

New Fluorination Methodology using a Hypervalent Fluoroiodane Reagent

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By

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List of abbreviations

α	Alpha
Ar	Aryl
ASAP	Atmospheric solids analysis probe
β	Beta
br	Broad peak
γ	Gamma
δ	Delta
DCM	Dichloromethane
DMF	Dimethylformamide
ESI	Electrospray Ionisation
Et ₂ O	Diethyl ether
MeOH	Methanol
<i>m</i> -CPBA	<i>meta</i> -Chloroperoxybenzoic acid
MS	Mass spectrometry
mp	Melting point
<i>m/z</i>	Mass / charge
NMR	Nuclear magnetic resonance
OAc	acetate
ppm	Parts per million
RT	Room temperature
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TfOH	Triflic acid
TREAT-HF	Triethylaminetris(hydrogenfluoride)

Abstract

In medicinal chemistry the incorporation of fluorine into the organic framework continues to be an important strategy for the development of new pharmaceutical products because of the beneficial properties imparted by fluorine such as increased metabolic stability, increased lipophilicity and/or to tune the pharmacokinetic properties.¹ The cyclic hypervalent fluoroiodane reagent **7** was introduced as a new, air and moisture stable, fluorinating reagent in 2013 and it can be prepared from cheap sources of nucleophilic fluoride. The fluoroiodane reagent **7** was used for an efficient transition metal catalysed fluorocyclisation of unsaturated carboxylic acids to prepare γ -lactones, containing tertiary alkyl fluorides. The reaction integrated a cyclisation, an aryl migration and a fluorination all in one step.

In contrast to the previous work reported in the literature, the metal catalysts (Ag(I), Cu(I) and Zn(II)) were used in catalytic rather than stoichiometric amounts in chapter 2 and the reactions were performed at room temperature for 4 hours generating the desired fluorinated γ -lactones in good yields. The scope of the unsaturated carboxylic acids was expanded from *geminal*-disubstituted alkenes to monosubstituted, *trans*-disubstituted and trisubstituted alkenes. Furthermore, it was discovered that the fluoroiodane reagent **7** can be activated by hydrogen bonding to hexafluoroisopropanol and so, metal-free fluorocyclisations of unsaturated carboxylic acids were developed. The efficiency of these new reaction conditions was demonstrated by the synthesis of eight fluorinated lactones in moderate to high yields.

In chapter 3, a new fluoroiodane reagent **91** containing an additional phenyl sidearm was synthesised and used to prepare a series of unsymmetrical diaryliodonium salts from Grignard reagents and arylboronic acids. The unsymmetrical diaryliodonium salts were fluorinated in the presence and absence of Cu(II) catalyst, generating fluorinated aromatics.

Finally, the novel fluoroiodane reagent **91** was reacted with terminal and internal alkyne substrates to form four β -fluorovinylidonium salts in good yields. Since the overall aim of chapter 4 was to develop new methodology for the synthesis of fluoroalkenes, a preliminary fluorination of (*E*)-(2-fluorooct-1-en-1-yl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate was attempted in the presence of a Cu(II) catalyst.

Chapter 1

Introduction

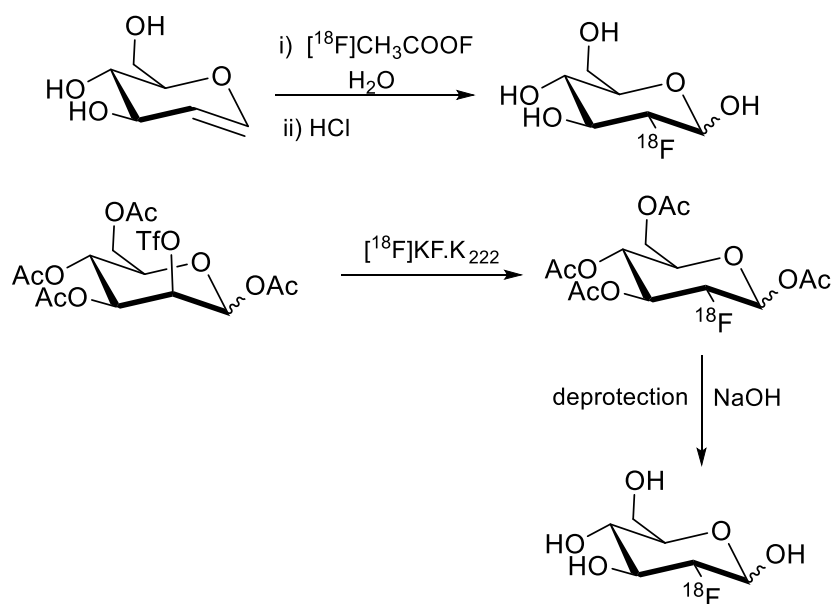


1. Introduction

1.1 Organofluorine chemistry

The first example of an organofluorine compound dates back to 1862 when Borodin, mostly famous for several symphonic poems and rather less for chemical investigations, carried out a nucleophilic displacement of chlorine by fluoride in benzoyl chloride using KHF_2 . Moissan later isolated elemental fluorine by electrolysis of a melt mixture of KHF_2 and HF . However, the area of organofluorine chemistry was relatively undeveloped until the early 20th century, mainly due to difficulties in the isolation and the hazardous nature of fluorine compounds. Historical consequences, such as the Manhattan project, where the first large scale synthesis of fluorine was carried out, laid the foundations for various industrial applications widely used nowadays.¹⁻²

Today, organic compounds containing fluorine play a significant role in medicinal chemistry, altering the metabolic stability, protein-ligand interactions and bioavailability.³ Moreover, organofluorine compounds exhibit radiochemical properties, enabling their use in PET scanning. Fluorine-18 ($t_{1/2} = 110$ min) is the most widely used radionuclide in PET because of its favourable physical and nuclear characteristics such as a short half-life which allows sufficient time for multiple labelling reactions and a short positron linear range in tissue (2.3 mm) giving the highest resolution PET images.⁴⁻⁷ The most common ^{18}F -labelling strategy is based on direct incorporation of ^{18}F and is divided into nucleophilic and electrophilic fluorination (**Scheme 1.1**).



Scheme 1.1 Electrophilic and nucleophilic ^{18}F -fluorination for the preparation of $[^{18}\text{F}]$ -fluorodeoxyglucose

1.2 Fluorine in Pharmaceuticals

Fluorine-containing molecules were not known to have any beneficial biological properties until 1943. Sodium monofluoroacetate, the first isolated fluorinated naturally occurring compound, was even found to be poisonous. Later, when naturally occurring compounds started to find their niches in biochemical sciences, O'Hagan demonstrated that the majority of fluorine-containing natural products were derived from a single precursor, 5'-fluoro-5'-deoxyadenosine, synthesised primarily from a single enzyme *fluorinase*.^{11,18} Interestingly, even though being one of the most common elements on Earth, fluorine is rarely found in natural products. This can be best explained by taking into account its physical properties. For example, a biochemical reaction involving enzymatic halogenation, in which hypohalous species are produced, requires vanadium-dependent halogenases and H_2O_2 . Fluorine, having the highest oxidation potential *ca.* -3.06 V cannot enter the reaction. Also, in contrast to other halogens, fluorine with a very high hydration energy *ca.* 117 kcal/mol, behaves as a very poor nucleophile under aqueous biological conditions.¹¹ Finally, knowing that the C-F bond is one of the strongest chemical bonds, the formation of reactive intermediates containing such bonds would be extremely difficult to generate under biological conditions.¹²⁻¹⁸

In drug design fluorine has a direct effect on the pharmacokinetic and pharmacodynamic properties as well as bioavailability. Modulation of lipophilicity can also be effectively done by introducing fluorine. Replacing hydrogen with fluorine on aromatic rings was found to be a very effective strategy for slowing down the oxidative metabolic step of a given drug by cytochrome P450 monooxygenases. Also, due to its electron withdrawing properties, fluorine directly affects the reaction rates and the stability of the intermediates.¹⁴ The number of fluorinated drugs within the drug market has now increased to *ca.* 25 %, whereas in the 1970's it only constituted 4 %. Lipitor, being amongst the top selling drugs globally with a revenue of \$5.9 billion, was registered in 2008. The antidepressant Prozac and the antibacterial agent Ciprobay have also been included in the top-selling list,¹⁴⁻¹⁷ showing that the importance of fluorine in pharmaceuticals is uncontested (**Figure 1.1**).

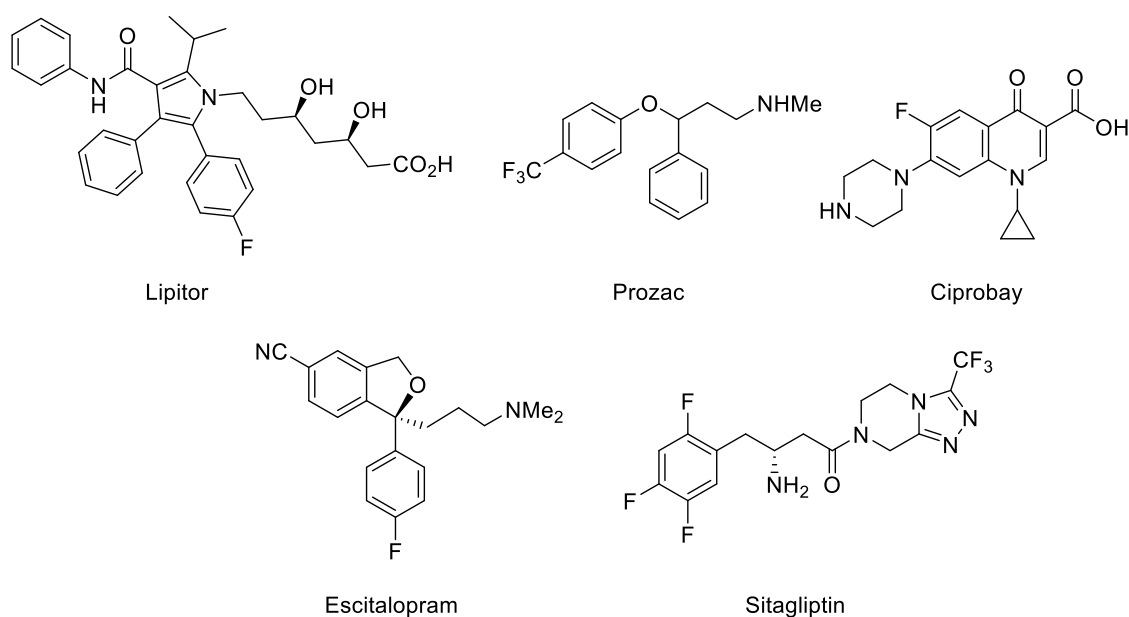


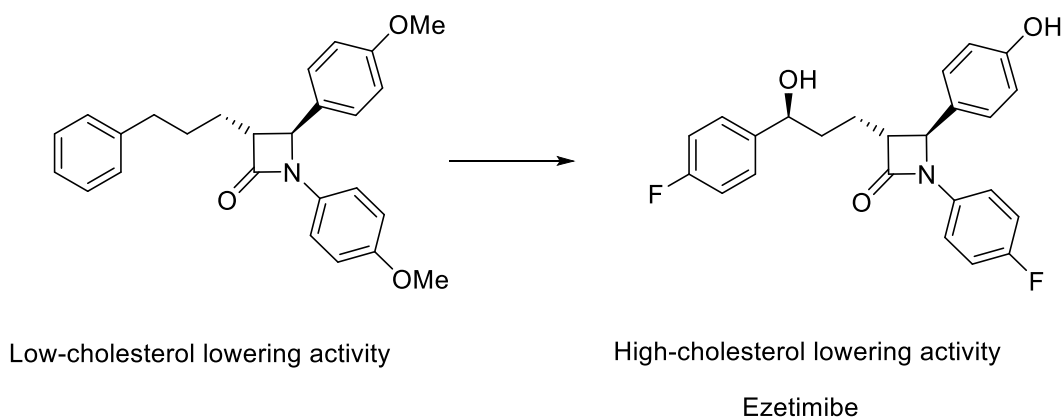
Figure 1.1 Fluorinated drugs

The beneficial properties related to fluorine substitution, such as increased blood brain barrier permeability due to changes in lipophilicity or enhanced binding to target molecules are especially important in central nervous system active drugs.⁷ Escitalopram (sold as Lexapro) was approved by the FDA to treat anxiety including panic and obsessive-compulsive disorders. Existing in the (*S*)-configuration and having a *p*-fluoro

substituent on the aromatic ring, the drug has shown a six-fold increase in potency for inhibition in contrast to the racemic drug Citalopram.¹¹

The antidiabetic drug Sitagliptin (*aka* Januvia) was first approved by the FDA in 2006 to treat type-2 diabetes mellitus, reaching a revenue of \$6 billion in 2015. The structural feature of Sitagliptin is the trifluorinated β -amino acid moiety linked to a trifluoromethyl-containing triazolopyrazine. Using X-ray crystallography, it was found that the 2,4,5-trifluorophenyl ring fits better in the active site than less fluorinated aromatic rings. The trifluoromethyl group in the triazole ring was also proved to be important for increased activities due to electrostatic interactions. Experimentally, it was demonstrated that the removal of the CF_3 group resulted in a 4-fold decrease in the inhibition activity. Interestingly, bulkier groups such as CF_3CF_2 were less effective.¹¹⁻¹⁴

An effective inhibitor of intestinal cholesterol uptake for the treatment of hypercholesterolaemia has been developed successfully. Ezetimibe has shown a much more potent reduction of high levels of cholesterol than statins alone. The insertion of fluorine due to its small steric demand and ability to deactivate P450-mediated aromatic hydroxylation blocked the sites in the drug molecule susceptible to metabolism.^{10,18}



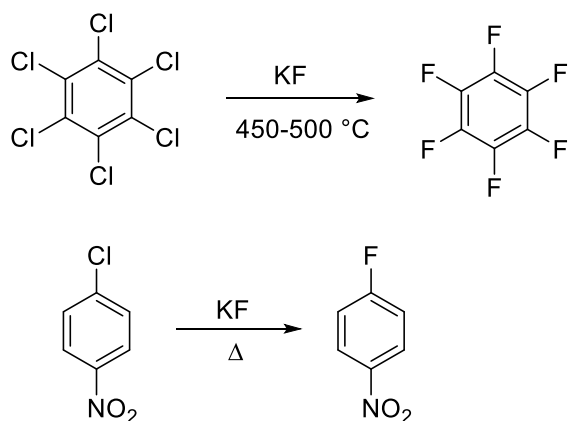
Scheme 1.2 *Drugs affecting the cardiovascular system*

1.3 Fluorination of Organic Molecules

1.3.1 Nucleophilic Fluorination

The introduction of fluorine into organic molecules by nucleophilic fluorination to form the C-F bond, the strongest carbon-heteroatom single bond known, is quite challenging. This can be attributed to high kinetic barriers derived from the high electronegativity of fluorine. The ability to form strong fluorine-hydrogen bonds tends to reduce its nucleophilicity and increase its basicity and side reactions.¹⁹⁻²⁰

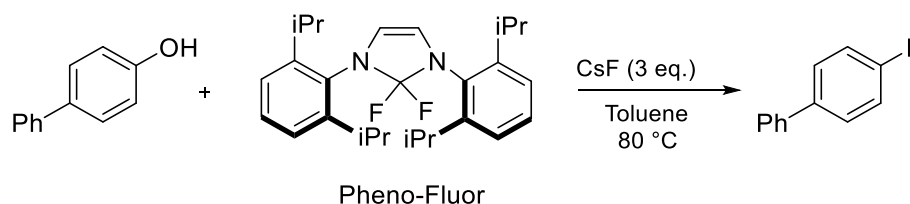
Most commonly, nucleophilic fluorination is achieved using alkali-metal fluorides, mainly due to their low cost, compared to electrophilic fluorinating reagents. However, when used alone, alkali-metal fluorides are rather weak nucleophiles being poorly soluble in organic solvents due to their strong lattice energy. However, in polar aprotic solvents, alkali-metal fluorides retain their nucleophilicity, simply by not forming any hydrogen bonds. The use of 18-crown-6 or other crown ethers can also increase the poor solubility of fluoride salts, leading to an increase in reactivity.¹⁹



Scheme 1.3 *Halex fluorination*

The Halex process,²⁰ developed in 1936 in which the chloride in 1-chloro-2,4-dinitrobenzene was exchanged with fluoride using anhydrous KF and later fluorodemetalation using toxic organothallium(III) sources were the very first examples of direct nucleophilic fluorination. The process is still technically most relevant, especially applicable in the preparation of specifically fluorinated aromatic compounds. Aromatic starting materials with electron withdrawing substituents, for example halogens or, sometimes, nitro groups are treated at moderate to high temperatures with inorganic fluoride sources to exchange these groups nucleophilically by fluorine (**Scheme 1.3**).²¹

Whilst the fluorination of simple aryl fluorides has been fully investigated, the preparation of functionalised fluoroarenes is still quite challenging. A palladium-catalysed nucleophilic fluorination using aryl triflates and a silver-catalysed fluorination of aryl stannanes were reported by Buchwald.²² Both methods lack practicality, either requiring anhydrous conditions, giving mixtures of constitutional isomers or involving the synthesis and use of toxic aryl stannanes. In 2011 Ritter developed a relatively simple fluorination method using Pheno-Fluor and caesium fluoride.²³ This method is very efficient for the fluorination of electron-poor, -neutral and -rich phenols (**Scheme 1.4**).



Scheme 1.4 Deoxyfluorination using Pheno-Fluor

Diethylaminosulfur trifluoride (DAST) has been commonly used for the fluorination of oxygen and sulphur-containing substrates. The reagent is, however, moisture sensitive and highly explosive. More recently, the Deoxo-Fluor was developed and it is considered a safer and thermally more stable alternative to DAST. However, upon decomposition Deoxo-Fluor generates HF. The group of nucleophilic fluorinating reagents termed Xtal-Fluor are much less moisture sensitive, crystalline, non-explosive and have better selectivity in contrast to DAST or Deoxo-Fluor (**Figure 1.2**).¹⁹⁻²³

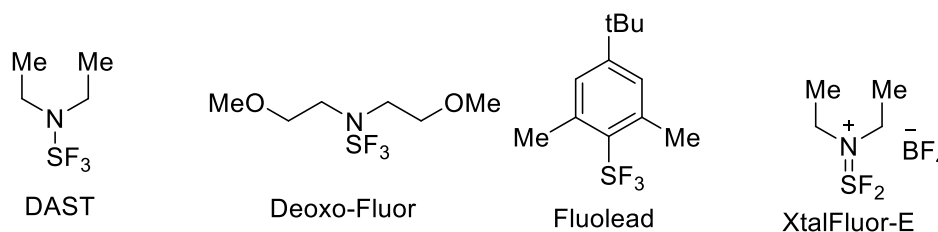


Figure 1.2 Deoxyfluorination reagents

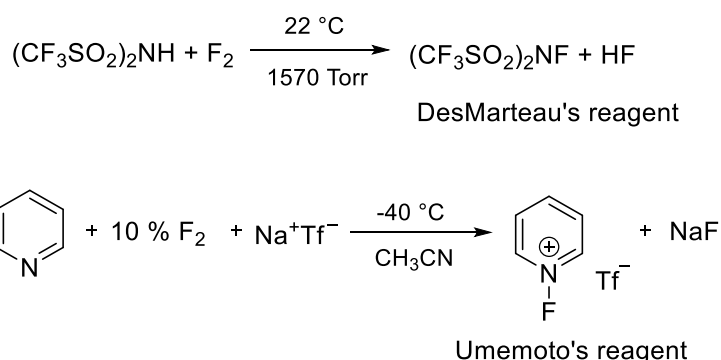
A cost effective nucleophilic fluorinating strategy using aqueous-HF and triethylamine-HF (TREAT-HF) can also be effectively used to fluorinate various substrates. However, aqueous HF is extremely dangerous and highly corrosive. Such

drawbacks limit its applications mainly due to safety reasons, but nevertheless, such reagents are still widely used in industry for the preparation of fluoropolymers such as PTFE or PFA which were developed by DuPont.²⁴

1.3.2 Electrophilic Fluorination

Even though the nucleophilic fluorination sources are much more cost effective and readily available, they cannot fluorinate electron rich substrates, therefore, the electrophilic fluorination strategy has been developed. The early electrophilic fluorinating reagents such as hypofluorites, perchloryl fluorides and fluorine gas were challenging to use, mainly due to their high reactivity. Xenon difluoride was developed as a more stable alternative, but it was still not very functional group tolerant and not very economical for large scale synthesis. The Fluoraza (NF) reagents have emerged as generally safer and easier to handle sources of electrophilic fluorine, however, they are still prepared from fluorine. Generally, NF reagents are either neutral R_2NF or quaternary ammonium salts $[R_3N^+F] X^-$. The R_2N^- and $R_3N^+ F$ fragments are chosen to be good leaving groups, promoting the bound fluorine to react with nucleophiles.¹⁹⁻²²

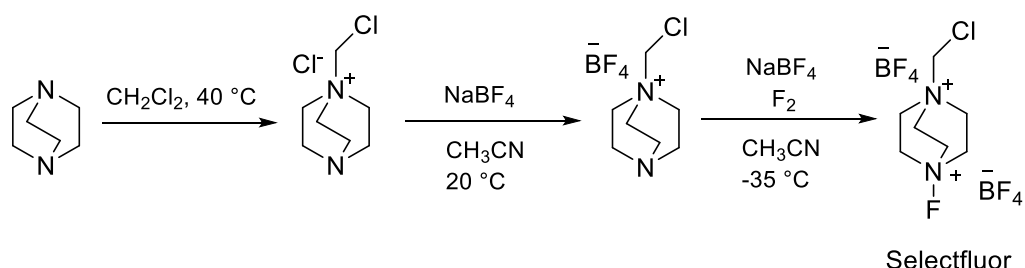
One of the first examples for the preparation of NF reagents was shown by DesMarteau²⁵ using elemental fluorine and releasing HF. Later, Umemoto²⁶ synthesised *N*-fluoropyridinium triflate using an amine precursor in the presence of an alkali metal salt (**Scheme 1.5**).



Scheme 1.5 Early examples of NF reagents

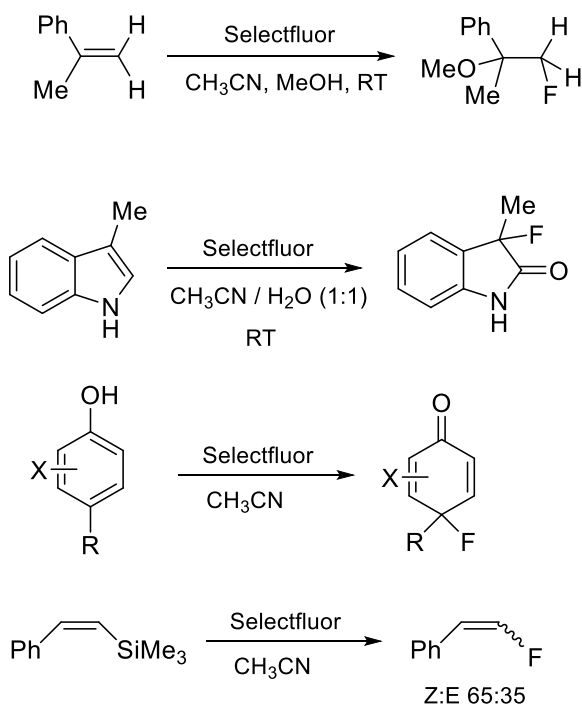
Since the discovery of Selectfluor, it quickly became one of the most popular reagents for the electrophilic fluorination of organic compounds. Being relatively harmless, it is widely used at the academic laboratory level as well as in industry.

Selectfluor is soluble in polar organic solvents, thermally stable (up to 195 °C) and is a crystalline material. The preparation of Selectfluor, which is produced in multiton quantities per year, was designed to be simple, flexible, and efficient (**Scheme 1.6**).^{26,27}



Scheme 1.6 *Synthesis of Selectfluor*

Selectfluor can be used successfully in the fluorinations of electron-rich carbon centres including sulphides, aromatic compounds, alkenes and indoles (**Scheme 1.7**). As reported by Wong, Selectfluor can also act as an excellent deprotection reagent in tetrahydropyranyl due to its Lewis acidity and can even be used as a substitute to toxic mercury salts in the deprotection of dithianes.²⁷



Scheme 1.7 *Fluorination reactions using Selectfluor*

A milder and no-less popular electrophilic fluorinating reagent than Selectfluor, NFSI (**Figure 1.3**) has been widely used for the fluorination of metal enolates, ethers, aromatics and silyl enol ethers. Moreover, NFSI is now quite successful not only as an electrophilic fluorinating reagent, but also as an oxidant for organometallic intermediates to promote reductive elimination through high-oxidation state transition metals.²³

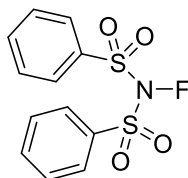


Figure 1.3 NFSI reagent

Despite their high efficiency in electrophilic fluorination, Selectfluor and NFSI still suffer from drawbacks such as their cost-ineffective synthesis strategy, involving the use of elemental fluorine. Because of its highly polar nature, Selectfluor is only soluble in solvents with high polarity index.^{19-22, 24}

1.4 Hypervalent Iodine Reagents

Since the development of hypervalent iodine compounds at the beginning of the 21st century, their non-toxic and mild reactivity patterns have received considerable attention.²⁹⁻³¹ Their chemical properties resemble those of transition metal derivatives, including mercury(II), thallium(III) and chromium(VI) without causing the environmentally-associated problems.^{29,34}

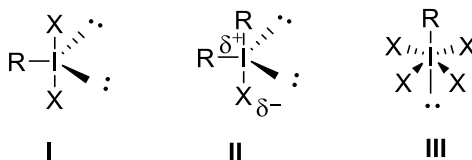


Figure 1.4 Common classes of hypervalent iodine compounds

Hypervalent iodine compounds belong to two general structural types. The iodine(III) compounds **I** and **II** are named λ_3 -iodanes whilst the iodine(V) compound **III** is a λ_5 -iodanes. The λ_3 -iodane has a total of 10 electrons and is generally described as a

distorted trigonal bipyramid with two heteroatom ligands (X) occupying the apical positions. The least electronegative, generally an aryl group, and two lone pairs of electrons reside in equatorial positions.³¹

Iodonium salts **II**, due to their highly electron-deficient nature and excellent leaving group ability, serve as versatile arylating agents with a variety of nucleophiles. They have similar pseudo trigonal bipyramidal geometry with two carbon ligands (R_2IX).³¹⁻³³

Iodine(III) compounds are electrophilic at iodine which is best explained by considering MO theory. The hypervalent bonding model in λ_3 -iodanes uses the non-hybridised 5p orbital of iodine in the linear X-I-X bond. This gives a linear 3-center-4-electron (3c-4e) bond which is longer, highly polarised and weaker than a regular covalent bond.²⁹⁻³³

In contrast to λ_3 -iodanes, λ_5 -iodanes have a distorted octahedral structure in which the organic R group and the lone pair of electrons are in the apical positions and four heteroatom ligands (X) reside in the equatorial positions. The apical group R is connected to iodine by a normal covalent bond using a 5sp-hybridised orbital whilst two 3c-4e bonds accommodate the heteroatom ligands (X).^{29,32-33,35}

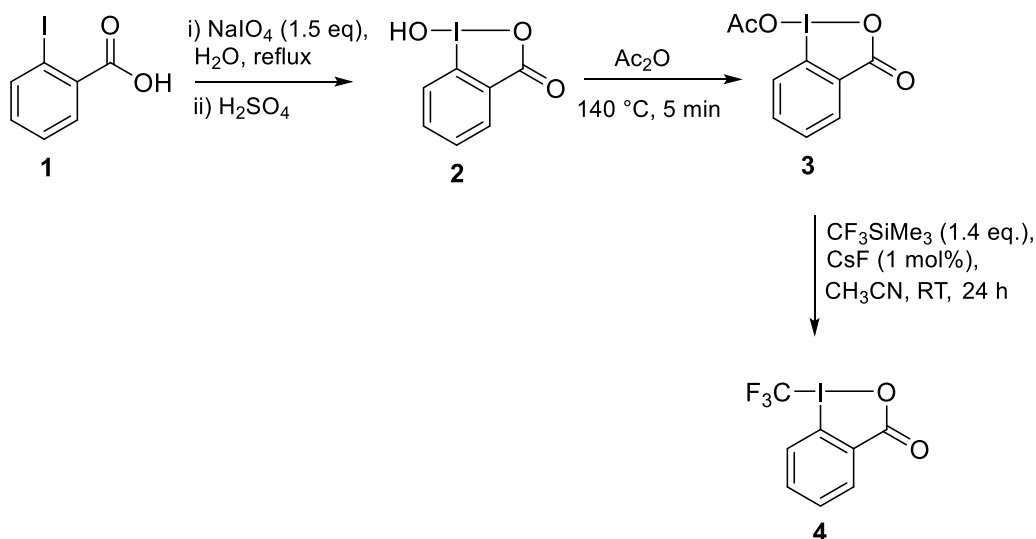
Iodine(III) compounds with two heteroatom ligands such as (diacetoxyiodo)benzene (PIDA) or iodosylbenzene are employed in oxidations of alcohols and alkenes, as well as in the α -functionalisation of carbonyl compounds. Iodine(V) reagents, such as Dess-Martin periodinane and 2-iodoxybenzoic acid (IBX) are used as mild oxidants of alcohols.²⁹

1.5 Electrophilic trifluoromethylation using hypervalent iodine compounds

1.5.1 Preparation of Togni's reagent

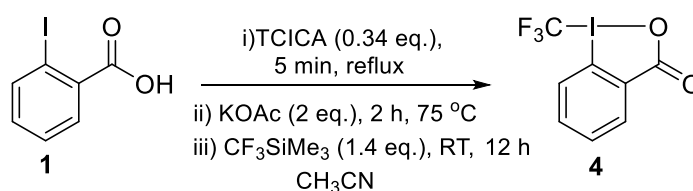
Since the development of a new class of hypervalent iodine compounds in 2006 by Togni,³⁶ their applications in organic synthesis has been undisputed. The original synthesis of **4** (**Scheme 1.8**) started from 2-iodobenzoic acid **1** which was reacted with sodium metaperiodate. A suspension of hydroxyiodobenzodioxolone **2** was then acetylated in hot, neat acetic anhydride. After cooling the solution to -20 °C, the intermediate **3** was obtained as a crystalline material which had to be dried thoroughly,

but this was a time consuming process, and limited its preparation on an industrial scale. In the last step of the synthesis, dry **3** was suspended in acetonitrile with the Ruppert-Prakash reagent (TMSCF_3) and 1 mol % of caesium fluoride.



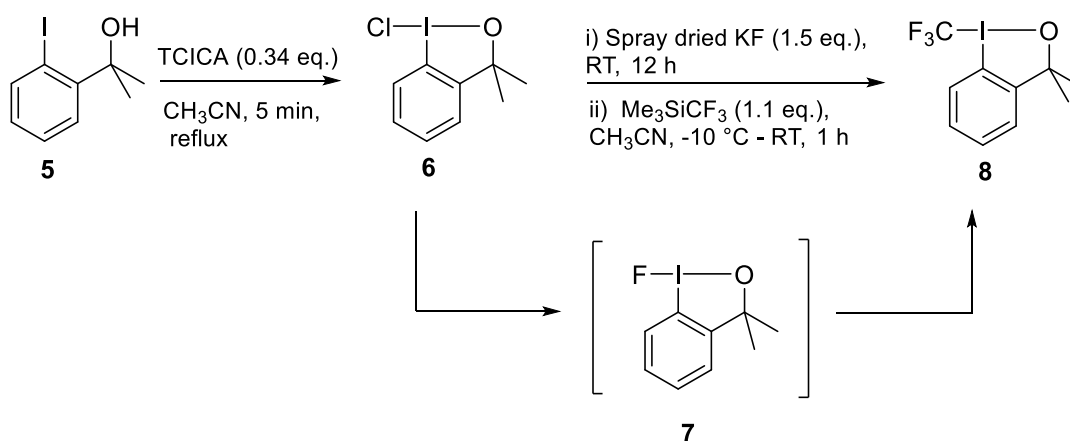
Scheme 1.8 *Synthesis of Togni's reagent 4*

The cost-effective, one-pot synthesis of **4** outlined in **Scheme 1.9** proposed more than a decade ago, found a niche in industry using the cheap oxidant, trichloroisocyanuric acid (TCICA).³⁶



Scheme 1.9 *Improved synthesis of Togni's reagent 4*

An alternative trifluoromethylating reagent based on an alcohol rather than the acid backbone was also prepared by Togni's group, using fluoroiodane **7** and trichloroisocyanuric acid, generating the trifluoromethyliodane (**Scheme 1.10**).³⁶⁻³⁷

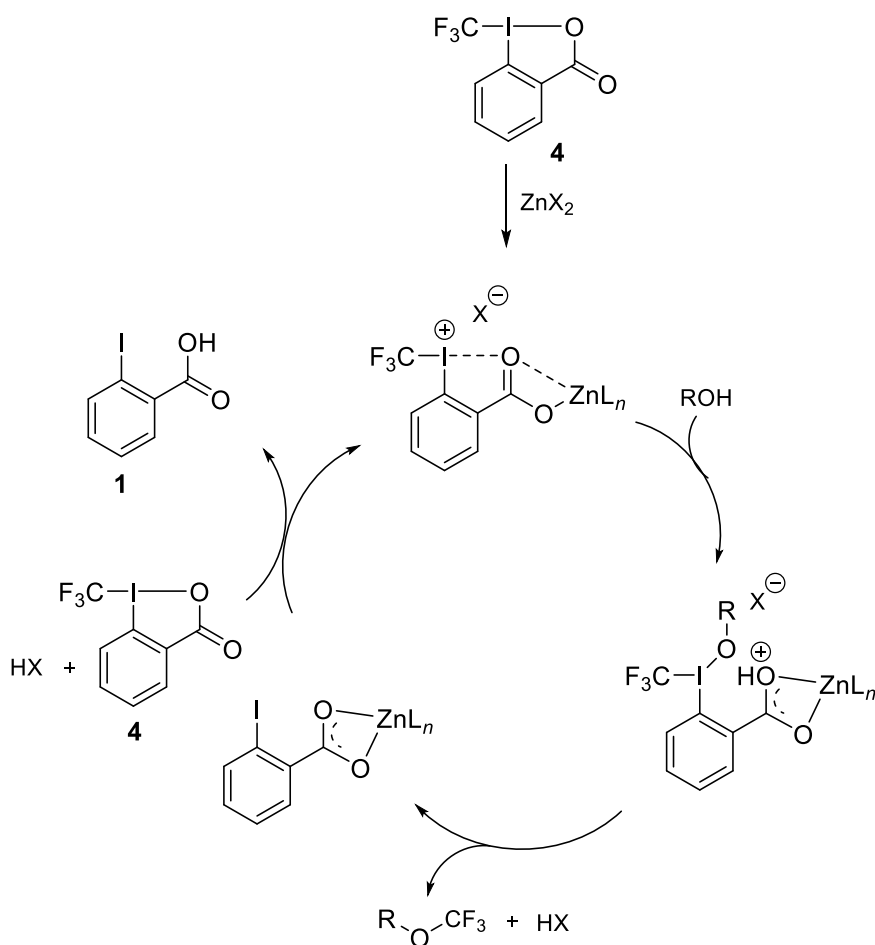


Scheme 1.10 *Synthesis of Togni's alcohol reagent 8*

The general applications of Togni's reagents have expanded considerably since their development 10 years ago. The trifluoromethylation of soft phosphorus-, sulphur- and carbon nucleophiles such as phosphines, thiols and β -ketoesters proved to be very efficient. Substrates with enolizable carbon centres were found to be good candidates for the stereoselective introduction of the CF_3 group, including enantioselective trifluoromethylation of cyclic β -keto esters or α -trifluoromethylation of aldehydes.³⁷

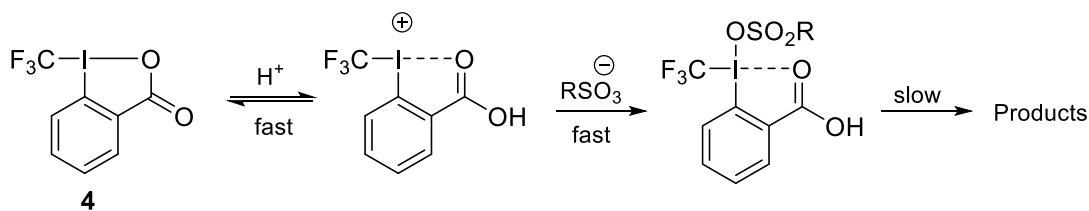
1.5.2 Mechanism of Togni's Reagents

Earlier reports based on the activation of Togni's reagent hypothesised that the mode of action of the trifluoromethylating reagent is based on the weakening of the I-O bond which promotes the release of the CF_3 unit in the presence of either Lewis or Brønsted acids. In the example of the trifluoromethylation of alcohols under Zn(II) catalysis reported by Togni, the activated complex is formed by reacting reagent **4** with the zinc salt, forming a carboxylate/iodonium complex.³⁷ Upon coordination to the metal, the I-O bond is weakened and the ligand exchange with the alcohol is facilitated. The deprotonation followed by reductive elimination generates the desired trifluoromethylated product (**Scheme 1.11**).



Scheme 1.11 Activation of Togni's reagent **4** by Lewis acids

In the same report the activation of the trifluoromethylating reagent by strong Brønsted acids such as aromatic or aliphatic sulfonic acids was also discussed. The activation was relatively easily monitored as the reaction generated less byproducts making the ^{19}F NMR spectroscopy observations clear. The kinetic experiments showed that the reaction was first-order in both reagent and substrate but independent of the substitution pattern on the sulfonic acid. The mechanism involved a fast protonation-deprotonation of the reagent **4** followed by the formation of a steady-state intermediate. Fast protonation-deprotonation of the carboxyl group weakens the I-O bond liberating the coordination site at the iodine which is occupied by the substrate. In the rate determining step the CF_3 group is transferred to the substrate forming trifluoromethyl sulfonates (**Scheme 1.12**).³⁷⁻³⁸



Scheme 1.12 Earlier predicted activation of Togni's reagent **4** by Brønsted acid

Transition metal-based activation of Togni's reagent **4** has also been widely discussed in the literature, including rhenium-catalysed trifluoromethylation of arenes using MTO (MeReO_3) involving $\cdot\text{CF}_3$ radical species (**Figure 1.5 A**).³⁹

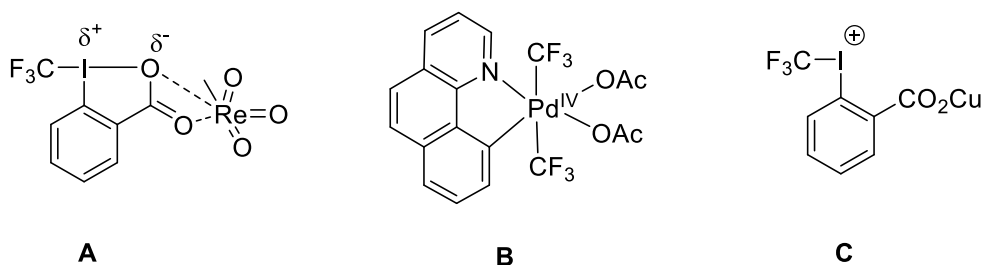


Figure 1.5 Transition metal based activation of Togni's reagent **4**

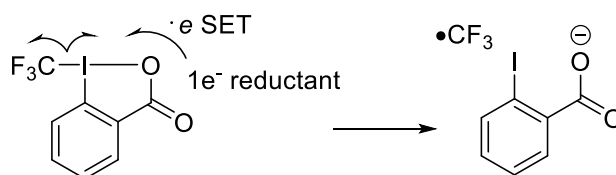
Palladium-mediated trifluoromethylation was reported by Sanford *et al.* from dinuclear palladium(II) complex which upon oxidation with Togni's reagent forms mononuclear palladium(IV)- CF_3 which was found to be an important intermediate in C- CF_3 bond-forming reactions (**Figure 1.5 B**).³⁹

Copper(I) salts have been the most commonly used transition metal-based reagents in the activation of reagent **4** mainly due to their lower price and relatively easy synthesis (**Figure 1.5 C**).³⁹ The plausible mechanism involved the SET/radical process which was tested by adding a radical scavenger TEMPO to the reaction mixture. However, the group led by Togni found that TEMPO itself underwent trifluoromethylation with the reagent **4** without the addition of the substrate. This could explain that the reaction does not necessarily involve the radical-based process, but shows that TEMPO is competing with the nucleophile present in the reaction mixture.³⁷⁻³⁸

More recent studies attempted by Ling *et al.* have provided $\cdot\text{CF}_3$ radical based mechanistic insights on the activation of the trifluoromethylating reagent **4** from DFT

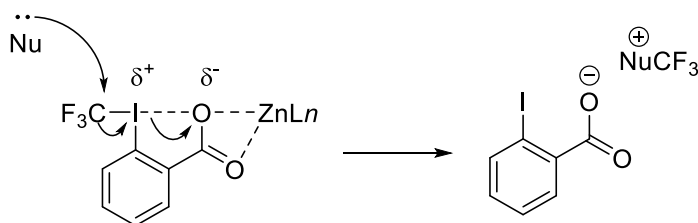
calculations. Two general reaction modes for the activation of the reagent have been found based on $\cdot\text{CF}_3$ acting as a free radical source or CF_3^+ acting as a cation source.⁴¹

The mechanism following the free radical pathway was attempted using terminal olefins as substrates and CuI as the activator which promotes the homo-cleavage of the $\text{F}_3\text{C-I}$ bond via single electron transfer (SET) to produce Cu(II) species and a free radical $\cdot\text{CF}_3$ (**Scheme 1.13**). The attack from the latter to the olefin lead to the formation of the trifluoromethyl alkyl radical intermediate and the Cu(II) species oxidised the alkyl radical to a carbocation intermediate. The final product was generated after deprotonation. Overall, the single electron transfer and the free radical generation proceeded in a concerted manner.



