conc. hydrochloric acid (0.1 mL, 1.19 mmol). The flask was then sealed and the contents stirred at 40 $^{o}$C for 24 hours. After this time, the reaction mixture was cooled to room temperature. Dichloromethane was added (5 mL) followed by water (5 mL). The organic layer was separated and the

aqueous layer extracted with more dichloromethane (3 x 5 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated on a rotary evaporator to give a colourless oil (0.198 g). Purification by column chromatography (100% petroleum ether 40-60) gave 1-iodo-2-(prop-1-en-2-yl)benzene **235** as a colourless oil (0.059 g, 55%). Further elution (5% EtOAc in petroleum ether 40-60) gave ethyl 2-chloro-3-oxo-3-phenylpropanoate **236a** as a colourless oil (0.095 g, 83%) and 2-(2-iodophenyl)propan-2-ol as a pale yellow oil (0.034 g, 29%).

The characterisation data for ethyl 2-chloro-3-oxo-3-phenylpropanoate **236a** was in agreement with the literature.[18] $\delta_H$ ($CDCl_3$, 400 MHz) 1.16 (3H, t, $^3J_{HH}$ = 7.1 Hz, $CH_3$), 4.21 (2H, q, $^3J_{HH}$ = 7.1 Hz, $OCH_2$), 5.54 (1H, s, CH), 7.42 (2H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 7.55 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 7.92 (2H, d, $^3J_{HH}$ = 7.4 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 13.9 ($CH_3$), 58.0 (CH), 63.2 ($CH_2$), 128.9 (CH), 129.2 (CH), 133.4 (C), 134.3 (CH), 165.3 (CO), 188.3 (CO). m/z (ASAP) 227.0467 ($M(^{35}Cl)H^+$, $C_{11}H_{12}O_3Cl$ requires 227.0475, 100%), 229.0460 ($M(^{37}Cl)H^+$, 30%).

### 7.3.23 Reaction between iodonium ylide 220 and AcOH



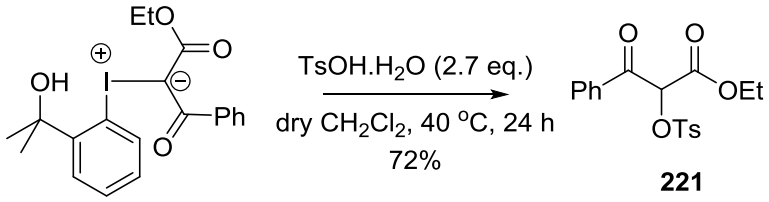

**220** **236b**

A solution of the ylide **220** (0.200 g, 0.44 mmol) in dry dichloromethane (0.9 mL) was prepared under nitrogen. To this was added glacial acetic acid (0.068 mL, 1.19 mmol). The flask was then sealed and the contents stirred at 40 °C for 24 hours. After this time, the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give a colourless oil (0.221 g). Purification by column chromatography (10% EtOAc in petroleum ether 40-60) gave 2-(2-iodophenyl)propan-2-ol **64** as a pale yellow oil (0.099 g, 86%) and ethyl 2-acetoxy-3-oxo-3-phenylpropanoate **236b** as a colourless oil (0.099 g, 93%).

The characterisation data for ethyl 2-acetoxy-3-oxo-3-phenylpropanoate **236b** was in agreement with the literature.[32] $\delta_H$ ($CDCl_3$, 400 MHz) 1.21 (3H, t, $^3J_{HH}$ = 7.0 Hz, $CH_3$), 2.22 (3H, s, $COCH_3$), 4.25 (2H, q, $^3J_{HH}$ = 7.0 Hz, $OCH_2$), 6.33 (1H, s, CH), 7.50 (2H, t,

$^3J_{HH}$ = 7.6 Hz, ArH), 7.63 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 8.00 (2H, d, $^3J_{HH}$ = 7.6 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 13.9 ($CH_3$), 20.5 ($CH_3$), 62.4 ($CH_2$), 74.5 (CH), 128.8 (CH), 129.2 (CH), 134.2 (CH), 134.2 (C), 165.1 (CO), 169.5 (CO), 189.6 (CO). m/z (ASAP) 251.0924 ($MH^+$, $C_{13}H_{15}O_5$ requires 251.0919, 100%).

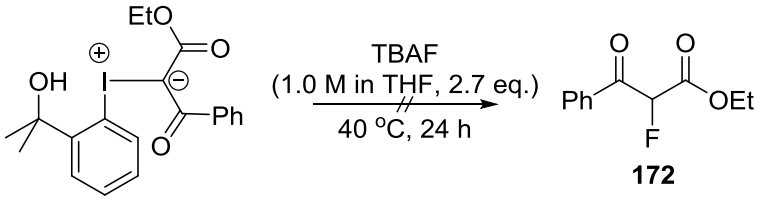
### 7.3.24 Reaction between iodonium ylide 220 and TsOH.$H_2O$




**220** **221**

A solution of the ylide **220** (0.150 g, 0.33 mmol) and TsOH.$H_2O$ (0.170 g, 0.90 mmol) in dry dichloromethane (0.75 mL) was prepared under nitrogen. The flask was then sealed and the contents stirred at 40 $^oC$ for 24 hours. After this time the reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to give a white solid (0.268 g). Purification by column chromatography (14% EtOAc in petroleum ether 40-60) gave 1-iodo-2-(prop-1-en-2-yl)benzene **235** as a colourless oil (0.075 g, 93%) and ethyl 3-oxo-3-phenyl-2-(tosyloxy)propanoate **221** (0.086 g, 72%).

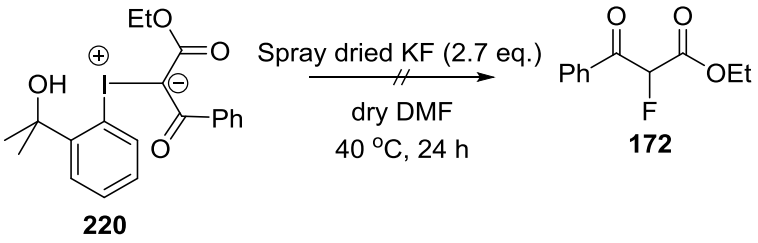
### 7.3.25 Reaction between iodonium ylide 220 and TBAF




**220** **172**

A solution of the ylide **220** (0.400 g, 0.88 mmol) in TBAF (2.4 mL, 2.4mmol, 1.0 M in THF) was prepared under nitrogen. The flask was then sealed and the contents stirred at 40 $^oC$ for 24 hours. After this time, the reaction mixture was concentrated on a rotary evaporator to give a brown oil (0.526 g). Analysis by $^1H$ and $^{19}F$ NMR spectroscopy revealed a complex mixture of products from which purification was not attempted.

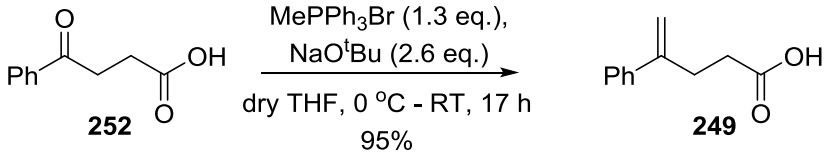
### 7.3.26 Reaction between iodonium ylide 220 and KF




A solution of the ylide **220** (0.200 g, 0.88 mmol) and spray dried KF (0.069 g, 1.19 mmol) in dry DMF (1 mL) was prepared under nitrogen. The flask was sealed and the contents heated to 40 $^{o}$C for 24 hours. After this time, the reaction mixture was concentrated on a rotary evaporator to give a brown oil (0.186 g). Analysis by $^{1}$H and $^{19}$F NMR spectroscopy revealed a complex mixture of products. Purification was not attempted.

## 7.4 Experimental for Chapter 4

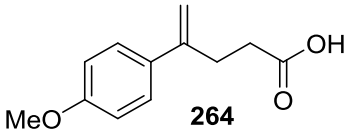
### 7.4.1 Preparation of the starting materials for fluorocyclisation reactions[33]




A suspension of methyltriphenylphosphonium bromide (13.0 g, 36.5 mmol) in dry THF (67 mL) was cooled to 0 °C. To this was added NaO$^t$Bu (7.00 g, 73.0 mmol) and the mixture was stirred at 0 °C for 30 mins. After adding 3-benzoylpropionic acid **252** (5.00 g, 28.1 mmol), the mixture was warmed to room temperature and stirred at this temperature for 17 hours. After this time, 1 M NaOH (170 mL) was added followed by dichloromethane (100 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL). The aqueous layer was then acidified to pH 2 using 12 M HCl and the product was extracted into dichloromethane (3 x 50 mL), dried ($MgSO_4$) and concentrated on a rotary evaporator to give 4-phenylpent-4-enoic acid **249** as a pale white solid (4.69 g, 95%). Characterisation of the crude product by $^1$H NMR spectroscopy showed that further purification was not required. The characterisation data was in agreement with the literature.[34] mp 93 – 95 °C (lit.,[34] 92 – 93 °C). $\delta_H$ ($CDCl_3$, 400 MHz) 2.46 (2H, t, $^3J_{HH}$ = 7.9 Hz, $CH_2$), 2.78 (2H, t, $^3J_{HH}$ = 7.9 Hz, $CH_2$), 5.04 (1H, br s, *H*HC=), 5.25 (1H, br s, *H*HC=), 7.18 – 7.35 (5H, m, ArH), 10.70 (1H, br s, COOH). $\delta_C$ ($CDCl_3$, 100 MHz) 30.2 ($CH_2$), 32.9 ($CH_2$), 113.0 ($CH_2$), 126.1 (CH), 127.7 (CH), 128.4 (CH), 140.9 (C), 146.6 (C), 178.8 (CO). m/z (ASAP) 177.0917 ($MH^+$, $C_{11}H_{13}O_2$ requires 177.0916, 100%), 83.0559 (40%).

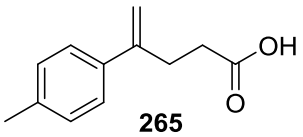
The other substrates for the fluorocyclisation reactions were also prepared using this procedure.

### 7.4.2 Characterisation Data for the Starting Materials



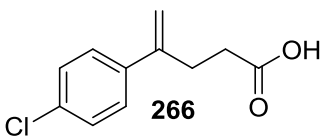
**264**

The reaction mixture was stirred at room temperature for 20 hours. The crude product was purified by column chromatography (50% EtOAc in petroleum ether 40 – 60) and recrystallisation from chloroform to give 4-(4-methoxyphenyl)pent-4-enoic acid **264** as a white solid (0.65 g, 22%). Product which was contaminated with starting material was retained for further purification (1.33 g). The characterisation data was in agreement with the literature.[35, 36] mp 142 – 143 °C (lit.,[35] 145 - 146 °C). $\delta_H$ ($CDCl_3$, 400 MHz) 2.53 (2H, t, $^3J_{HH}$ = 7.5 Hz, $CH_2$), 2.82 (2H, t, $^3J_{HH}$ = 7.5 Hz, $CH_2$), 3.82 (3H, s, $OCH_3$), 5.03 (1H, d, $^2J_{HH}$ = 1.2 Hz, *H*HC=), 5.26 (1H, br s, *H*HC=), 6.87 (2H, d, $^3J_{HH}$ = 9.0 Hz, ArH), 7.35 (2H, d, $^3J_{HH}$ = 9.0 Hz, ArH), 10.49 (1H, br s, COOH). $\delta_H$ (DMSO, 400 MHz) 2.35 (2H, t, $^3J_{HH}$ = 7.5 Hz, $CH_2$), 2.68 (2H, t, $^3J_{HH}$ = 7.5 Hz, $CH_2$), 3.75 (3H, s, $OCH_3$), 4.97 (1H, d, $^2J_{HH}$ = 1.2 Hz, *H*HC=), 5.26 (1H, br s, *H*HC=), 6.91 (2H, d, $^3J_{HH}$ = 9.0 Hz, ArH), 7.38 (2H, d, $^3J_{HH}$ = 9.0 Hz, ArH), 12.15 (1H, br s, COOH). $\delta_C$ (DMSO, 100 MHz) 29.6 ($CH_2$), 32.6 ($CH_2$), 55.0 ($OCH_3$), 110.5 ($CH_2$), 113.7 (CH), 126.9 (CH), 132.2 (C), 145.6 (C), 158.8 (C), 173.9 (CO). m/z (ASAP) 207.1025 ($MH^+$, $C_{12}H_{15}O_3$ requires 207.1021, 100%), 189.0925 ($(M\text{-}OH)^+$, 65%), 161.0974 ($(M\text{-}CO_2H)^+$, 70%).



**265**

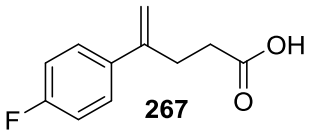
The reaction mixture was stirred at room temperature for 21 hours. Characterisation by $^1$H NMR spectroscopy showed that further purification was not required. 4-(*p*-Tolyl)pent-4-enoic acid was obtained as a white solid (2.95 g, 100%). The characterisation data was in agreement with the literature.[35] mp 92 – 94 °C (lit.,[35] 89 - 90 °C). $\delta_H$ ($CDCl_3$, 400 MHz) 2.35 (3H, s, $CH_3$), 2.53 (2H, t, $^3J_{HH}$ = 7.7 Hz, $CH_2$), 2.83 (2H, t, $^3J_{HH}$ = 7.7 Hz, $CH_2$), 5.06 (1H, d, $^2J_{HH}$ = 1.0 Hz, *H*HC=), 5.30 (1H, br s, *H*HC=), 7.15 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 7.30 (2H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 11.32 (1H, br s, COOH). $\delta_C$ ($CDCl_3$, 100 MHz) 21.1 ($CH_3$), 30.1 ($CH_2$), 33.0 ($CH_2$), 112.3 ($CH_2$), 126.0 (CH), 129.2 (CH), 137.4 (C), 137.5 (C), 146.3 (C), 179.2 (CO). *m/z* (ASAP) 191.1065 ($MH^+$, $C_{12}H_{15}O_2$ requires 191.1072, 65%), 173.0954 ($(M\text{-}OH)^+$, 100%), 145.1010 ($(M\text{-}CO_2H)^+$, 90%).



**266**

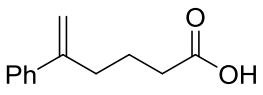
The reaction mixture was stirred at room temperature for 21 hours. The crude product was purified by column chromatography to give 4-(4-chlorophenyl)pent-4-enoic acid **266** as a white solid (3.12 g, 63%). The characterisation data was in agreement with the literature.[35] mp 87 – 88 °C (lit.,[35] 76 - 78 °C). $\delta_H$ ($CDCl_3$, 400 MHz) 2.52 (2H, t, $^3J_{HH}$ =

7.6 Hz, $CH_2$), 2.80 (2H, t, $^3J_{HH}$ = 7.6 Hz, $CH_2$), 5.11 (1H, br s, *H*HC=), 5.31 (1H, br s, *H*HC=), 7.29 (2H, d, $^3J_{HH}$ = 8.6 Hz, ArH), 7.32 (2H, d, $^3J_{HH}$ = 8.6 Hz, ArH), 11.49 (1H, br s, COOH). $\delta_C$ ($CDCl_3$, 100 MHz) 30.0 ($CH_2$), 32.9 ($CH_2$), 113.6 ($CH_2$), 127.4 (CH), 128.6 (CH), 133.5 (C), 138.9 (C), 145.4 (C), 179.8 (CO). m/z (ASAP) 213.0514 ($M(^{37}Cl)H^+$, 20%), 211.0523 ($M(^{35}Cl)H^+$, $C_{11}H_{12}{}^{35}ClO_2$ requires 211.0526, 70%), 195.0401 ($(M(^{37}Cl)\text{-}OH)^+$, 40%), 193.0418 ($(M(^{35}Cl)\text{-}OH)^+$, 100%), 167.0453 ($(M(^{37}Cl)\text{-}CO_2H)^+$, 20%), 165.0472 ($(M(^{35}Cl)\text{-}CO_2H)^+$, 60%), 153.0304 ($(M(^{37}Cl)\text{-}CO_2H\text{-}CH_2)^+$, 10%), 151.0313 ($(M(^{35}Cl)\text{-}CO_2H\text{-}CH_2)^+$, 10%).