Scheme 1.13 Homo-cleavage releasing free $\cdot\text{CF}_3$ radical

The activation of the Lewis acids discussed earlier is rather more complicated than just the weakening of the I-O bond leading to the release of the CF_3 unit. The DFT calculations suggested that the released trifluoromethyl unit acts as a CF_3^+ cation source (**Scheme 1.14**). In the example provided, the activated reagent **4** was found to undergo an $\text{S}_{\text{N}}2$ type nucleophilic attack at the CF_3 group by pentanol acting as a nucleophile.

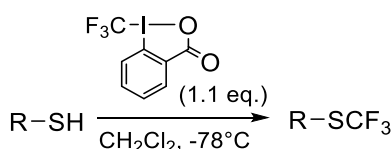


Scheme 1.14 Hetero-cleavage releasing CF_3^+ cation via nucleophilic attack

1.5.3 Applications of Togni's reagent

The electrophilic trifluoromethylating reagents are extremely versatile in synthetic chemistry and tolerate various functional groups. The trifluoromethylation of

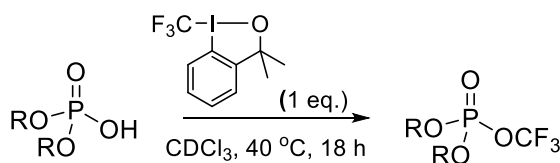
non-carbon-centered nucleophiles, in particular, sulphur-containing nucleophiles was investigated using thiols as substrates. It was observed that the trifluoromethylation of a thiol proceeded very quickly even at low temperatures and no competing side reactions were observed (**Scheme 1.15**). The facile formation of the SCF₃ group was not impeded by the presence of any functional groups including amines, amides, alcohols, carboxylic acids or alkynes.³⁷⁻³⁸



R = aromatic or aliphatic (65-99 %) ¹⁹F NMR yield

Scheme 1.15 Trifluoromethylation of thiols

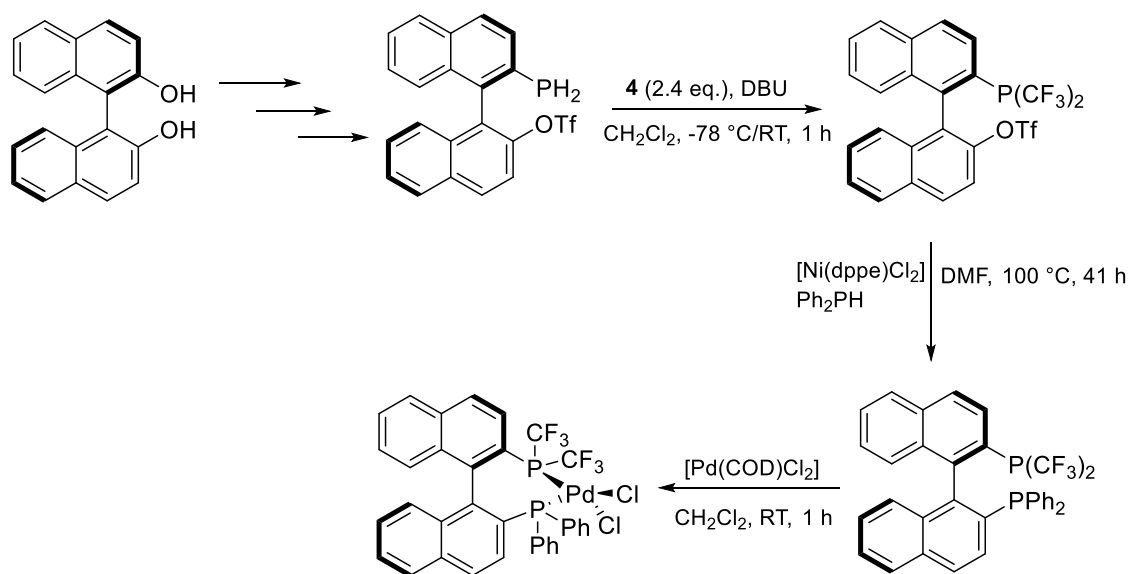
The direct monotrifluoromethylation of primary and secondary phosphates was reported by Togni in 2008 (**Scheme 1.16**).⁴¹



R = alkyl (21-44 %) ¹⁹F NMR yield

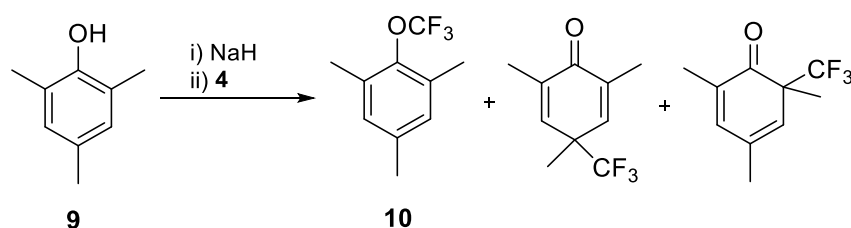
Scheme 1.16 Trifluoromethylation of phosphates

The scope of the reaction is broad with both aryl and alkyl phosphines. The incorporated trifluoromethyl group alters the electronic properties of the phosphorus atom. Also, the steric demand arising from the mono- or bis-trifluoromethylated phosphines in perfluoroalkylphosphorus ligands is becoming interesting in transition metal and organometallic chemistry (**Scheme 1.17**).³⁸



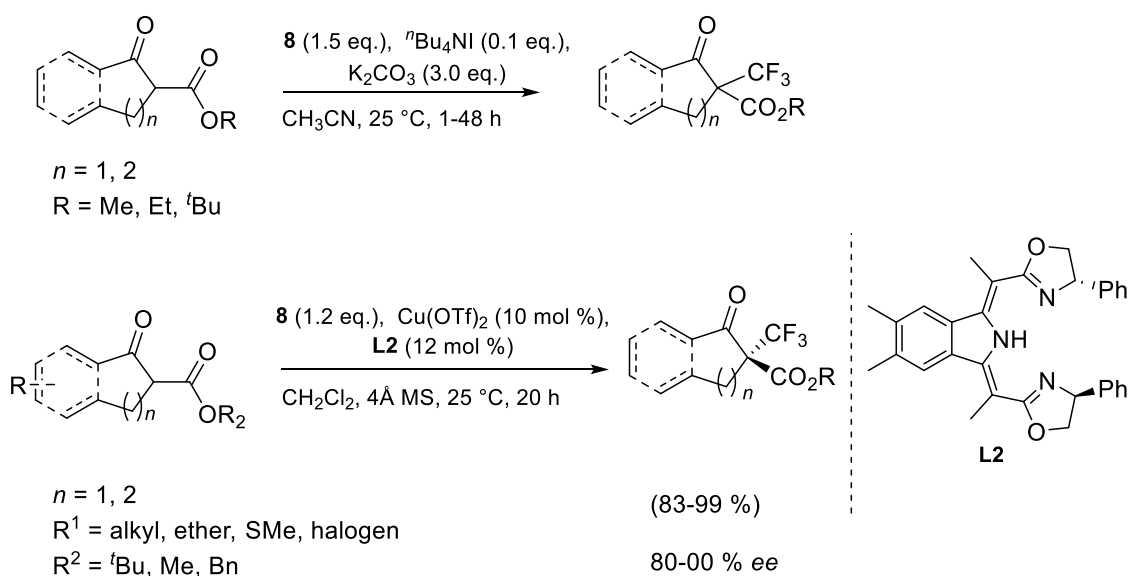
Scheme 1.17 *Synthesis and coordination of BINAP-derived bistrifluoromethylated phosphine*

The introduction of the trifluoromethoxy group by functional group interconversion often requires harsh reaction conditions and hazardous reagents such as CCl_4/HF , CoF_2 , SF_4 or SbF_4 . Togni showed that the attempted O-trifluoromethylation of phenols resulted in only electrophilic aromatic substitution being observed. When 2,4,6-trimethylphenol was used, the desired product was obtained in low yield (**Scheme 1.18**). Further investigations with other aromatic substrates confirmed that blocking the *ortho/para* positions is essential in order to obtain O-trifluoromethylation.⁴³



Scheme 1.18 *O-Trifluoromethylation of 2,4,6-trimethylphenol*

The trifluoromethylation of β -ketoesters using reagent **8** was one of the first examples performed under phase-transfer catalysis. The reaction, however, was only feasible for 5- or 6-membered cyclic substrates and required a large excess of base for deprotonation at the α -position. Later, Gade showed that the enantioselective trifluoromethylation of β -ketoesters could give up to 99 % ee using reagent **8** in combination with a copper(II) catalyst and boxmi ligand (**Scheme 1.19**).⁴⁴

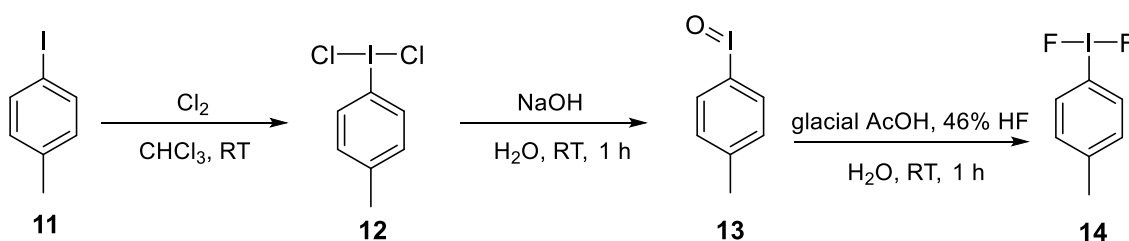


Scheme 1.19 Trifluoromethylation of β -ketoesters

1.6 Electrophilic fluorination using hypervalent iodine compounds

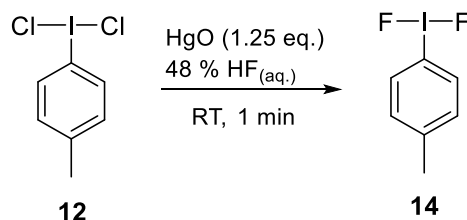
1.6.1 Preparation of difluoroiodoarenes

The very first example of a difluoroiodoarene dates back to the early 20th century. Despite many routes described in the literature, these reagents are not easy to make and require special storage precautions. In 1937 Garvey showed that difluoroiodoarene could be prepared by a three step synthesis from 4-iodotoluene, however, it was light and heat sensitive. The final product was only stable in chloroform for 2 days, which, clearly was not practical. Later, the procedure was improved, using dichloroiodotoluene (**Scheme 1.20**).⁴⁶⁻⁴⁷



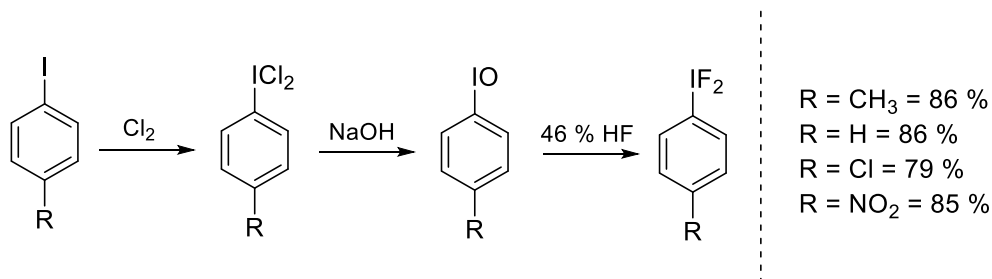
Scheme 1.20 Preparation of difluoroiodotoluene **14**

Alternatively, Carpenter showed a direct conversion of dichloriodotoluene **12** to difluoriodotoluene **14** using HgO and 48 % HF (**Scheme 1.21**).⁴⁷ Although the method was less time-consuming, the major disadvantage of the synthesis was the use of toxic mercury salts.



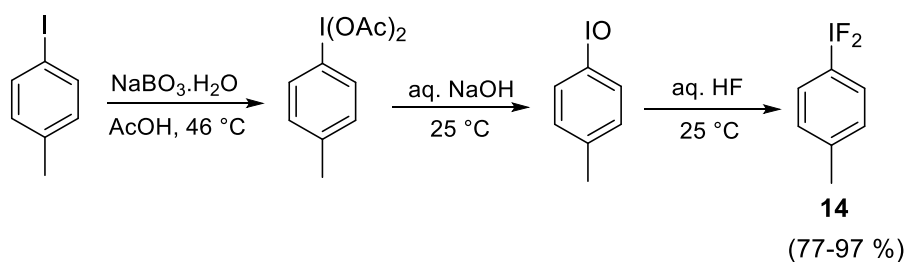
Scheme 1.21 Preparation of difluoriodotoluene from dichloriodotoluene

A new method that does not require the use of elemental fluorine or toxic mercury reagents was highly sought-after. Hara *et al.* reported the synthesis of difluoriodotoluene **14** from iodosyltoluene in the presence of 46 % aqueous hydrofluoric acid. As stated in the report, the improved method generated the final product **14** in a good 67 % overall yield and was applicable to various iodoarene difluoride substrates (**Scheme 1.22**).⁴⁸



Scheme 1.22 Improved synthesis of difluoroiodoarenes

A similar procedure that does not require the use of mercury oxide (HgO) or xenon difluoride (XeF₂) to generate difluoriodotoluene was reported by Wirth.⁴⁹ The three-step synthetic route involved perborate oxidation, hydrolysis with sodium hydroxide and reaction with 40 % aqueous HF. The target difluoriodotoluene was obtained in good yield (77-97 %). Interestingly, attempts to prepare the desired product upon treating (diacetoxyiodo)toluene with nucleophilic fluoride sources (LiF, NaF) were unsuccessful and therefore aqueous HF was used instead (**Scheme 1.23**).⁴⁹



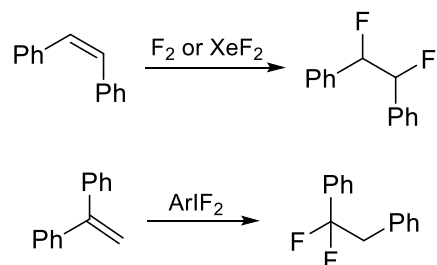
Scheme 1.23 *Synthesis of difluoroiodotoluene*

Reported methods have shown a big improvement in the preparation of difluoroiodoarenes. The elimination of dangerous to use mercury salts, elemental F₂ or chlorine is particularly important for the large scale synthesis. However the use of hydrogen fluoride which is highly corrosive and toxic reagent is undesirable, therefore new synthetic approaches utilising mild reagents are in need.

1.6.2 Reactivity of difluoroiodoarenes

Difluoroiodoarenes have been used as electrophilic fluorinating reagents with a large variety of substrates. In contrast to Selectfluor, the difluoroiodoarenes are particularly attractive fluorinating reagents because of their cheap synthetic preparation, however the use of aqueous HF, as stated above, is hazardous.

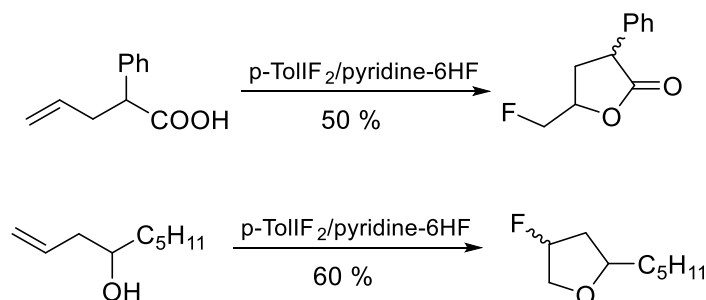
Hara showed that difluoroiodoarenes can fluorinate alkenes. In contrast to elemental fluorine or XeF₂ where simple 1,2-addition was observed, the difluoroiodoarenes gave exclusively *gem*-difluoroproducts in which phenyl migration was observed (**Scheme 1.24**).⁴⁹⁻⁵⁰



Scheme 1.24 *Fluorination of alkenes using difluoroiodoarenes*

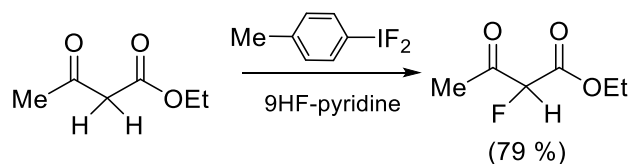
The same group also demonstrated that unsaturated alcohols and carboxylic acids can undergo intramolecular fluorocyclisations with difluoroiodotoluene **14**

(**Scheme 1.25**). The monofluorinated cyclic ethers and lactones were obtained in moderate yields (50 – 60 %).⁵⁰



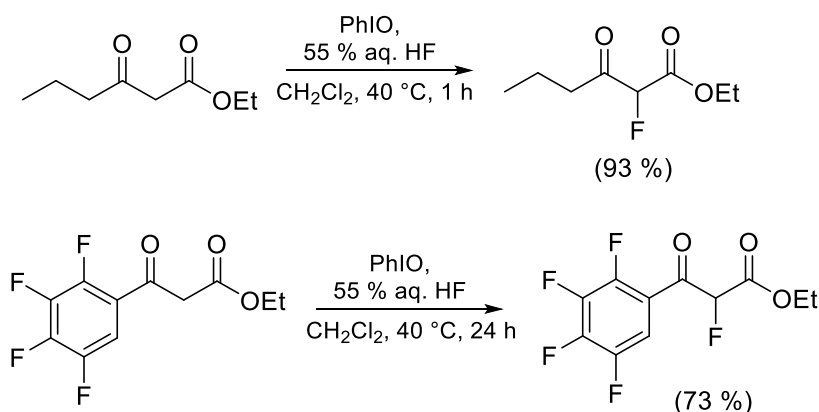
Scheme 1.25 Fluorination of unsaturated alcohols and carboxylic acids using difluoroiodotoluene

The first example of the fluorination of 1,3-dicarbonyl compounds was reported by Hara in 1996.⁵¹ The fluorination of butyl acetoacetate was carried out using difluoroiodoarenes and a variety of amine-HF complexes. Difluoroiodoarene alone showed no reactivity towards the substrate but in the presence of amine-HF complexes, the fluorination took place selectively at the α -position (**Scheme 1.26**).



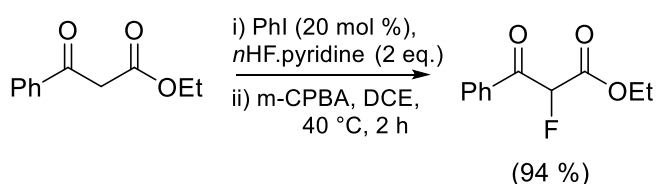
Scheme 1.26 Fluorination of 1,3-ketoesters

Since the preparation of difluoroiodoarenes and the fluorination of 1,3-dicarbonyls required the use of pyridine-HF complexes, a one-pot synthesis was reported by Kitamura in 2011.⁵² It was found that 1,3-ketoesters, 1,3-diketones and 1,3-ketoamides were monofluorinated in good yields using a practical and convenient method (**Scheme 1.27**).



Scheme 1.27 Fluorination of 1,3-dicarbonyls with iodosylbenzene and aq. HF

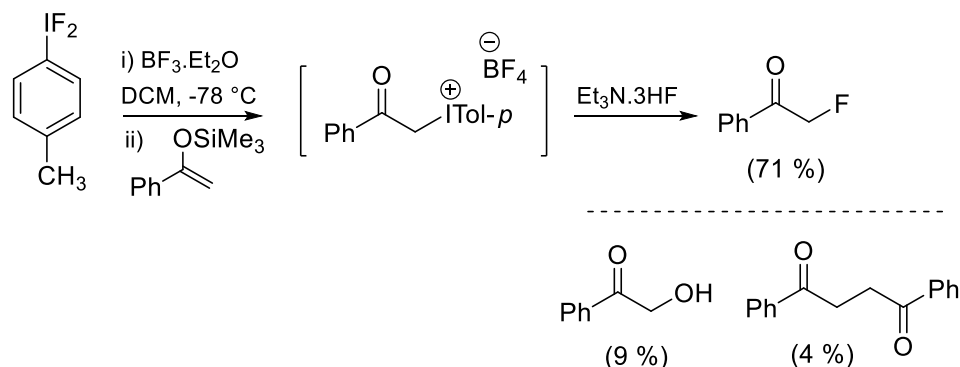
However, a stoichiometric amount of iodosylarene was still required. Even though iodosylarenes are reasonably stable they tend to decompose during long term storage which is particularly important on industrial-scale synthesis. In the fluorination using hydrofluoric acid and iodosylbenzene reagent, the latter was reduced to iodobenzene via (difluoroiodo)benzene and so it was hypothesised whether the resulting iodobenzene could be re-oxidised to iodosylbenzene *in situ* and participate in the fluorination again. The postulation was proved correct by showing that 1,3-dicarbonyl compounds were successfully fluorinated using aqueous HF as a cheap HF source and *m*-CPBA as oxidant (**Scheme 1.28**).⁵³ High catalytic efficiency of the iodoarenes including *o*-iodotoluene, *o*-iodoanisole and *o*-ethyliodobenzene was observed. The catalytic fluorination also reduced the drawbacks caused by the stoichiometric reaction with iodosylarenes, it was cost-effective and suitable for large-scale synthesis.



Scheme 1.28 Catalytic fluorination of 1,3-dicarbonyl compounds

The less reactive monocarbonyl compounds were also successfully fluorinated using difluoroiodotoluene. In the reported example by Hara *et al.*, the reaction between difluoroiodotoluene and silyl enol ethers of various acyclic and cyclic ketones in the presence of BF₃.Et₂O and the fluoride source (Et₃N.3HF, Et₃N.2HF, Et₃N.HF, TBAF, KF) generated the desired monofluorinated compounds in good yields.⁵⁴ It was noticed

that the addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and low reaction temperatures were essential, resulting in the activation of the difluoroiodotoluene. The best yields and minimal generation of byproducts were obtained with either $\text{Et}_3\text{N} \cdot 3\text{HF}$ or $\text{Et}_3\text{N} \cdot 2\text{HF}$ (**Scheme 1.29**). Other fluoride sources such as KF , CsF or TBAF were much less efficient.



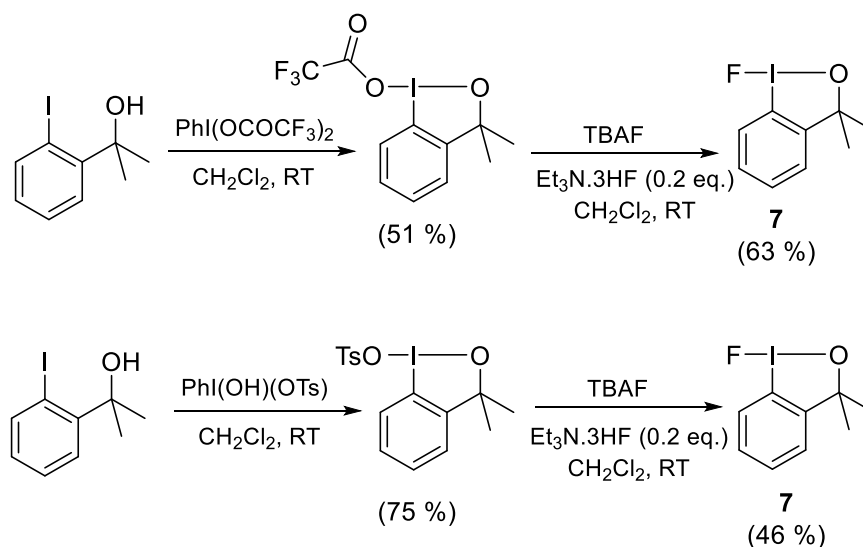
Scheme 1.29 Fluorination of monocarbonyl compounds

Despite many successful applications in electrophilic fluorination and the cost-effective preparation reported to date, the use of difluoroiodoarenes is limited. The major disadvantage of the difluoroiodoarenes is that their preparation requires pyridine-HF or aqueous-HF which cannot be used in normal laboratory glassware. Also, since these reagents are often unstable and moisture sensitive, they are normally prepared *in situ*.

1.7 The Fluoroiodane reagent

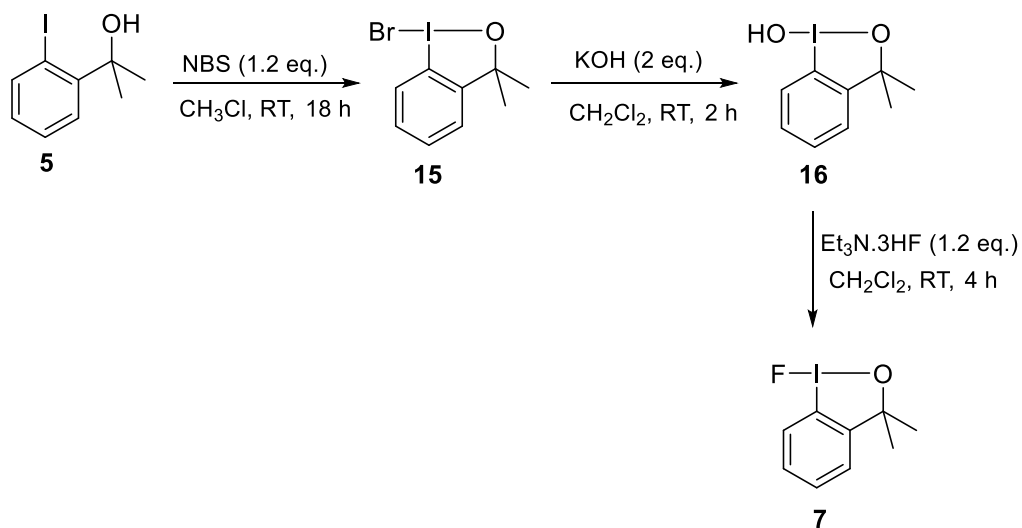
1.7.1 Synthesis of fluoroiodane reagent 7

The synthesis of fluoroiodane reagent **7** was first developed by Legault using Selectfluor in acetonitrile.⁵⁵ A year later the fluoroiodane reagent was prepared by halogen exchange of chloroiodane with spray dried potassium fluoride in acetonitrile.³⁷ Stuart showed that the fluoroiodane reagent could also be prepared using other nucleophilic sources of fluoride rather than KF .⁵⁶ In order to facilitate the nucleophilic displacement onto the hypervalent iodine reagent, a good leaving group, *e.g.* $(\text{CF}_3\text{CO}_2^-)$ was introduced, which was easily replaced by the incoming fluoride anion from TBAF (**Scheme 1.30**).



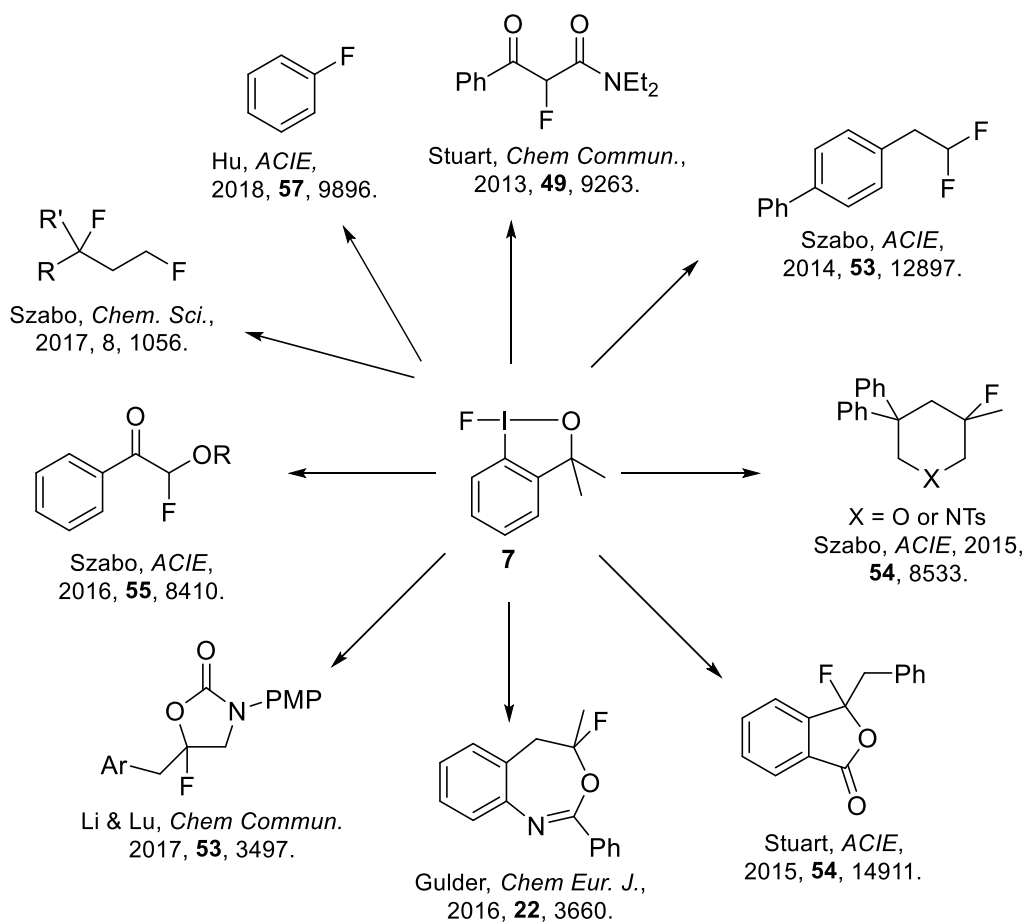
Scheme 1.30 Synthesis of the fluoroiodane reagent using TBAF

Following the same nucleophilic strategy, Stuart showed that the fluorinating reagent could be prepared by an alternative synthesis (**Scheme 1.31**). In the key step the hydroxyiodane **16** was reacted with triethylamine tris(hydrogen fluoride) (TREAT-HF) at room temperature. This method, in contrast to the other methods, is performed under very mild conditions and does not require purifications by column chromatography, making it time and yield efficient.



Scheme 1.31 Synthesis of fluoroiodane **7**

1.7.2 Applications of fluoroiodane reagent **7**



Scheme 1.32 Applications of fluoroiodane reagent **7**

Being relatively easily prepared, easy to handle and store, fluoroiodane reagent **7** has quickly secured its position as a versatile and efficient fluorinating reagent involved in fluorocyclisation reactions, fluorination of alkenes, dicarbonyl compounds and cyclopropanes (**Scheme 1.32**).

The group led by Stuart showed that fluoroiodane reagent **7** can be successfully used in the electrophilic fluorination reactions of 1,3-diketones and 1,3-ketoesters. The reactivity of the fluoriodane as an electrophilic fluorinating reagent was tested with various substrates, giving monofluorinated products with 1,3-diketoesters and difluorinated products with 1,3-diketones (**Table 1.1**).⁵⁷

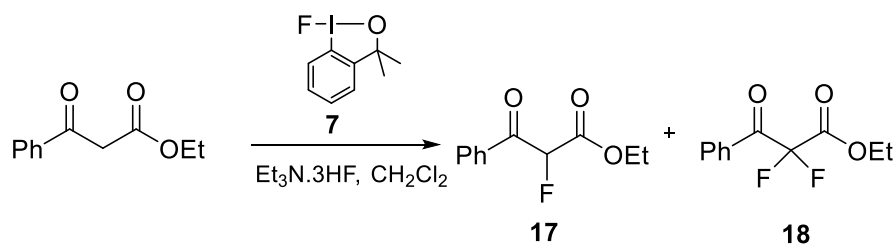
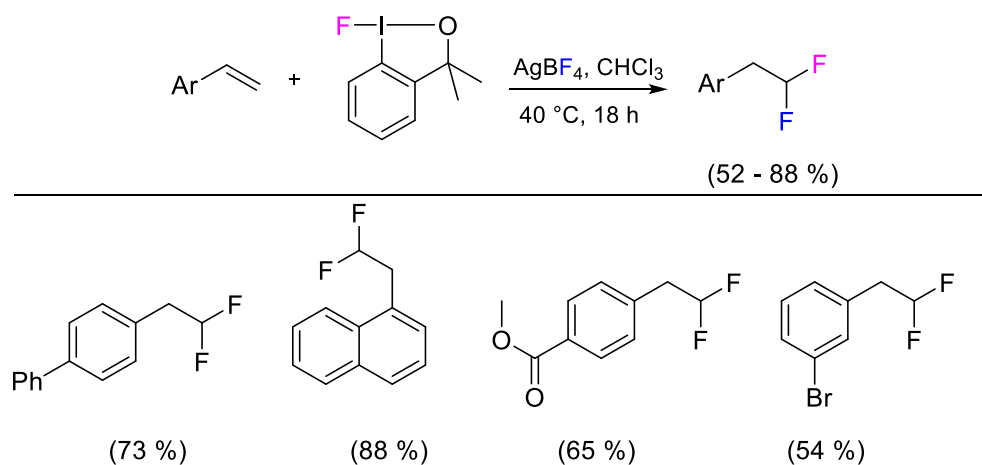


Table 1.1 Fluorination of 1,3-dicarbonyl substrates

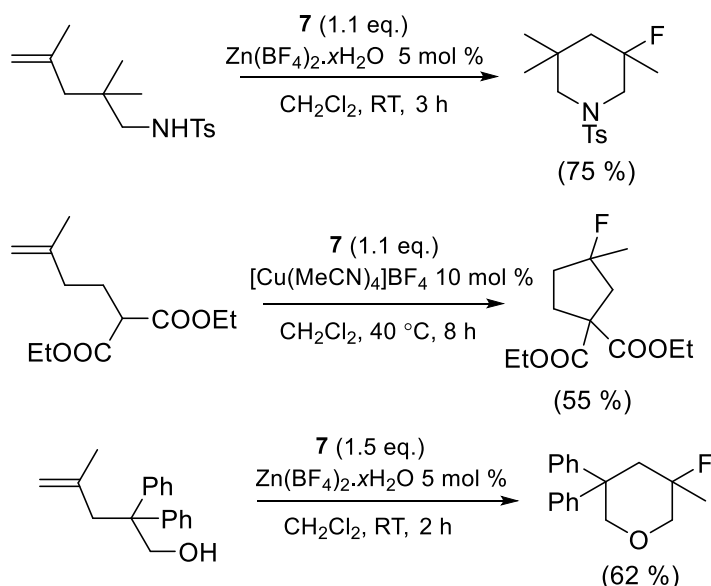
Entry	Substrate	7 (eq.)	T °C	Time (h)	17 (%)	18 (%)
1		2	40	24	89 (63)	6
2		3	60	24	0	100 (71)
3		2	60	168	62 (55)	—
4		2	60	48	100 (55)	—

Szabó investigated the geminal difluorination of styrenes using fluoroiodane reagent **7** and AgBF_4 (**Scheme 1.33**). It was shown that mixing equimolar amounts of various styrene substrates, fluoroiodane **7** and AgBF_4 resulted in difluorinated products under mild reaction conditions. In the geminally difluorinated product it was thought that one of the fluorine atoms was derived from **7** whilst the other one originated from the BF_4^- counterion.⁵⁸



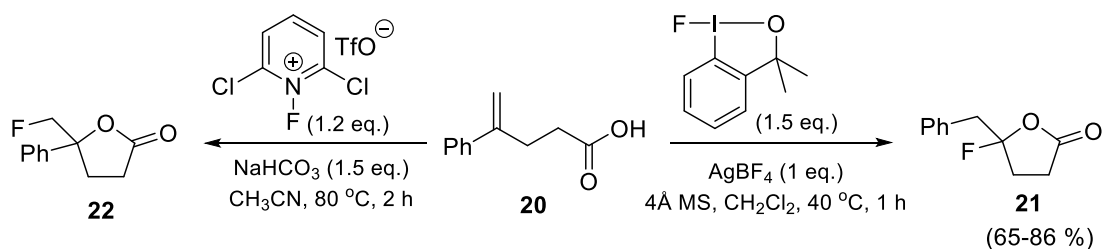
Scheme 1.33 Fluorination of styrenes

Szabó also demonstrated that the fluorinating reagent **7** can efficiently induce fluorocyclisation-based aminofluorinations, oxyfluorinations and carbofluorinations (**Scheme 1.34**).⁵⁹ In the presence of a transition metal catalyst (Zn, Cu, Ag or Pd) which was required to activate fluorinating reagent **7**, a range of functionalised hetero- and carbocyclic compounds containing a tertiary fluorine substituent were obtained.



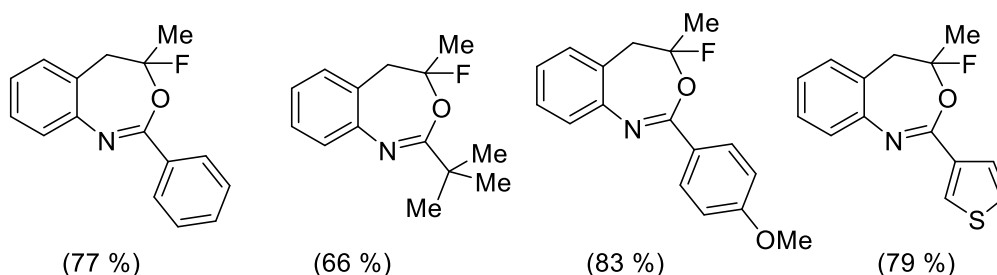
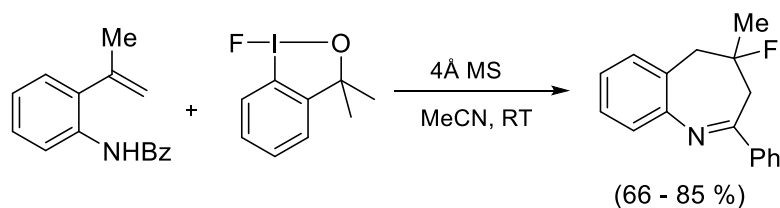
Scheme 1.34 Fluorocyclisation-based amino-, oxy-, and carbo-fluorination reactions

The preparation of γ -lactones by intramolecular fluorocyclisations was investigated by Stuart using unsaturated carboxylic acids and the stable fluoroiodane reagent **7** in combination with AgBF_4 (**Scheme 1.35**).⁶⁰ Interestingly, this method also involved an aryl migration which was not observed in Szabó's reported fluorocyclisations of amines, alcohols and malonates.⁵⁹ In contrast to the fluoraza reagents, where primary alkyl fluorides were formed, this method generated lactones with tertiary alkyl fluorides. Moreover, the transition metal catalyst was not essential in the intramolecular fluorocyclisation reactions. The fluoroiodane **7** was successfully used alone, generating the target products in moderate yields (50-54 %) in just 1 hour.