**267**

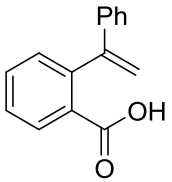
The reaction mixture was stirred at room temperature for 20 hours. The crude product was purified by column chromatography (50% EtOAc in petroleum ether 40 – 60) to give 4-(4-fluorophenyl)pent-4-enoic acid **267** as a white solid (4.56 g, 92%). The characterisation data was in agreement with the literature.[35] mp 86 - 88 °C (lit.,[35] 83 – 85 °C). $\delta_H$ ($CDCl_3$, 400 MHz) 2.52 (2H, t, $^3J_{HH}$ = 7.6 Hz, $CH_2$), 2.81 (2H, t, $^3J_{HH}$ = 7.6 Hz, $CH_2$), 5.09 (1H, d, $^2J_{HH}$ = 0.9 Hz, *H*HC=), 5.27 (1H, br s, *H*HC=), 7.02 (2H, dd, $^3J_{HF}$ = 8.8 Hz, $^3J_{HH}$ = 8.8 Hz, ArH), 7.36 (2H, dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{HF}$ = 5.4 Hz, ArH), 11.18 (1H, br s, COOH). $\delta_F$ ($CDCl_3$, 376 MHz) -114.8 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 30.2 ($CH_2$), 32.8 ($CH_2$), 112.9 ($CH_2$), 115.3 (CH, d, $^2J_{CF}$ = 21.0 Hz), 127.7 (CH, d, $^3J_{CF}$ = 7.5 Hz), 136.5 (C, d, $^4J_{CF}$ = 3.5 Hz), 145.6 (C), 162.4 (C, d, $^1J_{CF}$ = 245.4 Hz), 179.0 (CO). m/z (ASAP) 195.0819 ($MH^+$, $C_{11}H_{12}FO_2$ requires 195.0821, 60%), 177.0704 ($(M\text{-}OH)^+$, 100%), 153.0725 (25%), 149.0757 ($(M\text{-}CO_2H)^+$, 90%), 135.0603 ($(M\text{-}CO_2H\text{-}CH_2)^+$, 70%).



**268**

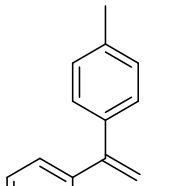
The reaction mixture was stirred at room temperature for 18 hours. The crude product was purified by column chromatography (50% EtOAc in petroleum ether 40 – 60) to give 5-phenylhex-5-enoic acid **268** as a white solid (2.28 g, 77%). The characterisation data was in agreement with the literature.[37] mp 47 - 48 °C (lit.,[37] 44 °C). $\delta_H$ ($CDCl_3$, 400 MHz) 1.72 (2H, quintet, $^3J_{HH}$ = 7.5 Hz, $CH_2$), 2.30 (2H, t, $^3J_{HH}$ = 7.5 Hz, $CH_2$), 2.49 (2H, t, $^3J_{HH}$ = 7.5 Hz, $CH_2$), 5.00 (1H, d, $^2J_{HH}$ = 1.3 Hz, *H*HC=), 5.23 (1H, d, $^2J_{HH}$ = 1.3 Hz, *H*HC=), 7.18 (1H, t, $^3J_{HH}$ = 7.0 Hz, ArH), 7.24 (2H, t, $^3J_{HH}$ = 7.0 Hz, ArH), 7.31 (2H, d, $^3J_{HH}$ = 7.0 Hz, ArH), 11.05 (1H, br s, COOH). $\delta_C$ ($CDCl_3$, 100 MHz) 23.0 ($CH_2$), 33.3 ($CH_2$), 34.5 ($CH_2$), 113.1 ($CH_2$), 126.1 (CH), 127.5 (CH), 128.4 (CH), 140.8 (C), 147.4 (C), 179.9 (CO). m/z (ASAP) 191.1066 ($MH^+$, $C_{12}H_{15}O_2$ requires

191.1072, 35%), 173.0945 ($(M\text{-}OH)^+$, 80%), 145.1099 ($(M\text{-}CO_2H)^+$, 35%), 131.0845 ($(M\text{-}CO_2H\text{-}CH_2)^+$, 100%).



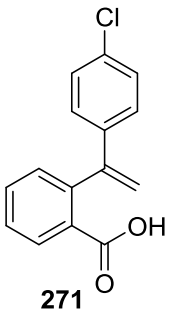
**269**

2-(1-Phenylvinyl)benzoic acid **269** was prepared using 2 equivalents of $MePPh_3Br$, and 3 equivalents of $NaO^tBu$. The reaction mixture was stirred at room temperature for 24 hours. Purification by recrystallization from petroleum ether 40 – 60 and ethyl acetate gave 2-(1-phenylvinyl)benzoic acid **269** as a white solid (1.73 g, 35%). The characterisation data was in agreement with the literature.[38] mp 133 – 135 $^oC$ (lit.,[38] 130 - 131 $^oC$). $\delta_H$ ($CDCl_3$, 400 MHz) 5.22 (1H, d, $^2J_{HH}$ = 0.8 Hz, *H*HC=), 5.66 (1H, d, $^2J_{HH}$ = 0.8 Hz, *H*HC=), 7.18 – 7.26 (5H, m, ArH), 7.37 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.43 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.56 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.92 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 11.14 (1H, br s, COOH). $\delta_C$ ($CDCl_3$, 100 MHz) 114.4 ($CH_2$), 126.8 (CH), 127.5 (CH), 127.7 (CH), 128.1 (CH), 129.4 (C), 130.7 (CH), 131.6 (CH), 132.5 (CH), 140.9 (C), 143.6 (C), 149.5 (C), 172.0 (CO). m/z (ASAP) 225.0918 ($MH^+$, $C_{15}H_{13}O_2$ requires 225.0916, 70%), 207.0805 ($(M\text{-}OH)^+$, 100%).



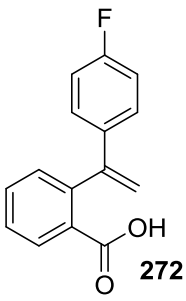
**270**

The reaction mixture was stirred at room temperature for 42 hours. The crude product was purified by column chromatography (50% EtOAc in petroleum ether 40 – 60) to give 2-(1-(p-tolyl)vinyl)benzoic acid **270** as a white solid (3.47 g, 70%). The characterisation data was in agreement with the literature.[38] mp 132 - 135 $^oC$ (lit.,[38] 133 - 134 $^oC$). $\delta_H$ ($CDCl_3$, 400 MHz) 2.29 (3H, s, $CH_3$), 5.15 (1H, d, $^2J_{HH}$ = 1.0 Hz, *H*HC=), 5.62 (1H, d, $^2J_{HH}$ = 1.0 Hz, *H*HC=), 7.04 (2H, d, $^3J_{HH}$ = 8.3 Hz, ArH), 7.10 (2H, d, $^3J_{HH}$ = 8.3 Hz, ArH), 7.34 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.41 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.54 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.91 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 10.84 (1H, br s, COOH). $\delta_C$ ($CDCl_3$, 100 MHz) 21.1 ($CH_3$), 111.2 ($CH_2$), 124.4 (CH), 125.2 (CH), 126.5 (CH), 127.2 (C), 128.3 (CH), 129.2 (CH), 130.0 (CH), 134.9 (C), 135.8 (C), 141.5 (C), 147.0 (C), 169.7 (CO). m/z (ASAP) 239.1070 ($MH^+$, $C_{16}H_{15}O_2$ requires 239.1070, 40%), 221.0973 ($(M\text{-}OH)^+$, 100%).



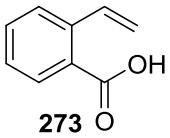
**271**

The reaction mixture was stirred at room temperature for 27 hours. The crude product was purified by recrystallization from chloroform to give 2-(1-(4-chlorophenyl)vinyl)benzoic acid **271** as a white solid (3.03 g, 61%). The characterisation data was in agreement with the literature.[38] mp 163 – 165 $^{o}$C (lit.,[38] 162 - 164 $^{o}$C). $\delta_H$ ($CDCl_3$, 400 MHz) 5.23 (1H, d, $^2J_{HH}$ = 0.8 Hz, *H*HC=), 5.65 (1H, d, $^2J_{HH}$ = 0.8 Hz, *H*HC=), 7.13 (2H, d, $^3J_{HH}$ = 8.7 Hz, ArH), 7.21 (2H, d, $^3J_{HH}$ = 8.7 Hz, ArH), 7.35 (1H, dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.45 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.58 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.95 (1H, dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 11.07 (1H, br s, COOH). $\delta_C$ ($CDCl_3$, 100 MHz) 114.8 ($CH_2$), 127.9 (CH), 128.0 (CH), 128.3 (CH), 129.1 (C), 130.9 (CH), 131.6 (CH), 132.7 (CH), 133.3 (C), 139.4 (C), 143.2 (C), 148.5 (C), 171.8 (CO). m/z (ASAP) 261.0503 (M($^{37}$Cl)$H^+$, 20%), 259.0525 (M($^{35}$Cl)$H^+$, $C_{15}H_{12}{}^{35}ClO_2$ requires 259.0526, 40%), 243.0410 ((M($^{37}$Cl)-OH)$^+$, 25%), 241.0409 ((M($^{35}$Cl)-OH)$^+$, 100%).



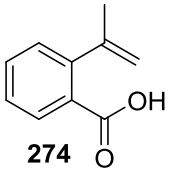
**272**

The reaction mixture was stirred at room temperature for 41 hours. The crude product was purified by column chromatography (50% EtOAc in petroleum ether 40 – 60) to give 2-(1-(4-fluorophenyl)vinyl)benzoic acid **272** as a white solid (2.85 g, 57%). mp 143 – 145 $^{o}$C. $\delta_H$ ($CDCl_3$, 400 MHz) 5.18 (1H, s, *H*HC=), 5.58 (1H, s, *H*HC=), 6.91 (2H, dd, $^3J_{HH}$ = 8.9 Hz, $^3J_{HF}$ = 8.9 Hz, ArH), 7.16 (2H, dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{HF}$ = 5.4 Hz, ArH), 7.35 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.42 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.55 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.92 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 10.28 (1H, br s, COOH). $\delta_F$ ($CDCl_3$, 376 MHz) -114.9 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 114.2 ($CH_2$), 114.9 (CH, d, $^2J_{CF}$ = 20.6 Hz), 127.8 (CH), 128.4 (CH, d, $^3J_{CF}$ = 8.4 Hz), 129.4 (C), 130.8 (CH), 131.5 (CH), 132.6 (CH), 137.1 (C, d, $^4J_{CF}$ = 2.9 Hz), 143.4 (C), 148.6 (C), 162.3 (C, d, $^1J_{CF}$ = 243.5 Hz), 172.5 (CO). m/z (ASAP) 243.0818 ($MH^+$, $C_{15}H_{12}FO_2$ requires 243.0821, 40%), 225.0601 ((M-OH)$^+$, 100%).



**273**

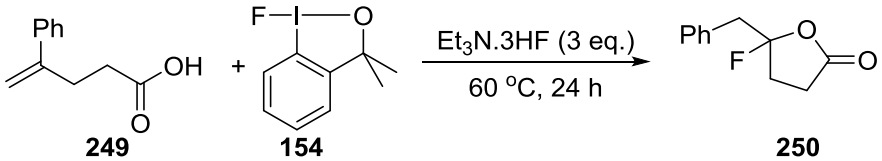
The reaction mixture was stirred at room temperature for 16 hours. Characterisation by $^{1}$H NMR spectroscopy showed that further purification was not required. 2-Vinylbenzoic acid **273** was obtained as a white solid (4.35 g, 88%). The characterisation data was in agreement with the literature.[39] mp 86 – 88 $^{o}$C (lit.,[39] 94 – 95 $^{o}$C). $\delta_H$ ($CDCl_3$, 400 MHz) 5.38 (1H, dd, $^{3}J_{HH}$ = 11.0 Hz, $^{2}J_{HH}$ = 1.3 Hz, *H*HC=), 5.67 (1H, dd, $^{3}J_{HH}$ = 17.5 Hz, $^{2}J_{HH}$ = 1.3 Hz, *H*HC=), 7.35 (1H, td, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.4 Hz, ArH), 7.52 – 7.66 (3H, m, 2 x ArH and C*H*=$CH_2$), 8.05 (1H, dd, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 1.4 Hz, ArH), 12.12 (1H, br s, COOH). $\delta_C$ ($CDCl_3$, 100 MHz) 116.9 ($CH_2$), 127.2 (C), 127.5 (CH), 127.6 (CH), 131.4 (CH), 133.2 (CH), 136.1 (CH), 140.7 (C), 173.4 (CO). m/z (ASAP) 149.0597 ($MH^+$, $C_9H_9O_2$ requires 149.0603, 100%), 131.0490 ($(M\text{-}OH)^+$, 70%).



**274**

The reaction mixture was stirred at room temperature for 26 hours. The crude product was purified by column chromatography (50% EtOAc in petroleum ether 40 – 60) to give 2-(prop-1-en-2-yl)benzoic acid **274** (0.76 g, 26%). mp 72 - 74 $^{o}$C (lit.,[40] 70 - 71 $^{o}$C). $\delta_H$ (DMSO, 400 MHz) 2.09 (3H, s, $CH_3$), 4.85 – 4.86 (1H, m, *H*HC=), 5.11 – 5.13 (1H, m, *H*HC=), 7.32 (1H, dd, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.3 Hz, ArH), 7.42 (1H, td, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.3 Hz, ArH), 7.55 (1H, td, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.3 Hz, ArH), 7.74 (1H, dd, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.3 Hz, ArH), 12.91 (1H, br s, COOH). $\delta_C$ (DMSO, 100 MHz) 23.9 ($CH_3$), 113.7 ($CH_2$), 127.0 (CH), 128.8 (CH), 129.1 (CH), 130.8 (C), 131.0 (CH), 143.7 (C), 145.8 (C), 169.0 (CO). m/z (ASAP) 163.0753 ($MH^+$, $C_{10}H_{11}O_2$ requires 163.0759, 70%), 145.0641 ($(M\text{-}OH)^+$, 100%).

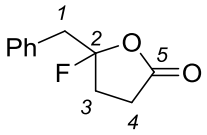
### 7.4.3 Reaction between 4-Phenyl-4-pentenoic acid and the Fluoroiodane with TREAT-HF



**249** **154** (2 eq.) **250** 86% (43%)

4-Phenylpent-4-enoic acid **249** (0.252, g, 1.43mmol), 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.800 g, 2.86 mmol), and TREAT-HF (0.7 mL, 4.26 mmol) were charged to a small Schlenk flask. The flask was then sealed and the contents were stirred at 60 $^{o}$C for 24 hours. After this time, the reaction mixture was

cooled to room temperature, diluted with dichloromethane (5 mL), washed with water (3 x 5 mL) and concentrated on a rotary evaporator to give a yellow oil. Purification by column chromatography (5% EtOAc in petroleum ether 40 – 60) gave 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one **250** as a colourless oil (0.120 g, 43%). The product was visualised on the TLC plate using a $KMnO_4$ stain.




$\delta_H$ ($CDCl_3$, 400 MHz) 2.15-2.30 (2H, m, $H_3$ and $H_3$'), 2.42 (1H, dm, on fluorine decoupling simplifies to ddd, $^2J_{HH}$ = 17.8 Hz, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 3.1 Hz, $H_4$), 2.74 (1H, ddd, $^2J_{HH}$ = 17.8 Hz, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 9.3 Hz, $H_4$'), 3.29 (2H, d, $^3J_{HF}$ = 14.7 Hz, $H_1$ and $H_1$'), 7.28 – 7.36 (5H, m, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -97.0 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 27.0 ($CH_2$, $C_4$), 30.9 ($CH_2$, d, $^2J_{CF}$ = 27.7 Hz, $C_3$), 42.7 ($CH_2$, d, $^2J_{CF}$ = 28.0 Hz, $C_1$), 119.2 (C, d, $^1J_{CF}$ = 230.7 Hz, $C_2$), 127.6 (CH), 128.6 (CH), 130.4 (CH), 133.0 (C, d, $^3J_{CF}$ = 5.1 Hz, $C_6$), 174.7 (CO, $C_5$). m/z (ASAP) 195.0822 ($MH^+$, $C_{11}H_{12}FO_2$ requires 195.0821, 20 %), 175.0722 ($(M-F)^+$, 100%).

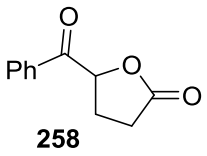
### 7.4.4 Procedure for Table 1

4-Phenylpent-4-enoic acid **249** (0.063, g, 0.36 mmol), 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.200 g, 0.71 mmol), the required amount of TREAT-HF and/or solvent (0.2 mL) were charged to a small Schlenk flask. The flask was then sealed and the contents were stirred at the required temperature for the stated amount of time. After this time, the reaction mixture was cooled to room temperature and naphthalene (0.046 g, 0.36 mmol) was added. The reaction mixture was diluted with dichloromethane (5 mL), washed with water (3 x 5 mL) and concentrated on a rotary evaporator to give a yellow oil. Conversion was calculated by $^1H$ and $^{19}F$ NMR spectroscopy using naphthalene as the internal standard.