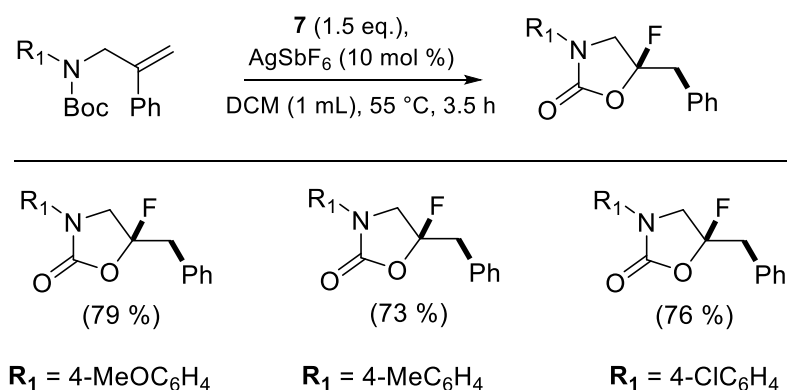
Scheme 1.35 Fluorocyclisation reactions of unsaturated carboxylic acids

Gulder investigated a metal-free synthesis of fluoro-benzoxazepines using fluoroiodane reagent **7**.⁶¹ When the conditions developed by Szabó using AgBF_4 as an additive were followed, the fluorinated product was not obtained.⁵⁸ Because of the mild reaction conditions, even substrates with electron-rich functionalities were tolerated, giving the desired products in high yields. Mechanistically, the reaction followed a fluorination and 1,2-aryl migration/cyclisation, producing fluorinated heterocycles.



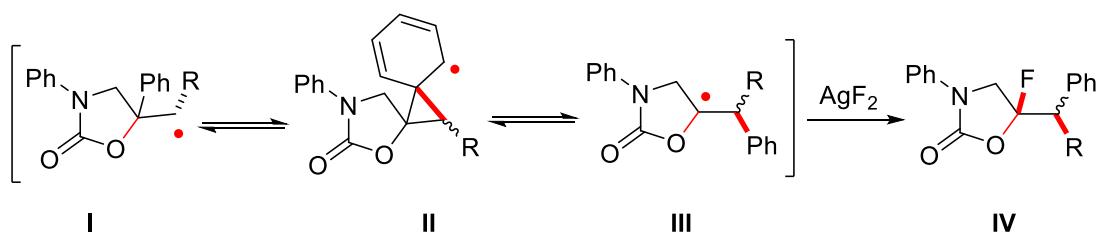
Scheme 1.36 Fluorination of unsaturated amides

The formation of a C-F bond in one step to form fluorinated cyclic structures that may serve as versatile bioactive compounds was expanded further by Lu *et al.* who reported the preparation of radiofluorinated oxazolidin-2-ones, oxazolidin-2,4-diones and 1,3-oxazinan-2-one under mild reaction conditions using fluoroiodane **7**.⁶² Following the fluorocyclisation strategies previously reported,⁵⁵⁻⁶⁰ the reaction underwent a silver promoted intramolecular fluorocyclisation with a 1,2-(hetero)aryl migration/fluorination cascade using (hetero)aryl-substituted olefins and acrylamides as substrates.



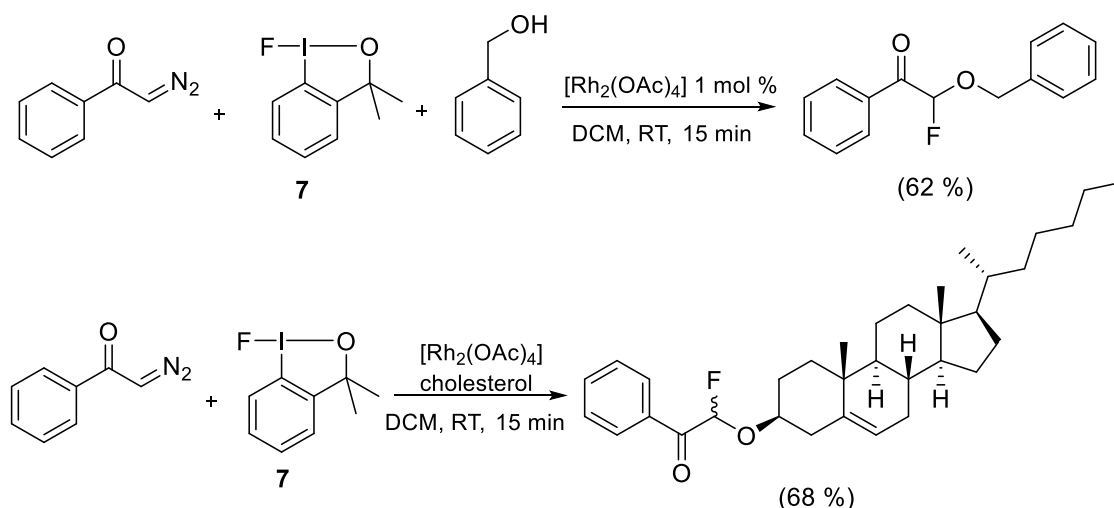
Scheme 1.37 Fluorination of unsaturated carbamates using the fluoroiodane **7**

Interestingly, the reaction was not very diastereoselective which was in contrast to other hypervalent iodine(III)-mediated fluorinations in which good to high diastereoselectivity is generally obtained. Therefore, a novel reaction mechanism was proposed for this intramolecular fluorocyclisation involving a methylene radical in the 5-position of oxazolidin-2-one. The rearrangement of a radical species **I** induced the formation of the intermediate radical species **III** via a three-membered ring cyclic structure **II** and the fluorine atom transfer to the methylene radical **III** resulted in the formation of the desired fluorinated compound **IV**.



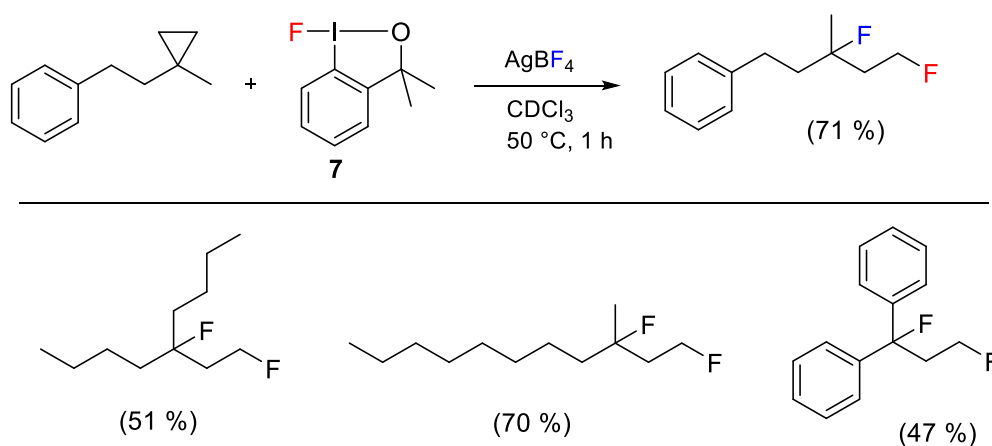
Scheme 1.38 Proposed radical mechanism for aryl transfer step

In 2016 Szabó reported the rhodium-catalysed geminal oxyfluorination of diazocarbonyl compounds using fluoroiodane reagent **7** (**Scheme 1.39**).⁶³ Interestingly, the fluorine and alkoxide sources were available from two different reagents, which increased the synthetic scope of the reaction. It was also found that NFSI can be successfully used as the fluorine source too, however, the fluoroiodane **7** was found to have a much broader synthetic scope, including cyclic substrates and carboxylic acids. The reactions were quick and performed at room temperature even with bulky substrates such as cholesterol.



Scheme 1.39 Oxyfluorination reaction

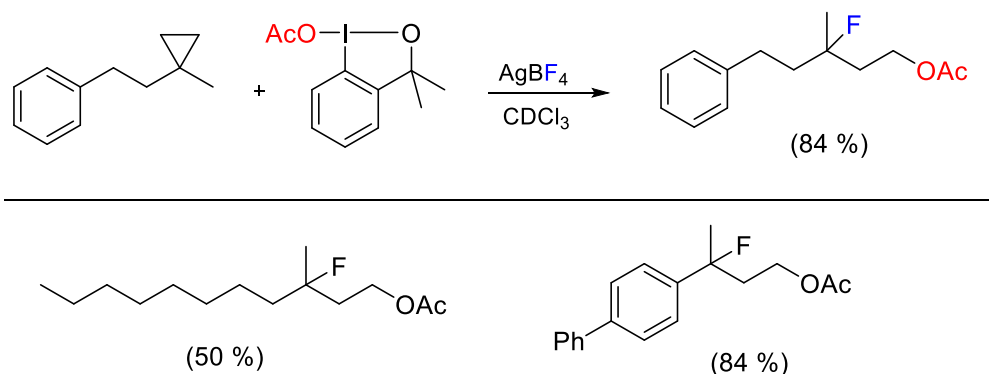
Szabó successfully employed the fluoroiodane reagent for the ring-opening of cyclopropanes leading to 1,3-difluorinations and 1,3-oxyfluorinations with high regio- and chemoselectivity under mild reaction conditions.⁶⁴ In the presence of 1 equivalent of AgBF_4 , a broad range of substrates underwent the 1,3-difluorination. Interestingly, neither SelectFluor nor NFSI could replace fluoroiodane reagent **7**. Even the alternative hypervalent iodine(III) compound Tol-IF_2 was found to be inactive in the absence of the metal catalyst and only 24 % of the desired product was obtained when it was reacted in the presence of AgBF_4 .



Scheme 1.40 1,3-Difluorination of cyclopropanes

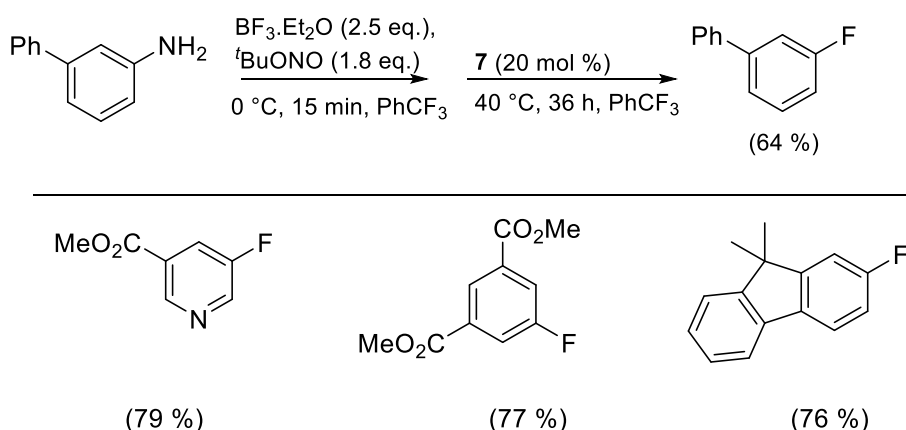
The 1,3-oxyfluorination of cyclopropane substrates was achieved when the original fluoroiodane reagent **7** was replaced by acetoxy- and benzyloxy iodanes in a similar

manner as the 1,3-difluorination using 1 equivalent of AgBF_4 , proceeding *via* electrophilic ring opening of cyclopropanes (**Scheme 1.41**).



Scheme 1.41 1,3-Oxyfluorination of cyclopropanes

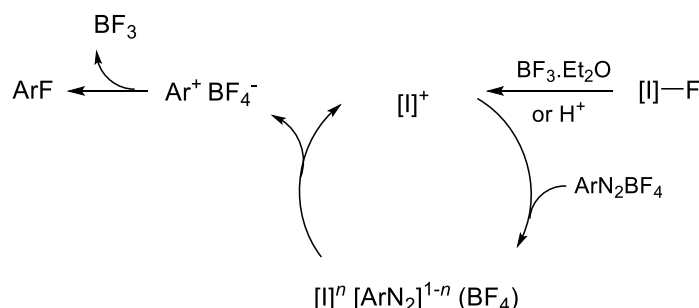
The synthesis of aryl fluorides, which are of particular importance in agrochemicals and medicinal chemistry, has been successfully achieved in the presence of the hypervalent iodine(III) reagents (*p*Tol-IF₂, **7**). Hu *et al.* reported that a Balz-Schiemann reaction which usually suffers from drawbacks such as high pressure and generation of gaseous N₂ and BF₃ can overcome safety hazards when attempted in the presence of a catalytic amount of the fluorinating reagent.⁶⁵ The overall reaction activation barrier in this new approach is much lower compared to the original Balz-Schiemann reaction which considerably reduces the reaction pressure and temperature as shown in **Scheme 1.42**.



Scheme 1.42 Synthesis of aryl fluorides using the fluoroiodane reagent

The proposed mechanism for the formation of the aryl fluorides is shown in **Scheme 1.43** and was proved to proceed through the arylodonium(III)-catalysed generation of an aryl

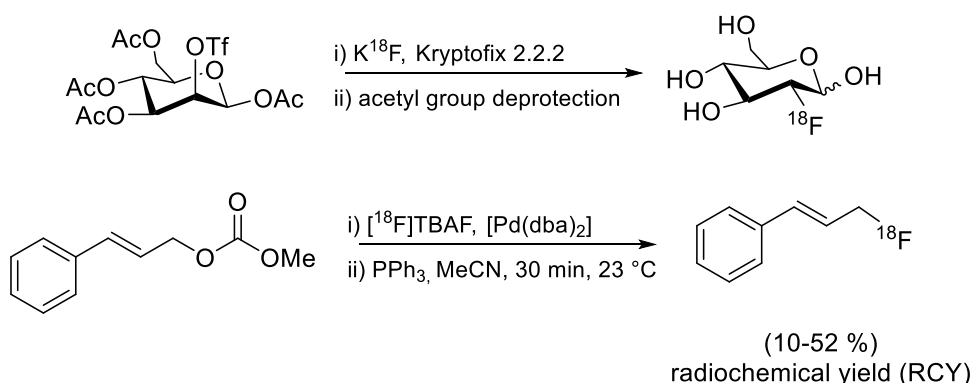
cation intermediate to give arylodonium(III) species which enhance the leaving ability of the diazo group of the arenediazonium salt to give $\text{Ar}^+ \text{BF}_4^-$, leading to the formation of aryl fluoride through nucleophilic fluorination.⁶⁵



Scheme 1.43 *Proposed mechanism for the synthesis of arylfluorides using the fluoroiodane*

1.7.3 Potential application in Positron Emission Tomography (PET)

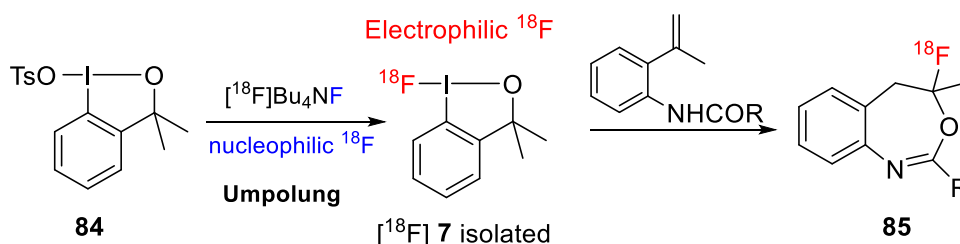
^{18}F -Fluorodeoxyglucose is widely known as a clinical tool in PET chemistry for cancer diagnosis, but PET chemistry can also be used to study pharmacological characteristics of drug molecules.⁶⁶⁻⁶⁸ Consequently, there is currently a lot of interest in developing new ^{18}F -labelled probes in medicinal chemistry. Therefore, an approach leading to a fast, highly specific and easily prepared ^{18}F source is highly desirable. As mentioned in the beginning of this chapter, a short half-life of ^{18}F ($t_{1/2}=110$ min) requires it to be introduced into the radiotracer at a late stage of the synthesis to avoid unproductive decay.^{67,70}



Scheme 1.44 *Nucleophilic radiochemical fluorination with $[^{18}\text{F}]$ -fluoride*

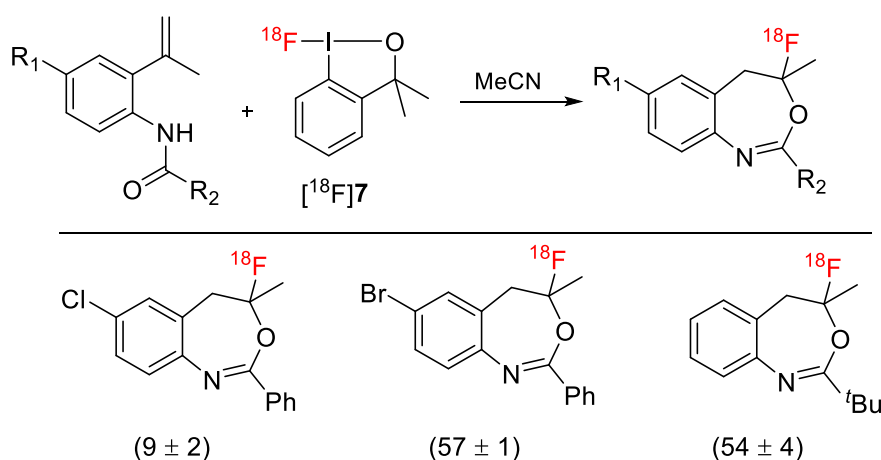
Various types of fluorinating reagents can be employed in the preparation of radiotracers such as nucleophilic (K^{18}F or $^{18}\text{F}[\text{TBAF}]$) and electrophilic ($[^{18}\text{F}]$ acetyl hypofluorite or $[^{18}\text{F}]\text{N}$ -fluoropyridinium salts) reagents (**Scheme 1.44**).⁷³ Several drawbacks such as slow

accumulation of the radiotracer and the use of metal catalyst for the preparation of radionuclides still require some experimental alterations.^{70,74-76}



Scheme 1.45 Electrophilic ^{18}F -labelling

The bench-stable and highly reactive tosyl derivative **84** was used as the precursor for the radiosynthesis of ^{18}F -labelled fluoroiodane (**Scheme 1.45**). Importantly, it was found that reagent **7** decomposes under chromatography due to high affinity of the iodine bound to fluorine to Si, Al and alkali metal ions and over 95 % of ^{18}F **7** was lost during attempts to purify it on Si or Al_2O_3 absorbents. However, the purification issues were overcome when reagent ^{18}F **7** was extracted into hexane. It was noticed that the starting materials and TBAF were insoluble in hexane and, therefore the entire amount of radioactivity in the hexane solution arose from ^{18}F **7**. The best conditions involved the reaction of **84** and ^{18}F TBAF in 500 μL of DCM for 5 minutes at room temperature followed by solvent evaporation and extraction of the solid residue by hexane for 1 minute at 70 ° C which gave the highest RCC value (56 ± 1). To test the feasibility of ^{18}F **7**, the electrophilic fluorocyclisation on *o*-styrylamides was attempted (**Scheme 1.46**).

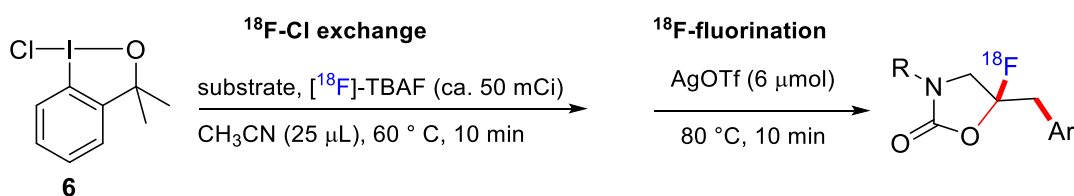


Scheme 1.46 Electrophilic fluorocyclisation affording ^{18}F -benzoxazepines

Using the optimum conditions developed by Gulder⁶¹ only low RCC levels of desired products were obtained. However, a significant increase (76 % RCC) for chlorine-substituted benzoxazepine was observed when the reaction temperature was raised from room temperature to 90 °C and the reaction time was reduced from 40 minutes to 7 minutes. The same conditions were applied to the other *o*-styrylamide substrates and showed that the products had a higher molar activity than those obtained from electrophilic ¹⁸F- labelling experiments (**Scheme 1.46**).⁷⁸

Interestingly, a *one-pot* synthesis of the fluorocyclisation using [¹⁸F]**7** was also attempted. The procedure involved the *in situ* formation of [¹⁸F]**7** followed by fluorocyclisation with *o*-styrylamide substrates. The reaction was shorter by 5 minutes than the one original styryl report because the purification step of [¹⁸F]**7** was skipped. Disappointingly, the RCC values for the *one-pot* synthesis were low.

Overall, reagent ¹⁸F**7** was prepared by an operationally simple three-step process in just 20 minutes. The purification of ¹⁸F**7** was essential which was proved by showing much higher RCC values compared to the non-purified ¹⁸F**7** analogue. Moreover, the reagent is very stable and therefore could be transported to PET facilities that are not equipped with on-site cyclotrons.⁷⁸



Scheme 1.47 Radiosynthesis of [¹⁸F]-heterocycles

The synthesis of [¹⁸F]-substituted heterocycles based on unsaturated carbamate precursors was investigated by Li.⁶² Aiming to minimise the radiosynthetic reaction time, short *one-pot* radiolabelling experiments were attempted. However, [¹⁸F]-fluorine containing heterocyclic products were not obtained.

Instead, AgCl was formed as a consequence of using chloroiodane and AgOTf in the *one-pot* synthetic approach (**Scheme 1.47**). To overcome the issue, a similar *one-pot* but two-step protocol was developed. It was noticed that increasing the reaction temperature to 60

°C in the first step for the ^{18}F -Cl exchange and to 80 °C in the following fluorination step was essential. Also, the reactions were only feasible with high substrate concentrations in MeCN and failed when the solvent system was changed to DMSO/DMF. The use AgSbF_6 or AgOTf was necessary as silver salts increased the radiochemical yields considerably. The *in vitro* and *in vivo* studies on the stability of radiolabelled compounds found that [^{18}F]-fluorocyclised products were extremely stable in aqueous solution for up to 3 hours after incubation in phosphate buffer solution.

The demand for novel [^{18}F] radiotracers in drug discovery and PET technology is rapidly increasing. Although designing and labelling various types of molecules with ^{18}F at a specific position is still challenging and requiring more indepth research, the few examples discussed here show that hypervalent iodine(III) reagent **7** has great potential to be employed in radiolabelling experiments.

1.7.4 Mechanism of the Fluoroiodane reagent **7**

1.7.5 Chemoselectivity in fluorocyclisation reactions with the fluoroiodane **7**

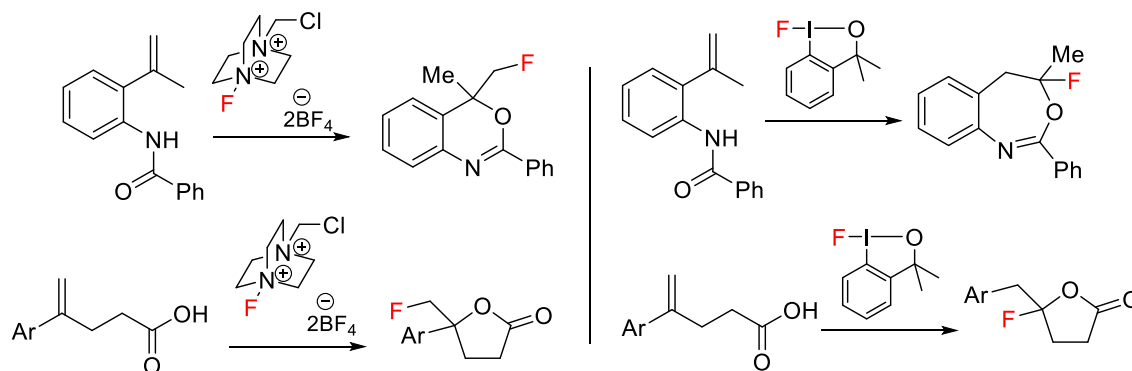


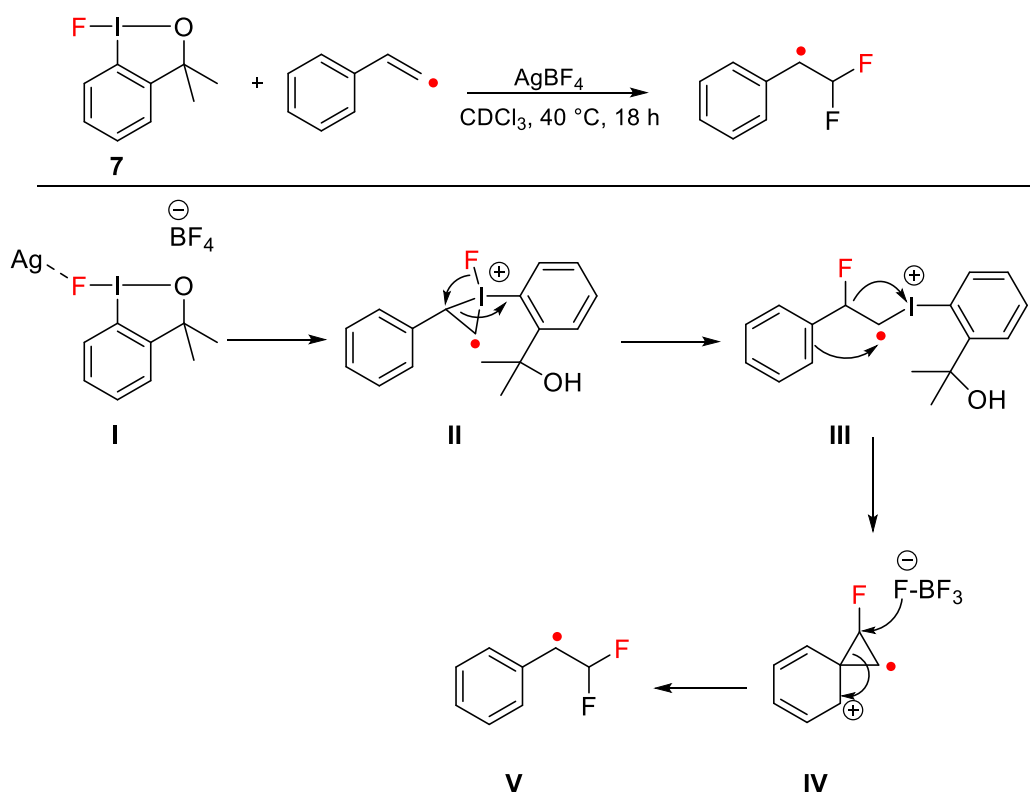
Figure 1.6 Different reactivity patterns of fluorinating reagents

A different reactivity pattern in the fluorocyclisations of unsaturated carboxylic acids and *o*-styryl benzamides was obtained with fluoroiodane **7** compared to traditional fluorinating reagents such as Selectfluor. The formation of tertiary over primary alkyl fluorides using the fluoroiodane reagent has been observed in the reactions generating γ -lactones and fluorobenzoxazepines shown in **Figure 1.6**.⁵⁹⁻⁶¹ To understand these differences, Cheng calculated the atomic charges on the F atom in both fluorinating reagents and found that Selectfluor carries the atomic charge of $0.243e$ whereas the

fluoroiodane has a negative charge of $-0.567e$. This indicates that electrophilic fluorine transfer will happen from Selectfluor but not from fluoroiodane which is electrophilic at the I(III) atom. Therefore, the fluorine atom in the fluoroiodane will act as a nucleophilic source of fluoride.⁷⁹

1.7.6 Activation of fluoroiodane by a transition metal coordination

The activation of the fluoroiodane reagent has been debated since the reagent became a potential substitute to well-known fluorinating reagents such as Selectfluor and NFSI. A few proposed mechanisms have been reported in the literature, however, none were fully confirmed until Zhou attempted DFT calculations based on the activation of reagent **7** by Lewis acids.⁸³



Scheme 1.48 Activation of the fluoroiodane by AgBF_4 – the DFT accepted model

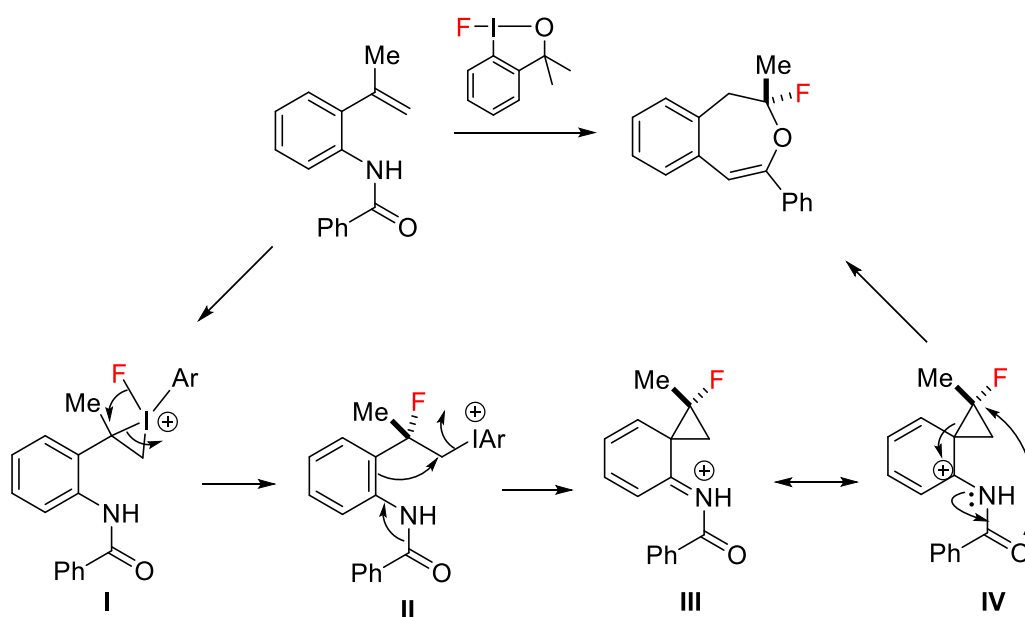
The most widely accepted Lewis-acid-activation model involved the polarisation of the I-O bond when the Lewis acid coordinated to the oxygen atom in reagent **7**. However, the activation mode through the fluorine atom was found to be much more energetically

preferred from the computational analysis of silver-mediated fluorination of styrenes with fluoroiodane **7**, reported by Szabo.⁷⁸

Considering the previously accepted mechanism which underwent the activation of reagent **7** through coordinating to the oxygen atom, it was found that the interaction between Ag-O was exoergic by 3.9 kcal mol⁻¹ which subsequently increased the activation energy barrier of **II** to 30.2 kcal mol⁻¹.⁸³

Alternatively, the activation through the F atom showed a similar stability pattern of the activated species **I**, but most importantly, the activation energy barrier after the nucleophilic attack from the olefinic double bond to form **II** was considerably reduced to 9.3 kcal mol⁻¹. The coordination to the fluorine atom leads to a more polarised I-F bond (2.543 vs. 2.310 Å), making it a more energetically preferred pathway.⁸³

1.7.7 Activation of fluoroiodane by hydrogen bonding to fluorine atom



Scheme 1.49 *Previously proposed mechanism for the fluorocyclisation*

In the original report the first step leading to the formation of a seven-membered benzoxazepine involved a nucleophilic attack of **7** from the olefinic double bond forming **I**. The three-membered heterocycle was opened selectively at the benzylic position going through an intramolecular 1,2-fluorine shift to form **II**. The formation of cyclopropyl compound **III** followed by ring opening which proceeded through a 6-*endo* cyclisation

and ring expansion lead to the desired seven-membered fluoro-benzoxazepine.⁶¹ Although the nucleophilic attack of fluoroiodane by the double bond was a facile process with an activation free energy of 18.2 kcal mol⁻¹ (**TS2**), the activation energy of the 1,2-fluorine shift was 30.2 kcal mol⁻¹ (**TS2'**). The formation of a seven-membered ring at room temperature having such a high free energy barrier would therefore not be possible.⁶⁹ In the absence of a Lewis acid, the amide functionality of the *o*-styryl benzamide in **I** served as an alternative activator, forming a hydrogen bond to the F atom and facilitating the 1,2-fluorine shift with the activation energy barrier of 18.2 kcal mol⁻¹ (**Figure 1.7**).⁷⁸⁻⁸⁰

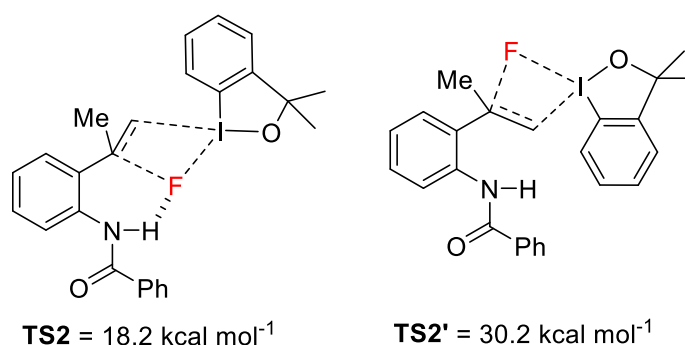


Figure 1.7 Accepted **TS2'** vs. previously proposed **TS2** in **I**

As reported by Gulder,⁶¹ the formation of intermediate **III** by the direct displacement of iodobenzene by nucleophilic attack of the aryl ring was calculated to have a high activation barrier of 30.4 kcal mol⁻¹ (**TS3'**). However, it could be substantially reduced by 23.4 kcal mol⁻¹ upon proton transfer from the N-H moiety of the *o*-styryl benzamide to the O atom of the fluoroiodane (**TS3**). The ring opening followed by expansion to form a seven-membered ring product occurred at the fluorine-substituted and more electrophilic carbon atom which was energetically favoured by 23.4 kcal mol⁻¹ over the attack on the unsubstituted and less electrophilic carbon atom (**Figure 1.8**).^{78,81,84}

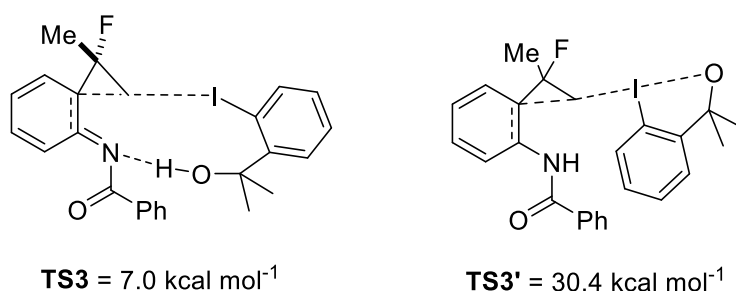


Figure 1.8 DFT supported **TS3** vs. energetically unfavourable **TS3'**

Overall, the formation of a seven-membered ring benzoxazepine as the only product was confirmed by DFT calculations. It was found that the amide group assisted C-F bond formation had a much lower overall reaction activation energy barrier of the transition state of 18.9 kcal mol⁻¹ which was in contrast to the original reaction mechanism.^{61,82}

1.8 Project Aims

Several big improvements in the development of new fluorinating reagents have been made to date. The efficiency of Togni's reagent **4** has been proved in many examples, showing the incorporation of the trifluoromethyl moiety (-CF₃) into a broad range of structures ranging from non-carbon centered nucleophiles such as sulfur and phosphorus to aryls/heteroaryls and hydrazones.³⁸ The electrophilic fluorinating reagent **7** developed by Stuart has successfully been employed in various reactions such as fluorination of 1,3-ketoesters, 1,3-diketones and 1,3-ketoamides.⁵⁶⁻⁵⁷ Being easily prepared, handled and stored in normal laboratory glassware, the reagent has shown a unique reactivity pattern in the development of fluorinated γ -lactones containing tertiary alkylfluorides. In contrast, the Fluoraza reagents generate fluorinated γ -lactones containing primary alkylfluorides. Moreover, the synthesis of reagent **7** does not require the use of aqueous HF, pyridine HF or elemental fluorine which contributes towards a safer working environment.

In chapter 2 the preparation of γ -lactones first reported by Stuart using AgBF₄ will be explored further.⁶⁰ The aim is to perform the fluorocyclisation reactions under catalytic conditions using a transition metal catalyst. With the optimum conditions found, the substrate scope will be expanded from *geminal*-disubstituted to monosubstituted, *trans*-disubstituted and trisubstituted alkenes. The next aim of this chapter was to investigate a metal-free fluorocyclisation reaction using a strong hydrogen bond donor with weak nucleophilic character, so it should not compete with the fluorinating reagent **7**. It is proposed that the synthesis of γ -lactones using fluoroiodane **7** under catalyst-free conditions will open new frontiers in Positron Emission Tomography (PET).

In chapter 3 of this thesis, a prototypical fluorinating reagent to **7** in which one of the methyl groups is replaced by a phenyl sidearm will be prepared. The new reagent will be used for the preparation of a series of unsymmetrical diaryliodonium salts from Grignard reagents and arylboronic acids. The overall aim of this chapter will investigate the fluorination reactions of diaryliodonium salts for the preparation of fluorinated aromatics in the presence and absence of a transition metal catalyst.

In chapter 4, the synthesis of β -fluorovinyliodonium salts from internal and terminal alkynes with the new fluoroiodane reagent will be discussed. A preliminary fluorination of one of the β -fluorovinyliodonium salts was investigated under copper-catalysed conditions to generate a difluoroalkene. The aim of this work was to generate β -fluorovinyliodonium salts and difluoroalkenes under mild reaction conditions.

Chapter 2

Intramolecular Fluorocyclisations of Unsaturated Carboxylic Acids using the Fluoriodane Reagent



2.1 Introduction

Intramolecular fluorocyclisation is an efficient one step approach leading to the formation of fluorinated heterocycles that are of particular interest to the pharmaceutical and agrochemical industries. Out of numerous examples reported, a few lactones shown in **Figure 2.1** exhibit remarkable biological activity. Valoneic acid dilactone, best known for its anti-inhibitory effect on 5 α -reductase involved in steroid metabolism and prostate cancer, is a naturally occurring lactone found in the heartwood of the European red oak and is also prepared on a large scale by Ullmann's condensation reaction.⁸⁶ Mysophenolic acid was found to inhibit the IMP dehydrogenase of adenocarcinoma of the colon more efficiently than enzymes found in murine tumours used in cancer treatment.⁸⁷ Naturally occurring Taiwanin A is a widely used pharmaceutical agent exhibiting excellent anti-inflammatory, anti-oxidant and anti-tumour properties.⁸⁸ Various synthetic routes for the preparation of benzyl-substituted lactones are known, however no procedures incorporating the fluorine atom have been reported yet.⁸⁹⁻⁹⁰

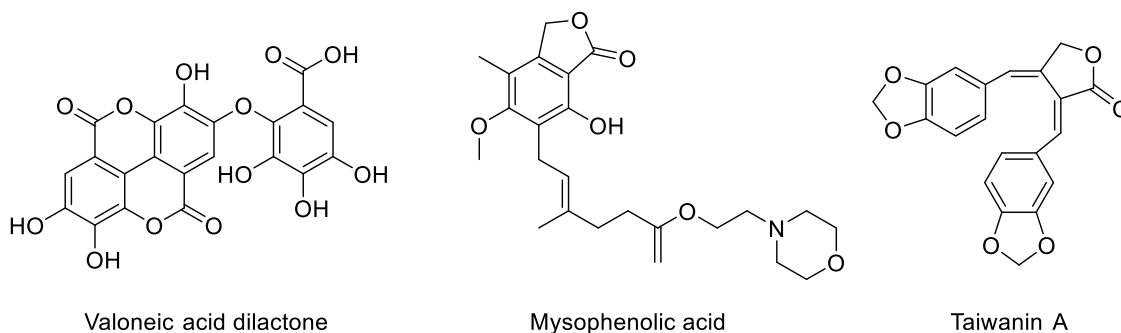


Figure 2.1 *Naturally occurring lactones*

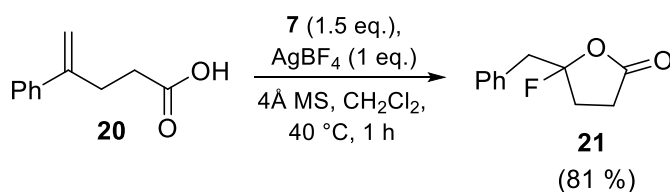
Electrophilic fluorinating reagents such as Selectfluor or NFSI have been used for the preparation of fluorinated lactones, tetrahydrofurans and isobenzofurans.⁹¹⁻⁹² However, the use of elemental fluorine required for the preparation of the electrophilic fluorinating reagents and high reagent cost make them unprofitable for industrial use.⁹³⁻⁹⁴

The readily available and less-costly nucleophilic fluorinating reagents can also be used for the preparation of fluorinated γ -lactones. Sawaguchi reported the fluorocyclisations of unsaturated alcohols and carboxylic acids using iodotoluene difluoride and amine-HF

complexes.⁹⁵ The reported procedure generated cyclised fluorinated lactones and furans in moderate yields (40-60 %) but required the use of pyridine-HF which cannot be handled and stored in normal laboratory glassware due to its highly corrosive nature.