### 7.4.5 Procedure for Table 2

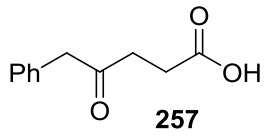
4-Phenylpent-4-enoic acid **249** (0.063, g, 0.36 mmol), 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.200 g, 0.71 mmol), the required amount of additive(s) and solvent (0.2 mL) were charged to a small Schlenk flask. In entry 6, 4 Å powdered molecular sieves (0.09 g) were also added. The flask was then sealed and the contents were stirred at the required temperature for the stated amount of time. After this time, the reaction mixture was cooled to room temperature and naphthalene (0.046

g, 0.36 mmol) was added. The reaction mixture was diluted with dichloromethane (5 mL), washed with water (3 x 5 mL) and concentrated on a rotary evaporator to give a yellow oil. Conversion was calculated by $^{1}H$ and $^{19}F$ NMR spectroscopy using naphthalene as the internal standard.



**258**

5-Benzoyldihydrofuran-2(3*H*)-one **258** was obtained a mixture with 4-oxo-5-phenylpentanoic acid **257** after column chromatography (5% EtOAc in petroleum ether 40 - 60) of the crude product from entry 4. The characterisation data was in agreement with the literature.[41] $\delta_H$ ($CDCl_3$, 400 MHz) 2.40 – 2.64 (4H, m, 2 x $CH_2$), 5.78 – 5.81 (1H, m, CH), 7.51 (2H, t, $^{3}J_{HH}$ = 7.5 Hz, ArH), 7.64 (1H, t, $^{3}J_{HH}$ = 7.5 Hz, ArH), 7.98 (2H, d, $^{3}J_{HH}$ = 7.5 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 25.0 ($CH_2$), 26.8 ($CH_2$), 78.3 (CH), 128.8 (CH), 129.0 (CH), 133.7 (C), 134.3 (CH), 176.3 (CO), 194.3 (CO). m/z (ASAP) 191.0703 ($MH^+$, $C_{11}H_{11}O_3$ requires 191.0708, 100%).



**257**

4-Oxo-5-phenylpentanoic acid **257** was isolated after column chromatography (5% EtOAc in petroleum ether 40 - 60) of the crude product from entry 5. The characterisation data was in agreement with the literature.[42] $\delta_H$ ($CDCl_3$, 400 MHz) 2.50 (2H, t, $^{3}J_{HH}$ = 6.4 Hz, $CH_2$), 2.66 (2H, t, $^{3}J_{HH}$ = 6.4 Hz, $CH_2$), 3.65 (2H, s, $CH_2$), 7.12 (2H, d, $^{3}J_{HH}$ = 7.5 Hz, ArH), 7.19 (1H, t, $^{3}J_{HH}$ = 7.5 Hz, ArH), 7.25 (2H, t, $^{3}J_{HH}$ = 7.5 Hz, ArH), 10.43 (1H, br s, COOH). $\delta_C$ ($CDCl_3$, 100 MHz) 27.9 ($CH_2$), 36.2 ($CH_2$), 50.0 ($CH_2$), 127.2 (CH), 128.8 (CH), 129.5 (CH), 133.9 (C), 178.6 (CO), 206.4 (CO). m/z (ASAP) 193.0871 ($MH^+$, $C_{11}H_{13}O_3$ requires 193.0865, 100%), 191.0657 (60%), 175.0752 ($(M\text{-}OH)^+$, 75%), 83.0512 (60%).

### 7.4.6 Procedure for Table 3

The required amount of $AgBF_4$ and 4 Å molecular sieves (0.09 g) were charged to a small Schlenk flask in the glove box. To this was added the required amount of 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154**, 4-phenylpent-4-enoic acid **249** (0.063, g, 0.36 mmol), and dry solvent (0.2 mL). The flask was then sealed and the contents stirred at the required temperature for the stated amount of time. After this time, the reaction mixture was cooled to room temperature and naphthalene (0.046 g, 0.36 mmol) was added. The reaction mixture was filtered through cotton wool and washed with water (3 x 5 mL). The reaction mixture was filtered through cotton wool

again and concentrated on a rotary evaporator to give a pale yellow oil. Conversion was calculated by $^{1}H$ and $^{19}F$ NMR spectroscopy using naphthalene as the internal standard.

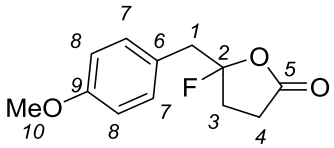
In entry 8 and 11 the following procedure was used:

The required amount of $AgBF_4$ and 4 Å molecular sieves (0.18 g) were charged to a small Schlenk flask in the glove box. To this was added 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.300 g, 1.07 mmol), 4-phenylpent-4-enoic acid **249** (0.126, g, 0.71 mmol), and dry dichloromethane (0.4 mL). The flask was then sealed and the contents stirred at 40 $^{o}$C for the required amount of time. After this time, the reaction mixture was cooled to room temperature and naphthalene (0.091 g, 0.71 mmol) was added. The reaction mixture was concentrated on a rotary evaporator to give a pale yellow solid. Conversion was calculated by $^{1}H$ and $^{19}F$ NMR spectroscopy using naphthalene as the internal standard. The crude product was purified by column chromatography (5% EtOAc in petroleum ether 40-60) to give 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one **250** as a colourless oil (entry 8, 0.112 g, 81%; entry 11, 0.071 g, 52%).

### 7.4.7 Procedure for the Reactions in Schemes 11, 12, 14, 16 and 17

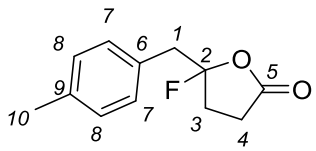
$AgBF_4$ (0.14 g, 0.71 mmol) and 4 Å molecular sieves (0.18 g) were charged to a small Schlenk flask in the glove box. To this was added 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole (0.300 g, 1.07 mmol), substrate (0.71 mmol), and dry dichloromethane (0.4 mL). The flask was then sealed and the contents stirred at 40 $^{o}$C for one hour. After this time, the reaction mixture was cooled to room temperature and naphthalene (0.091 g, 0.71 mmol) was added. The reaction mixture was then concentrated on a rotary evaporator to give a pale yellow solid. Conversion was calculated by $^{1}H$ NMR spectroscopy using naphthalene as the internal standard.

### 7.4.8 Characterisation Data for the Products in Schemes 11, 12, 14, 16 and 17



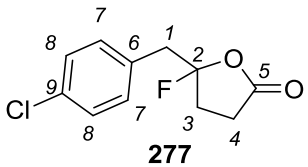

**275**

The crude product was purified by column chromatography (10% EtOAc in petroleum ether 40-60) to give 5-fluoro-5-(4-methoxybenzyl)dihydrofuran-2(3*H*)-one **275** as a colourless oil (0.103 g, 65%). $\delta_H$ ($CDCl_3$, 400 MHz) 2.14-2.31 (2H, m, $H_3$ and $H_3$'), 2.42 (1H, dm, on fluorine decoupling simplifies to ddd, $^2J_{HH}$ = 18.0 Hz, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 3.1 Hz, $H_4$), 2.74 (1H, ddd, $^2J_{HH}$ = 18.0 Hz, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 9.4 Hz, $H_4$'), 3.23 (2H, d, $^3J_{HF}$ = 14.1 Hz, $H_1$ and $H_1$'), 3.80 (3H, s, $H_{10}$), 6.87 (2H, d, $^3J_{HH}$ = 8.6 Hz, $H_{7/8}$), 7.20 (2H, d, $^3J_{HH}$ = 8.6 Hz, $H_{7/8}$). $\delta_F$ ($CDCl_3$, 376 MHz) -97.4 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 27.1 ($CH_2$, $C_4$), 30.8 ($CH_2$, d, $^2J_{CF}$ = 27.7 Hz, $C_3$), 41.8 ($CH_2$, d, $^2J_{CF}$ = 29.2 Hz, $C_1$), 55.3 ($OCH_3$, $C_{10}$), 114.0 (CH, $C_{7/8}$), 119.4 (C, d, $^1J_{CF}$ = 232.2 Hz, $C_2$), 142.9 (C, d, $^3J_{CF}$ = 6.5 Hz, $C_6$), 131.4 (CH, $C_{7/8}$), 159.0 (C, $C_9$), 174.8 (CO, $C_5$). m/z (ASAP) 205.0861 ($(M-F)^+$, $C_{12}H_{13}O_3$ requires 205.0865, 100%), 177.0934 (30%), 163.0774 (40%), 159.0813 (55%), 121.0652 (55%).




**276**

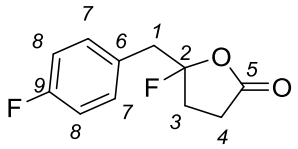
The crude product was purified by column chromatography (1% EtOAc in petroleum ether 40-60, then 5% EtOAc in petroleum ether) to give 5-fluoro-5-(4-methylbenzyl)dihydrofuran-2(3*H*)-one **276** as a colourless oil (0.101 g, 68%). $\delta_H$ ($CDCl_3$, 400 MHz) 2.14-2.29 (2H, m, $H_3$ and $H_3$'), 2.34 (3H, s, $H_{10}$), 2.41 (1H, dm, on fluorine decoupling simplifies to ddd, $^2J_{HH}$ = 18.0 Hz, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 3.4 Hz, $H_4$), 2.73 (1H, ddd, $^2J_{HH}$ = 18.0 Hz, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 9.4 Hz, $H_4$'), 3.25 (2H, d, $^3J_{HF}$ = 14.4 Hz, $H_1$ and $H_1$'), 7.14 (2H, d, $^3J_{HH}$ = 8.3 Hz, $H_{7/8}$), 7.17 (2H, d, $^3J_{HH}$ = 8.3 Hz, $H_{7/8}$). $\delta_F$ ($CDCl_3$, 376 MHz) -97.1 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 21.1 ($CH_3$, $C_{10}$), 27.1 ($CH_2$, $C_4$), 30.8 ($CH_2$, d, $^2J_{CF}$ = 27.1 Hz, $C_3$), 42.2 ($CH_2$, d, $^2J_{CF}$ = 28.6 Hz, $C_1$), 119.3 (C, d, $^1J_{CF}$ = 230.8 Hz, $C_2$), 129.3 (CH, $C_{7/8}$), 129.9 (C, d, $^3J_{CF}$ = 5.3 Hz, $C_6$), 130.2 (CH, $C_{7/8}$), 137.3 (C, $C_9$), 174.9 (CO, $C_5$). m/z (ASAP) 189.0912 ($(M-F)^+$, $C_{12}H_{13}O_2$ requires 189.0916, 100%), 143.0862 (80%), 105.0686 (40%).




**277**

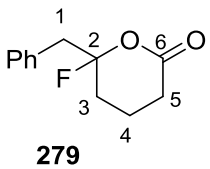
The crude product was purified by column chromatography (10% EtOAc in petroleum ether 40-60) to give 5-(4-chlorobenzyl)-5-fluorodihydrofuran-2(3*H*)-one **277** as a colourless oil (0.128 g, 79%). $\delta_H$ ($CDCl_3$, 400 MHz) 2.12-2.34 (2H, m, $H_3$ and $H_3$'), 2.46 (1H, ddd, $^2J_{HH}$ = 18.0 Hz, $^3J_{HH}$ = 9.5 Hz, $^3J_{HH}$ = 2.1 Hz, $H_4$), 2.76 (1H, ddd, $^2J_{HH}$ = 18.0 Hz, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 9.3 Hz, $H_4$'), 3.26 (2H, d,

$^3J_{HF}$ = 14.9 Hz, $H_1$ and $H_1$'), 7.23 (2H, d, $^3J_{HH}$ = 8.3 Hz, $H_{7/8}$), 7.31 (2H, d, $^3J_{HH}$ = 8.3 Hz, $H_{7/8}$). $\delta_F$ ($CDCl_3$, 376 MHz) -97.6 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 24.5 ($CH_2$, $C_4$), 28.6 ($CH_2$, d, $^2J_{CF}$ = 28.2 Hz, $C_3$), 39.7 ($CH_2$, d, $^2J_{CF}$ = 29.2 Hz, $C_1$), 116.3 (C, d, $^1J_{CF}$ = 233.4 Hz, $C_2$), 126.5 (CH, $C_{7/8}$), 129.0 (C, d, $^3J_{CF}$ = 4.7 Hz, $C_6$), 129.3 (CH, $C_{7/8}$), 131.3 (C, $C_9$), 172.1 (CO, $C_5$). m/z (ASAP) 211.0355 ((M($^{37}$Cl)-F)$^+$, 30%), 209.0368 ((M($^{35}$Cl)-F)$^+$, $C_{11}H_{10}O_2Cl$ requires 209.0369, 100%), 125.0140 (45%), 127.0134 (15%).



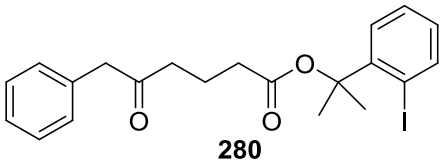
**278**

The crude product was purified by column chromatography (10% EtOAc in petroleum ether 40-60) to give 5-fluoro-5-(4-fluorobenzyl)dihydrofuran-2(3*H*)-one **278** as a colourless oil (0.115 g, 77%). $\delta_H$ ($CDCl_3$, 400 MHz) 2.14-2.34 (2H, m, $H_3$ and $H_3$'), 2.42 – 2.49 (1H, m, on fluorine decoupling simplifies to ddd, $^2J_{HH}$ = 18.1 Hz, $^3J_{HH}$ = 9.3 Hz, $^3J_{HH}$ = 2.3 Hz, $H_4$), 2.75 (1H, ddd, $^2J_{HH}$ = 18.1 Hz, $^3J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 9.4 Hz, $H_4$'), 3.26 (2H, d, $^3J_{HF}$ = 14.8 Hz, $H_1$ and $H_1$'), 7.02 (2H, dd, $^3J_{HF}$ = 8.7 Hz, $^3J_{HH}$ = 8.7 Hz, $H_8$), 7.26 (2H, dd, $^3J_{HH}$ = 8.7 Hz, $^3J_{HF}$ = 5.5 Hz, $H_7$). $\delta_F$ ($CDCl_3$, 376 MHz) -97.8 (1F, s, CF), -114.9 (1F, s, ArF). $\delta_C$ ($CDCl_3$, 100 MHz) 26.9 ($CH_2$, $C_4$), 30.9 ($CH_2$, d, $^2J_{CF}$ = 28.8 Hz, $C_3$), 41.8 ($CH_2$, d, $^2J_{CF}$ = 28.1 Hz, $C_1$), 115.5 (CH, d, $^2J_{CF}$ = 22.2 Hz, $C_8$), 118.9 (C, d, $^1J_{CF}$ = 231.4 Hz, $C_2$), 128.7 (C, $C_6$), 131.9 (CH, d, $^3J_{CF}$ = 8.0 Hz, $C_7$), 162.3 (C, d, $^1J_{CF}$ = 245.9 Hz, $C_9$), 174.7 (CO, $C_5$). m/z (ASAP) 193.0664 ((M-F)$^+$, $C_{11}H_{10}FO_2$ requires 193.0665, 100 %).



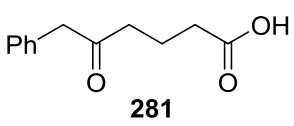
**279**

The crude product was purified by column chromatography (5% EtOAc in hexane, then 20% EtOAc in hexane) to give 6-benzyl-6-fluorotetrahydro-2*H*-pyran-2-one as a colourless oil (0.056 g, 38%). $\delta_H$ ($CDCl_3$, 400 MHz) 1.63 – 1.82 (2H, m, $H_3$ and $H_4$), 1.96 – 2.11 (2H, m, $H_3$' and $H_4$'), 2.35 – 2.45 (1H, m, $H_5$), 2.69 (1H, dm, $H_5$'), 3.20 (2H, d, $^3J_{HF}$ = 14.8 Hz, $H_1$ and $H_1$'), 7.26 – 7.34 (5H, m, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -96.7 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 14.2 ($CH_2$, d, $^3J_{CF}$ = 3.2 Hz, $C_4$), 28.8 ($CH_2$, d, $^2J_{CF}$ = 26.9 Hz, $C_3$), 29.1 ($CH_2$, $C_5$), 45.2 ($CH_2$, d, $^2J_{CF}$ = 26.7 Hz, $C_1$), 115.5 (C, d, $^1J_{CF}$ = 228.0 Hz, $C_2$), 127.4 (CH), 128.5 (CH), 130.5 (CH), 133.5 (C, d, $^3J_{CF}$ = 5.5 Hz), 174.7 (CO, $C_6$). m/z (ASAP) 189.0923 ((M-F)$^+$, $C_{12}H_{13}O_2$ requires 189.0916, 5%), 161.0948 ((PhCH$_2$COCH$_2$CH$_2$CH$_2$)$^+$, 100%).