Despite the undisputed significance of the aforementioned reagents that gave first insights into the generation of fluorinated lactones, safety and economical concerns have triggered the search for an easily prepared, stable and cost-efficient prototypical reagent.

The fluoroiodane reagent made successfully in Stuart's group using TREAT-HF, can be used to form C-F bonds under mild reaction conditions and it is safer to handle compared to alternative fluorinating reagents which use either elemental fluorine or pyridine-HF for their preparation.⁵⁶ The group demonstrated that the fluoroiodane reagent can be used to prepare fluorinated γ -lactones from unsaturated carboxylic acids using stoichiometric amounts of AgBF_4 (**Scheme 2.1**).⁶⁰ The reported procedure involved an intramolecular fluorocyclisation with an aryl migration delivering fluorinated γ -lactones. As discussed in the introduction, this method generated exclusively fluorocyclised lactones containing tertiary alkylfluorides which is in contrast to fluoraza reagents which result in the formation of γ -lactones having primary alkylfluorides. The difference in regioselectivity was explained by the calculated atomic charge of the fluorine atom in the fluorinating reagents resulting in different mechanisms.⁹⁷ It was found that the calculated atomic charge of the fluorine atom in the fluoraza reagent being 0.243e resulted in an electrophilic fluorine transfer, whereas in fluoroiodane the calculated atomic charge is -0.567e indicating a nucleophilic fluorination.



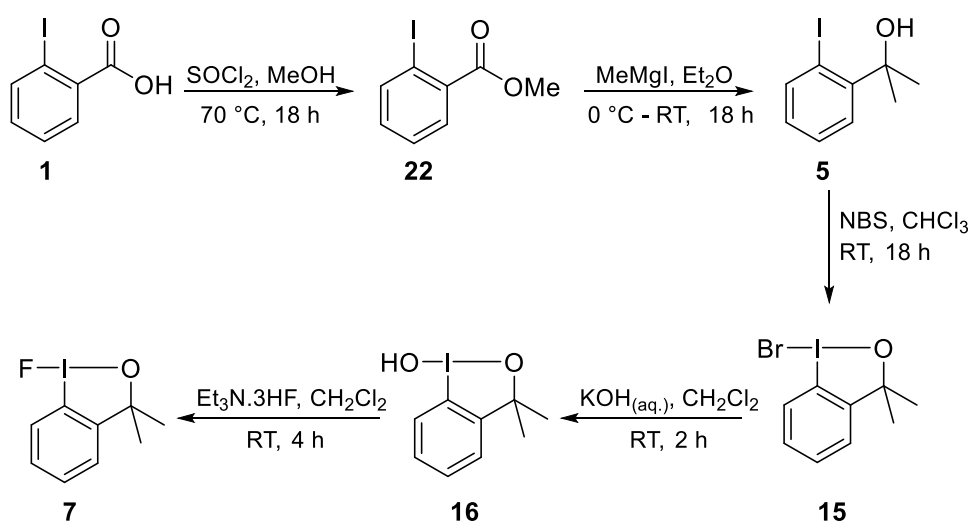
Scheme 2.1 Fluorocyclisation with fluoroiodane and AgBF_4

In this chapter the reactivity of the fluoroiodane reagent was first tested with 4-phenyl-4-pentenoic acid **20** using a stoichiometric amount of AgBF_4 . The overall aim of this chapter was to test the feasibility of promoting the reaction with catalytic quantities of transition metal catalysts (Ag(I) , Cu(I) , Zn(II)). Building on this work, the chapter also explored the substrate scope of the fluorocyclisations with a range of unsaturated carboxylic acids.

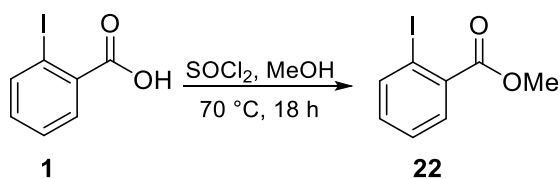
Finally, a new concept was introduced whereby the fluoroiodane reagent was activated by hydrogen bonding to hexafluoroisopropanol and metal-free fluorocyclisations were developed.

2.2 Synthesis of the fluoroiodane reagent 7

The first part of the project was focussed on the synthesis of 1-fluoro-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole **7**. The synthetic pathway is depicted in **Scheme 2.2** starting from commercially available 2-iodobenzoic acid **1**.



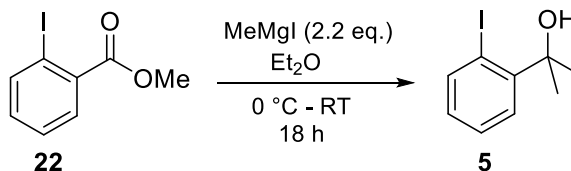
Scheme 2.2 Synthetic route for the preparation of the fluoroiodane reagent **7**



Scheme 2.3 Esterification of 2-iodobenzoic acid

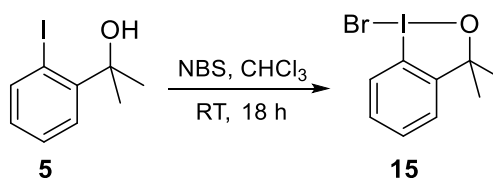
The esterification of commercially available 2-iodobenzoic acid **1** was carried out by reacting **1** with thionyl chloride (SOCl_2) in methanol (MeOH).⁹⁷ The reaction did not require dry solvents and was performed in an open system, generating the desired product in high yield. By increasing the amount of SOCl_2 from 1.3 to 1.5 equivalents, the yield increased from 72 % to 92 %. The appearance of the singlet at 3.94 ppm in the ^1H NMR spectrum and a singlet at 52.6 ppm in the ^{13}C NMR spectrum for the methoxy group

confirmed the formation of the ester. A fragment in the ASAP-MS spectrum at m/z 262.96 corresponded to MH^+ .



Scheme 2.4 Synthesis of 2-(2-iodophenyl)propan-2-ol **5**

The preparation of the tertiary alcohol, 2-(2-iodophenyl)propan-2-ol **5**, followed the synthetic route reported by Togni *et al.*⁹⁶ The Grignard reagent (MeMgI) was prepared from methyl iodide (MeI) and Mg turnings in dry diethyl ether. After the formation of the Grignard reagent, it was transferred to a new flask using cannula and cooled to 0 °C before a solution of **22** in diethyl ether was added dropwise forming a biphasic solution which was allowed to warm to room temperature and stirred for a further 18 h. The desired product was obtained as an orange oil in 85 % yield and no purification was required. The formation of the tertiary alcohol **5** was proved by ^1H and ^{13}C NMR spectroscopy as well as mass spectrometry. In the ^1H NMR spectrum, the two methyl group singlet appeared at 1.64 ppm. A broad singlet corresponding to the OH group was found at 2.52 ppm. In the ^{13}C NMR spectrum the quaternary carbon bearing an OH group appeared at 72.5 ppm whilst the quaternary carbon of the carbonyl group in **22** was found at 166.8 ppm. The ASAP-MS spectra confirmed the formation of the tertiary alcohol **3** by showing a peak at m/z 247 corresponding to $[M-\text{CH}_3]^+$.

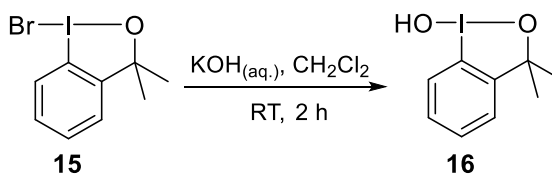


Scheme 2.5 Preparation of 1-bromo-3,3-dimethyl-1,3-dihydro- λ^3 benzo[d][1,2]iodoxole **15**

The bromoiodane **15** was prepared by following the procedure reported by Braddock (Scheme 2.5).⁹⁷ The tertiary alcohol **5** was dissolved in chloroform to which

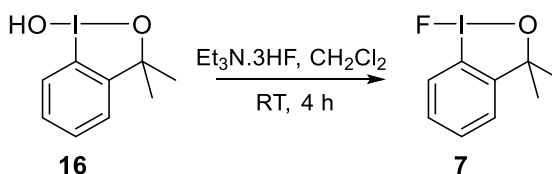
N-bromosuccinimide (NBS) was added portionwise and the reaction mixture was stirred at room temperature for 18 hours. The crude product was purified by re-crystallisation from warm ethyl acetate and washed with methanol in order to remove small impurities observed in the aromatic region of the ^1H NMR spectrum.

The key data from the ^1H and ^{13}C NMR spectra confirmed the formation of 1-bromo-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole **15**, showing a slight downfield shift of the aromatic protons and carbon atoms *cf.* 2-(2-iodophenyl)propan-2-ol **5** which was caused by the oxidation of iodine(I) to iodine(III). The proton closest to the iodine atom in compound **5** showed a peak at 7.51 ppm, whereas the proton at the same position in bromiodane **15** appeared at 7.98 ppm. The absence of the OH peak at 2.52 ppm indicated that the starting material was fully consumed. The quaternary carbon atom containing the hydroxyl group was shifted from 72.5 ppm for **5** to 84.2 ppm for **15** in the ^{13}C NMR spectrum. In the ASAP-MS spectrum, the isotopic pattern for bromine was observed for the parent cation peak at m/z 340.9047 and m/z 342.9037 showing a 1:1 ratio between ^{79}Br and ^{81}Br , respectively.



Scheme 2.6 Preparation of 1-hydroxy-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole **16**

1-Hydroxy-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole **16** was prepared by nucleophilic attack on the hypervalent λ^3 -iodine centre of bromoiodane **15**.⁵⁶ Mild reaction conditions and a short reaction time of 2 hours, generated the desired compound in a good 63 % yield. The formation of the product was confirmed by ^1H and ^{13}C NMR spectroscopy as well as ASAP-MS mass spectrometry which showed a peak at m/z 278.9880 for the MH^+ . A slight upfield shift for the aromatic protons was observed in **16** compared to the bromoiodane **15**. For example, the proton found closest to the iodine(III) in compound **15** appeared at 7.98 ppm whereas in compound **16** it was shifted to 7.75 ppm.



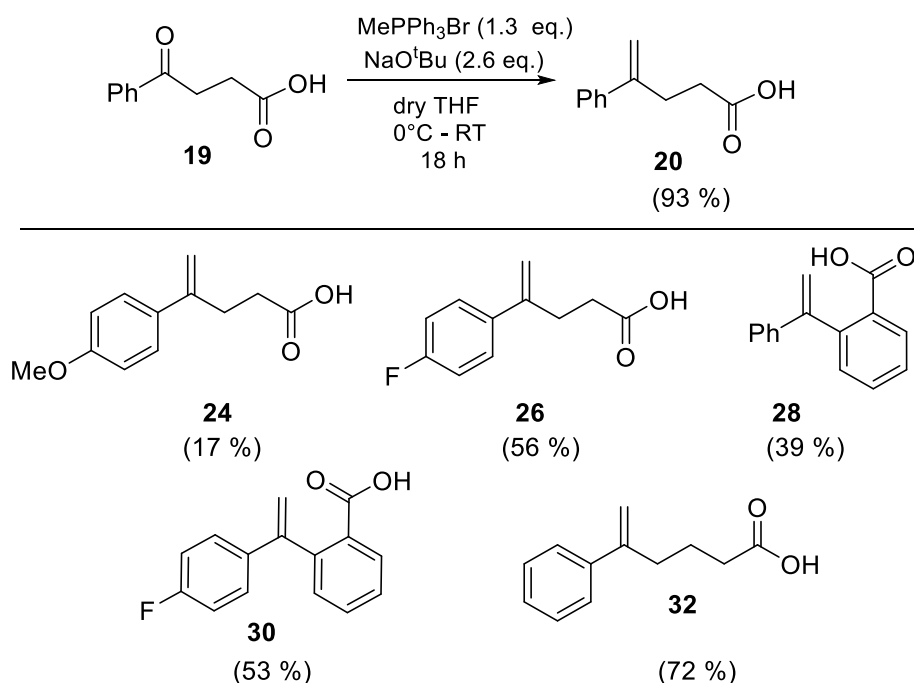
Scheme 2.7 *Synthesis of the fluoroiodane reagent*

The synthesis of the final reagent **7** was carried out by reacting 1-hydroxy-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole **16** with TREAT-HF in dichloromethane as reported by Stuart.⁵⁶ Mild reaction conditions and a short reaction time gave the target compound in an excellent 98 % yield. The characteristic singlet at -143.1 ppm in the ^{19}F NMR spectrum confirmed the formation of the fluoroiodane **7**. Additionally, the ASAP-MS showed a peak for MH^+ at m/z 280.98.

The preparation of the stable, easy to handle and store, fluoroiodane reagent **7** proceeded under mild reaction conditions, did not require time-consuming purification by column chromatography and produced the desired fluorinating reagent in an excellent yield.

2.3 Preparation of unsaturated carboxylic acids

2.3.1 Synthesis of *geminal*-disubstituted alkenes 20-32

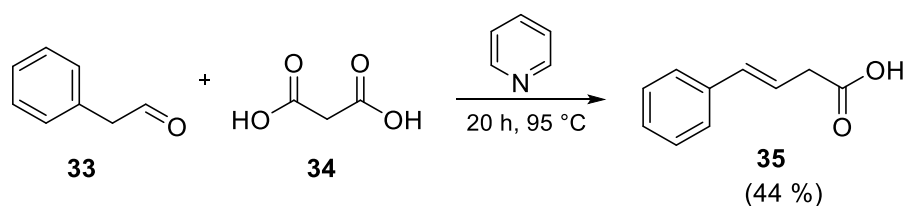


Scheme 2.8 *Preparation of unsaturated carboxylic acids*

To test the feasibility of the intramolecular fluorocyclisations using the fluorinating reagent **7**, a series of unsaturated carboxylic acids was prepared by a Wittig reaction using methyl triphenylphosphonium bromide and NaO^tBu. The model substrate, 4-phenyl-4-pentenoic acid **20**, was prepared from 4-oxo-4-phenylbutanoic acid **19** in an excellent 93 % yield following the literature procedure.⁶⁰ An immediate colour change from white to bright yellow was observed after the addition of NaO^tBu and indicated the formation of the ylide which is a key intermediate in the Wittig reaction. The two typical alkene singlets in the ¹H NMR spectrum appeared at 5.11 and 5.32 ppm. The CH₂ alkene carbon was found at 112.9 ppm in the ¹³C NMR spectrum.

The other substrates were prepared by the same route and obtained as white solids. However, substrates (**24**, **26**, **28** and **32**) had to be purified by either column chromatography using ethyl acetate (50 %):petroleum ether (40-60) or re-crystallization from ethyl acetate/hexane (1:5), which explains their lower overall yields compared to substrate **20**. A much lower 17 % yield was obtained for 4-(4-methoxyphenyl)pent-4-enoic acid **24** because it required purification by column chromatography, but it was only moderately soluble in organic solvents. The characterisation data for *gem*-disubstituted alkenes was in agreement with the literature.^{60, 98-99}

2.3.2 Synthesis of *trans*-disubstituted alkene **35**

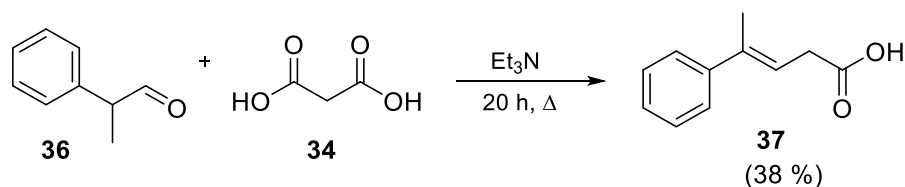


Scheme 2.9 Preparation of (*E*)-4-phenylbut-3-enoic acid **35**

To broaden the scope of the fluorocyclisations, the synthesis of the *trans*-disubstituted alkene **35** was attempted following the literature procedure (**Scheme 2.9**).¹⁰⁰⁻¹⁰³ (*E*)-4-Phenylbut-3-enoic acid **35** was prepared by reacting phenylacetaldehyde **33** with malonic acid **34** in pyridine. The ¹H NMR spectrum of the crude reaction mixture revealed the formation of the desired product along with some impurities. The crude product was purified by re-crystallisation from toluene/hexane (1/10), resulting in a 44 % yield of the desired product. The two alkene peaks appeared at 6.28 and 6.48 ppm in the

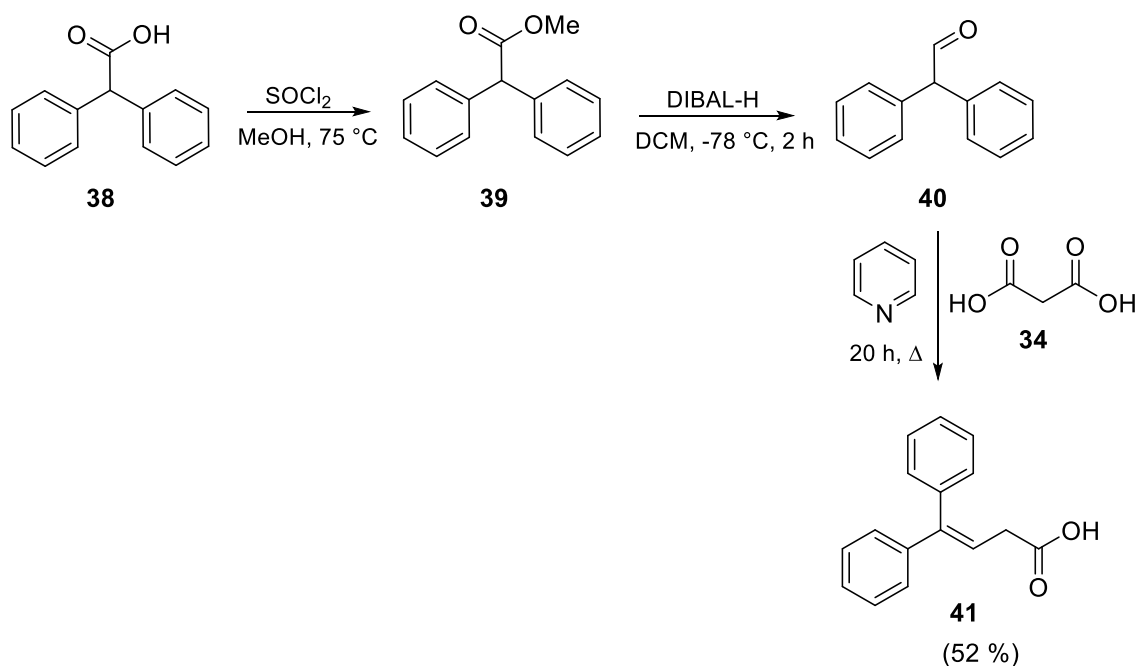
^1H NMR spectrum with $^3J_{\text{HH}}$ coupling constants of 15.8 Hz, confirming the *trans* configuration. The alkene carbons were found at 120.8 and 134.0 ppm in the ^{13}C NMR spectrum. The peak at m/z 162.09 for $(\text{M}-\text{H})^+$ was found by ASAP-MS.

2.3.3 Synthesis of trisubstituted alkenes **37** and **41**



Scheme 2.10 Preparation of (*E*)-4-phenylpent-3-enoic acid **37**

(*E*)-4-Phenylpent-3-enoic acid **37** was prepared following a similar method to **35** using malonic acid and 2-phenylpropanal in triethylamine. After re-crystallisation from ethyl acetate and petroleum ether (40-60) (1:5), the desired product was isolated in 38 % yield. The characterisation data for **37** was in agreement with the literature.¹⁰¹



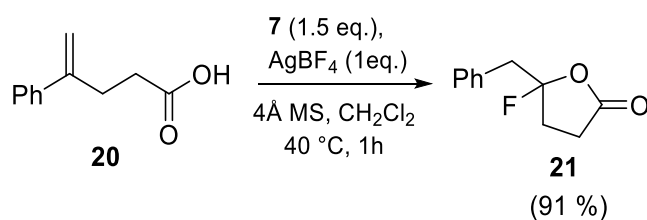
Scheme 2.11 Preparation of 4,4-diphenylbut-3-enoic acid **41**

4,4-Diphenylbut-3-enoic acid **41** was prepared according to the literature procedure from methyl-2,2-diphenylacetate **39**.¹⁰³ The ester **39** was obtained from 2,2-diphenylacetic acid **38** in a high 91 % yield. The reduction of **39** using an excess of

DIBAL-H resulted in **40** which was obtained as a pale yellow oil in an excellent 94 % yield. The singlet at 9.90 ppm corresponding to the $-CHO$ indicated the formation of the desired compound and no $-OCH_3$ singlet at 3.72 ppm was found. The target compound **41** was then obtained by refluxing **40** with malonic acid **34** in triethylamine (Et_3N) for 20 hours. The crude product was purified by column chromatography using diethyl ether (10 %) : petroleum ether (40-60). The CH_2 doublet at 3.21 ppm with a $^3J_{HH}$ coupling constant of 7.4 Hz and the CH triplet at 7.23 ppm with $^3J_{HH}$ coupling constant of 7.4 Hz were confirmed by 1H NMR spectroscopy. The carbonyl singlet at 176.6 ppm was found in the ^{13}C NMR spectrum.

2.4 Transition metal-assisted fluorocyclisations of unsaturated carboxylic acids

2.4.1 Reactions using $AgBF_4$



Scheme 2.12 Intramolecular fluorocyclisation using $AgBF_4$ (1 eq.)

The feasibility of the fluorocyclisation using $AgBF_4$ was tested on the unsaturated carboxylic acid **20** using a stoichiometric amount of silver tetrafluoroborate, 4Å molecular sieves and fluoroiodane **7** in dry dichloromethane. The reaction was carried out at 40 °C for 1 hour (**Scheme 2.12**). The final product was characterised by 1H , ^{13}C and ^{19}F NMR spectroscopy and ASAP mass spectrometry. The data was in agreement with the literature, showing a characteristic 2H doublet at 3.29 ppm in the 1H NMR spectrum for the CH_2CF protons with a $^3J_{HF}$ coupling constant of 14.7 Hz.¹¹ A quaternary carbon at 118.1 ppm coupled to the fluorine atom with coupling constant of 229.0 Hz was found in the ^{13}C NMR spectrum. The formation of the tertiary alkyl fluoride was also confirmed by ^{19}F NMR spectroscopy which showed a singlet at -97.0 ppm which is in sharp contrast to the primary alkyl fluoride found at -232.0 ppm.¹⁰⁵

The preparation of γ -lactones using the fluoroiodane reagent undergoes a unique reaction pathway involving a cyclisation, phenyl migration and fluorination.⁶⁰ As described by Szabó, the activation of the fluoroiodane reagent **7** is essential in the intramolecular

fluorocyclisation reactions which in this work was done by the Lewis acid AgBF_4 .⁵⁸ However, the original proposed mechanism only considered the Lewis acid coordination through the oxygen atom. However, as discussed previously, the DFT calculations proved that the most accepted form of activation is through the fluorine atom, making the I-F bond longer and more polarised. The electrophilic iodine centre is therefore more susceptible to undergo the nucleophilic attack from the alkene.⁷⁹⁻⁸³

The modified mechanism for the intramolecular fluorocyclisation is shown in (**Figure 2.2**). Activated fluoroiodane **7** induced the formation of the cyclic intermediate **43** in which the hypervalent iodine accepted π electrons from the substrate molecule **20**. The intramolecular nucleophilic attack of the hydroxyl group occurs at the more substituted carbon which is better able to stabilise the positive charge. The excellent leaving group ability of the iodoaryl group triggers the π donation of the aromatic ring in **44**. Lastly, the regioselective ring opening of the cyclopropane ring in **45** induces the phenyl migration and generates the final fluorinated product **21** having a tertiary alkyl fluoride.

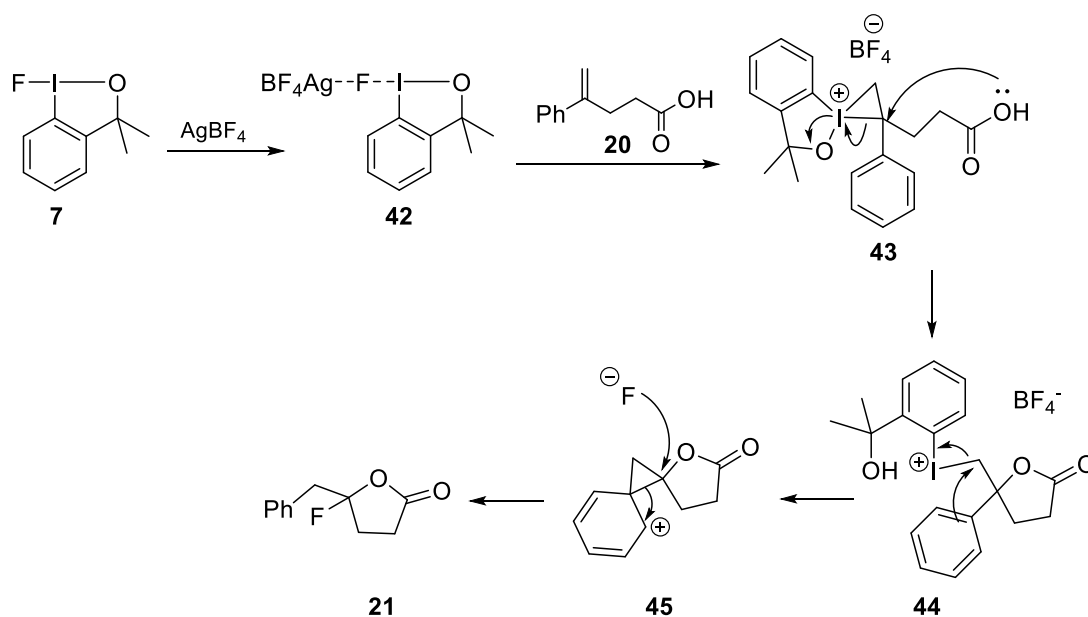


Figure 2.2 *Proposed mechanism for the intramolecular fluorocyclisation reaction*

Encouraged by the initial result which resulted in a 99 % conversion from the starting material and a 91 % overall yield using a stoichiometric amount of the Lewis acid, the feasibility of a catalytic reaction was investigated using 10 mol % of AgBF_4 . The percent conversion was found to be slightly lower (86 %) than using the stoichiometric amount of AgBF_4 (99 %). Interestingly, the 10 mol % catalysed reaction

generated not only the iodoalcohol by-product **5**, but also the iodoalkene **46** which probably resulted from the dehydration of **5**. The crude reaction mixture was purified successfully by column chromatography, yielding the desired product **21** in 63 % yield with a trace amount (< 5 %) of **46** (Table 2.1).

Table 2.1 *AgBF₄ catalysed fluorocyclisations*

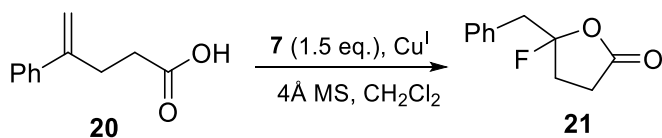
Entry	AgBF ₄	T (°C)	Time (h)	Conversion (%) ^{a, b} 21	20
1	1	40	1	99 (91)	1
2	10 mol %	40	1	86 (63)	14

^a Conversion calculated by ¹H NMR spectroscopy, refers to the consumption of the starting material **20**. ^b Isolated yields in parenthesis.

2.4.2 Catalyst optimisations

Instead of using AgBF₄, which proved to be an efficient reagent for fluorocyclisations under stoichiometric and catalytic conditions, [Cu(MeCN)₄]PF₆ was chosen as an alternative catalyst. The potential of a Cu^I catalyst to participate in catalytic intramolecular aminofluorination and carbofluorination reactions was reported by Szabó⁵⁹ and so it was thought that these catalytic species would work well for the intramolecular fluorocyclisations with unsaturated carboxylic acids. The reaction times, temperatures and catalytic amounts of Cu^I were monitored respectively (Table 2.2).

Table 2.2 Optimisation of the fluorocyclisation of 4-phenyl-4-pentenoic acid **20** with fluoroiodane using a Cu^I catalyst



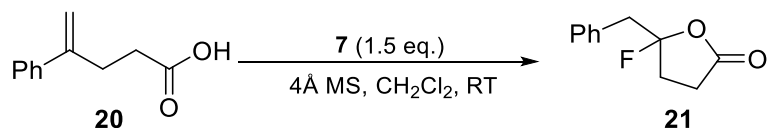
Entry	[Cu(MeCN) ₄]PF ₆ (mol %)	T (°C)	Time (h)	Conversion (%) ^{a,b}	
				21	20
1	10	40	1	99 (71)	1
2	5	40	1	84	16
3	10	RT	18	90 (70)	10
4	5	RT	18	67	33
5	10	RT	8	90	10
6	5	RT	8	33	67
7	10	RT	4	85	15
8	10	RT	2	86	14
9^c	10	RT	18	89 (74)	11

^a Conversion calculated by ¹H NMR spectroscopy, refers to the consumption of the starting material **20**. ^b Isolated yields in parenthesis. ^c [Cu(MeCN)₄]BF₄

In entry 1 4-phenyl-4-pentenoic acid **20** was reacted with 1.5 equivalents of fluoroiodane reagent **7**, 10 mol % of [Cu(MeCN)₄]PF₆ and 4Å molecular sieves at 40 °C for 1 hour. A 99 % conversion to the fluorinated product was observed (entry 1). When the amount of catalyst was reduced to 5 mol %, the percentage conversion dropped to 84 % (entry 2). It was then decided to make the reaction conditions milder, *i.e.* perform the fluorocyclisation reactions at room temperature, and keep the same catalytic amounts of the Cu^I catalyst. Only a small drop in conversion to 90 % was observed for the 10 mol % catalysed reaction (entry 3). However, the 5 mol % catalysed reaction showed a larger

decrease to 67 % (entry 4). When the time was reduced to 8 hours, the 10 mol % catalysed reaction was found to be efficient, showing a 90 % conversion from the starting material. However, the 5 mol % catalysed reaction conversion dropped significantly (entry 6) and so, further reactions were only performed using 10 mol % of the Cu^I catalyst. Interestingly, when the reaction time was reduced even more to 4 h, the conversion was found to be as high as 85 % (entry 7). However, a further reduction in time to 2 hours led to a small drop in the percent conversion, but it was still surprisingly good at 86 % (entry 8). As the price of the metal catalyst was quite high, a cheaper alternative of the same metal *i.e.* [Cu(MeCN)₄]BF₄ was used instead (entry 9). A high percent conversion (89 %) and isolated yield (74 %) were obtained with the new Cu^I catalyst (entry 9) when the reaction was stirred for 18 hours at room temperature.

Table 2.3 Optimisation of the reaction conditions with Cu^I catalyst

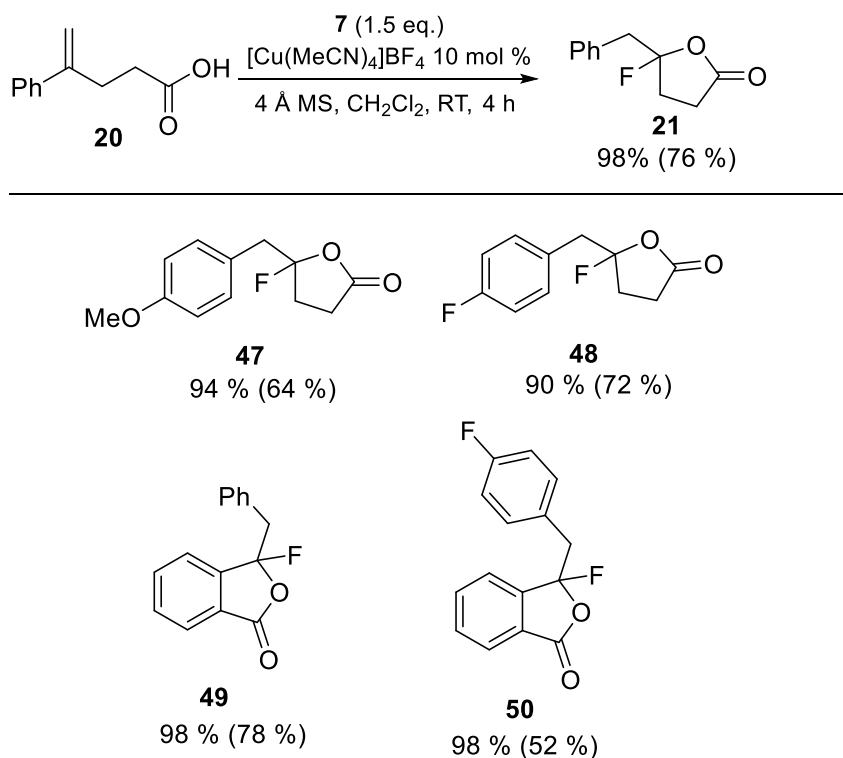


Entry	Cu ^I (10 mol %)	T (°C)	Time (h)	Conversion (%) ^{a,b} 21	20
1	[Cu(MeCN) ₄]PF ₆	40	1	99 (71)	1
2	[Cu(MeCN) ₄]PF ₆	RT	18	90 (70)	10
3	[Cu(MeCN) ₄]BF ₄	RT	18	89 (74)	11
4	[Cu(MeCN) ₄]BF ₄	RT	4	98 (76)	2

^a Conversion calculated by ¹H NMR spectroscopy, refers to the consumption of the starting material **20**. ^b Isolated yields in parenthesis.

Satisfied with the results under catalytic conditions using copper salts, it was intended to see whether a shorter reaction time would be efficient with the new [Cu(MeCN)₄]BF₄ catalyst. As shown in entry 4, a reduced time to four hours generated the desired fluorocyclisation product **21** in an excellent conversion and even higher yield than when it was attempted for 18 hours at room temperature (entry 3) or for 1 hour at 40 °C (entry 1).

2.4.3 Catalytic fluorocyclisation with optimised conditions using [Cu(MeCN)₄]BF₄

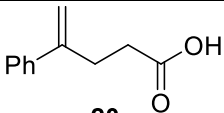
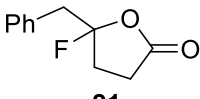
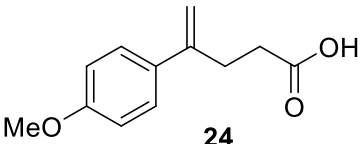
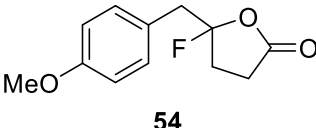
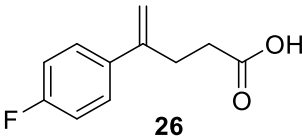
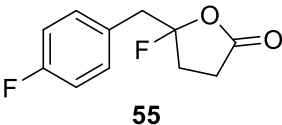
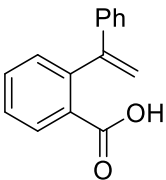
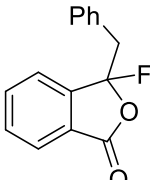
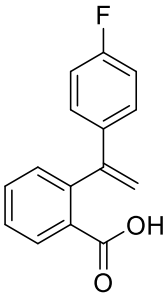
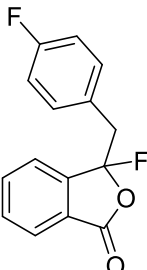


Scheme 2.13 *Synthesis of γ -lactones*

Having developed the optimum conditions for the fluorocyclisation reaction of **20** which used $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (10 mol %), 4 Å molecular sieves and 1.5 equivalents of the fluorinating reagent **7** in dry dichloromethane, the substrate scope of the intramolecular fluorocyclisation was tested with four different substrates and the resulting γ -lactones were formed in good isolated yields (52–78 %), as shown in **Scheme 2.13**. Interestingly, the electron donating groups on the aromatic ring did not have a direct effect on the reactivity of the substrates towards fluorocyclisations. The γ -lactones were fully characterised by ^1H , ^{13}C and ^{19}F NMR spectroscopy as well as ASAP mass spectrometry. Their characterisation data was in agreement with the literature.⁶⁰

Compared to the reactions attempted in the presence of AgBF_4 (1 eq.) at 40 °C for 1 hour reported by Stuart,⁶⁰ the fluorocyclisations performed under catalytic Cu^{I} conditions were of near equal efficiency. The conversion from the starting material reaching over 90 % was observed in this work, whereas in the reactions using AgBF_4 (1 eq.) it was slightly less efficient. The isolated yields after purification by column chromatography were very similar to those reported (**Table 2.4**).⁶⁰

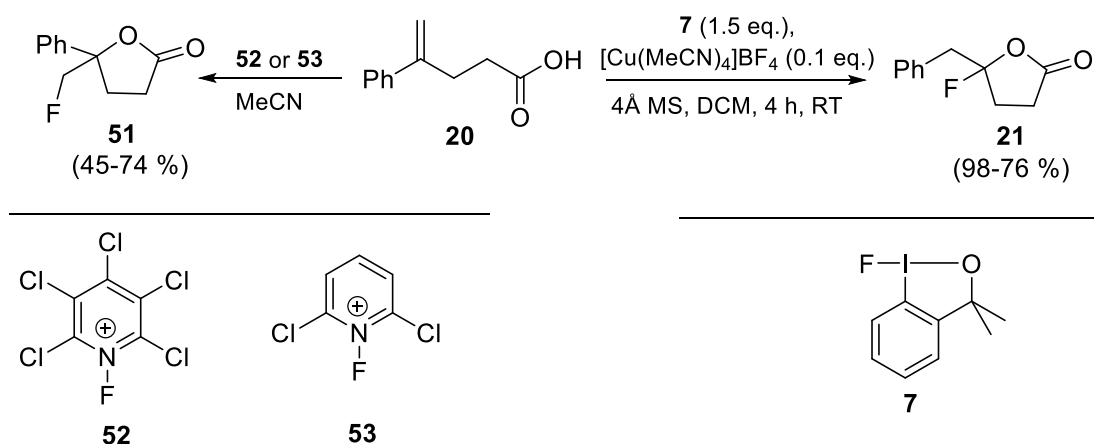
Table 2.4 Fluorocyclisation reactions with AgBF_4 and $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$

Substrate	Product	AgBF_4 (1 eq.) Conversion ^a (%) ^b	$[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (0.1 eq.) Conversion ^a (%) ^b
 20	 21	88 (81)	98 (76)
 24	 54	79 (65)	94 (64)
 26	 55	85 (77)	90 (72)
 28	 56	90 (86)	98 (78)
 30	 57	67 (48)	98 (52)

^a Conversion calculated by ^1H NMR spectroscopy, refers to the consumption of the starting materials. ^b Isolated yields in parenthesis.

A characteristic feature of the fluoroiodane reagent **7** was the formation of γ -lactones containing a tertiary alkyl fluoride which was in sharp contrast to the fluorolactonisation reactions utilising *N*-fluoropyridinium triflates (**Scheme 2.14**). Overall, high reaction conversions and good isolated yields were obtained in this work, showing that the intramolecular fluorocyclisations can be promoted successfully with a catalytic amount

of Cu^I salts. Additionally, the reduced amount of the catalyst and lowered reaction temperature did not induce the formation of the iodoalkene byproduct which was observed in reactions with AgBF₄ at 40 °C for 1 hour.

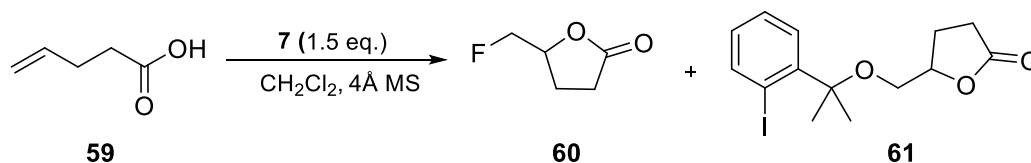


Scheme 2.14 Fluorocyclisation with fluoraza reagents and the fluoroiodane

2.5 Substrate scope of the fluorocyclisation reaction

2.5.1 Fluorocyclisation reactions of 4-pentenoic acid **59**

Having seen positive results in the intramolecular fluorocyclisation reactions of unsaturated carboxylic acids under both stoichiometric and catalytic conditions, the aim was to expand the reaction scope further by testing the reactivity of monosubstituted alkenes. The commercially available 4-pentenoic acid **59** was studied to investigate if the lactone 5-(fluoromethyl)dihydrofuran-2(3*H*)-one **60** could be formed.