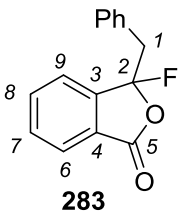

**280**

The ring opened by-product **280** was also isolated from this reaction (0.028 g, 9%) as a mixture with 2-(2-iodophenyl)propan-2-ol **64**. $\delta_H$ ($CDCl_3$, 400 MHz) 1.81 (6H, s, $CH_3$), 1.83 (2H, quintet, $^3J_{HH}$ = 7.2 Hz, $CH_2$), 2.42 (2H, t, $^3J_{HH}$ = 7.2 Hz, $CH_2$), 2.52 (2H, t, $^3J_{HH}$ = 7.2 Hz, $CH_2$), 3.66 (2H, s, $CH_2$), 6.90 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.8 Hz, ArH), 7.18 (2H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.23 – 7.28 (1H, m, ArH), 7.30 – 7.35 (3H, m, ArH), 7.40 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.8 Hz, ArH), 7.94 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.8 Hz, ArH). $\delta_C$ ($CDCl_3$, 125 MHz) 18.5 ($CH_2$), 27.7 ($CH_3$), 33.5 ($CH_2$), 40.9 ($CH_2$), 50.1 ($CH_2$), 81.2 (C), 91.8 (CI), 126.8 (CH), 127.0 (CH), 128.1 (CH), 128.7 (CH), 128.7 (CH), 129.4 (CH), 134.2 (C), 142.9 (CH), 145.4 (C), 171.5 (CO), 207.7 (CO). m/z (ASAP) 473.0599 ($(M+Na)^+$, $C_{21}H_{23}O_3NaI$ requires 473.0590, 100%), 207.1012 (50%), 189.0916 ($(M-C_9H_{10}IO)^+$, 45%).

**279** decomposed in $CDCl_3$ over several hours to give 5-oxo-6-phenylhexanoic acid **281**:

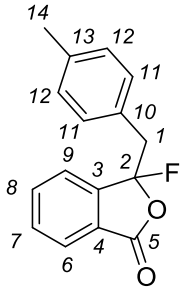

**281**

mp 42 – 44 °C (lit.,[43, 44] 265 °C or 58 °C). $\delta_H$ ($CDCl_3$, 400 MHz) 1.79 (2H, quintet, $^3J_{HH}$ = 7.4 Hz, C*H*$_2$), 2.26 (2H, t, $^3J_{HH}$ = 7.4 Hz, $CH_2$), 2.47 (2H, t, $^3J_{HH}$ = 7.4 Hz, $CH_2$), 3.61 (2H, s, $CH_2$), 7.12 (2H, d, $^3J_{HH}$ = 7.3 Hz, ArH), 7.19 (1H, t, $^3J_{HH}$ = 7.3 Hz, ArH), 7.25 (2H, t, $^3J_{HH}$ = 7.3 Hz, ArH), 10.38 (1H, br s, COOH). $\delta_C$ ($CDCl_3$, 100 MHz) 17.4 ($CH_2$), 31.8 ($CH_2$), 39.4 ($CH_2$), 49.1 ($CH_2$), 126.1 (CH), 127.7 (CH), 128.3 (CH), 133.0 (C), 178.3 (CO), 206.6 (CO). m/z (ASAP) 189.0909 ($(M-OH)^+$, $C_{12}H_{13}O_2$ requires 189.0916, 55%), 161.0941 (60%), 175.0752 (75%), 161.0941 ($(M-CO_2H)^+$, 60%).


**283**

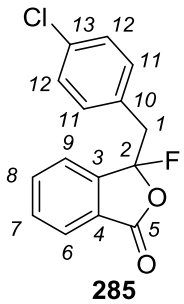
The crude product was purified by column chromatography (10% EtOAc in petroleum ether 40-60) to give 3-benzyl-3-fluoroisobenzofuran-1(3*H*)-one **283** as a colourless oil (0.148 g, 86%). $\delta_H$ ($CDCl_3$, 400 MHz) 3.52 (1H, dd, $^2J_{HH}$ = 14.4 Hz, $^3J_{HF}$ = 14.3 Hz, $H_1$), 3.63 (1H, dd, $^2J_{HH}$ = 14.4 Hz, $^3J_{HF}$ = 12.3 Hz, $H_1$'), 7.19-7.26 (5H, m, Ph), 7.34 (1H, d, $^3J_{HH}$ = 7.5 Hz, $H_9$), 7.59 (1H, t, $^3J_{HH}$ = 7.5 Hz, $H_7$), 7.69 (1H, t, $^3J_{HH}$ = 7.5 Hz, $H_8$), 7.80 (1H, d, $^3J_{HH}$ = 7.5 Hz, $H_6$). $\delta_F$ ($CDCl_3$, 376 MHz) -100.7 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 40.6 ($CH_2$, d, $^2J_{CF}$ = 28.2 Hz, $C_1$), 113.4 (C, d, $^1J_{CF}$ = 232.2 Hz, $C_2$), 121.4 (CH, $C_9$), 124.0 (CH, $C_6$), 124.5 (C, $C_4$), 125.9 (CH), 126.7 (CH), 128.8 (CH), 129.8 (CH, $C_7$), 130.2 (C, d, $^3J_{CF}$ = 4.5 Hz, $C_{10}$), 132.9 (CH, $C_8$), 142.8 (C, d, $^2J_{CF}$ =

21.2 Hz, $C_3$), 164.8 (CO, $C_5$). m/z (ASAP) 223.0758 ($(M-F)^+$, $C_{15}H_{11}O_2$ requires 223.0759, 100%), 195.0813 ($(M-F-CO)^+$, 70%).



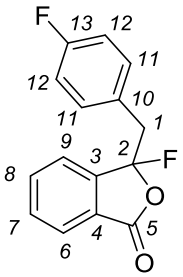
**284**

The crude product was purified by column chromatography (5% EtOAc in petroleum ether 40 – 60) to give 3-fluoro-3-(4-methylbenzyl)isobenzofuran-1(3*H*)-one **284** as a colourless oil (0.088 g, 48%). $\delta_H$ ($CDCl_3$, 400 MHz) 2.28 (3H, s, $H_{14}$), 3.50 (1H, dd, $^3J_{HF}$ = 15.4 Hz, $^2J_{HH}$ = 14.5 Hz, $H_1$), 3.58 (1H, dd, $^2J_{HH}$ = 14.5 Hz, $^3J_{HF}$ = 12.3 Hz, $H_1$'), 7.03 (2H, d, $^3J_{HH}$ = 8.1 Hz, $H_{12}$), 7.07 (2H, d, $^3J_{HH}$ = 8.1 Hz, $H_{11}$), 7.35 (1H, d, $^3J_{HH}$ = 7.7 Hz, $H_9$), 7.57 (1H, tt, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.4 Hz, $H_7$), 7.66 (1H, t, $^3J_{HH}$ = 7.7 Hz, $H_8$), 7.78 (1H, d, $^3J_{HH}$ = 7.7 Hz, $H_6$). $\delta_F$ ($CDCl_3$, 376 MHz) -100.6 (s). $\delta_C$ ($CDCl_3$, 100 MHz) 21.0 ($CH_3$, $C_{14}$), 41.9 ($CH_2$, d, $^2J_{CF}$ = 30.8 Hz, $C_1$), 115.3 (CF, d, $^1J_{CF}$ = 232.4 Hz, $C_2$), 123.2 (CH, $C_9$), 125.7 (CH, $C_6$), 126.4 (C, $C_4$), 128.9 (C, d, $^3J_{CF}$ = 6.4 Hz, $C_{10}$), 129.1 (CH, $C_{11/12}$), 130.5 (CH, $C_{11/12}$), 131.5 (CH, $C_7$), 134.6 (CH, $C_8$), 137.3 (C, $C_{13}$), 144.7 (C, d, $^2J_{CF}$ = 20.8 Hz, $C_3$), 166.6 (CO, $C_5$). m/z (ASAP) 237.0924 ($(M-F)^+$, $C_{16}H_{13}O_2$ requires 237.0916, 100%), 209.0974 ($(M-F-CO)^+$, 70%).



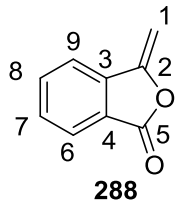
**285**

The crude product was isolated by column chromatography (5% EtOAc in petroleum ether 40 – 60) to give 3-(4-chlorobenzyl)-3-fluoroisobenzofuran-1(3*H*)-one **285** as a colourless oil (0.148 g, 76%). $\delta_H$ ($CDCl_3$, 400 MHz) 3.51 (1H, dd, $^2J_{HF}$ = 14.2 Hz, $^3J_{HH}$ = 14.2 Hz, $H_1$), 3.57 (1H, dd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HF}$ = 12.7 Hz, $H_1$'), 7.14 (2H, d, $^3J_{HH}$ = 8.4 Hz, $H_{11}$), 7.22 (2H, d, $^3J_{HH}$ = 8.4 Hz, $H_{12}$), 7.38 (1H, d, $^3J_{HH}$ = 7.6 Hz, $H_9$), 7.61(1H, tt, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz, $H_7$), 7.70 (1H, t, $^3J_{HH}$ = 7.6 Hz, $H_8$), 7.82 (1H, d, $^3J_{HH}$ = 7.6 Hz, $H_6$). $\delta_F$ ($CDCl_3$, 376 MHz) -100.7 (s). $\delta_C$ ($CDCl_3$, 126 MHz) 41.7 ($CH_2$, d, $^2J_{CF}$ = 31.4 Hz, $C_1$), 114.8 (CF, d, $^1J_{CF}$ = 232.7 Hz, $C_2$), 123.0 (CH, $C_9$), 125.9 (CH, $C_6$), 126.3 (C, $C_4$), 128.6 (CH, $C_{12}$), 130.5 (C, d, $^3J_{CF}$ = 4.7 Hz, $C_{10}$), 131.7 (CH, $C_7$), 131.9 (CH, $C_{11}$), 133.8 (C, $C_{13}$), 134.8 (CH, $C_8$), 144.4 (C, d, $^2J_{CF}$ = 22.1 Hz, $C_3$), 166.3 (CO, $C_5$). m/z (ASAP) 259.0346 ($(M(^{37}Cl)-F)^+$, 40%), 257.0369 ($(M(^{35}Cl)-F)^+$, $C_{15}H_{10}{}^{35}ClO_2$ requires 257.0369, 100%), 231.0440 ($(M(^{37}Cl)-F-CO)^+$, 20%), 229.0409 ($(M(^{35}Cl)-F-CO)^+$, 50%).



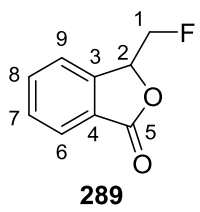
**286**

The crude product was purified by column chromatography (5% EtOAc in petroleum ether 40 – 60) and trituration with hexane to give 3-fluoro-3-(4-fluorobenzyl)isobenzofuran-1(3*H*)-one **286** as a white solid (0.128 g, 69%). mp 69 – 71 $^{o}$C. $\delta_H$ ($CDCl_3$, 400 MHz) 3.51 (1H, dd, $^2J_{HH}$ = 14.5 Hz, $^3J_{HF}$ = 14.3 Hz, $H_1$), 3.57 (1H, dd, $^2J_{HH}$ = 14.5 Hz, $^3J_{HF}$ = 12.7 Hz, $H_1$'), 6.93 (2H, dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HF}$ = 8.8 Hz, $H_{12}$), 7.17 (2H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HF}$ = 5.5 Hz, $H_{11}$), 7.37 (1H, d, $^3J_{HH}$ = 7.5 Hz, $H_9$), 7.60 (1H, t, $^3J_{HH}$ = 7.6 Hz, $H_7$), 7.69 (1H, t, $^3J_{HH}$ = 7.5 Hz, $H_8$), 7.81 (1H, d, $^3J_{HH}$ = 7.5 Hz, $H_6$). $\delta_F$ ($CDCl_3$, 376 MHz) –101.0 (1F, s, CF), -114.6 (1F, s, ArF). $\delta_C$ ($CDCl_3$, 126 MHz) 41.6 ($CH_2$, d, $^2J_{CF}$ = 31.3 Hz, $C_1$), 115.0 (CF, d, $^1J_{CF}$ = 233.2 Hz, $C_2$), 115.4 (CH, d, $^2J_{CF}$ = 21.7 Hz, $C_{12}$), 123.0 (CH, $C_9$), 125.8 (CH, $C_6$), 126.3 (C, d, $^3J_{CF}$ = 1.4 Hz $C_4$), 127.8 (C, dd, $^3J_{CF}$ = 5.6 Hz, $^4J_{CF}$ = 3.2 Hz, $C_{10}$), 131.7 (CH, d, $^5J_{CF}$ = 2.3 Hz, $C_7$), 132.2 (CH, d, $^4J_{CF}$ = 8.3 Hz, $C_{11}$), 134.8 (CH, $C_8$), 144.5 (C, d, $^2J_{CF}$ = 21.2 Hz, $C_3$), 162.3 (CF, d, $^1J_{CF}$ = 246.9 Hz, $C_{13}$), 166.4 (CO, d, $^3J_{CF}$ = 2.1 Hz, $C_5$). m/z (ASAP) 241.0656 ((M-F)$^+$, $C_{15}H_{10}O_2F$ requires 241.0665, 100%), 213.0694 ((M-F-CO)$^+$, 95%).



**288**

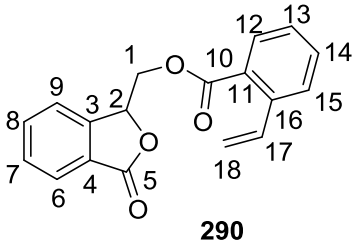
3-Methyleneisobenzofuran-1(3*H*)-one **288** was also isolated from this reaction as a pale yellow solid (0.041 g, 40%). The characterisation data was in agreement with the literature.[45] The sample decomposed below 200 $^{o}$C, there was insufficient sample to repeat melting point (lit.,[45] 55 - 56 $^{o}$C). $\delta_H$ ($CDCl_3$, 400 MHz) 5.24 (1H, d, $^2J_{HH}$ = 3.0 Hz, $H_1$), 5.25 (1H, d, $^2J_{HH}$ = 3.0 Hz, $H_1$'), 7.56 – 7.62 (1H, m, $H_7$), 7.72 (1H, d, $^3J_{HH}$ = 8.2 Hz, $H_9$), 7.75 (1H, d, $^3J_{HH}$ = 8.2 Hz, $H_8$), 7.92 (1H, dt, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 0.9 Hz, $H_6$). $\delta_C$ ($CDCl_3$, 125 MHz) 89.7 ($CH_2$, $C_1$), 117.0 (CH, $C_8$), 123.4 (C, $C_4$), 123.7 (CH, $C_6$), 128.9 (CH, $C_7$), 132.9 (CH, $C_9$), 137.3 (C, $C_3$), 150.1 (C, $C_2$), 165.3 (CO, $C_5$). m/z (ASAP) 147.0545 ($MH^+$, $C_9H_7O_2$ requires 147.0446, 100%), 129.0553 ((M-OH)$^+$, 35%).



**289**

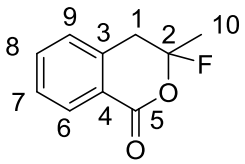
The crude product was purified by column chromatography (5% EtOAc in hexane) to give 3-(fluoromethyl)isobenzofuran-1(3*H*)-one **289** as a colourless oil (0.013 g, 11%). The product was isolated as a mixture with **290** (see below) and therefore the yield given is approximate. $^1$H and $^{13}$C NMR data is given, however, the assignments are not 100% accurate since it was difficult to determine which peaks corresponded to which product. $\delta_H$ ($CDCl_3$, 400 MHz) 4.73 (1H, ddd, $^2J_{HF}$ = 46.5 Hz, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 5.0 Hz, $H_1$), 4.80 (1H, ddd, $^2J_{HF}$ = 47.1 Hz, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 3.9 Hz, $H_1$'), 5.67 (1H, dt,

$^{3}J_{HF}$ = 18.6 Hz, $^{3}J_{HH}$ = 4.5 Hz, $H_2$), 7.54 (1H, t, $^{3}J_{HH}$ = 7.6 Hz, ArH), 7.61 (1H, t, $^{3}J_{HH}$ = 7.6 Hz, ArH), 7.73 (1H, dd, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.1 Hz, ArH), 7.95 (1H, d, $^{3}J_{HH}$ = 7.6 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -228.9 (s). $\delta_C$ ($CDCl_3$, 125 MHz) 78.7 ($CH_2$, d, $^{2}J_{CF}$ = 21.2 Hz, $C_2$), 82.3 ($CH_2$, d, $^{1}J_{CF}$ = 178.3 Hz, $C_1$), 122.3 (CH), 126.1 (CH), 130.0 (CH), 134.4 (CH), 145.1 (C, d, $^{3}J_{CF}$ = 5.1 Hz), 145.9 (C), 169.7 (CO, $C_5$). m/z (ASAP) 167.0509 ($MH^+$, $C_9H_8FO_2$ requires 167.0508, 100%).