Table 2.5 Fluorocyclisation of 4-pentenoic acid **59**

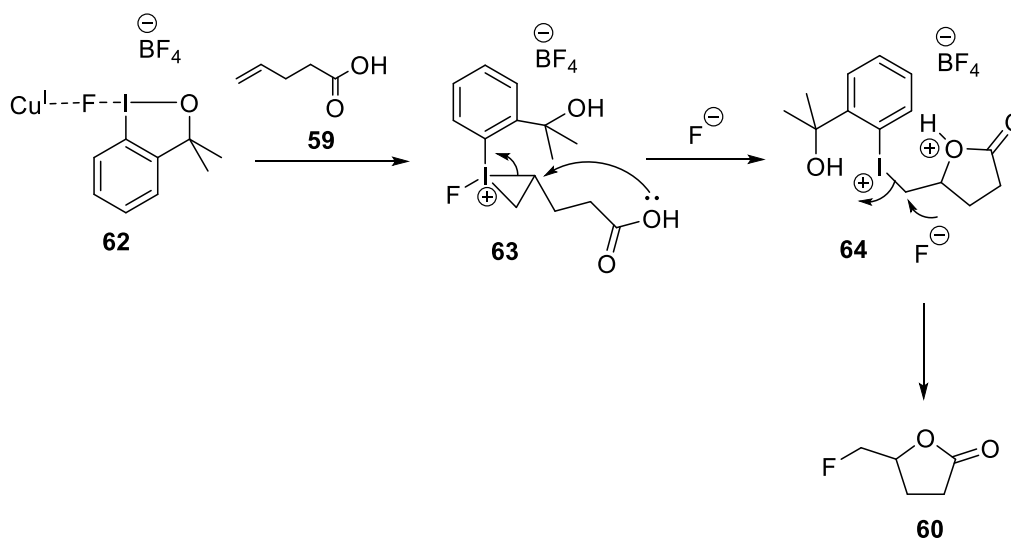
Entry	Additive (eq.)	T (°C)	Time (h)	Consumption ^a 59	Yield 60 (%) ^b	Yield 61 (%) ^b
1	AgBF ₄ (1)	40	1	96	40	26
2	AgBF ₄ (0.2)	40	1	85	37	15
3	Cu (0.2) ^c	40	1	86	38	16
4	AgBF ₄ (0.2)	RT	4	75	37	5
5	Cu (0.2) ^c	RT	4	73	38	5
6	Cu (0.2) ^c	40	4	83	55	9

^a Consumption calculated by ¹H NMR spectroscopy. ^b Isolated yield after column chromatography. ^c[Cu(MeCN)₄]BF₄

Firstly, the standard reaction conditions developed by Stuart (entry 1) were applied, which resulted in a 96 % conversion of the starting material. The desired lactone **60** was isolated in 40 % yield along with the byproduct **61** (26 %). The singlet in the ¹⁹F NMR spectrum at -232.6 ppm was characteristic for the primary alkyl fluoride. The amount of catalyst was reduced to 0.2 equivalents in entry 2, resulting in a drop in the consumption of the starting material and the isolated yield of the desired product to 85 % and 37 % respectively. The byproduct **61** was also isolated in a lower 15 % yield. Aiming to find the best reaction conditions, Cu^I was used instead of Ag^I, but the reaction did not show any significant changes yielding 38 % of the fluorinated product **60** along with 16 % of the byproduct **61** in entry 3.

Interestingly, when the temperature of the reaction was reduced to RT using 0.2 equivalents of both Lewis acid catalysts (entries 4-5), the fluorinated product was still formed successfully in similar yields, but the amount of byproduct **61** dropped to 5 %. In a final attempt (entry 6) using 0.2 equivalents of Cu^I reagent, the reaction was conducted at 40 °C for 4 hours giving a similar 83 % conversion to entry 3 (86 %), but a much better isolated yield of 55 % was achieved.

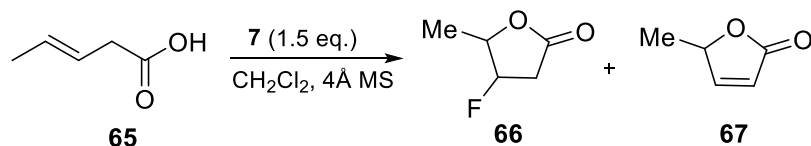
It is important to note that purification by column chromatography in most cases generated mixed fractions of the fluorinated lactone **60** together with the iodoalcohol **5**. The complete separation was achieved by re-crystallisation in hexane. Compounds **60** and **61** were fully characterised by ¹H, ¹³C and ¹⁹F NMR spectroscopy as well as ASAP mass spectrometry and was in agreement with the literature.⁵⁰ The byproduct **61** had a singlet at 1.69 ppm in ¹H NMR spectrum which corresponded to two CH₃ groups on the iodoalcohol backbone as well as three sets of multiplets from CH₂ groups on the lactone moiety. The carbonyl carbon singlet (C=O) appeared at 177.6 ppm in the ¹³C NMR spectrum.



Scheme 2.15 Proposed copper-catalysed reaction mechanism for the formation of **60**

2.5.2 Fluorocyclisation reactions of 3-pentenoic acid **65**

Table 2.6 Fluorocyclisation of 3-pentenoic acid **65**



Entry	Additive (eq.)	T (°C)	Time (h)	Conversion ^a (%)	Yield of 67 (%) ^b
1	$[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (0.1)	RT	4	2	0
2	$[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (0.2)	40	4	8	0
3	AgBF_4 (1.0)	40	4	48	0
4	-	RT	20	0	0
5	$[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (0.2)	40	20	73	69

^a Conversion calculated by ^1H NMR spectroscopy, refers to the consumption of the starting material **65**. ^b Isolated yield after column chromatography.

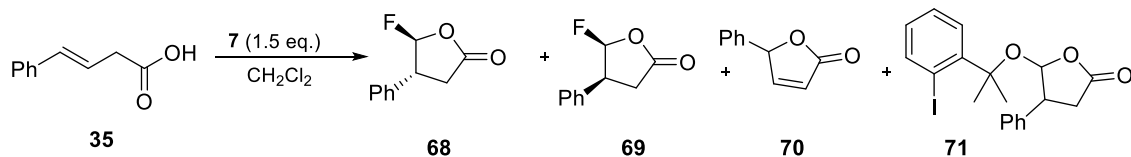
The reactivity of the *trans*-disubstituted alkene, 3-pentenoic acid **65**, was tested next. In entry 1 3-pentenoic acid was treated with 1.5 equivalents of the fluoroiodane reagent **7**, 0.1 equivalents of $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ and 4Å molecular sieves at room temperature for 4 hours. The ^1H and ^{19}F NMR spectra confirmed that the fluorinated product **66** was not formed. The crude reaction mixture showed the unreacted starting material **65** along with fluoroiodane **7** and traces of iodoalcohol **5**. Aiming to increase the activation of the fluoroiodane reagent, the reaction conditions were changed by increasing the amount of the Lewis acid catalyst from 0.1 to 0.2 equivalents as well by raising the reaction temperature from RT to 40 °C. However, only a slight increase in the conversion from the starting material to the unsaturated lactone **67** was observed (entry 2) without any evidence for the desired fluorinated product **66**. Instead of using $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$, AgBF_4 was chosen as an alternative Lewis acid which induced efficiently the fluorocyclisations of geminal disubstituted alkenes. In entry 3, 1 equivalent of AgBF_4

along with 1.5 equivalents of the reagent **7** was reacted at 40 °C for 4 hours. A significant increase in the consumption of the starting material was observed, forming the unsaturated lactone **67** in 48 % conversion, as monitored by ¹H NMR spectroscopy. However, the change in the Lewis acid catalyst did not show any progress towards the formation of the desired fluorinated product **66**. Seeing no evidence in the formation of **66** using both Lewis acids, an additive-free reaction was performed at room temperature for a much longer reaction time (entry 4). Unfortunately, the reaction did not show any progress towards the fluorination or elimination, resulting mainly in the unreacted starting material **65** and the fluorinating reagent **7**. The desired product was not formed because the secondary alkyl fluoride was more susceptible to undergo elimination generating an alkene in conjugation with the carbonyl group.

Since there was no evidence for the formation of the fluorinated lactone **66** in any attempted reaction, the aim was to increase the formation of the eliminated product **67** instead. By comparing entries 1 and 2, it seemed that the reaction temperature and a slight increase in the amount of the Cu^I showed a higher consumption of the starting material. Therefore, the reaction time was increased from 4 to 20 hours and the reaction was conducted at 40 °C using 0.2 equivalents of the Cu^I catalyst. The reaction resulted in 73 % conversion and 69 % isolated yield. The isolated compound **67** was characterised fully by ¹H and ¹³C NMR spectroscopy as well as ASAP mass spectrometry. A characteristic doublet of doublets at 6.0 ppm with coupling constants of 5.6 Hz and 1.9 Hz and a doublet at 7.36 ppm with a coupling constant of 5.7 Hz was assigned for the two alkene protons in the ¹H NMR spectrum. The ASAP-MS showed a peak at *m/z* 97 corresponding to (M-H)⁺.

2.5.3 Fluorocyclisation reactions of (*E*)-4-phenylbut-3-enoic acid **35**

Table 2.7 Fluorocyclisation reactions of (*E*)-4-phenylbut-3-enoic acid **35**



Entry	Additive (eq.)	Time (h)	Conversion 35 / 68-69 (%) ^a	d.r.	Yield of 68/ 69 (%) ^b	Yield of 70 (%) ^b	Yield of 71 (%) ^b
1	AgBF ₄ (1.0)	4	95	1.9:1	45	7	11
2^c	AgBF ₄ (1.0)	4	87	1.7:1	49	12	0
3^d	AgBF ₄ (0.2)	4	2	1.8:1	0	0	0
4^c	AgBF ₄ (1.0)	1	4	1.6:1	0	0	0
5	Cu (0.2) ^e	4	47	2:1	33	26	4
6^{c, f}	Cu (0.2) ^e	4	3	2:1	0	0	0

^a Conversion calculated by ¹H NMR spectroscopy, refers to the consumption of the starting material **35**. ^b Isolated yield after column chromatography; ^c Without 4Å MS. ^d 23 % conversion to **70** (not purified). ^e [Cu(MeCN)₄]BF₄. ^f 25 % conversion to **70** (not purified).

The reactivity of a second, *trans*-disubstituted alkene, (*E*)-4-phenylbut-3-enoic acid **35**, was tested in the fluorocyclisations (**Table 2.7**). The feasibility of the reaction was first investigated with the already developed conditions at 40 °C for 4 hours using 4Å molecular sieves in dichloromethane (entry 1). The ¹H and ¹⁹F NMR spectra of the crude reaction mixture confirmed a high conversion of the starting material and the formation of the fluorinated product as a mixture of diastereomers **68/69** at -114.9 and -134.2 ppm in a 1.9:1 ratio in the ¹⁹F NMR spectrum. The crude product was purified by column

chromatography using DCM as eluent and two byproducts **70** (7 %) and **71** (11 %) were also isolated in low yields. The ^1H NMR spectrum showed a distinctive doublet for the *CHF* proton coupling to the fluorine atom with a $^2J_{\text{HF}}$ coupling constant of 61 Hz at 5.98 ppm confirming that phenyl migration had occurred.

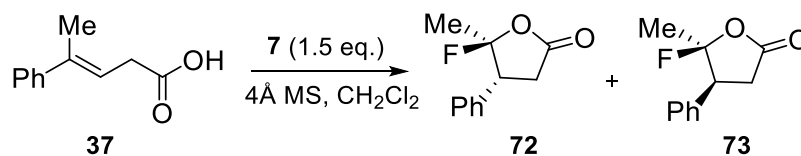
When the same reaction was attempted without 4Å molecular sieves (entry 2), the reaction generated the desired mixture of fluorinated lactones **68** and **69** in 49 % overall yield along with the byproduct **70** obtained in 12 % yield. Stuart found that the ring opened byproduct was formed in the intramolecular fluorocyclisation reactions of *geminal*-disubstituted alkenes attempted in the absence of molecular sieves. Interestingly, the predicted byproduct was not formed in this reaction with a *trans*-disubstituted substrate, presumably because the less substituted secondary alkyl fluoride is more stable than the tertiary alkyl fluoride, and is therefore less likely to undergo ring opening.

The amount of AgBF_4 reagent was lowered to 0.2 equivalents in entry 3, but unfortunately, the reaction did not work, showing mainly the unreacted starting material **35** with traces of **70**. Since the isolated yield of the desired mixture of diastereomers **68/69** was best achieved with the stoichiometric amount of the AgBF_4 , the reaction was repeated for 1 hour (entry 4). Disappointingly, the reaction did not work.

As a direct comparison to the Ag^{I} induced reactions, 0.2 equivalents of Cu^{I} were also tested (entry 5). Surprisingly, the conversion of the starting material was considerably higher reaching 47 % compared to 2 % using Ag^{I} (entry 3). The fluorinated product was isolated in 33 % yield along with byproducts **70** and **71** in 26 % and 4 % yields respectively. The same reaction was repeated without molecular sieves (entry 6), however, the crude ^1H NMR spectrum did not show any evidence of either ring opened compound or the desired fluorinated product. Only the unreacted starting material **35** along with the fluoroiodane **7** was observed.

2.5.4 Fluorocyclisation reactions of (*E*)-4-phenylpent-3-enoic acid **37**

Table 2.8 Fluorocyclisation reactions of (*E*)-4-phenylpent-3-enoic acid **37**



Entry	Additive (eq.)	T (°C)	Time (h)	Conversion 37 / 72-73 (%) ^a	d.r.	Yield of 72/ 73 (%) ^b
1	Ag (1.0)	40	4	100	1 / 2.2	64 (24 / 40)
2	Ag (1.0)	40	1	100	1 / 2.4	50 (22 / 28)
3	Ag (0.2)	40	1	41	1 / 2.6	36 (16 / 20)
4	Ag (0.2)	40	4	77	1 / 2.7	56 (21 / 35)
5	Cu (0.2)	40	1	42	1 / 2.6	0
6	Cu (0.2)	40	4	59	1 / 2.2	0
7	Ag (1.0)	RT	4	100	1 / 2.4	54 (31 / 23)

^aConversion calculated by ¹H NMR spectroscopy, refers to the consumption of the starting material **37**. ^bIsolated yield after column chromatography.

A trisubstituted unsaturated carboxylic acid **37** was next tested in the intramolecular fluorocyclisation reaction using fluoroiodane **7**. Applying the standard reaction conditions in entry 1, a 100 % conversion from the starting material to the desired fluorinated product was obtained as a mixture of diastereomers in a 1 : 2.2 ratio. The two diastereomers were isolated successfully by column chromatography on silica gel using dichloromethane as eluent. The first diastereomer had a singlet at -86.3 ppm in the ¹⁹F NMR spectrum and was a yellow oil, whilst the second one was a solid with a singlet at -107.7 ppm in the ¹⁹F NMR spectrum. The latter **73** was submitted for X-ray crystallography which confirmed that the structure exists in the *syn* configuration with respect to fluorine atom and the Ph group (**Figure 2.3**). Characteristic bond lengths (Å)

and bond angles ($^{\circ}$) are shown in **Table 2.9**. The two structures also showed slight differences in their ^1H NMR spectra. The CH_3 group in the *anti*-configuration **72** appeared as a doublet at 1.37 ppm due to coupling to the fluorine atom with a $^3J_{\text{HF}}$ coupling constant of 18.9 Hz. The same methyl group in the *syn*-configuration **73** was shifted to 1.69 ppm and had a $^3J_{\text{HF}}$ coupling constant of 17.8 Hz. A $^1\text{H}\{^{19}\text{F}\}$ NMR spectrum was obtained and, as expected, showed a singlet CH_3 peak only.

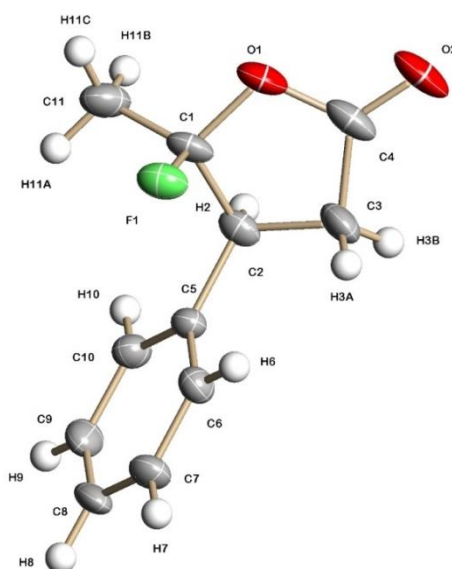


Figure 2.3 Molecular structure of **73** with atom labelling and ellipsoids at 50 % probability.

Table 2.9 Selected bond lengths (\AA) and angles ($^{\circ}$) for **73**

Atoms	Bond lengths (\AA)	Atoms	Bond angles ($^{\circ}$)
F(1)-C(1)	1.404(3)	F(1)-C(1)-O(1)	105.4(2)
O(1)-C(1)	1.421(3)	O(1)-C(1)-C(11)	109.9(2)
O(1)-C(4)	1.372(4)	C(4)-O(1)-C(1)	110.4(2)
O(2)-C(4)	1.198(4)	O(2)-C(4)-O(1)	120.5(3)

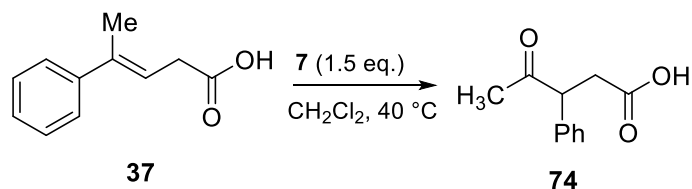
In entry 2, the reaction time was reduced to 1 hour at 40°C , but although the reaction conversion reached 100 %, the isolated yield dropped slightly to 50 %. When the amount of the Lewis acid was lowered to 0.2 equivalents in entry 3, a considerable drop in conversion to 41 % was observed, which also resulted in a lower overall yield of 36 %.

When the same reaction was repeated for 4 hours (entry 4), the consumption of the starting material increased significantly to 77 % giving the fluorinated product in 56 % yield.

As a comparison to AgBF_4 , a copper(I) reagent was used in entry 5 and no significant changes were observed with a 42 % consumption of the starting material. When the reaction time was increased to 4 hours, the conversion was increased by 17 %, concluding that Ag^{I} was a better reagent and a more powerful activator towards the fluoroiodane **7**. Trace amounts of the ring opened product **74** were observed in the crude ^1H NMR spectrum when the reaction time was increased to 4 hours in entry 6. It was thought that the slightly acidic silica could facilitate the ring opening even further, therefore the purification was attempted on Al_2O_3 . However, the separation was not successful and the desired product was not isolated.

Finally, the reaction was performed at room temperature using 1 equivalent of the Ag^{I} reagent for 4 hours. Surprisingly, the reaction went to completion and the fluorinated product was isolated in 54 % overall yield.

Table 2.10 Formation of the ring opened compound **74**



Entry	Additive (eq.)	Time (h)	Conversion (%) ^a	Yield of 74 (%) ^b
1	$\text{Zn}(\text{BF}_4)_2 \cdot x\text{H}_2\text{O}$ (0.2)	4	100	84
2^c	AgBF_4 (1.0)	1	100	65

^a Conversion calculated by ^1H NMR spectroscopy, refers to the consumption of the starting material **37**. ^b Isolated yield after column chromatography. ^c Without 4Å MS.

Since a zinc(II) hydrate was discussed in the literature as an efficient additive in the fluorocyclisation reactions,⁵⁹ it was also tested in this work. Interestingly, the molecular sieves did not prevent the ring opening reaction and resulted in the formation of **74** in 84 % yield (entry 1). No signs of the desired fluorinated lactone were detected in the ^1H

NMR spectrum of the crude reaction mixture. Previously it was proved that the molecular sieves act as a water scavenger and so the reaction was attempted using Ag^{I} reagent as the only additive (entry 2). As expected, only the ring-opened product was formed and isolated in 65 % yield which was characterised by ^1H and ^{13}C NMR spectroscopy as well as mass spectrometry. Yellow crystals were grown in DCM : petroleum ether (40-60) and the solid-state structure is shown in **Figure 2.4**.

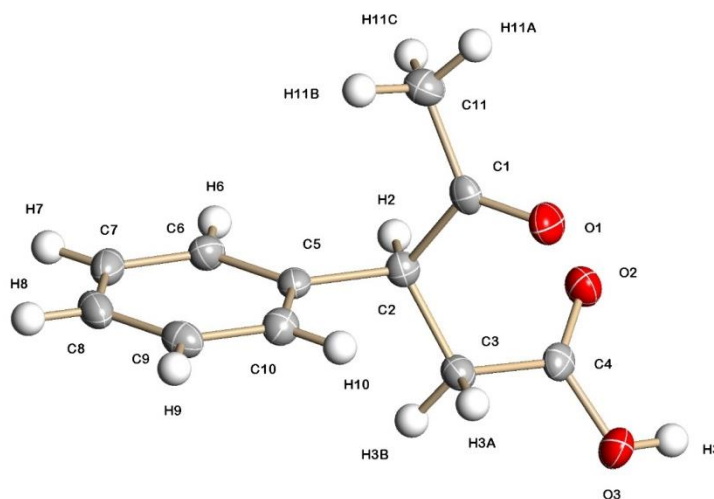


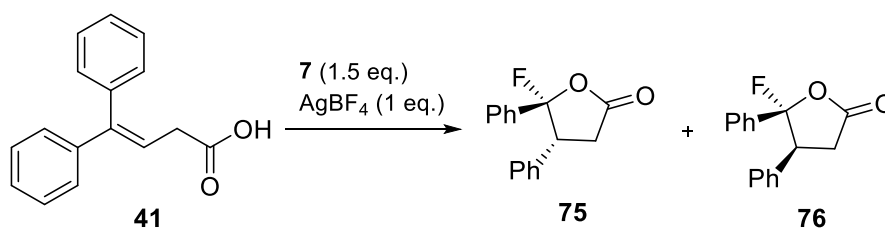
Figure 2.4 Molecular structure of **74** with atom labelling and ellipsoids at 50 % probability

Table 2.11 Selected bond lengths (\AA) and angles ($^\circ$) for **74**

Atoms	Bond lengths (\AA)	Atoms	Bond angles ($^\circ$)
O(2)-C(4)	1.203(3)	O(2)-C(4)-O(3)	123.9(3)
O(1)-C(1)	1.218(3)	O(1)-C(1)-C(2)	120.3(2)
O(3)-C(4)	1.335(3)	O(3)-C(4)-C(3)	111.5(2)

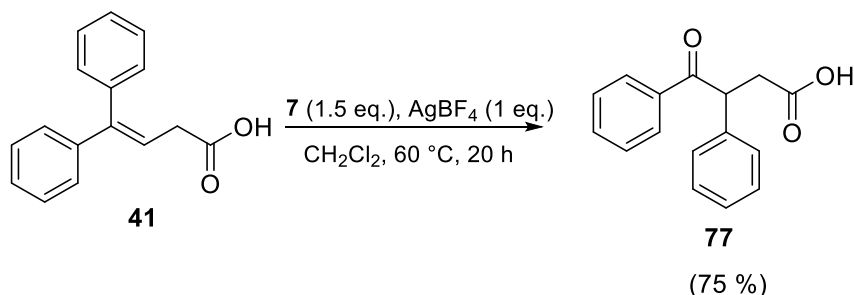
The O(2)-C(4) and O(1)-C(1) bond lengths of the ring opened product **74** ranged from (1.203(3) - 1.218(3) \AA) and the O(3)-C(4) bond length was 1.335(3) \AA . The bond angles of O(1)-C(1)-C(2) and O(2)-C(4)-O(3) were (120.3(2) - 123.9(3) $^\circ$). The O(3)-C(4)-C(3) bond angle was 111.5(2) $^\circ$.

2.5.5 Fluorocyclisation reaction of 4,4-diphenylbut-3-enoic acid **41**



Scheme 2.16 Fluorocyclisation reaction of 4,4-diphenylbut-3-enoic acid **41**

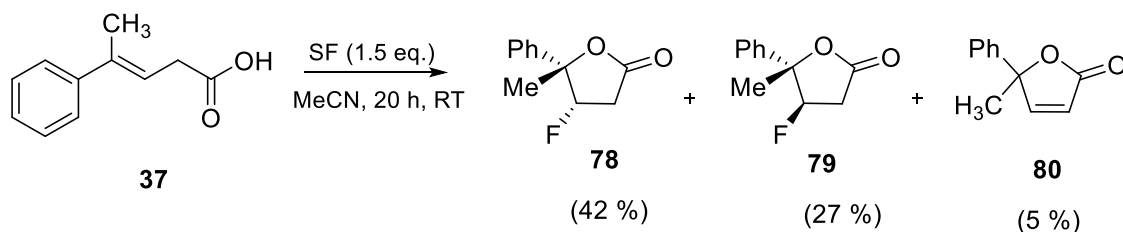
The standard conditions using 1 equivalent of AgBF_4 at 40 °C for 4 hours were first applied to the fluorocyclisation of trisubstituted acid **41** and mainly showed the unreacted starting material in the ^1H NMR spectrum (**Scheme 2.16**). To increase the solubility of the starting material, acetonitrile was used instead of dichloromethane, but no improvements were observed. The reaction temperature was then increased to 60 °C, but even that did not show any significant changes. Lastly, the reaction time was extended to 20 hours, but that did not show any conversion to the desired product.



Scheme 2.17 Formation of a ring opened product **77**

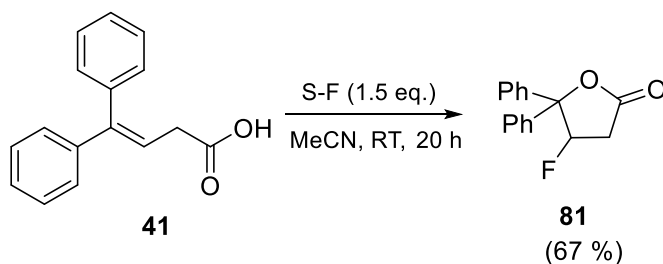
When substrate **41** was reacted with 1 equivalent of AgBF_4 at 60 °C for 20 hours in the absence of 4Å MS, the reaction generated the ring opened product **77** in 75 % isolated yield. A doublet of doublets corresponding to the CHPh proton was found at 5.05 ppm in the ^1H NMR spectrum and had $^3J_{\text{HH}}$ coupling constants of 9.7 Hz and 4.8 Hz, respectively. The two CH_2 protons appeared at 2.75 ppm and 3.41 ppm in the proton NMR spectrum as separate doublet of doublets. The two carbonyl peaks were found at 171.2 ppm and 198.3 ppm in the ^{13}C NMR spectrum. The ASAP-MS confirmed the structure of the ring opened product with a mass of m/z 237.0921 for $(\text{M}-\text{OH})^+$.

2.5.6 Fluorocyclisation reaction of (*E*)-4-phenylpent-3-enoic acid **37** and 4,4-diphenylbut-3-enoic acid **41** with SelectFluor



Scheme 2.18 Fluorocyclisation reaction of (*E*)-4-phenylpent-3-enoic acid **37** with Selectfluor

To confirm that the fluoroiodane reagent **7** was inducing a phenyl migration, generating a tertiary alkyl fluoride, the reaction was attempted using the conventional electrophilic fluorinating reagent, SelectFluor (1.5 eq.). The desired fluorinated lactones were successfully formed in 42 % and 27 % yields, respectively and were in agreement with the literature. As in the previous case using fluoroiodane **7**, one isomer was obtained as a white solid, and the solid-state structure confirmed the *anti*-configuration **79** (**Figure 2.5a**). The two diastereomers showed singlets at -176.1 ppm and -182.1 ppm in the ^{19}F NMR spectrum. The doublet peak at 1.79 ppm in the ^1H NMR spectrum corresponded to the CH_3 group which was coupling to the fluorine with a $^4J_{\text{HF}}$ coupling constant of 3.7 Hz. Such a small coupling was not found in the *syn*-configuration **78** and only showed a singlet CH_3 peak at 1.62 ppm. The elimination product **80** was isolated together with **79** in 5 % yield. The structure of **80** was confirmed by ^1H NMR spectroscopy, showing two separate doublets at 5.98 ppm and 7.59 ppm with a $^3J_{\text{HH}}$ coupling constant of 5.6 Hz.²⁶



Scheme 2.19 Fluorocyclisation reaction of 4,4-diphenylbut-3-enoic acid **41** with Selectfluor

As the fluorocyclisation reaction using fluoroiodane **7** and AgBF₄ did not work with substrate **41**, the reaction was tested with SelectFluor (**Scheme 2.19**). The reaction generated a single product, which after purification by column chromatography was obtained in 67 % yield and had a singlet at -180.6 ppm in the ¹⁹F NMR spectrum. In the ¹H NMR spectrum there was a doublet of doublets at 5.85 ppm for the CHF proton with a ²J_{HF} coupling constant of 46.7 Hz. The structure of the cyclised product **81** was confirmed by X-ray crystallography (**Figure 2.5b**). The key bond lengths and angles are presented in (**Table 2.12**).

Figure 2.5 Solid-state structures for fluorolactones **79** and **81**

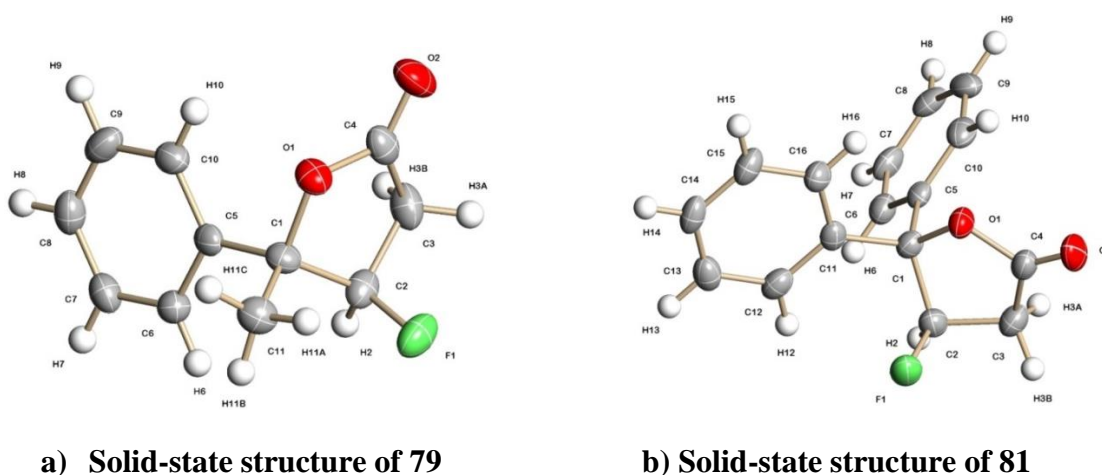
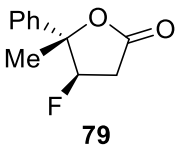
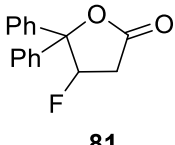


Table 2.12 Selected bond lengths (Å) and angles (°) for **79** and **81**

	Atoms	Bond lengths (Å)	Atoms	Bond angles (°)
 <p>79</p>	F(1)-C(2)	1.407 (2)	F(1)-C(2)-C(1)	109.5(2)
	O(1)-C(4)	1.360(3)	C(4)-O(1)-C(1)	111.3(2)
	O(1)-C(1)	1.468(3)	O(1)-C(1)-C(5)	109.6(1)
	O(2)-C(4)	1.197(3)	O(2)-C(4)-O(1)	120.7(2)
 <p>81</p>	F(1)-C(2)	1.422 (5)	F(1)-C(2)-C(1)	106.0(3)
	O(1)-C(4)	1.390(5)	C(4)-O(1)-C(1)	109.9(3)
	O(1)-C(1)	1.468(5)	O(1)-C(1)-C(2)	103.0(3)
	O(2)-C(4)	1.203(5)	O(2)-C(4)-O(1)	119.2(4)

2.6 Transition metal-free fluorocyclisations

2.6.1 Fluorocyclisation reactions using fluoroalcohols

The efficiency of **7** as a fluorinating reagent has been proven with a wide range of substrates. The pioneering work by Szabó showed that **7** can be employed successfully in the fluorination reactions of styrenes, cyclopropanes and diazocarbonyls.^{59, 63-64} The same group investigated the intramolecular fluorocyclisations of unsaturated alcohols, amines and malonates. A unique feature using the fluoroiodane reagent was the preparation of γ -lactones containing tertiary alkyl fluorides which was reported by Stuart and has been shown in this work. However, all of the above mentioned strategies require the activation of the fluoroiodane reagent by a transition metal. Gulder developed the synthesis of fluoro-benzoxazepines based on a similar reaction mechanism involving a fluorination, an aryl migration and cyclisation, and showed that in the presence of a hydrogen bond donor, no other external activators were required for the initiation of the fluorocyclisation.⁶¹ DFT calculations showed that the intramolecular hydrogen bond donor-activated the fluorinating reagent through its fluorine atom.⁷⁹

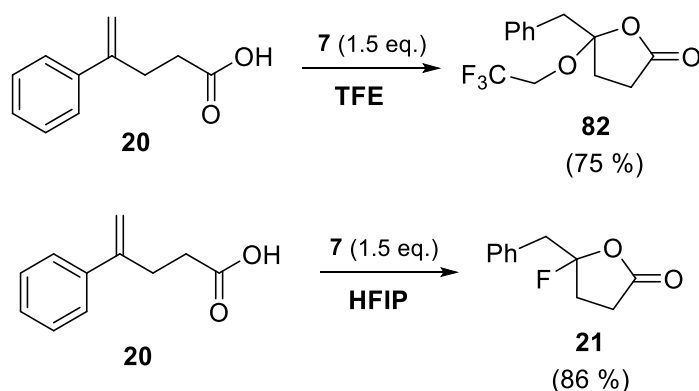
This unusual finding prompted the exploration of the potential of the fluoroiodane reagent **7** for intramolecular fluorocyclisations in the absence of a transition metal. Therefore, in this work it is proposed that the strong hydrogen bonding ability and reduced nucleophilicity of hexafluoroisopropanol (HFIP) makes it an excellent substitute to transition metal activators to perform fluorinations with the hypervalent fluoroiodane reagent **7**.

The use of the fluoroalcohol, HFIP, has been found crucial for the activation of reaction intermediates in the synthesis of polyenes reported by Gulder.¹⁰⁶ Due to the strong hydrogen-bond donor ability, HFIP has proved to be an efficient solvent for the regioselective halogenation of arenes and heterocycles with *N*-halosuccinimides without requiring any additional catalyst or activator. This allowed the sequential halogenation of arenes followed by Suzuki cross-coupling without removal of the solvent.¹⁰⁷ Furthermore, HFIP has also been successfully utilised in the metal-free oxidative cross-coupling of thiophenes and pyrroles with hypervalent iodine reagents, generating the desired products in high yields and regioselectivities.¹⁰⁸ Therefore, the aim of this section was to perform the intramolecular fluorocyclisations of unsaturated carboxylic acids using HFIP as a

hydrogen bond donor to activate the fluoroiodane reagent **7**. It is proposed that within this activation, the external Lewis acid is not required.

2.6.2 Preliminary work with fluoroalcohols (HFIP and TFE)

The fluoroalcohols exhibit unique properties that are remarkably different from regular alcohols due to the fluoroalkyl groups. Their high polarity index, low nucleophilicity and excellent hydrogen bond donor ability make them exclusive reagents or solvents in various reactions.¹⁰⁹ Following Gulder's work based on the fluorocyclisation reaction induced by intramolecular hydrogen bonding,⁶¹⁻⁷⁹ it was decided to test the reactivity of the fluoroalcohols for the preparation of γ -lactones.



Scheme 2.20 Preliminary fluorocyclisation using Fluoroalcohols

The investigation started with the use of 4-phenyl-4-pentenoic acid **20** and fluoroiodane **7** in trifluoroethanol (TFE) in the presence of 4Å molecular sieves for 1 hour at 40 °C. Although the cyclised lactone was formed, the trifluoroethanol underwent the nucleophilic attack instead of fluoride and formed compound **82** in 75 % yield. The singlet in the ¹⁹F NMR spectrum at -74.4 ppm confirmed the structure of the cyclised lactone containing the trifluoroethanol moiety. The quartet at 4.03 ppm in the ¹H NMR spectrum had a ³J_{HF} coupling constant of 17.2 Hz and corresponded to the CH₂ group coupling to the CF₃ moiety. A quartet having a coupling constant of 276.7 Hz corresponding to the CF₃ group appeared at 122.1 ppm in the ¹³C NMR spectrum.

In the next fluorocyclisation HFIP was used under the same reaction conditions, leading to the formation of the desired fluorinated γ -lactone in a high, 86 % yield. The ¹H and ¹⁹F NMR spectra of the crude product showed the full consumption of both the starting material **20** and the fluoroiodane **7**. The purification by column chromatography was

required in order to separate product **21** from iodoalcohol **5**. In contrast, the fluorocyclisation using 1 equivalent of AgBF_4 generated the same product in a slightly lower 81 % yield.

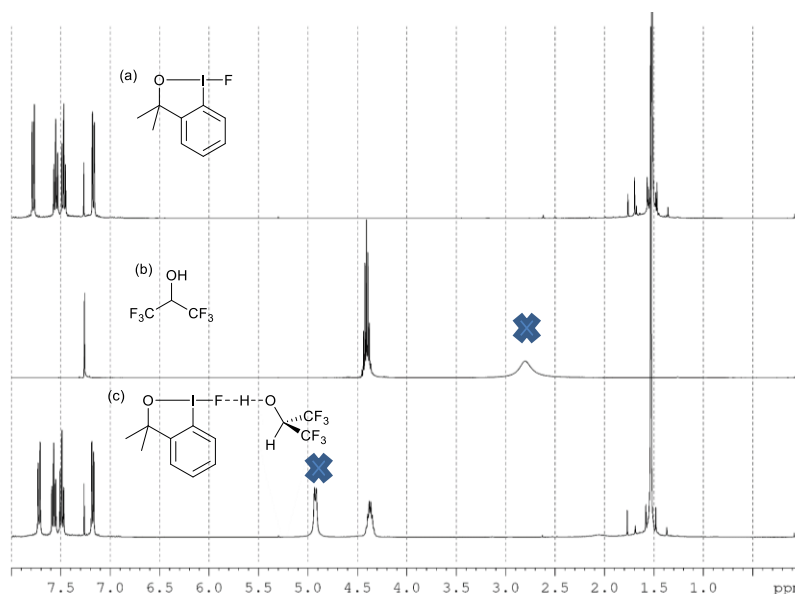
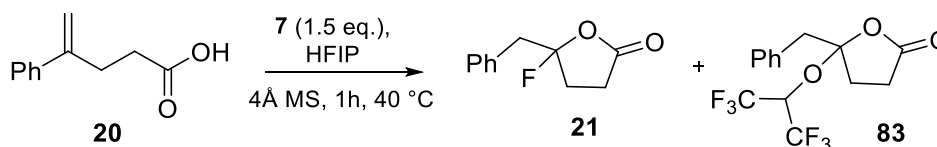


Figure 2.6 ^1H NMR spectra of (a) fluoroiodane **7**, (b) HFIP and (c) a 1:1 mixture of fluoroiodane:HFIP, showing a plausible structure of an adduct. The blue cross indicates the position of the deshielded OH signal of interest.¹¹⁰

DFT studies on the activation of the fluoroiodane reagent in the presence of transition metal additives were investigated in detail, confirming that the most accepted form of the activated fluoroiodane is based on the metal binding to the fluorine rather than the oxygen atom.⁸³ As no additional additives were used in this reaction, it was important to investigate how the activation is achieved using HFIP. Therefore, a series of ^1H ^{19}F and ^{13}C NMR experiments were recorded, providing insights into the activation mode of the fluorinating reagent. In the ^1H NMR of HFIP the broad OH singlet appeared at 2.80 ppm. Interestingly, when the ^1H NMR experiment was recorded for a 1:1 adduct of **7** and HFIP, the same OH signal was significantly shifted to 4.92 ppm and appeared as a doublet having a 7.8 Hz coupling, forming a hydrogen-bonded adduct between the HFIP and the fluoroiodane. The ^{13}C NMR spectrum showed a slight downfield shift in the carbon bonded to the oxygen in fluoroiodane from 85.2 ppm to 86.1 ppm in the 1:1 adduct, possibly due to a change in the F-I-O hypervalent bonding orbital upon activation.¹¹⁰

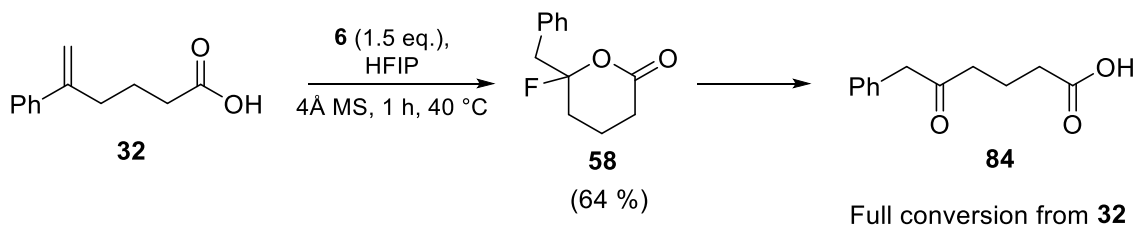
2.6.3 Substrate scope of the fluorocyclisation reactions using HFIP

Having found the optimum conditions for the fluorocyclisations using HFIP, other unsaturated carboxylic acid substrates were tested to prove the efficiency of the metal-free fluorocyclisations. As seen in **Table 2.13**, reactions of *geminal*-disubstituted alkenes (entries 1-4) generated the fluorinated γ -lactones in high yields (79-84 %) with similar or even better yields compared to those under AgBF_4 conditions (69-86 %). A small amount of the hexafluoroisopropoxy-substituted lactone was observed as a minor side product (<5 %) formed due to the competitive O-H insertion (**Scheme 2.21**).



Scheme 2.21 Formation of the hexafluoroisopropoxy-substituted lactone **83**

The silver promoted reaction of **32** reported previously generated the δ -lactone in a low 38 % yield,⁶⁰ but when the same substrate was used in the reaction with HFIP, a much higher 66 % yield was obtained. However, lactone **58** is unstable and decomposed to the ring opened by-product, 5-oxo-6-phenylhexanoic acid **84** over 2-3 hours in CDCl_3 .



Scheme 2.22 Formation of the ring opened **84**

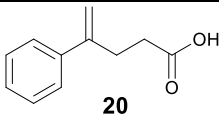
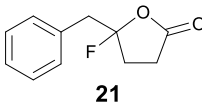
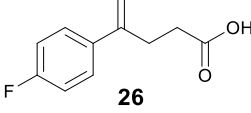
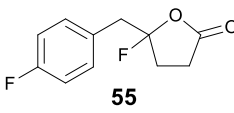
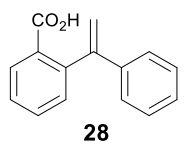
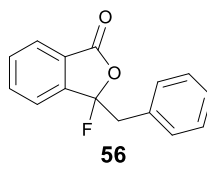
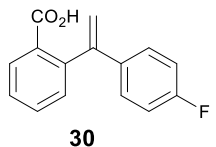
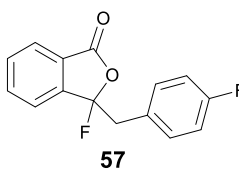
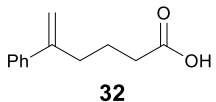
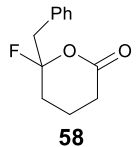
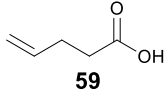
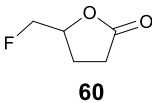
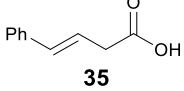
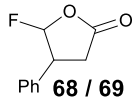
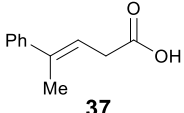
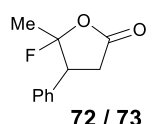
The intramolecular fluorocyclisation of the monosubstituted alkene, 4-pentenoic acid **59** generated 5-(fluoromethyl)dihydrofuran-2(3*H*)-one **60** in a high 82 %. When the same reaction was attempted in the presence of 1 equivalent of AgBF_4 , only a moderate 40 % yield was obtained.

The reactivity of the *trans*-disubstituted alkene, (*E*)-4-phenylbut-3-enoic acid **35**, was quite low under both sets of conditions. The mixture of fluorinated diastereomers was generated in only 36 % yield with HFIP and 45 % with AgBF_4 . Interestingly, from all the

substrates tested in this work, the (*E*)-4-phenylbut-3-enoic acid was the only one that benefited from activation with AgBF₄.

5-Fluoro-5-methyl-4-phenyl-dihydrofuran-2-one was generated as a mixture of diastereoisomers **72/73** in an excellent 86 % yield using HFIP. In contrast, a lower yield of 69 % was obtained in the presence of AgBF₄. The reaction with HFIP generated a very clean crude mixture of diastereomers that only required separation from the iodoalcohol byproduct **5** and from each other to be assigned as individual compounds **72/73**.

Table 2.13 Fluorocyclisations using **7** with and without AgBF₄

Entry	Substrate	Product	Yield with AgBF ₄ (%) ^{a,c}	Yield in HFIP (%) ^{b,c}
1	 20	 21	81 ^d	84
2	 26	 55	77 ^d	80
3	 28	 56	86 ^d	79
4	 30	 57	69 ^d	81
5	 32	 58	38 ^d	66
6	 59	 60	40	82
7	 35	 68 / 69	43 dr = 1.8:1	36 dr = 1.6:1
8	 37	 72 / 73	69 dr = 1:2	86 dr = 2.2:1

^a Reaction conditions: substrate (0.7 mmol), fluoroiodane **7** (1.1 mmol), AgBF₄ (0.7 mmol) and 4 Å molecular sieves (0.18 g) were stirred in dry CH₂Cl₂ (0.4 mL) at 40 °C for 1 h. ^b Reaction

conditions: substrate (0.9 mmol), fluoroiodane (1.36 mmol) and 4 Å molecular sieves (0.11 g) were stirred in HFIP (3 mL) at 40 °C for 1 h. ^c Isolated yield. ^d Result taken from reference 11.

2.6.4 Catalytic fluorocyclisation reactions using HFIP

As the original aim of this chapter was to perform the fluorocyclisations with a catalytic amount of the transition metal, the same hypothesis was raised for the reactions using HFIP. Moreover, as the reactions in the presence of a good hydrogen bond donor generated much cleaner results in excellent isolated yields, the idea of reducing the amount of the additive seemed rational.

Table 2.14 *Optimisation of reaction conditions using HFIP*

Reaction scheme: 4-phenyl-4-pentenoic acid (**20**) reacts with reagent **7** (1.5 eq.) in HFIP, with 4Å MS and CH₂Cl₂ at 40 °C, to produce fluorinated lactone **21** and hexafluoroisopropoxy-substituted lactone **83**.

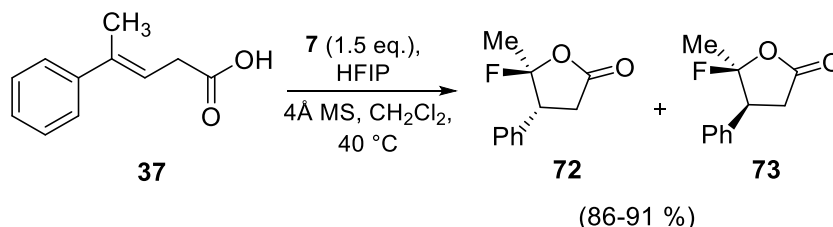
Entry	HFIP	T (C °)	Time (h)	Conversion ^a (%)	Yield (%) ^b of 21	Yield (%) ^b of 83
1	2 eq.	40	4	100	90	5
2	1 eq.	40	1	100	93	4
3	0.25 eq.	40	1	100	91	2

^a Conversion calculated by ¹H NMR spectroscopy, refers to the consumption of the starting material **20**. ^b Isolated yield.

The model substrate, 4-phenyl-4-pentenoic acid **20**, was reacted with fluoroiodane in dichloromethane with 2 equivalents of HFIP. As the amount of HFIP was reduced from 3 mL to 0.18 mL, the time of the reaction was increased to 4 hours at 40 °C. Fortunately, the reaction went to completion which was confirmed by ¹H and ¹⁹F NMR spectroscopy of the crude product and the fluorinated lactone **21** was isolated in an excellent 90 % yield.

In entry 2 the amount of HFIP was reduced to 1 equivalent and the reaction time was reduced to 1 hour. After purification by column chromatography, the desired product was obtained in 93 % yield and the hexafluoroisopropoxy-substituted lactone was observed as a minor side product in 4 % yield.

Finally, the amount of HFIP was reduced to 0.25 equivalents in a one hour reaction at 40 °C. A very exciting result was generated in which the desired product was formed in 91 % isolated yield. Also, compared to the previous reactions, the byproduct hexafluoroisopropoxy-substituted lactone was produced in just 2 % compared to 5 % using 3 mL of HFIP and 4 % with 1 equivalent of HFIP.



Scheme 2.25 Catalytic fluorocyclisation of **37** using HFIP

To test the feasibility of the reaction with a more complicated substrate, the trisubstituted alkene **37** was reacted with 1 equivalent of HFIP at 40 °C for 4 hours. The excellent 91 % yield for the desired mixture of lactones was obtained after purification by column chromatography. When the amount of HFIP was reduced to 0.25 equivalents, a slightly lower 86 % yield was obtained. Under both sets of conditions, the results obtained were higher than using AgBF₄ which resulted in 69 % overall yield.

2.7 Conclusion

In this chapter, it has been shown that the fluoroiodane reagent **7** efficiently promotes the fluorocyclisation reactions of unsaturated carboxylic acids under mild reaction conditions under copper(I) catalysis in good yields (52-78 %) with *geminal*-disubstituted alkenes. The reaction involves the activation of the fluoroiodane reagent by the transition metal which undergoes nucleophilic attack from the alkene, followed by the intramolecular fluorocyclisation with an aryl migration delivering γ-lactones with tertiary alkyl fluorides.⁶⁰ In contrast, the traditional electrophilic fluorinating reagents generate lactones with primary alkyl fluorides.

The fluorocyclisation reaction of 4-pentenoic acid **59** was very efficient using 0.2 equivalents of Cu(I) catalyst at 40 °C for 4 hours, resulting in a 55 % isolated yield. The same reaction using a stoichiometric amount of AgBF₄ generated lactone **60** in a lower

40 % along with byproduct **61** formed in 26 % yield. It is proposed that iodoalcohol **5** acted as a competing nucleophile forming **61** under stoichiometric conditions using AgBF₄ and was minimal under copper catalysed conditions.

The 3-pentenoic acid substrate **65** did not generate the fluorinated lactone under any reaction conditions. Instead, the elimination of the fluoride occurred forming an alkene in conjugation with the carbonyl group, resulting in the formation of **67**. The *trans*-disubstituted alkene **35** was also a less efficient substrate in fluorocyclisations. A low 33 % yield of **68/69** was obtained under copper(I) catalysed reaction conditions. In contrast, the reaction with 1 equivalent of Ag(I) generated the desired lactone in 49 % yield.

The trisubstituted alkene, **37**, worked well with 1 equivalent of AgBF₄ at 40 °C for 4 hours to generate the product a mixture of diastereomers in 56 % yield and was not efficient under copper catalysed reaction conditions, resulting in low reaction conversions. As a comparison, the reaction with **37** was attempted with Selectfluor which confirmed that the fluoroiodane reagent undergoes a completely different reaction mechanism to other available fluorinating reagents. The reaction with Selectfluor generated lactones **72** and **73** which did not undergo the phenyl migration, resulting in the formation of secondary alkylfluoride.

The substrate **41** was unreactive using either the stoichiometric or the catalytic amount of the transition metal additives. However, the fluorocyclised product was obtained when the fluoroiodane reagent was substituted with Selectfluor. The lactone with a secondary alkyl fluoride was obtained in 67 % yield, however as predicted, the mechanism did not involve the phenyl migration.

The efficiency of HFIP acting as a solvent to promote fluorinations with the hypervalent fluoroiodane reagent **7** without the need of a transition metal has been demonstrated clearly. In the reactions of *geminal*-disubstituted alkenes with HFIP at 40 °C for 1 hour, the desired fluorinated γ -lactones were obtained in excellent conversions and very good isolated yields (79-84 %). The δ -lactone **58** generated from the reaction of 5-phenyl-5-hexenoic acid **32** with HFIP was obtained in a 66 % isolated yield which was much higher than the AgBF₄ promoted reaction which resulted in a moderate 38 % yield.

The reaction of 4-pentenoic acid **59** in the presence of HFIP was much more efficient compared to the reaction using 1 equivalent of AgBF₄. The fluorocyclisation product **60**

was obtained in a good 82 % yield. The *trans*-disubstituted alkene, (*E*)-4-phenylbut-3-enoic acid **35** was the least reactive substrate tested in this work under both sets of conditions. In the reaction using HFIP, the desired mixture of diastereomers **68** / **69** was generated in a low 36 % yield and that was the only case where AgBF₄ was found to be more efficient than HFIP.

The trisubstituted alkene **37** generated the fluorinated γ -lactone 5-fluoro-5-methyl-4-phenyldihydrofuran-2-one as a mixture of diastereomers in a high 86 % overall yield in the presence of HFIP. Moreover, the reaction using HFIP resulted in the formation of the γ -lactone containing tertiary alkyl fluoride as in the original reaction with AgBF₄.

Preliminary studies, based on using a catalytic amount of HFIP, gave excellent conversions and isolated yields. Therefore, HFIP can act as a hydrogen bond donor to activate fluoroiodane **7** under mild reaction conditions with a broad substrate scope.

Chapter 3

Synthesis and Fluorination of Unsymmetrical Diaryliodonium Salts using a Hypervalent Iodine(III) Reagent



3.1 Introduction

Since the discovery of diaryliodonium salts in 1894, they have received great attention across the chemical society due to their relatively easy preparation and broad range of applications. Due to their highly electron-deficient nature and excellent leaving group ability, diaryliodonium salts serve as efficient arylating reagents, photoinitiators and precursors to ^{18}F -labelled radioligands.^{111,123}

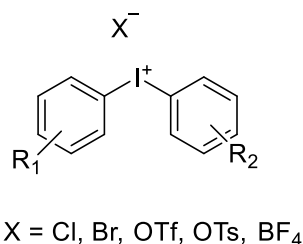


Figure 3.1 General structure of a diaryliodonium salt (diaryl- λ^3 -iodane)

Iodonium salts are generally classified as hypervalent λ^3 -iodanes with two carbon ligands (R_2IX) and can either be symmetrical when $\text{R}_1=\text{R}_2$ or unsymmetrical if $\text{R}_1 \neq \text{R}_2$. X-ray studies have confirmed the geometry of diaryliodonium salts as pseudo trigonal bipyramid with a bond angle ($\text{R}-\text{I}-\text{R}$) being close to 90° .² An important structural aspect of diaryliodonium salts in the solid state is the experimentally-found secondary bonding interaction between the iodine and the counteranion with average bond distances within a range of 2.3 to 2.7 Å. The nature of the counteranion plays an important role in determining the solubility of diaryliodonium salts in organic solvents. Tetrafluoroborate (BF_4^-) or triflate (^-OTf) salts are generally more soluble than those with halide counteranions (Cl^- , Br^- , I^-).¹¹²⁻¹¹⁴

The configuration of diaryliodonium salts in solution is still disputable, however, a definite amount of dissociation is expected depending on the anion of the salt and the solvent used. However, in the solid state the majority of diaryliodonium salts show a secondary bonding interaction between the anion and the iodine atom and, as confirmed by X-ray crystallography, exist in a T-shape configuration (**Figure 3.2**).¹²⁰

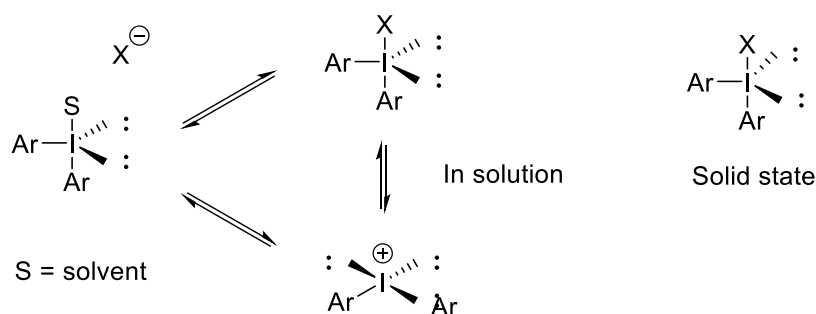
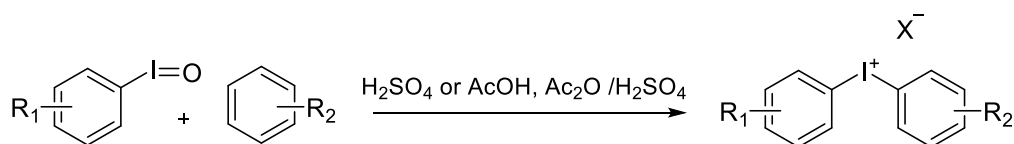


Figure 3.2 *General structure of a diaryliodonium salts in solution and solid state*

Due to their highly electrophilic character and excellent leaving group ability, diaryliodonium salts serve as versatile arylating agents with a broad range of nucleophiles. They also share similar properties to transition metals but are non-toxic and highly selective. Consequently, diaryliodonium salts can be successfully employed in reactions most commonly assigned to environmentally non-benign compounds, adding a significant value to the pharmaceutical industry.¹¹⁸

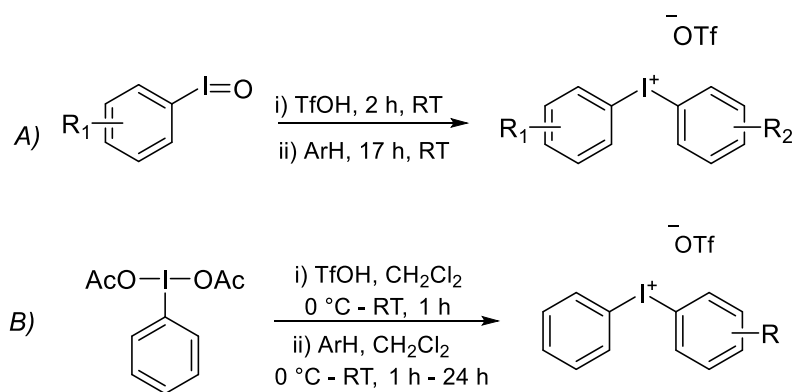
3.1.2 Synthesis of diaryliodonium salts

The first synthesis of diaryliodonium salts was reported by Meyer in 1894 and involved the use of iodosylarenes (ArI=O) and iodoxyarenes (ArIO_2) in a condensation reaction.¹²⁰ Lacking synthetic benefits such as high reaction yields, atom-efficiency and short reaction times, diaryliodonium salts did not receive much attention for several decades until Beringer and co-workers reported numerous improved synthetic preparations in the 1950s. Treating arenes with hypervalent iodine compounds in the presence of various acids yielded a range of symmetrical and unsymmetrical diaryliodonium salts. The use of different acid mixtures resulted in different reactivity patterns and variable reaction yields. The mixture of acetic acid together with trifluoroacetic acid was found to be efficient for electron rich arene substrates, whereas sulphuric acid was mostly efficient with electron-deficient substrates (**Scheme 3.1**).^{120-121, 123-124,128}



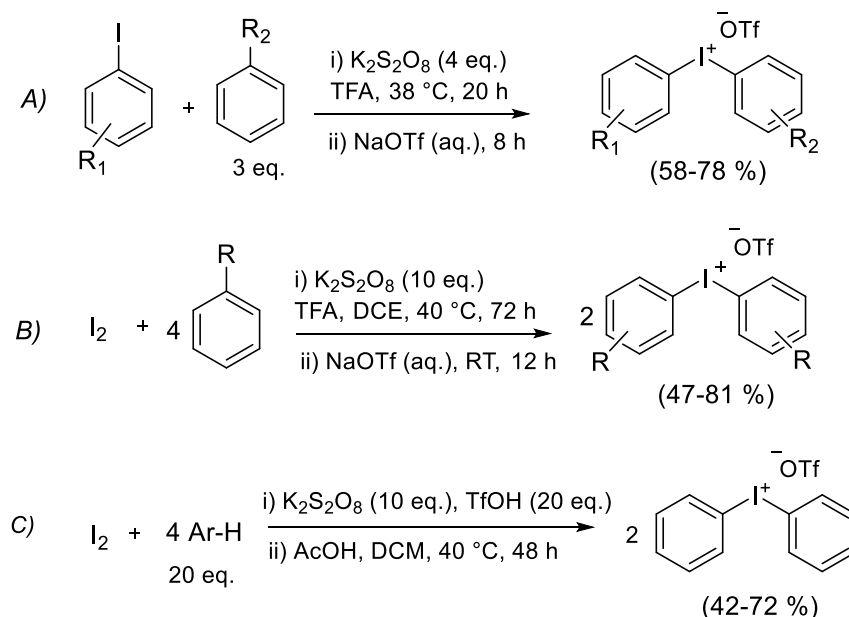
Scheme 3.1 Early synthesis of diaryliodonium salts

Later it was found that triflic acid could serve as an efficient alternative to the inorganic acids, generating triflate salts without needing anion exchange. In the report by Kitamura, triflic acid acted as an activator of iodosylbenzene towards ligand exchange reactions with arenes. The method was further improved by employing (diacetoxyiodo)benzene, forming $[\text{PhI}(\text{OAc})_2 \cdot 2\text{TfOH}]$ *in situ* followed by addition of electron-rich arenes, giving diaryliodonium triflate.^{117,137} (**Scheme 3.2 A, B**).



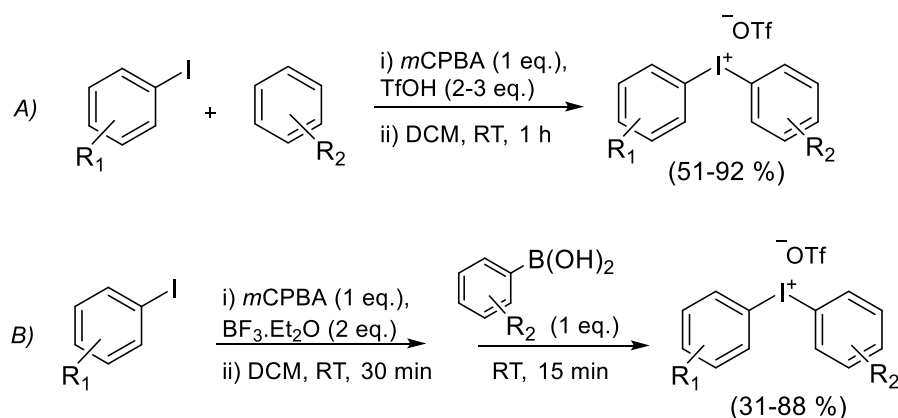
Scheme 3.2 Early synthesis of diaryliodonium salts using TfOH

Several improvements in the development of diaryliodonium salts have been made over the last decade such as *one-pot* synthetic strategies to make triflate and tetrafluoroborate salts. Particular attention has been brought to reactions between arene substrates and molecular iodine, eliminating the use of expensive aryl iodides and resulting in excellent reaction yields. Such examples include the work attempted by Kitamura *et al.*, who reported the synthesis of diaryliodonium salts from arenes which were treated with potassium persulfate and trifluoroacetic anhydride (TFA) (**Scheme 3.3 A**).¹¹⁷



Scheme 3.3 *One-pot synthesis of diaryliodonium salts*

The synthesis of (diacetoxy)iodoarene from arenes and molecular iodine was developed by the same group.¹¹⁸ Although the scope of the method was limited and only applicable to benzene, *tert*-butylbenzene and halobenzenes, it avoided the use of costly aryl iodides. The anion exchange was also circumvented by adding TfOH to the reaction, resulting in slightly shorter reaction times (**Scheme 3.3 B, C**).

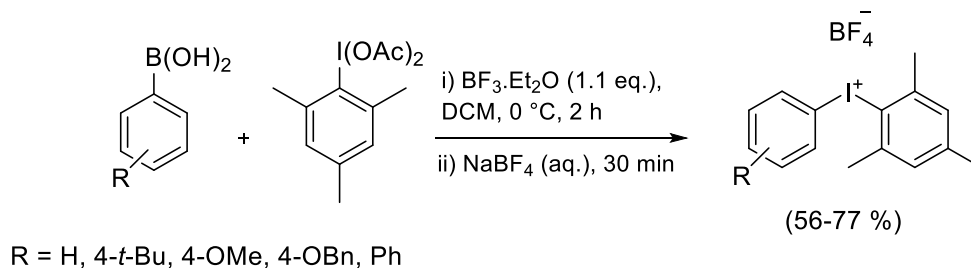


Scheme 3.4 *Preparation of diaryliodonium salts from aryl iodides*

Olofsson *et al.* has reported several efficient *one-pot* synthesis of diaryliodonium salts for both, symmetrical and unsymmetrical diaryliodonium triflates from electron-rich and deficient arenes and aryl iodides using an oxidant *m*CPBA and triflic acid.¹¹⁹⁻¹²⁰ The latter was used to activate the iodosoarene intermediate and to deliver a triflate anion to the final salt. An oxidant *m*CPBA was a good alternative to previously reported¹²⁰ analogues

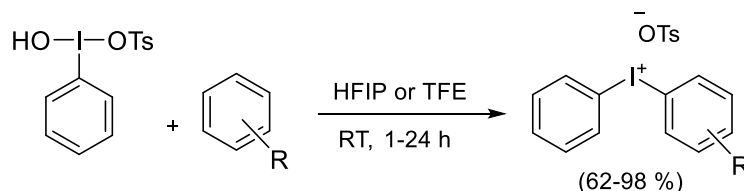
as it was easily soluble in organic solvents, simplifying the purification of the final product. A similar procedure has also been reported employing aryl boronic acids, aryl iodides, *m*CPBA and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ for a regioselective synthesis of unsymmetrical diaryliodonium tetrafluoroborates. The reported method increases reaction scope as a wide range of electron-deficient and -rich symmetrical and unsymmetrical salts can be obtained in a regio-specific manner with varied substitution patterns (**Scheme 3.4**).

Another example employing aryl boronic acids was reported by Sanford and co-workers who reacted aryl boronic acids with (diacetoxyiodo)mesitylene ($\text{MesI}(\text{OAc})_2$) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in dichloromethane. A range of diaryliodonium tetrafluoroborates were successfully generated in high yields (56-77 %) (**Scheme 3.5**).¹²¹⁻¹²²

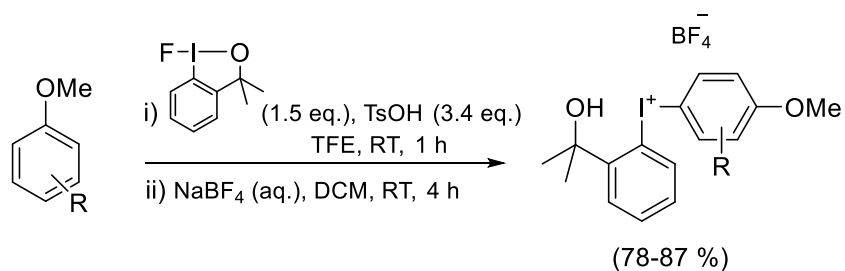


Scheme 3.5 Preparation of diaryliodonium salts from aryl boronic acids

Kita and co-workers demonstrated that fluoroalcohols (HFIP and TFE) can be successfully employed in the preparation of diaryliodonium salts in the presence of Koser's reagent (**Scheme 3.6**). The fluoroalcohols greatly enhanced the efficiency of the condensation, resulting in a larger product scope compared to previously reported methods. The reaction was attempted using either unsubstituted or electron-rich arenes under neutral conditions. The anion of the salt can be easily modified by substituting the Koser's reagent to triflate or tosylate.¹²³

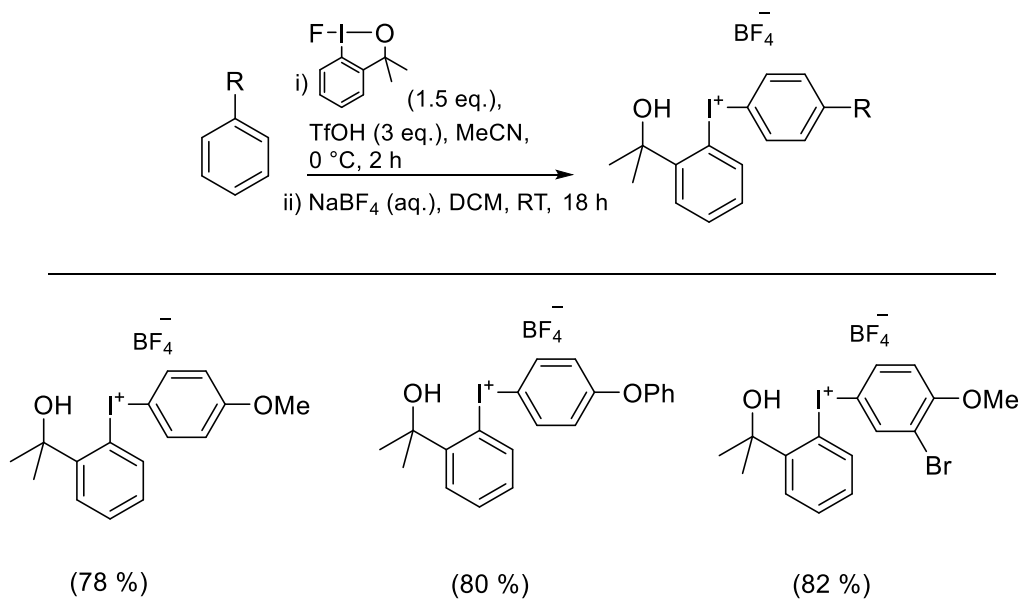


Scheme 3.6 Synthesis of diaryliodonium salts in fluoroalcohols



Scheme 3.7 Synthesis of diaryliodonium salts using fluoroiodane reagent **7**

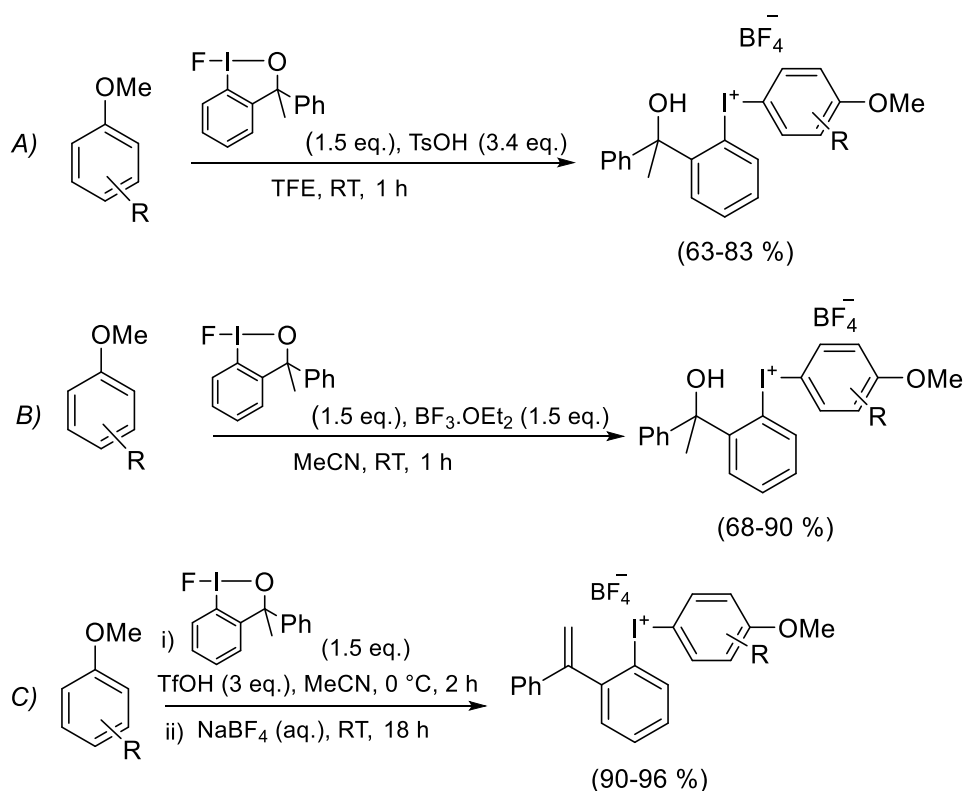
Research performed in Stuart's group has shown that a hypervalent iodine reagent **7** can be employed in the synthesis of diaryliodonium salts (**Scheme 3.7**).¹²⁴ When reacted with activated aromatics in the presence of *p*-toluensulfonic acid and trifluoroethanol as solvent at room temperature for just 1 hour, four unsymmetrical diaryliodonium salts were prepared in high yields (78-87 %). Although yield and time efficient, the scope of the method was very limited and therefore was not suitable for substituted aromatics other than anisole derivatives.



Scheme 3.8 Preparation of diaryldiodonium triflates

Alternatively, triflic acid can be used to activate the fluoroiodane reagent **7**. Requiring only 1.5 equivalents of TfOH in acetonitrile (MeCN) for 1 hour at room temperature, this method was applied to highly activated aromatics (anisole, mesitylene). When the amount of the triflic acid was increased to 3 equivalents and the reaction temperature was lowered to 0 °C, less activated aromatic systems such as 2-bromoanisole, *m*-xylene and methyl-2-methoxybenzoate were successfully reacted, generating unsymmetrical diaryliodonium salts in high yields (78-82 %) (**Scheme 3.8**).

The X-ray crystallographic data showed that the diaryliodonium salts formed short intramolecular I \cdots O(1) distances in the solid-state structures of the salts prepared from the fluoroiodane reagent **7** and this interaction was presumed to have a direct influence on the subsequent fluorinations. To overcome this drawback, a slight modification of the fluoroiodane reagent was attempted. It was found that the introduction of a phenyl group, which replaced one of the methyl groups in the sidearm, facilitated a dehydration reaction resulting in the formation of an alkene sidearm. The alkene formed was in conjugation with two aromatic rings and facilitated the subsequent fluorinations with potassium fluoride to form the desired fluoroaromatics.¹²⁴



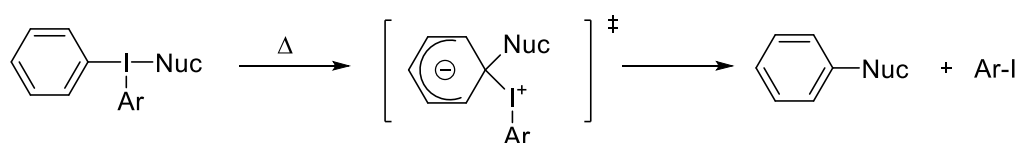
Scheme 3.9 Synthesis of diaryliodonium salts with either A) *TsOH*, B) *BF₃.Et₂O* or C) *TfOH*

Recent developments made over the last decade have proved the synthetic practicality of diaryliodonium salts. Being relatively easily prepared from a broad range of substrates, these compounds add significant value to the industrial and academic chemical society as being environmentally benign, cost-effective and versatile reagents.

3.1.3 Fluorination of diaryliodonium salts

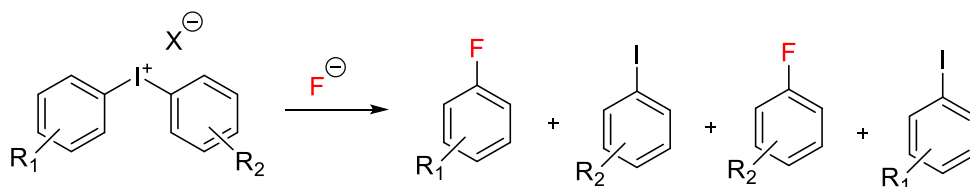
A variety of functionalised arenes can be obtained when utilizing diaryliodonium salts in reactions with nucleophiles. Their facile reactivity patterns with both strong and weak nucleophiles have been widely examined in both transition metal-catalysed and catalyst-free processes. However, a more challenging task using diaryliodonium salts is the fluorination of aromatic species, as the fluoride anion exhibits very poor nucleophilic properties. Nevertheless, reports to date have shown that a number of aromatic compounds can still be prepared successfully using the diaryliodonium salts with the fluoride nucleophile.¹²⁵⁻¹²⁶

A simple method generating the functionalised electron rich and poor arenes by a metal-free mediated pathway based on thermolysis of diaryliodonium salts was reported by Yamada and co-workers.¹²⁶ Upon heating, the nucleophile is directed towards the electron-deficient arene, which enables the build-up of the negative charge in the Meisenheimer-like transition state. The reported procedure successfully generated functionalised aromatics at the *ortho*-, *meta*- and *para*-positions.



Scheme 3.10 Thermolysis of diaryliodonium salts

The fluorination of unsymmetrical diaryliodonium salts is challenging as it leads to the formation of a number of possible products (**Scheme 3.11**). Symmetrical counterparts are therefore generally preferred over unsymmetrical analogues as chemoselectivity issues are overcome. Generally, when diaryliodonium salts are employed in transition metal-free mediated fluorination reactions, the most electron-deficient arene is usually transferred which is attributed to the electronic factor, as the more electron deficient group has a higher partial positive charge δ^+ .¹²⁷ Reports from Grushin and Beringer state that electron withdrawing groups are known to increase the reactivity of diaryliodonium salts towards nucleophiles, while electron donating substituents on aryl rings exert the opposite effect.¹²⁷⁻¹²⁹

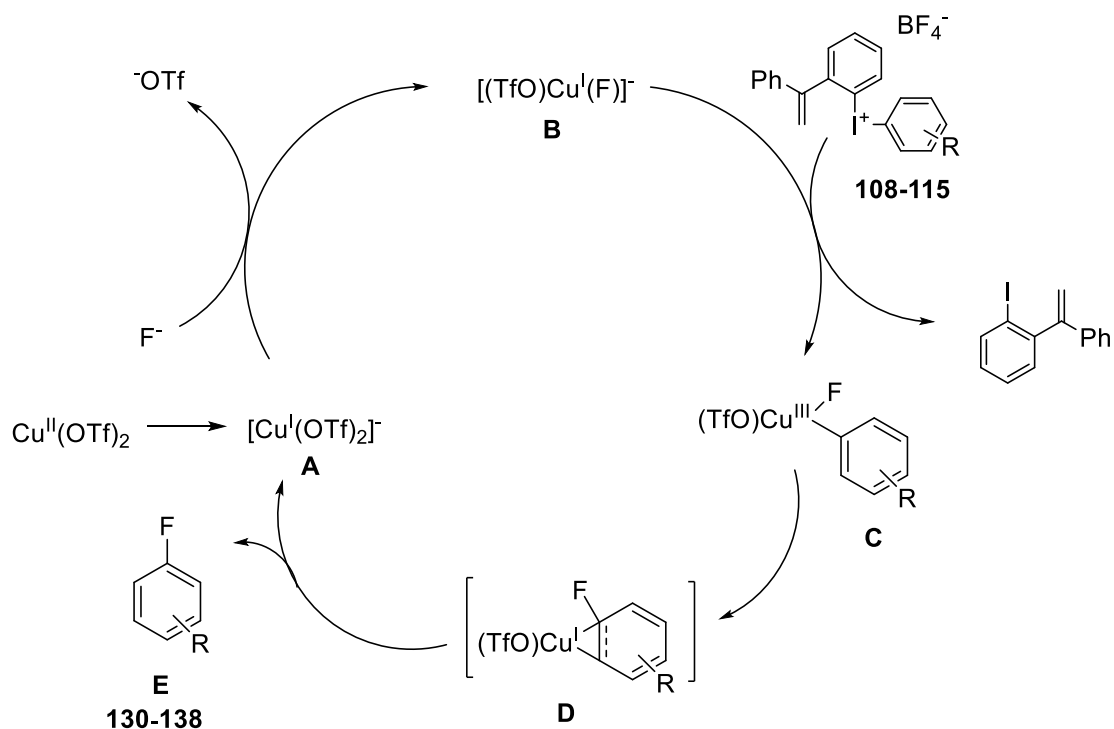


Scheme 3.11 Fluorination of diaryliodonium salts

Steric cases where the nucleophile preferentially attacks an *ortho*-substituted aryl group of diaryliodonium salts have been observed. A rational explanation given in several reports of the *ortho-effect* in diaryliodonium salts states that the nucleophilic attack on the iodine gives a tricovalent iodine(III) complex which is believed to be T-shaped. The bulkier of the two aryl groups together with two lone pairs tend to occupy the less encumbered equatorial positions. The formed complex undergoes intramolecular S_NAr , and being closer to the nucleophile, the equatorial aryl group is subsequently attacked.