**290**

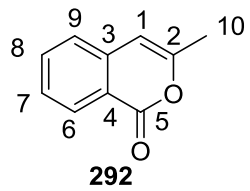
Partial $^{1}H$ and $^{13}C$ NMR data is presented. It was not possible to identify all of the peaks as **290** was isolated as a complex mixture. $\delta_H$ ($CDCl_3$, 400 MHz) 4.66 (1H, dd, $^{2}J_{HH}$ = 12.3 Hz, $^{3}J_{HH}$ = 5.7 Hz, $H_1$), 4.82 (1H, dd, $^{2}J_{HH}$ = 12.3 Hz, $^{3}J_{HH}$ = 3.5 Hz, $H_1$'), 5.30 (1H, dd, $^{3}J_{HH}$ = 11.0 Hz, $^{2}J_{HH}$ = 1.3 Hz, $H_{18}$), 5.59 (1H, dd, $^{3}J_{HH}$ = 17.4 Hz, $^{2}J_{HH}$ = 1.3 Hz, $H_{18}$'), 5.81 (1H, dd, $^{3}J_{HH}$ = 5.7 Hz, $^{3}J_{HH}$ = 5.7 Hz, $H_2$). $\delta_C$ ($CDCl_3$, 125 MHz) 64.6 ($CH_2$, $C_1$), 78.6 (CH, $C_2$), 116.9 ($CH_2$, $C_{18}$), 166.7 (CO).




**291**

The crude product was isolated by column chromatography to give 3-fluoro-3-methylisochroman-1-one **291** as a colourless oil (0.041 g, 32%). It was not possible to obtain this product completely pure. The NMR spectra were contaminated with trace amounts of 2-(2-iodophenyl)propan-2-ol **64** and 3-methyl-1*H*-isochromen-1-one **292**. $\delta_H$ ($CDCl_3$, 400 MHz) 1.77 (3H, d, $^{3}J_{HF}$ = 17.7 Hz, $H_{10}$), 3.17 – 3.34 (2H, m, collapses to 2 x 1H d on $^{19}F$ decoupling, $^{2}J_{HH}$ = 16.9 Hz, $H_1$ and $H_1$'), 7.20 (1H, d, $^{3}J_{HH}$ = 7.6 Hz, $H_9$), 7.35 (1H, t, $^{3}J_{HH}$ = 7.6 Hz, $H_7$), 7.51 (1H, td, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.3 Hz, $H_8$), 8.05 (1H, d, $^{3}J_{HH}$ = 7.6 Hz, $H_6$). $\delta_F$ ($CDCl_3$, 376 MHz) -98.6 (s). $\delta_C$ ($CDCl_3$, 125 MHz) 25.7 ($CH_3$, d, $^{2}J_{CF}$ = 26.8 Hz, $C_{10}$), 36.8 ($CH_2$, d, $^{2}J_{CF}$ = 29.1 Hz, $C_1$), 113.9 (C, d, $^{1}J_{CF}$ = 224.5 Hz, $C_2$), 123.5 (C, $C_3$/$_4$), 128.0 (2 x CH, $C_9$ and $C_7$), 130.2 (CH, $C_6$), 134.4 (CH, $C_8$), 135.4 (C, $C_3$/$_4$), 162.4 (CO, $C_5$). m/z (ASAP) 181.0665 ($MH^+$, $C_{10}H_{10}FO_2$ requires 181.0665, 25%), 161.0591 ($(M-F)^+$, 100%), 133.0641 ($(M-F-CO)^+$, 40%).

3-Methyl-1*H*-isochromen-1-one **292** was also isolated from this reaction (0.014 g, 12%):



**292**

The characterisation data was in agreement with the literature.[46] mp 69 – 71 °C (lit.,[46] 66 - 69 °C). $\delta_H$ ($CDCl_3$, 400 MHz) 2.29 (3H, d, $^4J_{HH}$ = 0.8 Hz, $H_{10}$), 6.26 (1H, s, $H_1$), 7.33 (1H, d, $^3J_{HH}$ = 7.6 Hz, $H_9$), 7.45 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, $H_7$), 7.67 (1H, td, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 8.25 (1H, d, $^3J_{HH}$ = 7.6 Hz, $H_6$). $\delta_C$ ($CDCl_3$, 125 MHz) 19.7 ($CH_3$, $C_{10}$), 103.5 (CH, $C_1$), 120.0 (C, $C_3$), 124.9 (CH, $C_9$), 127.6 (CH, $C_7$), 129.5 (CH, $C_6$), 134.7 (CH, $C_8$), 137.7 (C, $C_4$), 154.6 (C, $C_2$), 163.0 (CO, $C_5$). m/z (ASAP) 161.0598 ($MH^+$, $C_{10}H_9O_2$ requires 161.0603, 100%).

### 7.4.9 Procedure for Table 4

4 Å Molecular sieves (0.09 g) were charged to a small Schlenk flask in the glove box. To this was added the required amount of 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **152**, 4-phenylpent-4-enoic acid **249** (0.063, g, 0.36 mmol), and dry solvent (0.2 mL). The flask was then sealed and the contents stirred at the required temperature for the stated amount of time. After this time, the reaction mixture was cooled to room temperature and naphthalene (0.046 g, 0.36 mmol) was added. The reaction was concentrated on a rotary evaporator to give a pale yellow solid. Conversion was calculated by $^1$H and $^{19}$F NMR spectroscopy using naphthalene as the internal standard.

In entries 1, 3, 5 and 6 the following procedure was used:

4 Å Molecular sieves (0.18 g) were charged to a small Schlenk flask in the glove box. To this was added 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.300 g, 1.07 mmol), 4-phenylpent-4-enoic acid **249** (0.126, g, 0.71 mmol), and dry solvent (0.4 mL). The flask was sealed and the contents stirred at 40 °C for the stated amount of time. After this time, the reaction mixture was cooled to room temperature and naphthalene (0.091 g, 0.71 mmol) was added. The reaction mixture was then concentrated on a rotary evaporator to give a pale yellow solid. Conversion was calculated by $^1$H and $^{19}$F NMR spectroscopy using naphthalene as the internal standard. The crude product was purified by column chromatography (5% EtOAc in petroleum

ether 40-60) to give 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one as a colourless oil (entry 1, 0.071 g, 52%; entry 3, 0.057 g, 41% ; entry 5, 0.074 g, 54%).

### 7.4.10 Procedure for Table 5

4 Å Molecular sieves (0.18 g) were charged to a small Schlenk flask in the glove box. To this was added 1-fluoro-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **154** (0.300 g, 1.07 mmol), substrate (0.126, g, 0.71 mmol), and dry acetonitrile (0.4 mL). The flask was then sealed and the contents stirred at 40 $^{o}$C for one hour. After this time, the reaction mixture was cooled to room temperature and naphthalene (0.091 g, 0.71 mmol) was added. The reaction mixture was then concentrated on a rotary evaporator to give a pale yellow solid. The conversion was calculated by $^{1}$H and $^{19}$F NMR spectroscopy using naphthalene as the internal standard.

Entry 1: The crude product was purified by column chromatography (5% EtOAc in petroleum ether 40-60) to give 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one **250** as a colourless oil (0.074 g, 54%).

Entry 2: The crude product was purified by column chromatography (10% EtOAc in petroleum ether 40-60) to give 5-fluoro-5-(4-fluorobenzyl)dihydrofuran-2(3*H*)-one **278** as a colourless oil (0.075 g, 50%).

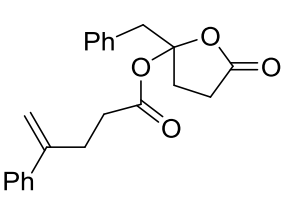
Entry 3: The crude product was purified by column chromatography (5% EtOAc in petroleum ether 40-60 increasing to 20% and then to 50%) to give 6-benzyl-6-fluorotetrahydro-2*H*-pyran-2-one **279** as a colourless oil (0.033 g, 22%). 5-Phenylhex-5-enoic acid **268** was also isolated (0.031 g, 23%) as a white solid.

Entry 4: The crude product was purified by column chromatography (5% EtOAc in petroleum ether 40-60) to give 3-benzyl-3-fluoroisobenzofuran-1(3*H*)-one **283** as a colourless oil (0.086 g, 50%).

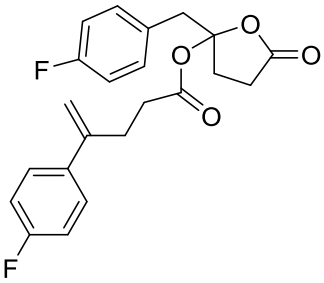
Entry 5: The crude product was purified by column chromatography (5% EtOAc in petroleum ether 40-60) to give 3-fluoro-3-(4-fluorobenzyl)isobenzofuran-1(3*H*)-one **286** as a white solid (0.061 g, 33%).

In all of the silver-free reactions, by-products **294** and **295** were formed in which the starting material had acted as the nucleophile. Due to the very small amounts of these products and the fact that they were isolated as mixtures with other products, full

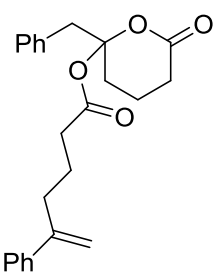
characterisation was not possible. Partial characterisation data is presented here. In some cases, overlapping peaks with other components in the mixture made assignments impossible.



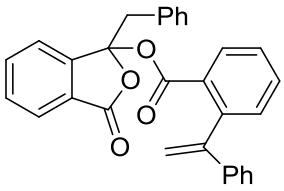
By-product obtained as a mixture with 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one **250** (0.018 g, 7%). $\delta_H$ ($CDCl_3$, 400 MHz) 2.16 – 2.28 (1H, m, $CH_2$), 2.32 – 2.49 (4H, m, $CH_2$), 2.68 – 2.80 (3H, m, $CH_2$), 3.23 (1H, d, $^2J_{HH}$ = 14.2 Hz, $CH_2$), 3.32 (1H, d, $^2J_{HH}$ = 14.2 Hz, $CH_2$), 5.06 (1H, d, $^2J_{HH}$ = 1.4 Hz, *H*HC=), 5.30 (1H, s, *H*HC=), 7.25 – 7.38 (10H, m, ArH).



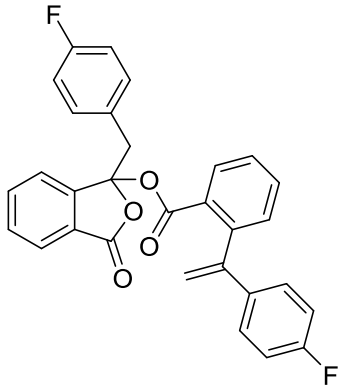
By-product isolated as a mixture with 5-fluoro-5-(4-fluorobenzyl)dihydrofuran-2(3*H*)-one **278** (0.010 g, 4%). $\delta_H$ ($CDCl_3$, 400 MHz) 2.12 – 2.50 (5H, m, $CH_2$), 2.70 – 2.85 (3H, m, $CH_2$), 3.19 (1H, d, $^2J_{HH}$ = 14.2 Hz, $CH_2$), 3.30 (1H, d, $^2J_{HH}$ = 14.2 Hz, $CH_2$), 5.03 (1H, d, $^2J_{HH}$ = 0.9 Hz, *H*HC=), 5.24 (1H, s, *H*HC=), 6.97 – 7.04 (4H, m, ArH), 7.21 – 7.27 (2H, m, ArH), 7.32 (2H, dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 5.3 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -114.6 (1F, s, ArF), -114.8 (1F, s, ArF).$\delta_C$ ($CDCl_3$, 100 MHz) 28.5 ($CH_2$), 30.1 ($CH_2$), 30.4 ($CH_2$), 33.6 ($CH_2$), 43.7 ($CH_2$), 109.1 (C), 113.2 ($CH_2$), 115.3 (CH, d, $^2J_{CF}$ = 22.4 Hz), 115.4 (CH, d, $^2J_{CF}$ = 20.8 Hz), 127.7 (CH, d, $^3J_{CF}$ = 7.2 Hz), 129.0 (C, d, $^4J_{CF}$ = 3.5 Hz), 132.2 (CH, d, $^3J_{CF}$ = 7.6 Hz), 136.4 (C, d, $^2J_{CF}$ = 4.7 Hz), 145.4 (C), 162.3 (C, d, $^1J_{CF}$ = 246.7 Hz), 162.4 (C, d, $^1J_{CF}$ = 246.2 Hz), 171.3 (CO), 175.1 (CO).



The by-product was isolated as a mixture with 5-phenylhex-5-enoic acid **268** (0.022 g, 8%). $\delta_H$ ($CDCl_3$, 400 MHz) 1.55 – 1.86 (5H, m, $CH_2$), 2.26 – 2.63 (7H, m, $CH_2$), 3.34 (1H, d, $^2J_{HH}$ = 14.0 Hz, $CH_2$), 3.39 (1H, d, $^2J_{HH}$ = 14.0 Hz, $CH_2$), 5.04 (1H, d, $^2J_{HH}$ = 1.4 Hz, *H*HC=), 5.29 (1H, d, $^2J_{HH}$ = 1.4 Hz, *H*HC=), 7.25 – 7.41 (10H, m, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 15.9 ($CH_2$), 28.4 ($CH_2$), 29.1 ($CH_2$), 34.2 ($CH_2$), 34.4 ($CH_2$), 44.4 ($CH_2$), 107.8 (C), 113.1 ($CH_2$), 126.1 (CH), 127.3 (CH), 127.5 (CH), 128.4 (CH), 130.8 (CH), 134.0 (CH), 140.7 (C), 147.3 (C), 169.5 (C), 171.4 (CO), 178.6 (CO).

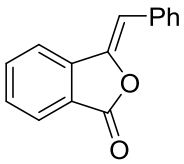


By-product isolated as a mixture with 2-(2-iodophenyl)propan-2-ol **64** (0.016 g, 5%). $\delta_H$ ($CDCl_3$, 400 MHz) 3.30 (1H, d, $^2J_{HH}$ = 14.3 Hz, $CH_2$), 3.42 (1H, d, $^2J_{HH}$ = 14.2 Hz, $CH_2$), 5.21 (1H, s, *H*HC=), 5.75 (1H, s, *H*HC=), 6.97 (2H, dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.7 Hz, ArH), 7.07 – 7.13 (3H, m, ArH), 7.20 – 7.26 (7H, m, ArH), 7.37 – 7.44 (3H, m, ArH), 7.52 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.7 Hz, ArH), 7.61 – 7.64 (1H, m, ArH), 7.74 (1H, dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.3 Hz, ArH).

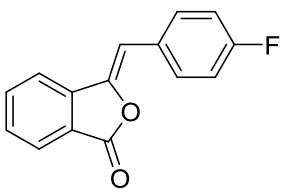


By-product isolated as a mixture with 2-(2-iodophenyl)propan-2-ol **64** and 3-fluoro-3-(4-fluorobenzyl)isobenzofuran-1(3*H*)-one **286** (0.040 g, 12%). $\delta_H$ ($CDCl_3$, 400 MHz) 3.33 (1H, d, $^2J_{HH}$ = 14.5 Hz, $CH_2$), 3.49 (1H, d, $^2J_{HH}$ = 14.5 Hz, $CH_2$), 5.18 (1H, s, *H*HC=), 5.60 (1H, s, *H*HC=), 6.80 – 7.12 (9H, m, ArH), 7.31 – 7.56 (5H, m, ArH), 7.67 (1H, d, $^3J_{HH}$ = 7.7 Hz ArH), 7.61 (1H, d, $^3J_{HH}$ = 8.0 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -114.4 (1F, s, ArF), -115.0 (1F, s, ArF).

Elimination by-products **296** were also observed in some of the silver-free reactions. Again, full characterisation was not possible due to the very small amounts of these products and the fact that they were isolated as mixtures with other products.



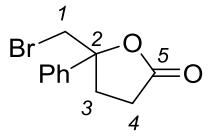
The by-product was isolated as a mixture with 3-benzyl-3-fluoroisobenzofuran-1(3*H*)-one **283** (0.006 g, 6%). The characterisation data was in agreement with the literature.[47] $\delta_H$ ($CDCl_3$, 400 MHz) 6.44 (1H, s, =CH), 7.32 (1H, m, ArH), 7.42 (2H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.54 – 7.56 (1H, m, ArH), 7.73 (2H, td, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.0 Hz, ArH), 7.86 (2H, d, $^3J_{HH}$ = 7.9 Hz, ArH), 7.95 (1H, dt, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.0 Hz, ArH).



The by-product was isolated as a mixture with 3-fluoro-3-(4-fluorobenzyl)isobenzofuran-1(3*H*)-one **286** (0.005 g, 3%). The characterisation data was in agreement with the literature.[48] $\delta_H$ ($CDCl_3$, 400 MHz) 6.40 (1H, s, =CH), 7.11 (2H, t, $^3J_{HH}$ = 8.9 Hz, ArH), 7.52 – 7.87 (5H, m, ArH), 7.95 (1H, d, $^3J_{HH}$ = 7.8 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz) -111.7 (s).

### 7.4.11 Procedure for bromination

4 Å Molecular sieves (0.15 g) were charged to a small Schlenk flask in the glove box. To this was added 1-bromo-3,3-dimethyl-1,3-dihydro-$\lambda^3$-benzo[d][1,2]iodoxole **65** (0.300 g, 0.88 mmol), 4-phenylpent-4-enoic acid **249** (0.103 g, 0.59 mmol), and dry dichloromethane (0.4 mL). The flask was then sealed and the contents stirred at 40 $^{o}$C for one hour. After this time, the reaction mixture was cooled to room temperature and naphthalene (0.075 g, 0.59 mmol) was added. The reaction mixture was then concentrated on a rotary evaporator to give a yellow solid (0.876 g). Purification by column chromatography (10% EtOAc in petroleum ether 40-60) gave 5-(bromomethyl)-5-phenyldihydrofuran-2(3*H*)-one **297** as a colourless oil (0.138 g, 92%).

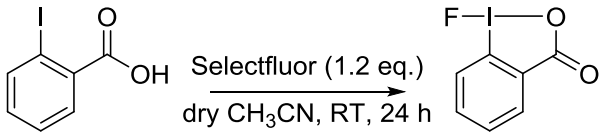


**297**

The characterisation data was in agreement with the literature.[34] $\delta_H$ ($CDCl_3$, 400 MHz) 2.48 – 2.60 (2H, m, $H_3$ and $H_4$), 2.75 – 2.87 (2H, m, $H_3$' and $H_4$'), 3.69 (1H, d, $^2J_{HH}$ = 11.4 Hz, $H_1$), 3.74 (1H, d, $^2J_{HH}$ = 11.4 Hz, $H_1$'), 7.33 – 7.42 (5H, m, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 29.1 ($CH_2$, $C_4$), 32.4 ($CH_2$, $C_3$), 41.0 ($CH_2$, $C_1$), 86.4 (C, $C_2$), 124.9 (CH), 128.7 (CH), 128.9 (CH), 140.6 (C), 175.5 (CO, $C_5$). m/z (ASAP) 175.0758 ($(M-Br)^+$, $C_{11}H_{11}O_2$ requires 175.0759, 100%), 129.0706 ($(M-Br-CO_2H)^+$, 80%). In the HMBC NMR spectrum, H1 and H1' correlate to C2, C3 and the aromatic ring C. There is no correlation between H1/H1' and the aromatic ortho proton therefore the structure is as assigned and no rearrangement has occurred.

## 7.5 Experimental for Chapter 5

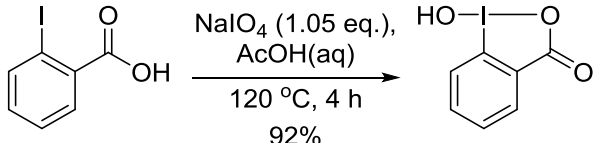
### 7.5.1 Reaction between 2-iodobenzoic acid and Selectfluor




**70** **299**

A solution of 2-iodobenzoic acid **70** (0.500 g, 2.01 mmol) in dry acetonitrile (40 mL) was prepared under nitrogen. To this was added Selectfluor (0.86 g, 2.42 mmol), upon addition of which the colourless solution turned bright blue. The solution was then stirred at room temperature for 24 hours. After this time, the blue colour had faded and a white precipitate formed which was collected by suction filtration (0.393 g, 74%). Due to the insolubility of the precipitate in common solvents (DMSO, methanol, acetone, chloroform, toluene, 2,2,2-trifluoroethanol), NMR spectroscopic data could not be obtained. m/z (ASAP) 494.8502 (15%), 282.9013 (12%), 266.9307 ($MH^+$, $C_7H_5O_2IF$ requires 266.9318, 15%), 248.9420 ($C_6H_5ICOOH^+$, 100%), 230.9283 ($C_6H_4CO$, 15%).

### 7.5.2 Preparation of 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one[15]

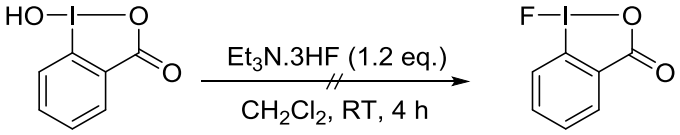



**70** **72**

A suspension of 2-iodobenzoic acid **70** (2.00 g, 8.06 mmol) and $NaIO_4$ (1.81 g, 8.46 mmol) in aqueous acetic acid (12 mL, 30% v/v) was prepared in a round bottomed flask. The reaction mixture was refluxed at 120 °C for 4 h. After this time, ice cold water (45 mL) was added and the mixture stirred in the dark for 1 h. The resultant white solid was collected by suction filtration, washed with cold water (3 x 5 mL) and acetone (3 x 5 mL) and air dried in the dark to give 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one **72** as a white solid (1.97 g, 92%). The characterisation data was in agreement with the literature.[15] mp 239-241 °C (lit.,[49] 254 °C). $\delta_H$ (DMSO, 400 MHz) 7.72 (1H, td, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 0.9 Hz ArH), 7.85 (1H, d, $^3J_{HH}$ = 8.1 Hz, ArH), 7.96 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 8.02 (1H, dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.4 Hz ArH). $\delta_C$ ($CDCl_3$, 100 MHz)

120.4 (CI), 126.3 (CH), 130.4 (CH), 131.1 (CH), 131.5 (C), 134.5 (CH), 167.9 (CO). m/z (ASAP) 264.9353 ($MH^+$, $C_7H_6O_3I$ requires 264.9362, 100 %).

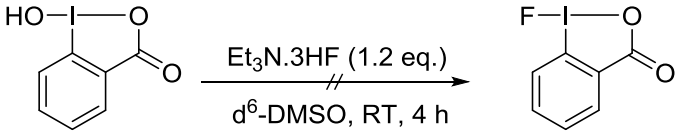
### 7.5.3 Reaction between 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one and TREAT-HF




**72** **299**

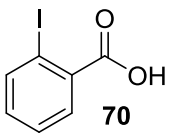
$Et_3N.3HF$ (0.07 mL, 0.45 mmol) was added to a suspension of 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one **72** (0.100 g, 0.38 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for four hours. After this time the reaction mixture was concentrated on a rotary evaporator to give a white solid (0.232 g). Analysis of the crude product by $^1H$ and $^{19}F$ NMR spectroscopy showed only the starting material and TREAT-HF.

### 7.5.3 Reaction between 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one and $Et_3N.3HF$ in $d^6$-DMSO




**72** **299**

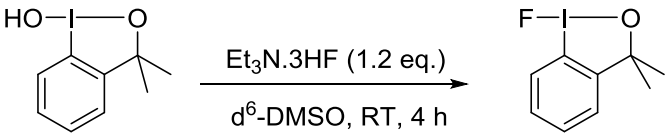
A solution of 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one **72** (0.018 g, 0.07 mmol) and $Et_3N.3HF$ (0.01 mL, 0.084 mmol) in $d^6$-DMSO was prepared in an NMR tube. After 4 hours at room temperature, no reaction had occurred. After heating the reaction mixture to 40 $^oC$ for 19 hours a 26% conversion to 2-iodobenzoic acid **70** was observed. This increased to 100% after 7 days.




**70**

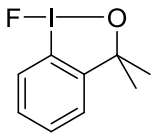
$\delta_H$ (DMSO, 400 MHz) 7.24 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.48 (1H, td, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.71 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.99 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.5 Hz ArH), 13.30 (1H, br s, COOH).

### 7.5.4 Reaction between 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole and $Et_3N.3HF$ in d$^6$-DMSO



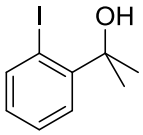

**166** **154**

A solution of 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole **166** (0.010 g, 0.036 mmol) and $Et_3N.3HF$ (0.007 mL, 0.043 mmol) in d$^6$-DMSO was prepared in an NMR tube. After four hours at room temperature, complete conversion to 1-fluoro-3,3-dimethyl-1,3-dihydro-λ$^3$-benzo[d][1,2]iodoxole **154** was observed. After heating the reaction mixture to 40 $^oC$ for 19 hours a 50% conversion to 2-(2-iodophenyl)propan-2-ol **64** was observed.




**154**

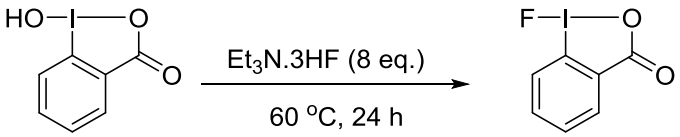
$\delta_H$ (DMSO, 400 MHz) 1.44 (6H, s, 2 x $CH_3$), 7.38 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH), 7.53 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.60 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.65 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz): -135.5 (s).




**64**

$\delta_H$ (DMSO, 400 MHz) 1.62 (6H, s, 2 x $CH_3$), 6.92 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.36 (1H, td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.76 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz, ArH), 7.93 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz ArH).

### 7.5.5 Reaction between 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one and $Et_3N.3HF$ (no solvent)

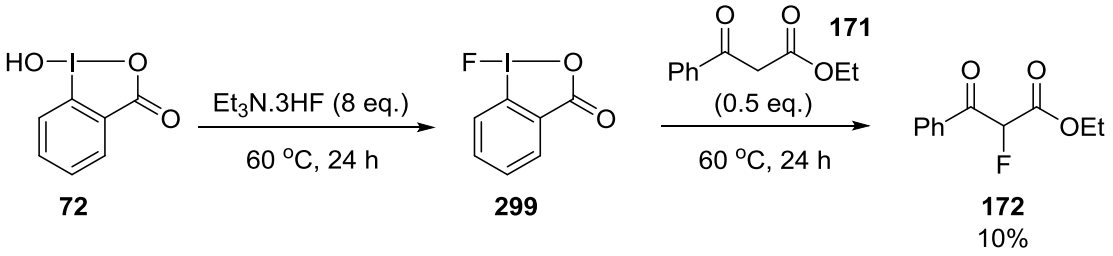



**72** **299**

1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one **72** (0.200 g, 0.76 mmol) and $Et_3N.3HF$ (1 mL, 6.14 mmol) were charged to a Schlenk flask. The flask was then sealed and the contents heated to 60 $^oC$ for 24 hours. After this time, the reaction mixture was cooled to room temperature and washed with water (3 x 5 mL) and acetone (3 x 5 mL) to give an insoluble white solid (0.140 g). Analysis of the crude product by ASAP mass

spectrometry showed peaks corresponding to the starting material and 2-iodobenzoic acid. m/z (ASAP) 248.9439 (2-iodobenzoic acid **70** $MH^+$, $C_7H_6O_2I$ requires 248.9413, 100%), 264.9374 (1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one **72** $MH^+$, $C_7H_6O_3I$ requires 264.9362, 90%).

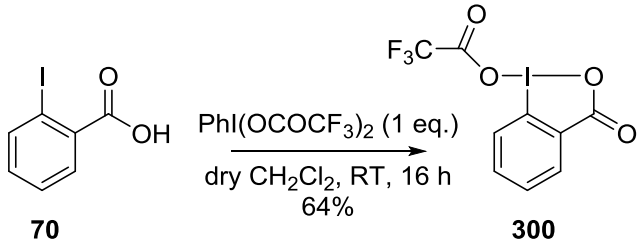
### 7.5.6 Reaction between 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one and $Et_3N.3HF$ (no solvent) followed by *in situ* fluorination




**72** **299** **172** 10%

1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one **72** (0.200 g, 0.76 mmol) and $Et_3N.3HF$ (1 mL, 6.14 mmol) were charged to a Schlenk flask. The flask was then sealed and the contents heated to 60 °C for 24 hours. After this time, the reaction mixture was cooled to room temperature, ethyl 3-oxo-3-phenylpropanoate **171** (0.066 mL, 0.38 mmol) was added and the flask was resealed. The contents were then heated to 60 °C for a further 24 hours. After this time, the reaction mixture was cooled to room temperature and washed with water (3 x 2 ml). The aqueous layer was extracted with dichloromethane (3 x 2 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated on the rotary evaporator to give a colourless oil (0.073 g). Analysis of the crude product by $^1H$ and $^{19}F$ NMR spectroscopy showed a 10% conversion to ethyl 2-fluoro-3-oxo-3-phenylpropanoate **172**.

### 7.5.7 Preparation of 1-trifluoroacetoxy-1,2-benziodoxol-3-(1*H*)-one

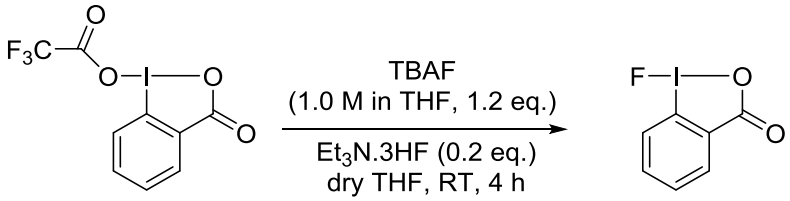



**70** **300**

A solution of 2-iodobenzoic acid **70** (2.00 g, 8.06 mmol) and $PhI(OCOCF_3)_2$ (3.47 g, 8.06 mmol) in dry dichloromethane (40 mL) was prepared under nitrogen. The reaction

mixture was stirred at room temperature for 16 h. After this time, the reaction mixture was cooled in ice and the white solid collected by suction filtration (1.86 g, 64%). The characterisation data for 1-trifluoroacetoxy-1,2-benziodoxol-3-(1*H*)-one **300** was *not* in agreement with the literature.[50] mp 196-199 $^{o}$C (lit.,[50] 210-212 $^{o}$C). $\delta_H$ (MeOD, 400 MHz) 7.77 (1H, t, $^3J_{HH}$ = 7.7 Hz), 7.90 (1H, d, $^3J_{HH}$ = 7.7 Hz), 8.02 (1H, t, $^3J_{HH}$ = 7.7 Hz), 8.18 (1H, d, $^3J_{HH}$ = 7.7 Hz). $\delta_F$ ($CDCl_3$, 376 MHz): -77.8. m/z (ASAP) 360.9170 ($MH^+$, $C_9H_5O_4IF_3$ requires 360.9185, 100 %), 246.9254 (M-$OCOCF_3^+$, 35%). Sample was not soluble enough to obtain a $^{13}$C NMR spectrum.

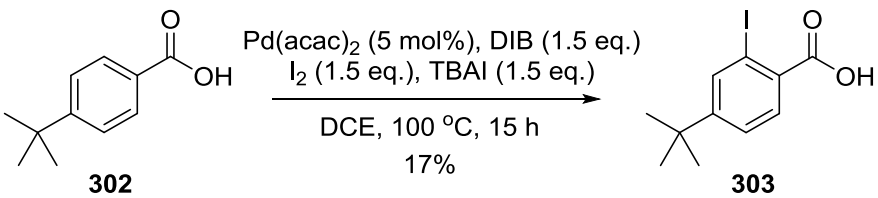
### 7.5.8 Reaction between 1-trifluoroacetoxy-1,2-benziodoxol-3-(1*H*)-one and TBAF




**300** **299**

TBAF (0.5 mL, 0.5 mmol, 1.0 M in THF) was added to $Et_3N.3HF$ (0.13 mL, 0.084 mmol, 0.64 M in THF) and the solution was stirred at room temperature for 1 hour. After this time, 1-trifluoroacetoxy-1,2-benziodoxol-3-(1H)-one **300** (0.150 g, 0.42 mmol) was added and the mixture was stirred at room temperature for 4 hours. This was then concentrated on a rotary evaporator to give a white solid which was insoluble in MeOD and $CDCl_3$. $^1$H and $^{19}$F NMR spectroscopy in d$^6$-DMSO revealed a complex mixture of products. m/z (ASAP) 266.9327 ($MH^+$, $C_7H_5O_2IF$ requires 266.9327, 100%), 264.9374 (1-hydroxy-1,2-benziodoxol-3-(1*H*)-one **72** $MH^+$, $C_7H_6O_3I$ requires 264.9362, 90%).