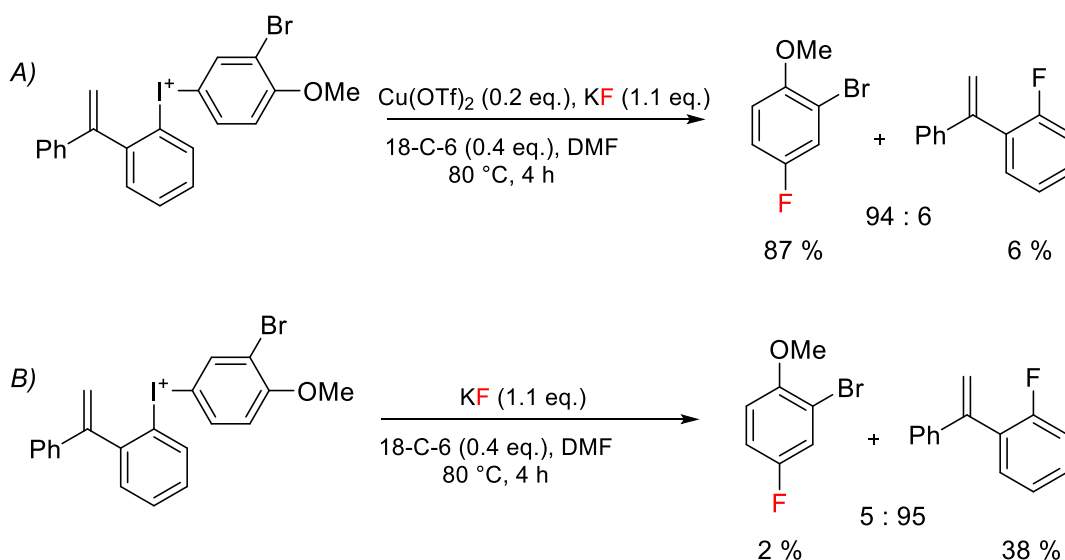
The use of diaryliodonium salts as reagents in combination with transition metal catalysts has been found to reverse the *ortho-effect*, leading to the formation of the desired fluorinated aromatic. Pioneering work in transition metal mediated fluorination reactions using Pd, Cu and Ni have been reported by Sanford and Buchwald.^{122,130} Later, Hartwig revealed the Cu(I)-Cu(III) catalysed fluorinations of aryl iodides with AgF, but the disclosed method required superstoichiometric amounts of Cu and high reaction temperatures.¹³¹

In 2013 Sanford investigated the use of copper catalysts in the fluorination reactions of diaryliodonium salts.¹²² Out of several advantages, it is worth emphasising that a fast and sterically controlled oxidative addition of the highly electrophilic Ar_2I^+ to Cu(I) led to much milder reaction conditions, even enabling substrates bearing electron-rich substituents to be fluorinated. Following this work, the Stuart group has successfully applied the use of various Cu salts ($Cu(OTf)_2$, $[Cu(CH_3CN)_4]BF_4$, $[Cu(CH_3CN)_4]OTf$) in the fluorination reactions of unsymmetrical diaryliodonium salts.¹²⁴ A suggested mechanism, based on Sanford's theoretical and experimental studies was proposed for this work (**Scheme 3.12**). In the first step the Cu(II) pre-catalyst is reduced to the Cu(I) active catalyst **A** in a disproportionation reaction.¹²² The formation of **B** by ligand exchange and a fast oxidative addition of unsymmetrical diaryliodonium salt leads to the formation of Cu(III) **C** which undergoes reductive elimination via the presumed π -complex to release the fluorinated product and regenerate the active catalyst Cu(I).



Scheme 3.12 Proposed $\text{Cu}(\text{OTf})_2$ catalytic cycle for the fluorination of unsymmetrical diaryliodonium salts

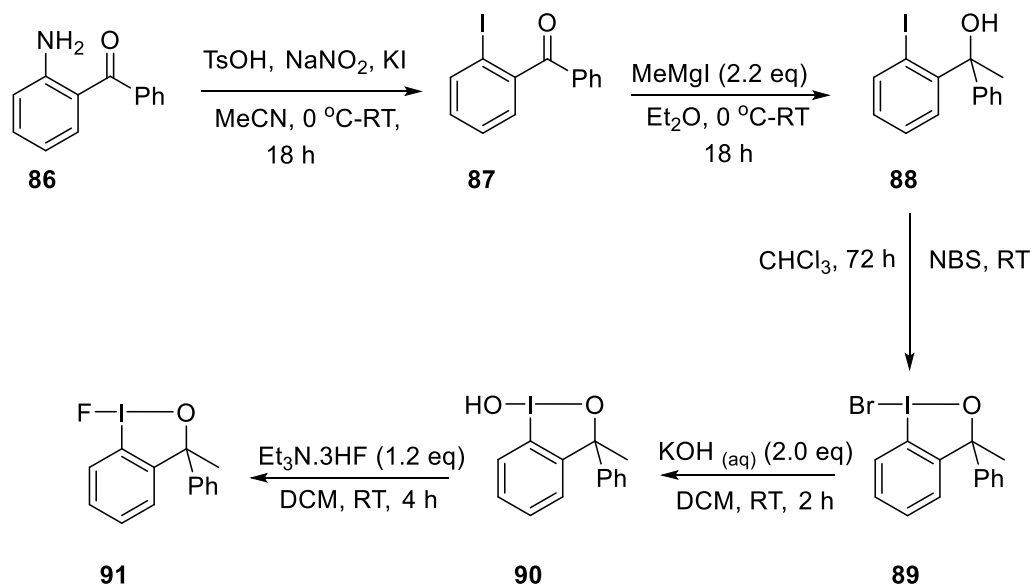
The fluorination reactions of unsymmetrical diaryliodonium salts were successfully achieved in Stuart's group and proved that the *ortho-effect* was reversed in the presence of the copper catalyst.¹²⁴ After several optimisation attempts, the fluorination reactions were successful at 80 °C for 4 hours using 1.1 equivalents of KF, 0.4 equivalents of 18-C-6 and 0.2 equivalents of $\text{Cu}(\text{OTf})_2$ in DMF. A range of unsymmetrical salts including 1,4-di and 1,2,4-trisubstituted substrates generated the desired fluorinated aromatics in good yields and high selectivity (61-87 %). As expected, the selectivity was reversed in the absence of the Cu catalyst, resulting in the formation of the *ortho* substituted fluoroaromatic (**Scheme 3.13**).



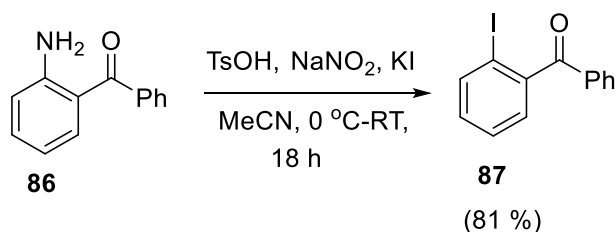
Scheme 3.13 $\text{Cu}(\text{OTf})_2$ catalysed (A) and non-catalysed (B) fluorination of unsymmetrical diaryliodonium salts

The initial aim of this chapter was to synthesise the hypervalent iodine(III) reagent **91** where one of the methyl groups in the side arm of the original fluoroiodane **7** was replaced by a phenyl group. The reagent **91** was used to prepare a range of unsymmetrical diaryliodonium salts from Grignard reagents and arylboronic acids. In contrast to the previous work done by the group which utilised aromatic compounds bearing electron donating groups, this work has expanded the substituent scope to weak electron withdrawing (*p*-F, *m*-F) and even strong electron withdrawing groups ($-\text{CF}_3$). Therefore, a range of 1,4-, 1,3- and 1,2-disubstituted diaryliodonium salts were successfully prepared. The results obtained in this work have shown that less activated aromatic structures are well tolerated under the developed reaction conditions, generating the desired products in good yields. The overall aim of this work was to investigate the fluorination reactions of unsymmetrical diaryliodonium salts to prepare a series of substituted fluorinated aromatics. The effect of the transition metal catalyst $\text{Cu}(\text{OTf})_2$, reaction temperature and time were investigated in order to find the optimum reaction conditions.

3.2 Synthesis of unsymmetrical diaryliodonium salts using a novel hypervalent iodine(III) reagent **91**



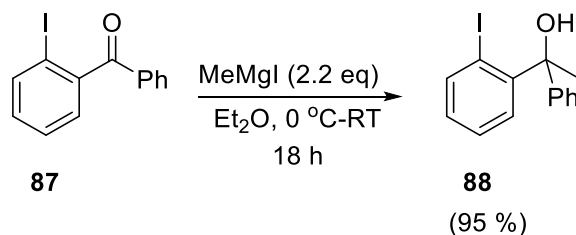
Scheme 3.14 Synthetic route for the preparation of the fluoroiodane reagent **91**



Scheme 3.15 Diazotisation of 2-aminobenzophenone

The hypervalent iodine(III) reagent **91** was prepared in a five step synthetic route from 2-aminobenzophenone **86** which is shown in **Scheme 3.14**. The first step is a diazotisation reaction (**Scheme 3.15**) generating 2-iodobenzophenone **87** and it was carried out by the dropwise addition of an aqueous solution of potassium iodide and sodium nitrite to a solution of *p*-toluenesulphonic acid and 2-aminobenzophenone **86** at 0 °C for 45 min. After the addition was complete, the dark red mixture was left to stir overnight at room temperature. The ^1H NMR spectrum of the crude product confirmed the full consumption of the starting material as the broad singlet peak at 6.10 ppm for the NH_2 group had disappeared completely. Moreover, the new C-I peak at 92.3 ppm in the ^{13}C NMR

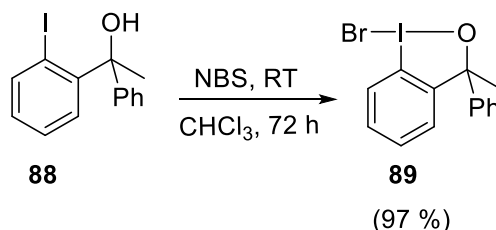
spectrum and the molecular ion peak M^+ at m/z 308.97 concluded that the desired product had been formed.



Scheme 3.16 Synthesis of iodoalcohol **88**

The *in situ* prepared Grignard reagent MeMgI, underwent a nucleophilic addition to 2-iodobenzophenone **87** resulting in the formation of the tertiary alcohol **88** (Scheme 3.16). The reaction was carried out under dry conditions in an inert atmosphere of nitrogen. To a cooled solution (0 °C) of MeMgI in dry diethyl ether **87** was added dropwise and the reaction mixture was left to stir overnight at room temperature. The desired product **88** was isolated in 95 % yield.

The formation of **88** was proved by 1H and ^{13}C NMR spectroscopy as well as by mass spectrometry. In the 1H NMR spectrum, the singlet for the methyl group was found at 1.92 ppm and the OH singlet appeared at 3.24 ppm. In the ^{13}C NMR spectrum, a new singlet was observed at 30.7 ppm corresponding to the methyl group and the quaternary carbon bearing an –OH group was found at 78.2 ppm which was in contrast to the quaternary carbonyl carbon peak at 197.3 ppm in compound **87**. The ASAP mass spectrum showed the formation of the product with the MH^+ fragment at m/z 322.99.

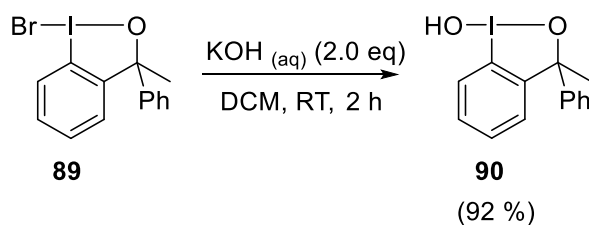


Scheme 3.17 Preparation of 1-bromo-3-methyl-3-phenyl-1,3-dihydro-1- λ^3 -benzo[d][1,2]iodoxole **89**

The formation of 1-bromo-3-methyl-3-phenyl-1,3-dihydro-1- λ^3 -benzo[d][1,2]iodoxole **89** from iodoalcohol **88** and *N*-bromosuccinimide in chloroform ($CHCl_3$) was carried out successfully in 72 hours generating the desired product in an excellent 97 % yield. Importantly, when the reaction was attempted overnight, the conversion to the desired

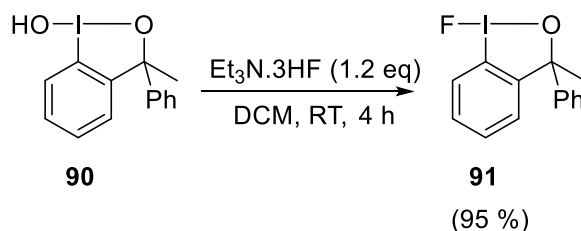
product was minimal reaching only 15 %. Increasing the reaction time to 32 hours resulted in considerable consumption of the iodoalcohol **88**, but the overall conversion was still lower than expected, reaching 45 %. Finally, when the reaction time was increased to 72 hours, 100 % conversion was achieved. The crude product was purified by re-crystallisation from ethyl acetate.

The oxidation of iodine(I) to iodine(III) resulted in the considerable downfield shift of the aromatic protons and carbon atoms in comparison to **88** which was confirmed by ^1H and ^{13}C NMR spectroscopy. Moreover, the loss of the OH singlet peak at 3.24 ppm in the ^1H NMR spectrum and the C-I peak shift to 113.9 ppm from 96.6 ppm in ^{13}C NMR spectrum were good indicators that the desired product had been formed. The ASAP-MS gave parent ion peaks at 398.88 m/z and 400.88 m/z , due to the isotope pattern for bromine.



Scheme 3.18 Synthesis of 3-methyl-3-phenyl-1 λ^3 -benzo[d][1,2]iodoxol-1(3H)-ol **90**

The hydroxyiodane **90** was prepared by the nucleophilic attack on the hypervalent iodine(III) centre of bromiodane **89** which was stirred in DCM with an aqueous solution of potassium hydroxide for 2 hours at room temperature (**Scheme 3.18**). Mild reaction conditions resulted in the formation of the desired product **90** in an excellent 92 % yield which was confirmed by ^1H and ^{13}C NMR spectroscopy as well as ESI mass spectrometry. The aromatic proton peaks were shifted upfield compared to the same group of protons in compound **89**.



Scheme 3.19 Synthesis of the fluoroiodane reagent **91**

The final product in the overall synthetic route was generated by reacting 3-methyl-3-phenyl-1- λ^3 -benzo[d][1,2]iodoxol-1(3*H*)-ol **90** with TREAT-HF in dichloromethane for 4 hours at room temperature (**Scheme 3.19**). The excess acid was removed by washing the crude product with water and the fluoroiodane was obtained as a red solid in 95 % yield. The residual water was removed by co-evaporation with toluene and **91** was re-crystallised from toluene to remove traces of aromatic impurities. A singlet peak at -143.2 ppm in the ^{19}F NMR spectrum confirmed the formation of the desired reagent **91**.

3.3 Synthesis of unsymmetrical diaryliodonium salts

3.3.1 Synthesis of unsymmetrical diaryliodonium salts from Grignard reagents

The preparation of unsymmetrical diaryliodonium salts was investigated initially by reacting reagent **91** with a series of aromatic Grignard reagents as shown in **Table 3.1**. The *in situ* prepared Grignard reagent was added to a cooled solution (0° C) of fluoroiodane **91** (1.8 equivalents.) in THF and after warming to room temperature, the reaction mixture was stirred at room temperature for 4 hours. Concentrated hydrochloric acid was added to quench the reaction and the mixture was stirred for 2 hours at room temperature. After washing the crude product with water to remove HCl, the salt was washed with hexane and diethyl ether, resulting in the formation of a white solid.

Table 3.1 *Synthesis of unsymmetrical diaryliodonium salts by Method A*

$ \begin{array}{c} \text{MgBr} \\ \\ \text{C}_6\text{H}_4\text{R} \end{array} \xrightarrow[\text{ii) HCl}_{(\text{conc.}), 2 \text{ h}}]{\text{i) } \begin{array}{c} \text{F-I-O} \\ \quad \\ \text{C}_6\text{H}_4 \quad \text{Ph} \end{array}} \begin{array}{c} \text{Ph} \\ \\ \text{C}(\text{OH})(\text{Ph})-\text{C}_6\text{H}_4-\text{I}^+-\text{C}_6\text{H}_4\text{R} \\ \\ \text{Cl}^- \end{array} $			
Entry	Substrate	Product	Yield ^a (%)
1	$ \begin{array}{c} \text{MgBr} \\ \\ \text{C}_6\text{H}_5 \end{array} \quad \mathbf{92} $	$ \begin{array}{c} \text{Ph} \\ \\ \text{C}(\text{OH})(\text{Ph})-\text{C}_6\text{H}_4-\text{I}^+-\text{C}_6\text{H}_5 \\ \\ \text{Cl}^- \end{array} \quad \mathbf{93} $	71
2	$ \begin{array}{c} \text{MgBr} \\ \\ \text{C}_6\text{H}_4\text{CH}_3 \end{array} \quad \mathbf{94} $	$ \begin{array}{c} \text{Ph} \\ \\ \text{C}(\text{OH})(\text{Ph})-\text{C}_6\text{H}_4-\text{I}^+-\text{C}_6\text{H}_4\text{CH}_3 \\ \\ \text{Cl}^- \end{array} \quad \mathbf{95} $	93
3	$ \begin{array}{c} \text{MgBr} \\ \\ \text{C}_6\text{H}_4\text{CH}_3 \end{array} \quad \mathbf{96} $	$ \begin{array}{c} \text{Ph} \\ \\ \text{C}(\text{OH})(\text{Ph})-\text{C}_6\text{H}_4-\text{I}^+-\text{C}_6\text{H}_4\text{CH}_3 \\ \\ \text{Cl}^- \end{array} \quad \mathbf{97} $	68
4	$ \begin{array}{c} \text{MgBr} \\ \\ \text{C}_6\text{H}_4\text{F} \end{array} \quad \mathbf{98} $	$ \begin{array}{c} \text{Ph} \\ \\ \text{C}(\text{OH})(\text{Ph})-\text{C}_6\text{H}_4-\text{I}^+-\text{C}_6\text{H}_4\text{F} \\ \\ \text{Cl}^- \end{array} \quad \mathbf{99} $	85
5	$ \begin{array}{c} \text{MgBr} \\ \\ \text{C}_6\text{H}_3\text{F} \end{array} \quad \mathbf{100} $	$ \begin{array}{c} \text{Ph} \\ \\ \text{C}(\text{OH})(\text{Ph})-\text{C}_6\text{H}_4-\text{I}^+-\text{C}_6\text{H}_3\text{F} \\ \\ \text{Cl}^- \end{array} \quad \mathbf{101} $	70
6	$ \begin{array}{c} \text{MgBr} \\ \\ \text{C}_6\text{H}_4\text{CF}_3 \end{array} \quad \mathbf{102} $	$ \begin{array}{c} \text{Ph} \\ \\ \text{C}(\text{OH})(\text{Ph})-\text{C}_6\text{H}_4-\text{I}^+-\text{C}_6\text{H}_4\text{CF}_3 \\ \\ \text{Cl}^- \end{array} \quad \mathbf{103} $	87
7	$ \begin{array}{c} \text{MgBr} \\ \\ \text{C}_6\text{H}_4\text{CF}_3 \end{array} \quad \mathbf{104} $	$ \begin{array}{c} \text{Ph} \\ \\ \text{C}(\text{OH})(\text{Ph})-\text{C}_6\text{H}_4-\text{I}^+-\text{C}_6\text{H}_4\text{CF}_3 \\ \\ \text{Cl}^- \end{array} \quad \mathbf{105} $	92
8	$ \begin{array}{c} \text{MgBr} \\ \\ \text{C}_6\text{H}_3\text{CF}_3 \end{array} \quad \mathbf{106} $	$ \begin{array}{c} \text{Ph} \\ \\ \text{C}(\text{OH})(\text{Ph})-\text{C}_6\text{H}_4-\text{I}^+-\text{C}_6\text{H}_3\text{CF}_3 \\ \\ \text{Cl}^- \end{array} \quad \mathbf{107} $	82

^a isolated yield

When the Grignard reagent **92** was reacted with fluoroiodane **91**, the ^1H NMR spectrum of the crude product indicated a full conversion to the desired product **93**. The ^{19}F NMR spectrum indicated that there was no fluoroiodane **91** remaining. The methyl group of the sidearm appeared at 2.09 ppm and the broad OH singlet was found at 6.26 ppm in the ^1H NMR spectrum. The ^{13}C NMR spectrum showed five quaternary carbon signals at 65.9, 110.0, 110.3, 143.7 and 145.5 ppm respectively, and the aliphatic CH_3 was found at 29.9 ppm. The parent cation M^+ in the ESI-MS had a mass of m/z 401.

When Grignard reagent **94** in entry 2 was reacted with **91**, the salt **95** was obtained in an excellent 93 % yield. The reaction fully went to completion, which was confirmed by the ^1H , ^{19}F and ^{13}C NMR spectra, and the desired salt was generated as a white powder. Two CH_3 singlets were found at 2.17 and 2.36 ppm in the ^1H NMR spectrum along with six quaternary carbons in the ^{13}C NMR spectrum.

In entry 3, *para*-bromotoluene was used to prepare the Grignard reagent, which was reacted with the fluoroiodane **91** following the same reaction conditions as previously described. The reaction went to completion, generating the desired salt **97** in a good 68 % isolated yield. ^{19}F NMR spectroscopy proved that the fluorinating reagent was consumed as the singlet at -143.2 ppm had disappeared. Furthermore, the ^1H and ^{13}C NMR spectra showed two methyl signals at 2.04 & 2.46 ppm and 21.2 & 29.9 ppm, respectively. Four quaternary carbon atom peaks at 65.8, 137.8, 143.9, 145.1 ppm and two C-I signals at 106.2 and 115.9 ppm were identified. The M^+ of the parent cation in the ESI-MS showed a peak at m/z 415.

When **98** was reacted with the fluoroiodane following the same method, full consumption of fluoroiodane **91** was proved by ^{19}F NMR spectroscopy. Instead, a singlet peak at -107.1 ppm was found. The ^{13}C NMR spectrum confirmed the structure of the desired salt showing a doublet at 164.7 ppm with a $^1J_{\text{CF}}$ coupling constant of 256.5 Hz. A two bond coupling of the CH to the fluorine atom was found at 119.5 ppm having a coupling constant of 22.1 Hz and a small three-bond coupling constant of 10.1 Hz for the CH group was also found at 138.1 ppm the ^{13}C NMR spectrum. The ESI-MS confirmed the mass of the diaryliodonium cation M^+ of m/z 420.

The reaction of **100** with **91** produced successfully the diaryliodonium salt **101** in 70 % yield. The ^{19}F NMR spectrum showed a singlet at -106.2 ppm for the aromatic fluoride. In the ^{13}C NMR spectrum a doublet at 162.9 ppm with a coupling constant of 244.5 Hz

corresponded to the carbon atom directly bonded to fluorine. Six additional quaternary carbon atoms were also found in the ^{13}C NMR spectrum at 62.8, 99.0, 104.5, 133.4, 147.3 and 151.6 ppm.

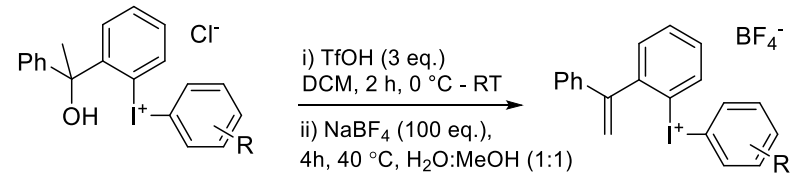
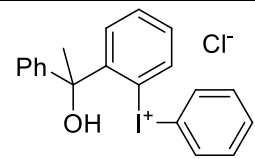
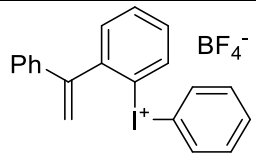
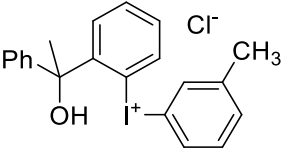
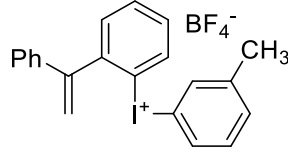
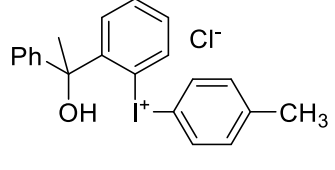
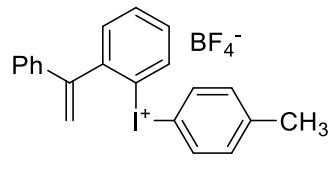
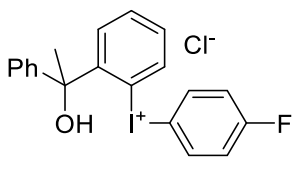
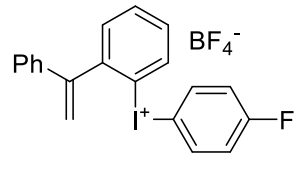
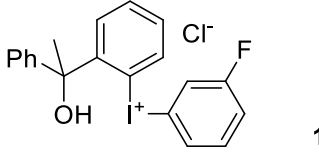
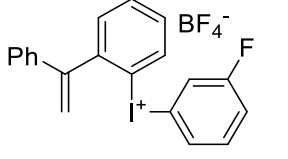
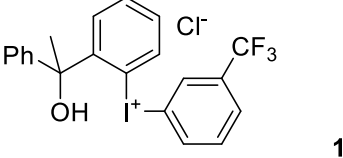
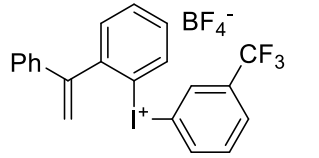
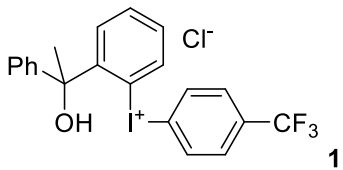
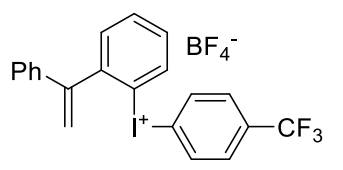
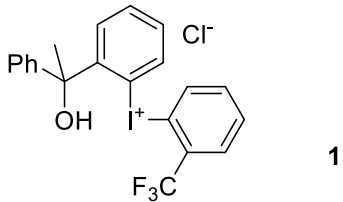
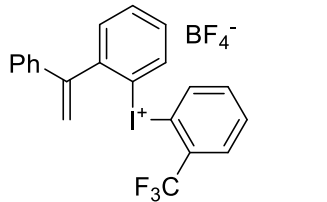
The reaction between fluoroiodane **91** and Grignard reagent **102**, resulted in the formation of the diaryliodonium salt **103** bearing a *m*-trifluoromethyl substituent on the aromatic ring. The reaction yielded the product in a high 87 % yield. The ^{19}F NMR spectrum showed a singlet peak at -64.3 ppm, corresponding to the CF_3 group. The ^{13}C NMR spectrum showed a quartet at 122.3 ppm, corresponding to the trifluoromethyl group. The quaternary carbon coupled to the $-\text{CF}_3$ was found at 138.6 ppm, with a $^2J_{\text{CF}}$ coupling constant of 24.1 Hz. The ESI-MS showed a peak at m/z 469 corresponding to the M^+ cation.

The *p*-trifluoromethyl substituted unsymmetrical diaryliodonium salt **105** was successfully prepared in 92 % yield from the reaction between Grignard reagent **104** and fluoroiodane **91** in tetrahydrofuran. The ^{19}F NMR spectrum showed a singlet at -64.6 ppm for the CF_3 group and there was no trace of the singlet at -143.2 ppm for the fluoroiodane reagent. The ^{13}C NMR spectrum confirmed the structure of the desired product by showing a quartet for the trifluoromethyl group at 122.0 ppm with a $^1J_{\text{CF}}$ coupling constant of 273.6 Hz. A smaller coupling constant of 32.2 Hz was also identified, which belonged to the carbon atom directly bonded to the CF_3 group. Furthermore, other quaternary carbon signals were successfully identified, including two separate singlets for the C-I groups. The structure was also confirmed by ESI-MS, giving the mass of the parent cation M^+ at m/z 462.

A similar result generating an *o*-trifluoromethyl substituted diaryliodonium salt **107** in a good 82 % yield was obtained in the reaction between the Grignard reagent **106** with the fluoroiodane **91**. The ^{19}F NMR spectrum showed a singlet peak at -60.3 ppm, corresponding to the CF_3 group and the ^{13}C NMR spectrum showed a quartet at 122.1 ppm with a $^1J_{\text{CF}}$ coupling constant of 274.6 Hz for the same trifluoromethyl group. The quaternary carbon coupled to the $-\text{CF}_3$ was found at 134.2 ppm, with a $^2J_{\text{CF}}$ coupling constant of 34.2 Hz. The ESI-MS showed a peak at m/z 469 corresponding to the parent cation M^+ .

3.3.2 Elimination and metathesis of diaryliodonium salts

Table 3.2 *Elimination and metathesis of unsymmetrical diaryliodonium salts*

<div style="text-align: center;">  </div>			
Entry	Substrate	Product	Yield ^a (%)
1	 93	 108	87
2	 95	 109	68
3	 97	 110	79
4	 99	 111	72
5	 101	 112	49
6	 103	 113	87
7	 105	 114	74
8	 107	 115	70

^a isolated yield

The elimination of the alcohol to form the alkene sidearm was attempted using 3 equivalents of triflic acid in dichloromethane over 2 hours. The anion exchange was achieved by stirring the triflate salt with 100 equivalents of NaBF₄ in an equimolar mixture of H₂O:MeOH (1:1) at 40 °C for 4 hours (**Table 3.2**).

In entry 1 the chloride salt **93** was dissolved in dichloromethane and cooled to 0 °C before 3 equivalents of triflic acid were added and the reaction mixture was stirred for 2 hours at RT. The counteranion exchange from triflate to tetrafluoroborate was investigated using NaBF₄ (100 eq.) in a homogenous mixture of H₂O:MeOH. A high 87 % isolated yield of the pure product as a white solid was obtained. The absence of the methyl (CH₃) group at 2.09 ppm was confirmed by ¹H NMR spectroscopy. Instead, two doublets at 5.40 and 6.05 ppm corresponding to the two protons of the alkene group were identified clearly and confirmed that the elimination had occurred. The CH₂ group of the alkene appeared at 119.9 ppm and the quaternary carbon was identified at 137.7 ppm in the ¹³C NMR spectrum. The ¹⁹F NMR spectrum showed a singlet at -148.9 ppm which corresponded to the tetrafluoroborate counteranion. The ESI-MS showed a peak at *m/z* 383 for the parent cation M⁺ of the desired salt **108**.

The *m*-tolyl based diaryliodonium salt **109** in entry 2 was formed in a moderate 68 % yield. The characterisation of the final salt was proved by multinuclear NMR spectroscopy, mass spectrometry and X-ray crystallography. The CH₂ alkene carbon atom was observed at 119.2 ppm and the quaternary alkene carbon was observed at 143.3 ppm in the ¹³C NMR spectrum. In the ¹⁹F NMR spectrum, the singlet for the tetrafluoroborate counteranion was found at -148.9 ppm.

The formation of the *p*-tolyl substituted diaryliodonium salt **110** was obtained in a higher 79 % yield compared to entry 2 and it was proved by ¹H, ¹⁹F and ¹³C NMR spectroscopy, as well as by mass spectrometry. The disappearance of the methyl singlet at 2.04 ppm and the formation of two alkene singlets at 5.43 and 6.06 ppm in the ¹H NMR spectrum indicated that the elimination process had occurred. All of the quaternary carbon atoms were successfully found in the ¹³C NMR spectrum. The M⁺ of the main cation was found at *m/z* 397

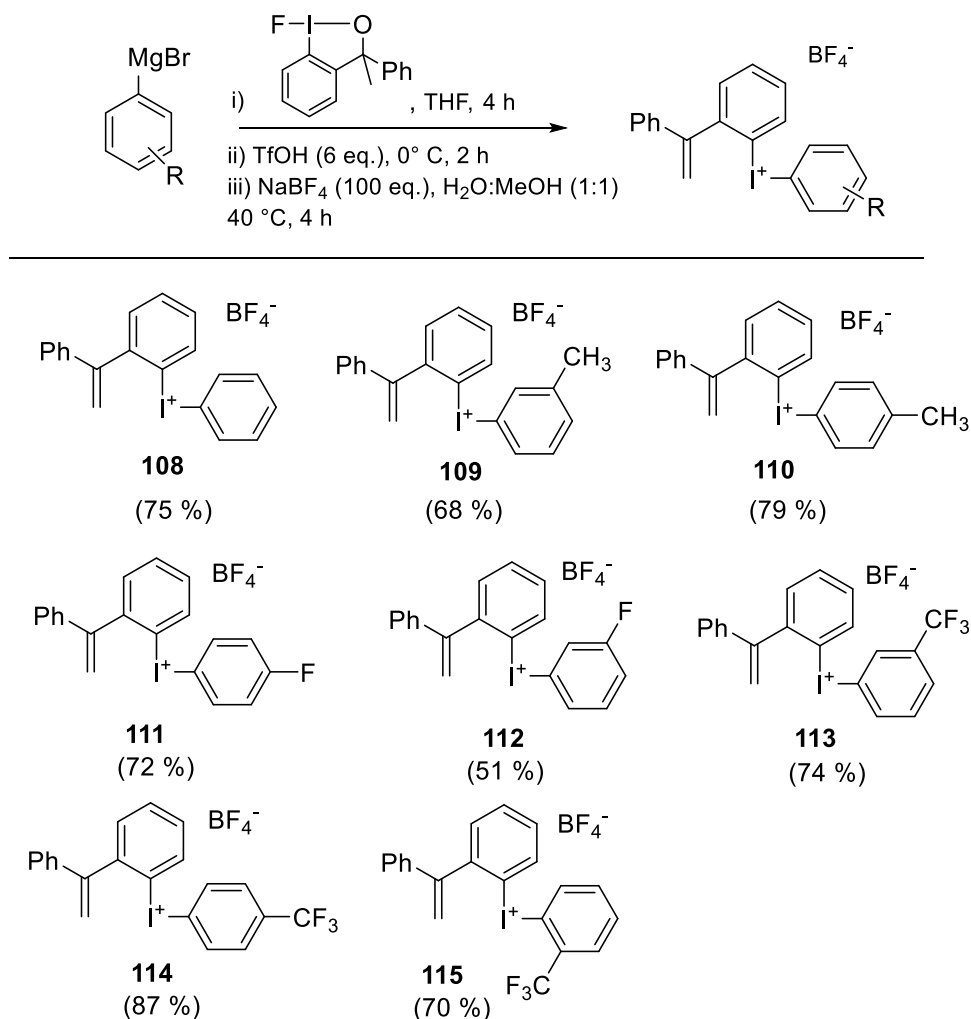
The reaction of **99** with triflic acid followed by metathesis with NaBF₄ in H₂O:MeOH mixture, generated the desired salt **111** in a good 72 % yield. The formation of the salt

was confirmed by ^1H NMR spectroscopy, showing the alkene singlets at 5.43 and 5.96 ppm, respectively. The singlet peak at 137.8 ppm corresponded to the quaternary alkene carbon atom and the disappearance of the peak at 60.4 ppm for the same atom in **99** was confirmed by ^{13}C NMR spectroscopy. The ^{19}F NMR spectrum showed two separate singlet peaks at -107.1 and -148.9 ppm, respectively in a 1:4 ratio. The ESI-MS gave a peak at m/z 401 for M^+ .

Following the same reaction conditions, **112** was formed as a white powder in a moderate 49 % yield. The yield of the final compound was considerably lower than the *p*-substituted analogue **111**, which was also observed for other diaryliodonium salts bearing *meta* substituents. The ^1H NMR spectrum proved the formation of the final product showing the appearance of the two alkene singlet peaks at 5.45 and 6.07 ppm. The peak at 137.8 ppm for the quaternary alkene carbon indicated that the final salt successfully underwent the elimination reaction as the same carbon atom in **101** appeared at 62.8 ppm in the ^{13}C NMR spectrum.

The *p*-CF₃, *m*-CF₃ and *o*-CF₃ substituted diaryliodonium salts, **113**, **114** and **115** were produced in good yields (87 %, 74 % and 70 % respectively) and were fully characterised by ^1H , ^{19}F and ^{13}C NMR spectroscopy, as well as mass spectrometry.

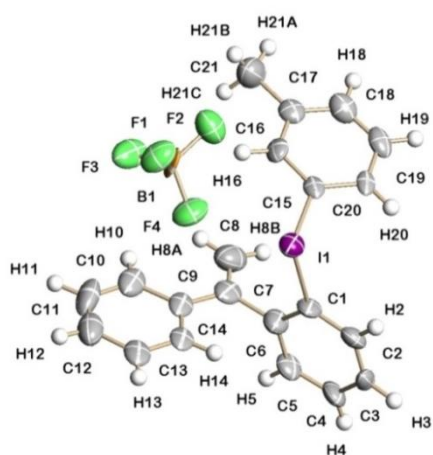
3.4 Synthesis of diaryliodonium salts with direct elimination / metathesis



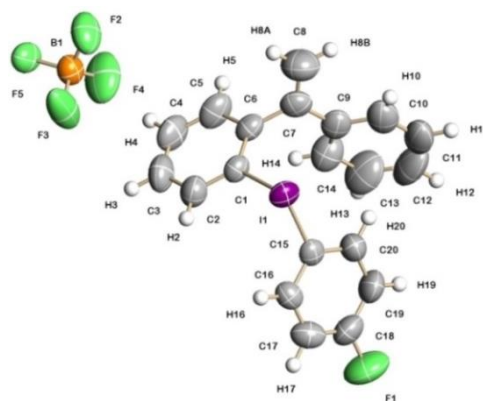
Scheme 3.20 Synthesis of unsymmetrical diaryliodonium salts with direct elimination by Method B

After the successful synthesis of unsymmetrical diaryliodonium salts from Grignard reagents forming **108-115** in three consecutive steps, it was found that the eliminated salt could be obtained by quenching the Grignard reaction with TfOH (6 eq.). The metathesis with NaBF₄ was achieved following the same procedure by stirring the diaryliodonium triflates for 4 hours at 40 °C (**Scheme 3.20**). The disappearance of the peak at -73.4 ppm in the ¹⁹F NMR spectrum corresponding to the triflate CF₃ group and the appearance of the singlet at -148.9 ppm for the tetrafluoroborate counteranion proved the formation of the desired salt.