### 7.5.9 Preparation of 4-(*tert*-butyl)-2-iodobenzoic acid[51]

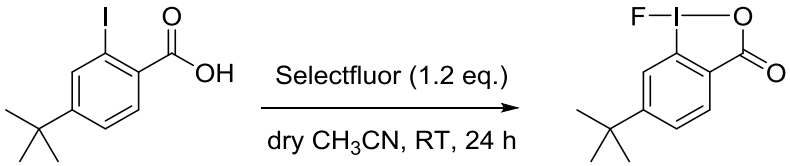



**302** **303**

A solution of 4-(*tert*-butyl)benzoic acid **302** (0.712 g, 4 mmol), $Pd(acac)_2$ (0.061 g, 0.2 mmol), (diacetoxyiodo)benzene (1.93 g, 6 mmol), $I_2$ (1.52 g, 6 mmol) and tetrabutylammonium iodide (2.21 g, 6 mmol) in DCE (20 mL) was refluxed at 100 $^{o}$C

for 15 hours. After this time, the reaction mixture was cooled to room temperature and washed with 2 M HCl (2 x 20 mL) and an aqueous solution of $Na_2S_2O_3$ (2 x 20 mL, 5% w/v). The organic layer was dried ($MgSO_4$) and concentrated on a rotary evaporator to give a brown oil (4.20 g). The crude product was purified by column chromatography (100% petroleum ether 40-60 then 10% ethyl acetate in petroleum ether 40-60) to give 4-(*tert*-butyl)-2-iodobenzoic acid **303** as a pale brown solid (0.212 g, 17%). mp 114-116 $^{o}$C. $\delta_H$ ($CDCl_3$, 400 MHz) 1.33 (9H, s, $CH_3$), 7.45 (1H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.9 Hz, ArH), 7.98 (1H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 8.05 (1H, d, $^4J_{HH}$ = 1.9 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 30.9 ($CH_3$), 34.9 (C), 95.2 (CI), 125.3 (CH), 130.0 (C), 132.0 (CH), 139.4 (CH), 157.7 (C), 171.0 (CO). m/z (ASAP) 305.0043 ($MH^+$, $C_{11}H_{14}O_2I$ requires 305.0039, 100%), 286.9944 ($M\text{-}OH^+$, 30%).

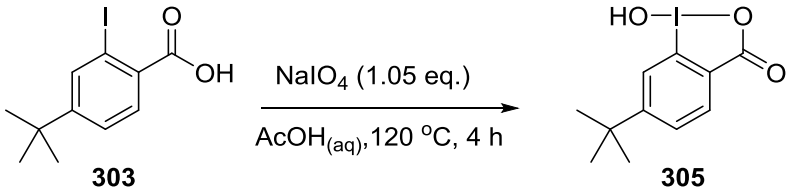
### 7.5.10 Reaction between 4-(*tert*-butyl)-2-iodobenzoic acid and Selectfluor




**303** **304**

A solution of 4-(*tert*-butyl)-2-iodobenzoic acid **303** (0.100 g, 0.33 mmol) and Selectfluor (0.140 g, 0.39 mmol) in dry acetonitrile (6.6 mL) was stirred under nitrogen at room temperature for 24 hours. After this time, the reaction mixture was concentrated on a rotary evaporator and the product was extracted into chloroform (3 x 2mL). The chloroform extracts were concentrated on a rotary evaporator to give a white solid (0.112 g). Analysis of the crude product by $^1$H NMR spectroscopy showed two major iodane products as well as minor impurities. A weak peak in the $^{19}$F NMR spectrum was observed at -166.3 ppm. m/z (ASAP) 322.9935 ($MH^+$, $C_{11}H_{13}O_2IF$ requires 322.9944, 100%).

### 7.5.11 Preparation of 4-(*tert*-butyl)-1-hydroxy-1,2-benziodoxol-3-(1*H*)-one

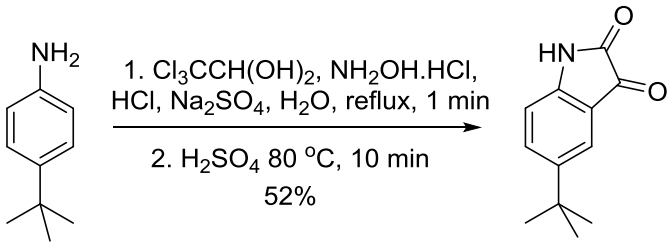



**303** **305**

4-(*Tert*-butyl)-2-iodobenzoic acid **303** (0.100 g, 0.33 mmol), $NaIO_4$ (0.074 g, 0.35 mmol) and glacial acetic acid (0.5 mL, 30% v/v) were heated to 120 °C in a sealed Schlenk flask for 4 hours. After this time, water (2 mL) was added and the mixture was stirred at 0 °C in the dark for 1 hour. The white precipitate was then filtered and washed with water (3 x 5 mL) and acetone (3 x 5 mL) to give a white solid (0.069 g). Analysis by $^1$H NMR spectroscopy showed an 81% conversion to an iodane species. Purification was not attempted. The characterisation data is given for the major component of the mixture.

$\delta_H$ ($CDCl_3$, 400 MHz) 1.35 (9H, s, $CH_3$), 7.74 (1H, dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.6 Hz, ArH), 7.81 (1H, d, $^4J_{HH}$ = 1.5 Hz, ArH), 7.93 (1H, d, $^3J_{HH}$ = 8.1 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 30.8 ($CH_3$), 35.5 (C), 120.6 (CI), 122.4 (CH), 127.8 (CH), 129.1 (C), 130.8 (CH), 158.0 (C), 167.6 (CO). m/z (ASAP) 908.9654 (($C_{33}H_{36}I_3O_6$)$^+$, 10%), 606.9811 (($C_{22}H_{25}I_2O_4$)$^+$, 100%), 305.0040 (($C_{11}H_{14}O_2I$)$^+$, $C_{11}H_{14}O_2I$ requires 305.0039, 90%).

### 7.5.12 Preparation of 5-(*tert*-butyl)indoline-2,3-dione[52]

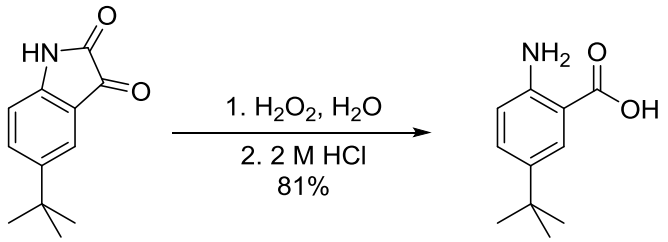



**309** **310**

A solution of choral hydrate (7.11 g, 43 mmol) in water (100 mL) was prepared in a 250 mL round bottomed flask. To this was added sodium sulphate (100 g, 704 mmol), 4-(*tert*-butyl)aniline **309** (5.96 g, 40 mmol), HCl (4 mL) and a solution of hydroxylamine hydrochloride (8.34 g, 120 mmol) in water (40 mL). The mixture was then heated gradually to reflux over 40 minutes and refluxed for one minute.

The reaction mixture was cooled to room temperature and the solution was decanted from the oily brown solid. The brown solid was then washed with water (3 x 50 mL). Warm $H_2SO_4$ (50 $^oC$, 20 mL) was added cautiously to the brown solid and the mixture was stirred at 80 $^oC$ for ten minutes before pouring into ice cold water (100 mL). The product was extracted into dichloromethane (4 x 100 mL) and the organic layers were combined, washed with water (2 x 100 mL), dried ($MgSO_4$) and concentrated on a rotary evaporator to give a brown solid (7.83 g). Purification by column chromatography (50% diethyl ether in petroleum ether 40-60) gave 5-(*tert*-butyl)indoline-2,3-dione **310** as an orange solid (4.24 g, 52%). The characterisation data was in agreement with the literature.[53] mp $^oC$ 146 – 148 $^oC$. (lit.,[54] 155-156 $^oC$). $\delta_H$ ($CDCl_3$, 400 MHz) 1.31 (9H, s, C(C$H_3$)), 6.87 (1H, d, $^3J_{HH}$ = 8.3 Hz, ArH), 7.61 (1H, dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 2.1 Hz, ArH), 7.66 (1H, d, $^4J_{HH}$ = 2.1 Hz, ArH), 8.39 (1H, br s, NH). $\delta_C$ ($CDCl_3$, 100 MHz) 31.1 ($CH_3$), 34.6 (C), 112.0 (CH), 118.0 (C), 122.8 (CH), 135.9 (CH), 146.9 (C), 147.6 (C), 159.8 (CO), 183.4 (CO). m/z (ASAP) 204.1023 ($MH^+$, $C_{12}H_{14}O_2N$ requires 204.1025, 55 %).

### 7.5.13 Preparation of 2-amino-5-(*tert*-butyl)benzoic acid[55]



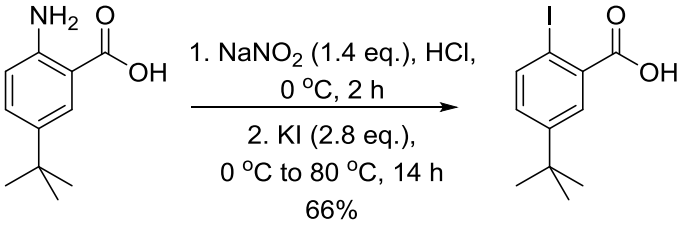

**310** **311**

A solution of 5-(t*ert*-butyl)indoline-2,3-dione **310** (4.24 g, 20.9 mmol) in 10% NaOH (76 mL) was heated to 90 $^oC$. To this was added 30% $H_2O_2$ (100 mL), dropwise over 15 minutes. The reaction mixture was cooled to room temperature and treated with activated charcoal. The solution was then acidified with 2M HCl (approx. 100 mL) and the product was extracted into dichloromethane (4 x 100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated on a rotary evaporator to give 2-amino-5-(*tert*-butyl)benzoic acid **311** as a pale brown solid (3.25 g, 81%).

mp 146 – 148 $^oC$ (lit.,[54] 153-154 $^oC$). $\delta_H$ ($CDCl_3$, 400 MHz) 1.29 (9H, s, C(C$H_3$)), 6.64 (1H, d, $^3J_{HH}$ = 8.6 Hz, ArH), 7.39 (1H, dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 2.4 Hz, ArH), 7.92 (1H, d, $^4J_{HH}$ = 2.4 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 31.2 ($CH_3$), 33.8 (C), 109.1 (C),

116.9 (CH), 127.9 (CH), 133.0 (CH), 139.3 (C), 149.1 (C), 173.5 (CO). m/z (ES) 194.1178 ($MH^+$, $C_{11}H_{16}NO_2$ requires 194.1181, 58%), 176.1073 ($M\text{-}OH^+$, 100 %).

### 7.5.14 Preparation of 5-(*tert*-butyl)-2-iodobenzoic acid[56]

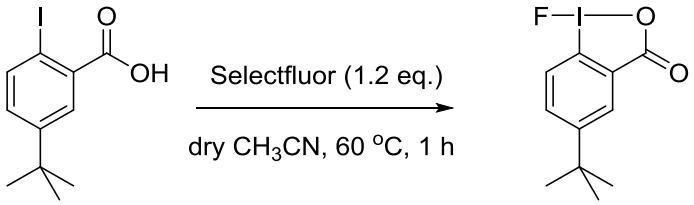



**311** **312**

A suspension of 2-amino-5-(*tert*-butyl)benzoic acid **311** (3.25 g, 16.8 mmol) in 3 M HCl (168 mL) was cooled to 0 °C. To this was added a solution of $NaNO_2$ (1.62 g, 23.5 mmol) in water (33 mL), drop wise over ten minutes. The solution was then stirred at 0 °C for 2 hours. After this time, the solution was added, drop wise over half an hour, to an ice cold solution of KI (7.81 g, 47.0 mmol) in water (66 mL). The mixture was stirred at 0 °C for 15 minutes before gradually warming to 80 °C and stirring at this temperature for 15 hours. The resultant solution was cooled to room temperature and $Na_2SO_3$ added until the colour turned from red to yellow. The product was then extracted into DCM (3 x 75 mL), washed with a saturated solution of $Na_2SO_3$ (2 x 75 mL), dried ($MgSO_4$) and concentrated on a rotary evaporator to give 5-(*tert*-butyl)-2-iodobenzoic acid **312** as a brown solid (3.37 g, 66%). mp 105 – 107 °C. $\delta_H$ ($CDCl_3$, 400 MHz) 1.33 (9H, s, $C(CH_3)$), 7.24 (1H, dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.5 Hz, ArH), 7.95 (1H, d, $^3J_{HH}$ = 8.5 Hz, ArH), 8.05 (1H, d, $^4J_{HH}$ = 2.5 Hz, ArH), 11.10 (br s, OH). $\delta_C$ ($CDCl_3$, 100 MHz) 31.0 ($CH_3$), 34.7 (C), 91.0 (CI), 129.4 (CH), 131.1 (CH), 132.8 (C), 141.6 (CH), 151.6 (C), 172.1 (CO). m/z (ASAP) 305.0038 ($MH^+$, $C_{11}H_{14}O_2I$ requires 305.0039, 100 %).

It was later found that higher yields could be obtained if the initial part of the reaction was stirred at 0 °C for 4 hours instead of 2.[57]

### 7.5.15 Reaction between 5-(*tert*-butyl)-2-iodobenzoic acid and Selectfluor

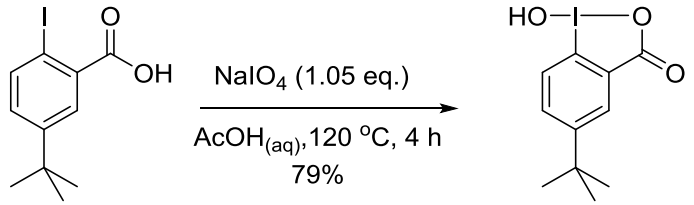



**312** **313**

A solution of 5-(*tert*-butyl)-2-iodobenzoic acid (0.400 g, 1.32 mmol) and Selectfluor (0.560 g, 1.58 mmol) in dry acetonitrile (26 mL) was stirred under nitrogen at 60 °C for 1 hour. After this time, the reaction mixture was concentrated and extracted into chloroform (3 x 10 mL). The chloroform extracts were concentrated on a rotary evaporator at 30 °C to give a yellow solid (0.435 g). The $^{1}$H NMR spectrum of the crude product showed two species (85%:15%). The data for the major product **313** is given. Due to the fast decomposition of this species in $CDCl_3$ it was not possible to obtain a $^{13}$C NMR spectrum.

$\delta_H$ ($CDCl_3$, 400 MHz) 1.34 (9H, s, $C(CH_3)$), 7.75 (1H, d, $^{3}J_{HH}$ = 8.5 Hz, ArH), 7.96 (1H, dd, $^{3}J_{HH}$ = 8.5 Hz, $^{4}J_{HH}$ = 2.0 Hz ArH), 8.18 (1H, t, $^{4}J_{HH}$ = 2.0 Hz, ArH). $\delta_F$ ($CDCl_3$, 376 MHz): -166.9 (s).

### 7.5.16 Preparation of 5-(*tert*-butyl)-1-hydroxy-1,2-benziodoxol-3-(1*H*)-one

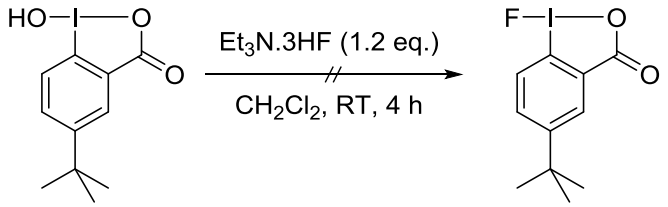



**312** **316**

5-(*Tert*-butyl)-2-iodobenzoic acid **312** (0.40 g, 1.32 mmol), $NaIO_4$ (0.30 g, 1.73 mmol) and glacial acetic acid (2 mL, 30% v/v) were heated to 120 °C in a sealed Schlenk flask for 4 hours. After this time, water (2 mL) was added and the mixture was stirred at 0 °C in the dark for 1 hour. The white precipitate was then filtered, washed with water (5 x 5 mL) and dried in air in the dark. 5-(*Tert*-butyl)-1-hydroxy-1,2-benziodoxol-3-(1H)-one **316** was obtained as a pale orange powder (0.33 g, 79%). Due to the fast decomposition of this species in $CDCl_3$ it was not possible to obtain a $^{13}$C NMR spectrum.

$\delta_H$ ($CDCl_3$, 400 MHz) 1.39 (9H, s, $C(CH_3)$), 7.86 (1H, d, $^3J_{HH}$ = 8.6 Hz, ArH), 7.92 (1H, dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 2.1 Hz, ArH), 8.25 (1H, d, $^4J_{HH}$ = 2.1 Hz, ArH). m/z (ASAP) 320.9991 ($MH^+$, $C_{11}H_{14}O_3I$ requires 320.9988, 40 %), 305.0013 ($(C_{11}H_{14}O_2I)^+$, 100%).

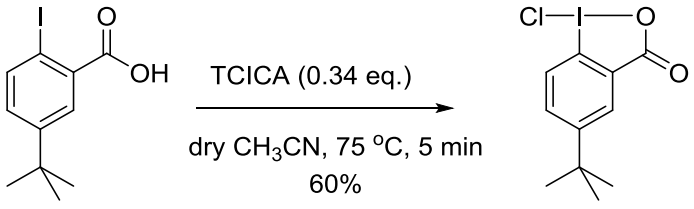
### 7.5.17 Reaction between 5-(*tert*-butyl)-1-hydroxy-1,2-benziodoxol-3-(1*H*)-one and TREAT-HF




**316** **313**

$Et_3N.3HF$ (0.04 mL, 0.24 mmol) was added to a suspension of the 5-(*tert*-butyl)-1-hydroxy-1,2-benziodoxol-3-(1H)-one **316** (0.065 g, 0.20 mmol) in dichloromethane (2.8 mL), upon which, a clear solution was formed. The solution was stirred at room temperature for four hours. After this time, water (3 mL) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (3 x 5 mL). The organic layers were then combined and concentrated on a rotary evaporator. Residual water was removed by coevaporation with toluene to give the product as a white solid (0.043 g). A very weak peak was observed in the expected position for the fluoroiodoxolone (-168 ppm) in the $^{19}F$ NMR spectrum of the crude product. The major product in the $^1H$ NMR spectrum, however, could not be identified.

### 7.5.18 Preparation of 5-(*tert*-butyl)-1-chloro-1,2-benziodoxol-3-(1*H*)-one



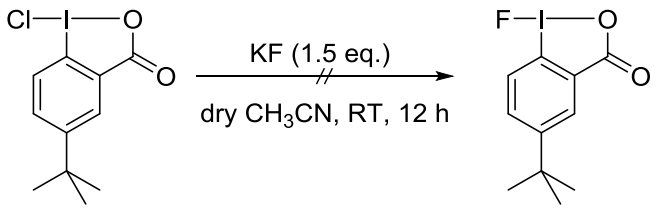

**312** **317**

A solution of 5-(*tert*-butyl)-2-iodobenzoic acid **312** (0.400 g, 1.32 mmol) in dry acetonitrile (2.5 mL) was heated to 75 $^oC$ in a sealed Schlenk flask. To this was added a solution of trichloroisocyanuric acid (0.104 g, 0.45 mmol) in dry acetonitrile (0.5 mL), quickly. The flask containing the trichloroisocyanuric acid solution was rinsed with a

further 0.2 mL of dry acetonitrile and this was also added to the reaction flask. The reaction mixture was then heated to 75 $^{o}$C for 5 minutes in a sealed Schlenk flask before hot filtration through celite. The solid was washed with hot acetonitrile (2 x 1 mL) and the filtrate concentrated almost to dryness on a rotary evaporator. The resultant solid was collected by suction filtration and washed with cold acetonitrile (2 x 1 mL). A second crop of crystals was obtained by repeating this process with the filtrate. The solids were combined and dried under high vacuum for 40 minutes to give the product as a yellow powder (0.27 g, 60%).

$\delta_H$ ($CDCl_3$, 400 MHz) 1.42 (9H, s, $C(CH_3)$), 8.03 (1H, dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.4 Hz ArH), 8.09 (1H, d, $^3J_{HH}$ = 8.8 Hz, ArH), 8.28 (1H, d, $^4J_{HH}$ = 2.4 Hz, ArH). $\delta_C$ ($CDCl_3$, 100 MHz) 29.4 ($CH_3$), 33.3 (C), 111.8 (CI), 124.7 (CH), 126.4 (C), 128.8 (CH), 132.6 (CH), 154.6 (C), 165.9 (CO). m/z (ASAP) 340.9774 (M($^{37}$Cl)$H^+$, 50%), 338.9660 (M($^{35}$Cl)$H^+$, $C_{11}H_{13}O_2{}^{35}ClI$ requires 338.9649, 100%).

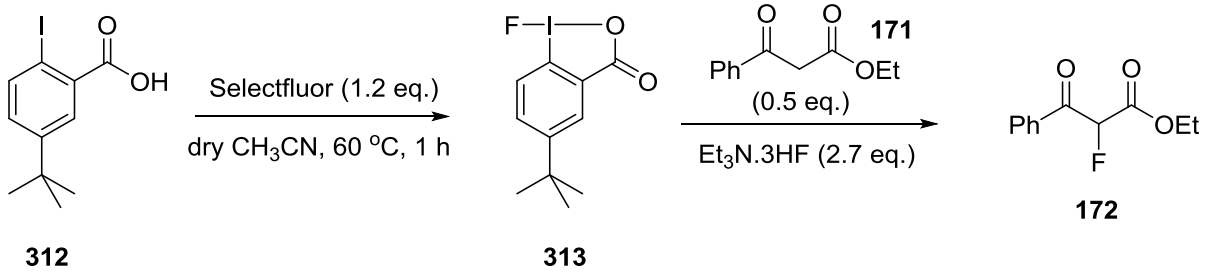
### 7.5.19 Reaction between 5-(*tert*-butyl)-1-chloro-1,2-benziodoxol-3-(1*H*)-one and KF




**317** **313**

Spray-dried KF (0.051 g, 0.89 mmol) was charged to a small Schlenk flask and heated under vacuum for two minutes. After cooling to room temperature under nitrogen, the 5-(*tert*-butyl)-1-chloro-1,2-benziodoxol-3-(1*H*)-one **317** was added (0.200 g, 0.59 mmol), followed by dry acetonitrile (1.8 mL). The flask was then sealed and the contents stirred vigorously at room temperature overnight. After this time, the reaction mixture was concentrated on a rotary evaporator to give a white solid. Analysis of the crude product by $^1$H and $^{19}$F NMR spectroscopy showed predominantly starting material accompanied by minor impurities. The formation of the fluoroiodoxolone **313** was not observed.

### 7.5.20 Formation of the fluoroiodoxolone and *in situ* fluorination




**312** **313**

A solution of 5-(*tert*-butyl)-2-iodobenzoic acid **313** (0.400 g, 1.32 mmol) and Selectfluor (0.560 g, 1.58 mmol) in dry acetonitrile (26 mL) was heated to 60 $^{o}$C in a sealed Schlenk flask under nitrogen for 1 hour. After this time, the reaction mixture was cooled to room temperature and concentrated on the Schlenk line. The product was extracted into $CHCl_3$ (5 x 10 mL) and concentrated on a rotary evaporator to give an orange solid (0.435 g). Analysis by $^{1}$H and $^{19}$F NMR spectroscopy showed an 85% conversion to **313** and a 15% conversion to the by-product **314**. No residual Selectfluor was remaining.

The orange solid containing **313** (0.270 g, 0.84 mmol) was then immediately charged to a Schlenk flask along with TREAT-HF (0.18 mL, 1.13 mmol), ethyl 3-oxo-3-phenylpropanoate (0.073 mL, 0.42 mmol) and dry dichloromethane (0.7 mL). The flask was sealed and the contents stirred at 40 $^{o}$C for 24 hours. After this time, the reaction mixture was cooled to room temperature and the product analysed by $^{1}$H and $^{19}$F NMR spectroscopy. This showed a 4% conversion to the ethyl 2-fluoro-3-oxo-3-phenylpropanoate **172**.

## 7.6 References for Chapter 7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# Appendix

**A1 Crystal Data and Structure Refinement for 154**

| | | |
|---|---|---|
| Identification code | 11022 | |
| Empirical formula | C9 H10 F I O | |
| Formula weight | 280.07 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 7.9834(19) Å | α= 83.119(4)°. |
| | b = 10.207(3) Å | β= 79.231(4)°. |
| | c = 11.705(3) Å | γ = 78.308(4)°. |
| Volume | 914.2(4) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 2.035 $Mg/m^3$ | |
| Absorption coefficient | 3.467 $mm^{-1}$ | |
| F(000) | 536 | |
| Crystal size | 0.11 x 0.10 x 0.03 $mm^3$ | |
| Theta range for data collection | 1.78 to 26.00°. | |
| Index ranges | -9<=h<=9, -12<=k<=12, -14<=l<=14 | |
| Reflections collected | 7214 | |
| Independent reflections | 3550 [R(int) = 0.0463] | |
| Completeness to theta = 26.00° | 98.6 % | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 0.969 and 0.650 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3550 / 0 / 221 | |
| Goodness-of-fit on $F^2$ | 0.894 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0383, wR2 = 0.0699 | |
| R indices (all data) | R1 = 0.0539, wR2 = 0.0748 | |
| Largest diff. peak and hole | 1.321 and -0.794 $e.Å^{-3}$ | |

**A2 Crystal Data and Structure Refinement for 167**

| | | |
|---|---|---|
| Identification code | 12085 | |
| Empirical formula | C11 H10 F3 I O3 | |
| Formula weight | 374.09 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/n | |
| Unit cell dimensions | a = 5.7763(13) Å | α= 90°. |
| | b = 16.159(4) Å | β= 95.205(4)°. |
| | c = 13.284(3) Å | γ = 90°. |
| Volume | 1234.8(5) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 2.012 $Mg/m^3$ | |
| Absorption coefficient | 2.629 $mm^{-1}$ | |
| F(000) | 720 | |
| Crystal size | 0.36 x 0.30 x 0.07 $mm^3$ | |
| Theta range for data collection | 1.99 to 26.00°. | |
| Index ranges | -7<=h<=7, -19<=k<=19, -16<=l<=16 | |
| Reflections collected | 9448 | |
| Independent reflections | 2422 [R(int) = 0.0507] | |
| Completeness to theta = 26.00° | 99.8 % | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 0.928 and 0.554 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2422 / 0 / 165 | |
| Goodness-of-fit on $F^2$ | 1.076 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0375, wR2 = 0.0918 | |
| R indices (all data) | R1 = 0.0403, wR2 = 0.0938 | |
| Largest diff. peak and hole | 2.449 and -0.860 $e.Å^{-3}$ | |

**A3 Crystal Data and Structure Refinement for 168**

| | | |
|---|---|---|
| Identification code | 12094 | |
| Empirical formula | C16 H17 I O4 S | |
| Formula weight | 432.26 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 8.2948(18) Å | α= 90°. |
| | b = 10.663(2) Å | β= 101.233(4)°. |
| | c = 18.336(4) Å | γ = 90°. |
| Volume | 1590.7(6) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.805 $Mg/m^3$ | |
| Absorption coefficient | 2.159 $mm^{-1}$ | |
| F(000) | 856 | |
| Crystal size | 0.34 x 0.21 x 0.13 $mm^3$ | |
| Theta range for data collection | 2.22 to 26.00°. | |
| Index ranges | -10<=h<=10, -13<=k<=13, -22<=l<=22 | |
| Reflections collected | 12066 | |
| Independent reflections | 3127 [R(int) = 0.0433] | |
| Completeness to theta = 26.00° | 99.8 % | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 0.928 and 0.682 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3127 / 0 / 202 | |
| Goodness-of-fit on $F^2$ | 1.057 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0253, wR2 = 0.0608 | |
| R indices (all data) | R1 = 0.0278, wR2 = 0.0620 | |
| Largest diff. peak and hole | 0.705 and -0.504 $e.Å^{-3}$ | |

**A4 Crystal Data and Structure Refinement for 220**

| | | |
|---|---|---|
| Identification code | 14028 | |
| Empirical formula | C20 H21 I O4 | |
| Formula weight | 452.27 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/n | |
| Unit cell dimensions | a = 15.062(3) Å | α= 90°. |
| | b = 8.1555(15) Å | β= 104.717(4)°. |
| | c = 15.606(3) Å | γ = 90°. |
| Volume | 1854.1(6) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.620 $Mg/m^3$ | |
| Absorption coefficient | 1.748 $mm^{-1}$ | |
| F(000) | 904 | |
| Crystal size | 0.16 x 0.11 x 0.04 $mm^3$ | |
| Theta range for data collection | 1.68 to 26.00°. | |
| Index ranges | -18<=h<=18, -10<=k<=10, -19<=l<=18 | |
| Reflections collected | 14049 | |
| Independent reflections | 3635 [R(int) = 0.1203] | |
| Completeness to theta = 26.00° | 99.9 % | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 0.928 and 0.673 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3635 / 0 / 229 | |
| Goodness-of-fit on $F^2$ | 0.869 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0497, wR2 = 0.0763 | |
| R indices (all data) | R1 = 0.0841, wR2 = 0.0841 | |
| Largest diff. peak and hole | 0.737 and -1.008 $e.Å^{-3}$ | |

**A5 Crystal Data and Structure Refinement for 226**

| | | |
|---|---|---|
| Identification code | 14118 | |
| Empirical formula | C24 H22 O6 | |
| Formula weight | 406.42 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 7.9106(16) Å | γ= 90°. |
| | b = 13.735(3) Å | β= 111.053(4)°. |
| | c = 9.861(2) Å | γ = 90°. |
| Volume | 999.9(4) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.350 $Mg/m^3$ | |
| Absorption coefficient | 0.097 $mm^{-1}$ | |
| F(000) | 428 | |
| Crystal size | 0.31 x 0.22 x 0.10 $mm^3$ | |
| Theta range for data collection | 2.66 to 25.00°. | |
| Index ranges | -9<=h<=9, -16<=k<=16, -11<=l<=11 | |
| Reflections collected | 7098 | |
| Independent reflections | 1760 [R(int) = 0.0568] | |
| Completeness to theta = 25.00° | 100.0 % | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 0.962 and 0.724 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1760 / 0 / 137 | |
| Goodness-of-fit on $F^2$ | 1.036 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0458, wR2 = 0.1039 | |
| R indices (all data) | R1 = 0.0620, wR2 = 0.1103 | |
| Largest diff. peak and hole | 0.270 and -0.181 $e.Å^{-3}$ | |

**A6 Crystal Data and Structure refinement for 301**

| | | |
|---|---|---|
| Identification code | 14034 | |
| Empirical formula | C8 H7 I O3 | |
| Formula weight | 278.04 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | Pbca | |
| Unit cell dimensions | a = 7.9729(14) Å | α= 90°. |
| | b = 13.463(2) Å | β= 90°. |
| | c = 15.151(3) Å | γ = 90°. |
| Volume | 1626.3(5) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 2.271 $Mg/m^3$ | |
| Absorption coefficient | 3.898 $mm^{-1}$ | |
| F(000) | 1056 | |
| Crystal size | 0.34 x 0.19 x 0.06 $mm^3$ | |
| Theta range for data collection | 2.69 to 27.00°. | |
| Index ranges | -10<=h<=10, -17<=k<=17, -19<=l<=19 | |
| Reflections collected | 12510 | |
| Independent reflections | 1766 [R(int) = 0.0470] | |
| Completeness to theta = 27.00° | 99.9 % | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 0.894 and 0.627 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1766 / 0 / 110 | |
| Goodness-of-fit on $F^2$ | 1.075 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0233, wR2 = 0.0493 | |
| R indices (all data) | R1 = 0.0267, wR2 = 0.0507 | |
| Largest diff. peak and hole | 0.596 and -0.579 $e.Å^{-3}$ | |

**A7 Publications from this Thesis**

1. G. C. Geary, E. G. Hope, K. Singh and A. M. Stuart, *Chem. Commun.*, 2013, **49**, 9263-9265.
2. G. C. Geary, E. G. Hope, K. Singh and A. M. Stuart, *RSC Adv.*, 2015, **5**, 16501-16506.
3. G. Geary, E. G. Hope and A. M. Stuart, *Angew. Chem., Int. Ed.*, 2015, **54**, 14911-14914.