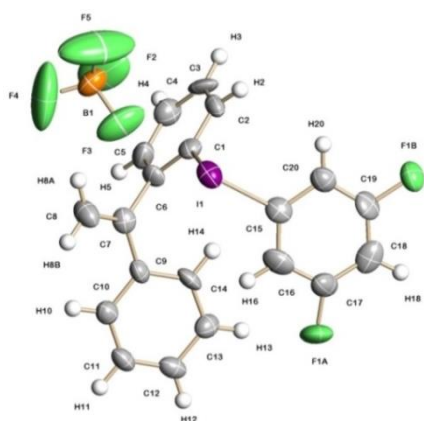
Crystals suitable for X-ray crystallography were obtained for salts **109**, **111**, **112** and **113** (**Figure 3.3**). The key bond lengths and angles are presented in **Table 3.3**. The C(1)-I(1) bond lengths of iodonium tetrafluoroborates ranged from 2.093(25) to 2.126(8) Å and were in close proximity to the bond lengths of C(15)-I(1) (2.071(14) - 2.109(5) Å). Moreover, the C(7)-C(8) bond lengths were 1.27(2) – 1.325(9) Å and were typical for a carbon-carbon double bond. The bond angles of C(1)-I(1)-C(15) ranged from 99.3(6) to 99.1(2) Å and are fairly typical for the pseudo T-shape of diaryliodonium salts. The C(6)-C(7)-C(9) bond angles were between 116.5(15) to 120.6(5) Å, confirming the presence of the alkene sidearm.



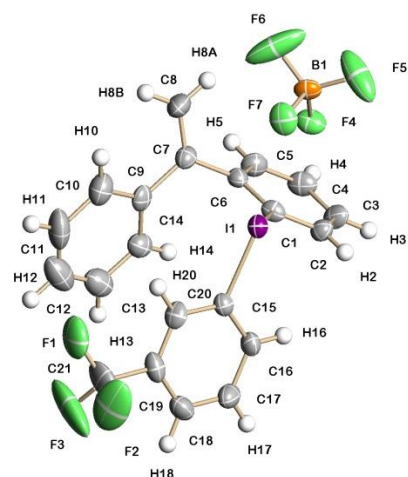
a) Solid-state structure of **109**



b) Solid-state structure of **111**



c) Solid-state structure of **112**



d) Solid-state structure of **113**

Figure 3.3 Solid-state structures for diaryliodonium tetrafluoroborates

Table 3.3 Key bond lengths (Å) and angles (°) for diaryliodonium tetrafluoroborates

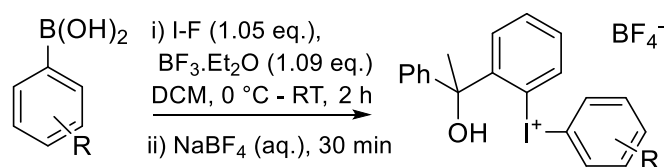
	109	111	112	113
C(1)-I(1)	2.107(5)	2.126(8)	2.093(15)	2.106(5)
C(15)-I(1)	2.086(6)	2.093(9)	2.071(14)	2.109(5)
C(7)-C(8)	1.325(9)	1.304(11)	1.273(2)	1.305(8)
C(1)-I(1)-C(15)	99.1(2)	97.0(3)	93.3(6)	98.5(2)
C(6)-C(7)-C(9)	117.5(7)	117.4(8)	116.5(15)	120.6(5)

3.5 Synthesis of diaryliodonium salts from aryl boronic acids

An alternative procedure for preparing unsymmetrical diaryliodonium salts was investigated by reacting aryl boronic acids with fluoroiodane and the Lewis acid $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (**Table 3.4**). Boron trifluoride was added to a cooled solution of the fluoroiodane **91** in dichloromethane and the solution was stirred at 0 °C for 10 min before the aromatic boronic acid (**116**, **117**, **118**, **119**, **120**, **121** and **122**) was added. After stirring the reaction mixture at room temperature for 2 hours, a saturated aqueous solution of NaBF_4 (20 mL) was added and the mixture was stirred vigorously for 30 min. The crude product was washed with water and then with hexane and diethyl ether to produce the salt as a stable white powder.

All the diaryliodonium salts, **123**, **124**, **125**, **126**, **127**, **128** and **129** were obtained in good yields (59-84 %) and were fully characterised by multinuclear NMR spectroscopy and mass spectrometry.

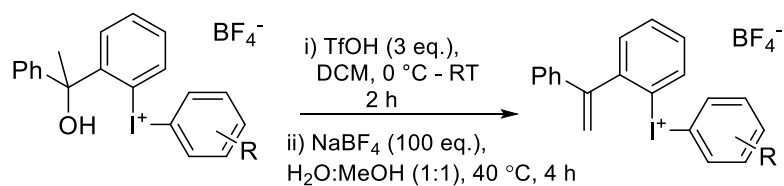
Table 3.4 *Synthesis of substituted diaryliodonium salts from boronic acids*



Entry	Substrate	Product	Yield ^a (%)
1	 116	 123	79
2	 117	 124	82
3	 118	 125	77
4	 119	 126	59
5	 120	 127	76
6	 121	 128	84
7	 122	 129	82

^a isolated yield

Table 3.5 Elimination and metathesis of substituted diaryliodonium salts from boronic acids



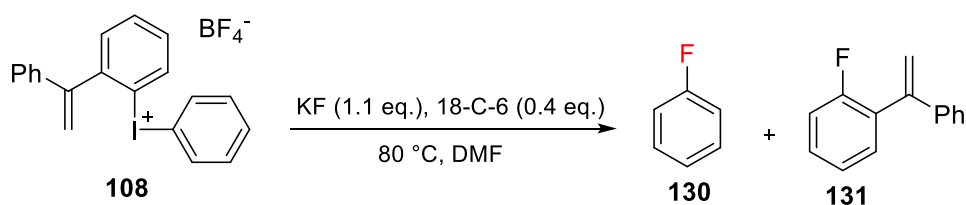
Entry	Substrate	Product	Yield ^a (%)
1	 123	 109	72
2	 124	 110	79
3	 125	 111	74
4	 126	 112	62
5	 127	 113	72
6	 128	 114	69
7	 129	 115	70

^a isolated yield

All the diaryliodonium salts in (**Table 3.4**) (entries 1-7) were reacted with TfOH in order to undergo elimination to form the alkene sidearm and then anion metathesis with NaBF₄ (**Table 3.5**). Although the overall yield of the diaryliodonium salt, generated from the aromatic boronic acid (**Method C**), was slightly lower than the yields obtained from the aromatic Grignard reagents (**Methods A and B**), the product salts were formed in higher purity and this was confirmed by multinuclear NMR spectroscopy.

3.6 Fluorination of unsymmetrical diaryliodonium salts

Table 3.6 Fluorination of 108



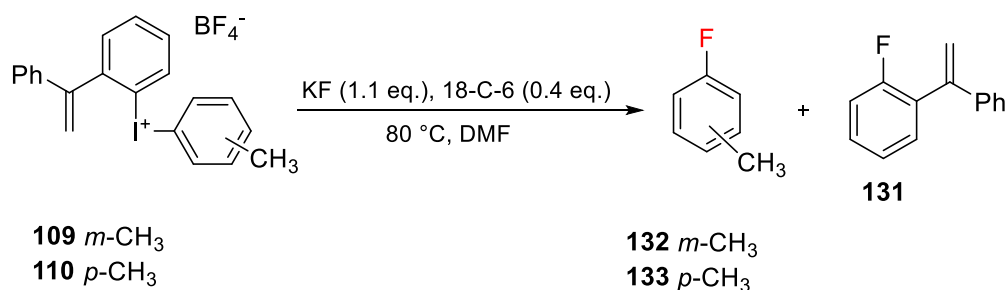
Entry	Ar-F	Time (h)	Cu(OTf) ₂ (eq.)	Yield of Ar-F ^a (%)	Yield of 131 ^a (%)	Ar-F:131
1		4	0.2	75	3	96:4
2		4	0	5	12	29:71
3	130	18	0	7	13	35:65

^a Determined by ¹⁹F NMR spectroscopy with internal standard, 1-fluoro-4-nitrobenzene

Initially, the fluorination conditions optimised by Dr. Abudken¹³⁰ in the Stuart group for the fluorination of unsymmetrical diaryliodonium salts containing an alkene sidearm were applied to the unsymmetrical salt **108** (**Table 3.6**). In entry 1 salt **108** was reacted with KF, 18-C-6 and Cu(OTf)₂ in DMF at 80 °C for 4 h to generate fluorobenzene **130** in 75 % yield. There was a very high selectivity towards the desired fluoroaromatic over **131** of 96:4. Exactly the same reaction conditions were repeated in entry 2, but without any copper catalyst. As expected, the selectivity was reversed and the *ortho-effect* dominated

forming fluoroalkene **131**. Surprisingly, not much fluorination occurred and essentially the same result was obtained in entry 3 when the reaction was repeated for 18 hours.

Table 3.7 Fluorination of *m*- and *p*-tolyl salts



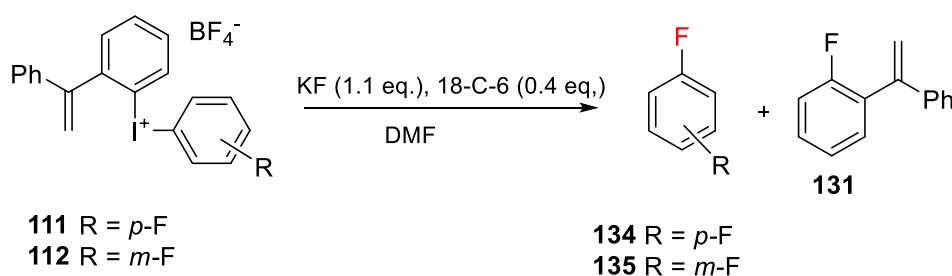
Entry	Ar-F	Time (h)	Cu(OTf) ₂ (eq.)	Yield of Ar-F ^a (%)	Yield of 131 ^a (%)	Ar-F: 131
1		4	0.2	46	1	98:2
2		8	0.2	70	7	91:9
3	132	8	0	0	58	0:100
4		8	0.2	71	8	90:10
5		8	0	0	55	0:100
	133					

^a Determined by ¹⁹F NMR spectroscopy with internal standard, 1-fluoro-4-nitrobenzene.

The fluorination reaction was investigated with electron rich substrates **109-110**. As shown in entry 1, the desired fluorinated product was obtained in a moderate 46 % yield and with 98:2 selectivity for **132:131**. When the reaction time was increased to 8 hours, the yield increased significantly to 70 % and the fluoroalkene was formed in only 7 %. As expected, the selectivity was reversed in the absence of the Cu catalyst (entry 3) and the reaction was driven by the *ortho*-effect, where the fluoroalkene **131** was formed as the only product.

Having seen that an increased reaction time generated the desired product in a higher yield, the fluorination of the *p*-tolyl salt **110** was conducted at 80 °C for 8 hours. The desired fluorinated product **133** was obtained in a high 71 % yield together with the fluoroalkene **131** (8 %) and with 90:10 selectivity. The selectivity was reversed when the non-catalysed reaction was attempted (entry 5). A 55 % yield of the fluoroalkene **131** was obtained and there was no sign of 4-fluorotoluene **133** in the $^{19}\text{F}\{^1\text{H}\}$ NMR spectrum.

Table 3.8 Fluorination of *m*- and *p*-fluorine substituted salts



Entry	Ar-F	Time (h)	Cu(OTf) ₂ (eq.)	Temp. (°C)	Yield of Ar-F ^a (%)	Yield of 131 ^a (%)	Ar-F: 131
1		4	0.2	80	41	4	91:9
2	 134	4	0.5	80	43	5	90:10
3		1	0.2	100	38	6	86:14
4		8	0.2	80	51	2	96:4
5		8	0	80	1	42	98:2
6	 135	4	0.2	80	7	3	98:2
7		8	0.2	80	29	19	60:40

^a Determined by ^{19}F NMR spectroscopy with internal standard, 1-fluoro-4-nitrobenzene.

In the fluorination of substituted aromatic salts **111-112** bearing weak electron donating substituents, the desired fluorinated products **134-135** were obtained in moderate yields (38-51 %) but in high selectivity over **131** in the presence of Cu(OTf)₂.

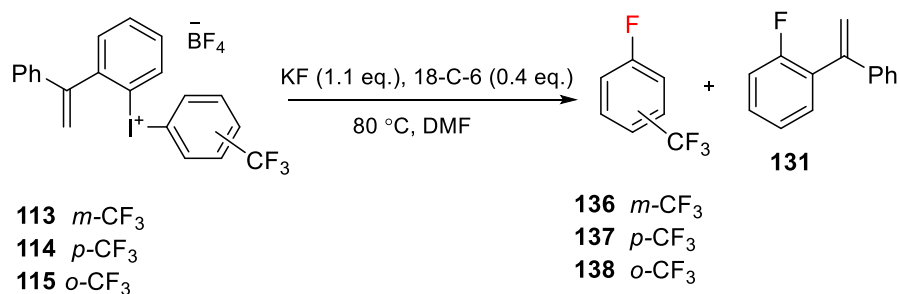
As shown in entry 1, *p*-difluorobenzene **134** was obtained in a 41 % yield along with 4 % of the fluoroalkene **131**. However, the reaction did not go to completion as 37 % of unreacted starting material **111** was found in the ¹⁹F{¹H} NMR spectrum, showing a singlet peak at -107.1 ppm. The formation of other side products was also observed, which included 4-fluoriodobenzene (20 %) at -115.2 ppm, 4,4'-difluorobiphenyl (6 %) at -116.3 ppm and 4-fluorophenol (10 %) at -127.3 ppm in the ¹⁹F{¹H} NMR spectrum.

Aiming to increase the conversion to **134** and reduce the formation of unwanted side products, the catalyst loading was increased from 0.2 to 0.5 equivalents. A similar yield of 43 % was observed and only 11 % of unreacted starting material **111** was observed from the ¹⁹F{¹H} NMR spectrum. The formation of 4-fluoriodobenzene (17 %), 4,4'-difluorobiphenyl (7 %) and 4-fluorophenol (4 %) side products was not reduced. The reaction also generated the fluoroalkene **131** in 5 % yield. Full consumption of the starting material was observed in the fluorination reaction attempted at 100 °C for 1 h as shown in entry 3. However, the formation of the 4-fluoriodobenzene side product increased to 45 % along with 27 % of 4-fluorophenol. Moreover, the yield and selectivity of the desired product dropped to 38 % and 86:14 (**134:131**), respectively.

When the reaction time was increased to 8 hours and the temperature was lowered to 80 °C, the fluorinated product **134** was obtained in a 51 % yield and the formation of the fluoroalkene was reduced to 2 % (entry 4). However, the reaction also generated 31 % of 4-fluoriodobenzene, 38 % of 4-fluorophenol and 29 % of fluorobenzene. Interestingly, the fluorinated product **134** was obtained in 1 % yield only in a catalyst-free fluorination reaction in entry 5. The fluoroalkene **131** was obtained in 46 % yield along with 22 % of 4-fluoriodobenzene.

Surprisingly, the *meta*-fluoro-substituted diaryliodonium salt **112** did not react well under Cu-catalysed conditions producing *meta*-difluorobenzene in very low yield when the reaction was attempted for 4 hours at 80 °C. When the reaction time was increased to 8 hours in entry 7, 29 % yield of the desired difluorinated product **135** was obtained. However, this also resulted in the formation of **131** in 19 % yield.

Table 3.9 Fluorination of 113, 114 and 115



Entry	Ar-F	Time (h)	Cu(OTf) ₂ (eq.)	Yield of Ar-F ^a (%)	Yield of 131 ^a (%)	Ar-F: 131
1		4	0.2	35	1	97:3
2		8	0.2	63	8	89:11
3		8	0	76	13	85:15
4		4	0	89	2	98:2
5		8	0.2	56	7	89:11
6		18	0.2	51	8	86:14
7		18	0	60	15	80:20
8		8	0	68	3	96:4
9		4	0	84	0	100:0
10		8	0.2	24	2	92:8
11		8	0	60	0	100:0
12		4	0	91	1	99:1

^a Determined by ¹⁹F NMR spectroscopy with internal standard, 1-fluoro-4-nitrobenzene.

The fluorination reactions of diaryliodonium salts bearing the electron-withdrawing trifluoromethyl group were first attempted in the presence of Cu(OTf)₂. As seen in entry 1, a four hour reaction generated the desired product **136** in a low 35 % yield along with

1 % of **131**. Although a low yield was observed, the selectivity of **136** over fluoroalkene was 97:3 (**136:131**). A considerable increase to 63 % was observed when the reaction time was increased to 8 hours. However, an increase to 8 % for the fluoroalkene side product was also noticed which reduced the selectivity to 89:11 (**136:131**).

For a direct comparison, the same reaction over 8 hours was attempted using the diaryliodonium salt bearing a trifluoromethyl substituent at the *para* position on the aromatic ring. The reaction generated the desired fluorinated aromatic **137** in a lower 56 % yield along with 7 % of the fluoroalkene **131** (entry 5). As the substrate seemed to be less reactive than the *meta*-substituted counterpart, the reaction time was prolonged to 18 hours which, unfortunately, resulted in a moderate 51 % yield (entry 6) and the side product **131** was formed in 8 % yield, which resulted in a lower selectivity of 86:14 (**137:131**).

The trifluoromethyl substituent at the *ortho* position in **115** was the least reactive under Cu-catalysed conditions. The standard 8 hour reaction generated the fluorinated aromatic **138** in a low 24 % yield along with the side product **131** which was formed in 2 % yield.

Interestingly, when the fluorination reactions of the trifluoromethyl substituted diaryliodonium salts were attempted in the absence of Cu(OTf)₂, the desired fluorinated aromatics were produced in much better yields. When the reactions were carried out at 80 °C for the standard 8 h, the *meta*-, *para*-, and *ortho*-fluoro products were prepared in 76 %, 68 % and 60 % yields, respectively. The yields were further improved to 89 %, 84 % and 91 % by using a short 4 h reaction time. In all three of these reactions only trace amounts of **131** were formed (0-2 %) and so there was exceptionally high selectivity towards the desired fluorinated aromatic (98:2 up to 100:0).

3.7 Conclusions

A novel fluorinating reagent **91**, containing a phenyl group in the sidearm compared to the original fluoroiodane **7**, was prepared from the commercially available 2-aminobenzophenone **86** in a five-step synthetic protocol.

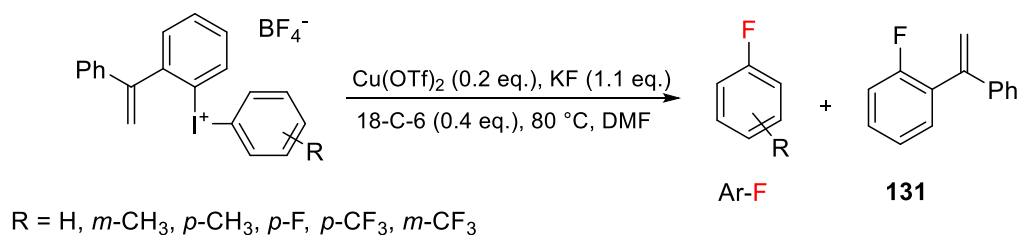
A range of unsymmetrical diaryliodonium salts were prepared using the fluoroiodane **91** and aromatic Grignard reagents. In the second step, the alcohol sidearm was eliminated

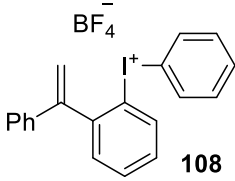
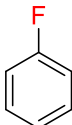
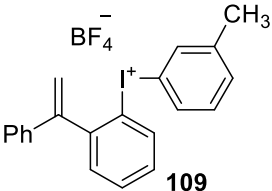
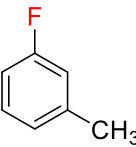
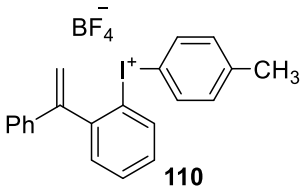
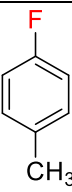
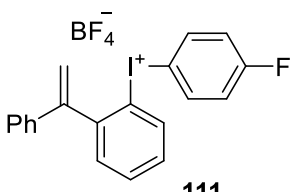
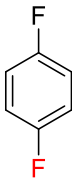
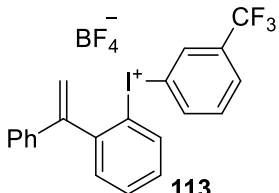
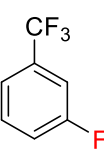
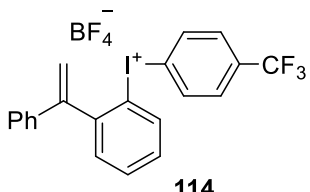
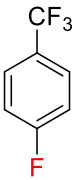
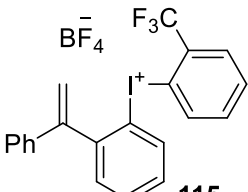
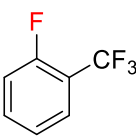
in the presence of triflic acid (3 equivalents), resulting in the formation of an alkene sidearm. Eight salts were prepared successfully in high yields (68-92 %). The diaryliodonium triflates then underwent metathesis with NaBF₄ (100 eq.) in a MeOH:DCM (1:1) homogenous mixture which was heated to 40 °C for 4 hours, forming the unsymmetrical diaryliodonium tetrafluoroborates in good yields (49-87 %).

Alternatively, the reaction process was accelerated when the Grignard reaction was quenched with 6 equivalents of TfOH, resulting in the formation of the eliminated product without generating the hydroxyl salt. The final tetrafluoroborate salts were obtained after the metathesis step with NaBF₄ (100 eq.) in a MeOH:DCM (1:1) homogenous mixture which was stirred for 4 hours at 40 °C. The advantage over the indirect elimination using 3 eq. of TfOH was that the reaction yields of the final tetrafluoroborate salts were as high as in the previous attempt (51-87 %) *cf.* (49-87 %), concluding that the shortened reaction sequence was both time and yield efficient.

The synthesis of unsymmetrical diaryliodonium salts was also attempted using commercially available arylboronic acids in the presence of the Lewis acid, BF₃.Et₂O, together with the fluoroiodane reagent **91** in DCM for 2 hours at 0 °C, generating the hydroxyl salts with the tetrafluoroborate counteranion. The resulting salts underwent elimination with TfOH (3 eq.) and metathesis as described above and generated the final unsymmetrical diaryliodonium salts bearing the alkene sidearm in good yields (62-79 %). Although the final tetrafluoroborate salts were obtained in slightly lower yields than those made from Grignard reagents, the final compounds were of higher purity as was confirmed by the multinuclear NMR spectroscopy.

Table 3.10 Summary of best fluorination results



Entry	Salt substrate	Ar-F	Cu(OTf) ₂ (eq.)	Yield of Ar- F ^a (%)	Yield of 131 ^a (%)	Ar- F:131
1 ^b	 108	 130	0.2	75	3	96:4
2 ^c	 109	 132	0.2	70	7	91:9
3 ^c	 110	 133	0.2	71	8	90:10
4 ^c	 111	 134	0.2	51	2	96:4
5 ^b	 113	 136	0	89	2	98:2
6 ^b	 114	 137	0	84	0	100:0
7 ^b	 115	 138	0	91	1	99:1

^a Determined by ¹⁹F NMR spectroscopy with internal standard, 1-fluoro-4-nitrobenzene

^b 4 h reaction; ^c 8 h reaction

Table **10** summarises the best fluorination results obtained in the presence and absence of the Cu(OTf)₂ catalyst using the unsymmetrical diaryliodonium salts **108-111**, **113-115**. As seen in entries 1, 2 and 3, the fluorinated products were obtained in high yields (70 – 75 %) in the presence of the copper catalyst and there was high selectivity over **131** (> 90:10). In entry 4, the less reactive substrate **111** was fluorinated in a moderate 51 % yield along with 2 % of the fluoroalkene **131**.

When the unsymmetrical diaryliodonium salts contained an electron-withdrawing trifluoromethyl group (entries 5-7), the non-catalysed fluorination produced the desired fluorinated aromatics in 84-91 % yield in just 4 hours. Only trace amounts of the competing **131** were observed (0-2 %) resulting in high selectivity towards the desired product (98:2 to 100:0). Presumably, these reactions undergo an S_NAr process with fluoride attacking the most electron deficient aryl group.

The electron rich substrates **109** and **110** again proved the reversibility of the *ortho* effect in the metal catalysed fluorination reaction. When **131** was fluorinated for 4 hours at 80 °C in DMF in the presence of 0.2 eq. of Cu(I), 46 % of the desired fluorinated product **132**. The increased reaction time to 8 hours successfully generated the final product in a high 70 % yield. Seeing that increased reactivity time resulted in higher yield, the *p*-tolyl substrate **110** was reacted for 8 hours following the same reaction conditions which resulted in a high 71 % yield of the final fluorinated product. As expected, the *ortho* effect was dominant in the uncatalysed reactions, generating fluoroalkene **131** as the only product in moderate yields (55-58 %).

The substrates having weak electron withdrawing groups **111** and **112** were less reactive towards fluorination and resulted in only moderate yields (38-51 %) under Cu(I) catalysed conditions. However, the selectivity over the fluorinated side product **134** was high each time >90 %. When **134** was tested in the fluorination reaction without a metal catalyst, the desired product was not formed. The *ortho* effect driven side product was obtained in 42 % yield along with 22 % of 4-fluoriodobenzene. The *meta*-substituted substrate **112** was even less reactive under metal catalysed conditions and only generated the fluorinated product in a low 29 % yield.

Chapter 4

Synthesis of β - Fluorovinylodonium Salts by the Reaction of Alkynes with a Hypervalent Iodine(III) Reagent

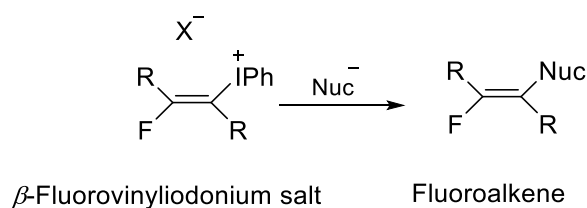


4.1 Introduction

The versatility of hypervalent iodine compounds described in previous chapters can be further expanded and show wide applications in medicinal chemistry and material science. Among such, alkenyl(phenyl)iodonium salts are considered to be highly reactive compounds which have broad applications in Michael addition-elimination reactions, ligand coupling and nucleophilic substitution (S_N1 and S_N2) processes.

The employment of alkenyl(phenyl)iodonium salts in the synthesis of organofluorine compounds, particularly fluoroalkenes, have attracted significant attention due to fluoroalkenes having similar properties to amide groups and being able to serve as isosteres for the amide moiety in peptides.¹³⁵ As the activity of biological structures is dependent on the position and stereochemistry of the fluorine atom, the regio- and stereo-specific introduction of the fluorine into biological structures is important.

Several methods for the preparation of fluoroalkenes have been reported and include the Horner-Wadsworth-Emmons reaction using fluorine-containing organophosphonates. However, the majority of procedures generate mixtures of stereoisomers and thus limit applications.¹³⁶ Reports based on hypervalent iodine-mediated fluorination reactions describe fluorovinylidonium salts as excellent building blocks for fluoroalkenes in which the phenyliodonio moiety can serve as a superleaving group under mild reaction conditions (**Scheme 4.1**).¹³⁷

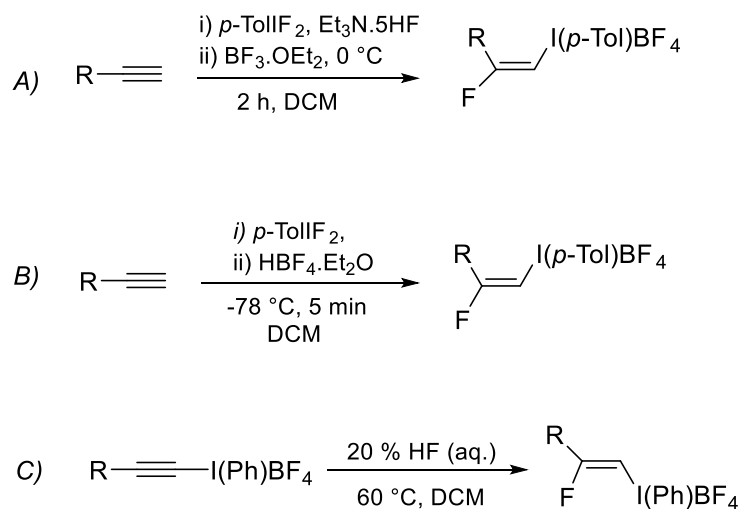


Scheme 4.1 β -Fluorovinylidonium salts – building blocks for fluoroalkenes

Several reports based on Pd-catalyzed cross coupling reactions using alkenyl halides have shown progress towards the stereoselective synthesis of fluoroalkenes. However, the preparation of fluoroalkenyl halides and the metal catalyst precursors was described as challenging. One of the earlier examples reported by Ochiai *et al.* utilised CsF for the preparation of (*Z*)-2-fluoro-1-alkenyl(phenyl)iodonium salts. However, due to the low nucleophilicity of the fluoride ion the yields were only 15-20 %.¹³⁸

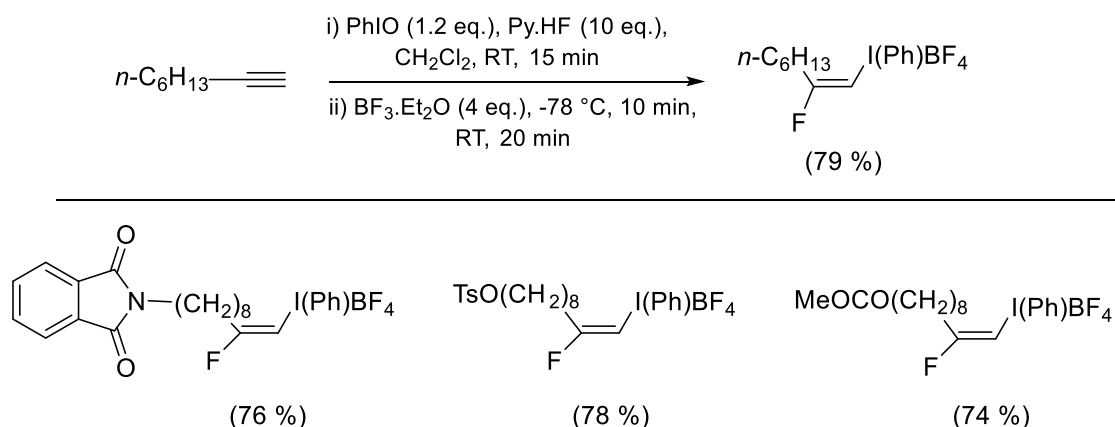
An improved stereoselective synthesis of (*E*)-2-fluoro-iodoalk-1-enes utilising pyridinium poly(hydrogen) fluoride for iodofluorination of alkynes was reported by Mestdagh *et al.*¹³⁹ Although only a few examples of this type of reaction were reported, it proved the synthetic practicality in the Pd-catalysed cross-coupling reactions, generating the desired products in high selectivity.¹³⁹ However, the use of highly toxic hydrogen fluoride or a more efficient HF-pyridine complex was required in the reported protocol.

Hara and co-workers developed a stereoselective synthesis of (*E*)- β -fluorovinyl-iodonium salts from the reaction of *p*-(difluoroiodo)toluene (*p*-TolIF₂) with alkynes in the presence of Et₃N.5HF under mild conditions. The reaction tolerated a variety of functional groups, therefore making the fluorovinylidonium salt a good synthon for the stereoselective synthesis of fluoroalkenes. Despite reaction efficiency, the preparation of Et₃N.5HF required handling of highly toxic anhydrous hydrogen fluoride (**Scheme 4.2 A**).¹⁴¹



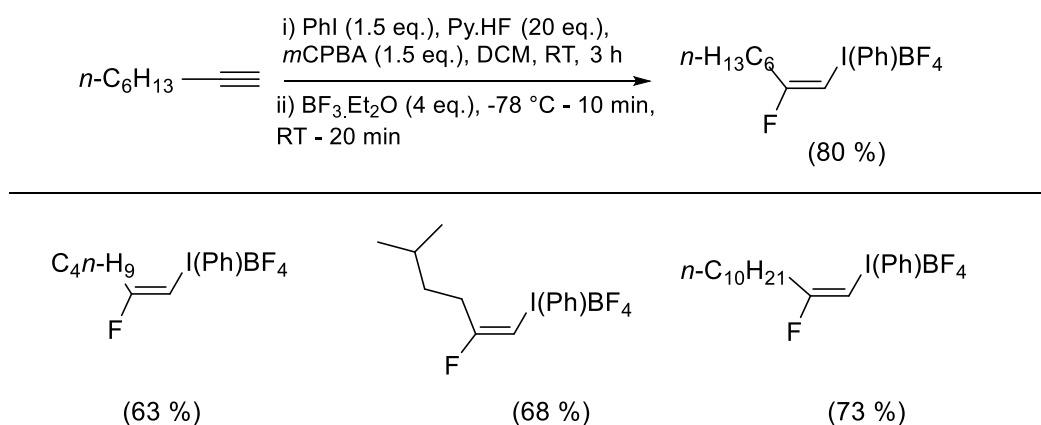
Scheme 4.2 Preparation of (*E*) and (*Z*)- β -fluorovinylidonium salts

The same group also reported an alternative synthetic preparation of (*E*)- β -fluorovinylidonium salts utilising *p*-(difluoroiodo)toluene (*p*-TolIF₂) with 1-alkynes in the presence of the commercially available and less toxic HBF₄·OEt₂ at -78 °C in just 5 minutes (**Scheme 4.2 B**).¹⁴² Similarly, the synthesis of (*Z*)- β -fluorovinylidonium salts can be prepared by adding HF to 1-alkynylidonium salts by Michael addition at 60 °C in dichloromethane (**Scheme 4.2 C**).¹⁴³



Scheme 4.3 *Synthesis of (E)-β-fluorovinylidonium salts with hypervalent iodine/HF reagents*

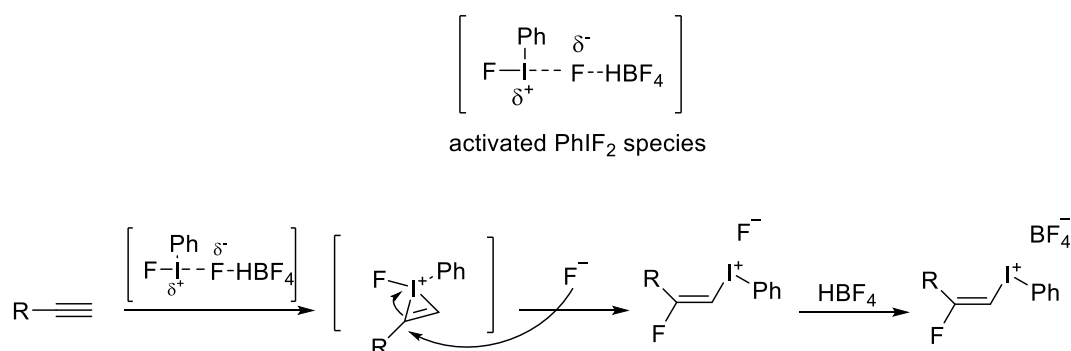
Kitamura and co-workers reported the synthesis of β-fluorovinylidonium salts by the reaction of alkynes with hypervalent iodine and HF reagents.¹⁴⁴ The studies were initiated using 1-octyne with several hypervalent iodine and HF reagents for the fluorination. The use of PhI(OAc)₂ and pyridine.HF complex followed by the addition of BF₃.Et₂O generated the desired salt in a moderate 58 % yield. When PhIO was used as an alternative hypervalent iodine source, the yield of the salt increased to 81 %. Further reaction optimisations such as increasing the amount of Py.HF from 5 equivalents to 10 equivalents improved the yield of the salt to 87 %. Interestingly, the reaction did not progress in the absence of BF₃.Et₂O, proving that PhIF₂ needed a stronger activating agent than Py.HF. Various terminal and internal alkyne substrates were used successfully for the preparation of β-fluorovinylidonium salts under the optimized conditions. Even functionalised alkynes bearing methyl ester, tosylate and phthalimide underwent fluorination reactions affording the desired salts in high yields (73-78 %). Although efficient, the reported synthesis of β-fluorovinylidonium used environmentally non-benign Py.HF which is highly toxic even at fairly low concentration and requires special handling and storing precautions.



Scheme 4.4 Synthesis of (*E*)- β -fluoroalkenylidonium salts from iodoarenes

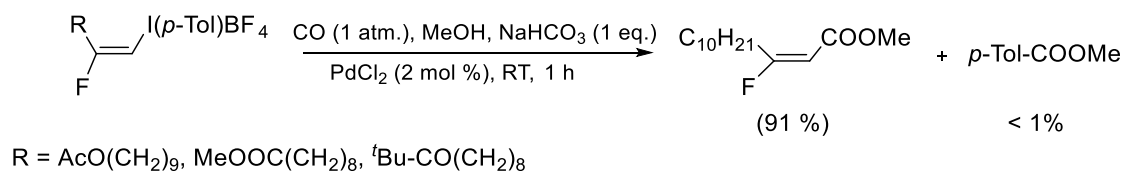
In 2018 the same group reported the preparation of β -fluorovinylidonium salts from iodoarenes in the presence of *m*-CBPA without requiring the synthesis of iodosylarenes or (diacetoxyiodo)arenes.¹³⁷ When 1-octyne was reacted with iodobenzene (1.5 eq.) in the presence of Py.HF (10 eq.), an oxidant *m*-CBPA (1.5 eq.) and the activator BF₃.Et₂O (4 eq.), the desired tetrafluoroborate salt was obtained in a good 73 % yield. Replacement of Py.HF by HF, TEA.3HF or TEA.5HF did not enhance the yield (64 %, 31%, 60 %), respectively. A considerable increase in the reaction yield was observed when the amount of HF was increased to 20 equivalents, resulting in a high 80 % of the final β -fluorovinylidonium salts (**Scheme 4.4**).

The vinylic proton in the β -fluorovinylidonium salt obtained from 1-octyne appeared at 6.70 ppm in the ¹H NMR spectrum and was coupled to the fluorine atom by 14.8 Hz coupling constant which was in agreement with previously reported data stating that the β -fluorovinylidonium tetrafluoroborate salt existed as the (*E*) isomer.^{147,149,151} The mechanistic explanation states that the *in situ* generated difluoroiodoarene (PhIF₂) is activated by HBF₄, formed after the addition of the Lewis acid BF₃.Et₂O, and undergoes electrophilic addition to the alkyne to form a bridged iodonium species which is attacked nucleophilically by fluoride ion forming the (*E*)- β -fluorovinylidonium salt. The key step determining the stereochemistry is the ring-opening of the bridged iodonium species by fluoride (**Scheme 4.5**).¹³⁷



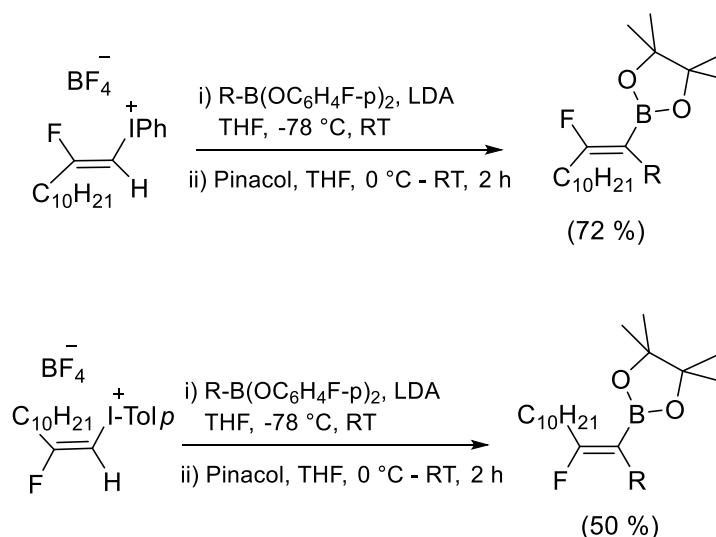
Scheme 4.5 Mechanism for stereoselective formation of (*E*)- β -fluorovinylidonium salts

The usefulness of fluorovinylidonium salts has been discussed in various reports with particular attention paid to the synthesis of fluorinated analogues of biological compounds which often show greater bioactivity than the original non-fluorinated compound.¹⁴⁸ Hara showed that fluorovinylidonium salts can be successfully employed in the Pd catalysed carbomethoxylation reaction (**Scheme 4.6**) which proceeded smoothly at room temperature in 1 hour to give (*E*)-3-fluorotridec-2-enoate in an excellent 91 % yield with retention of stereochemistry (*E* / *Z* > 98 / 2).¹⁴⁷⁻¹⁴⁹



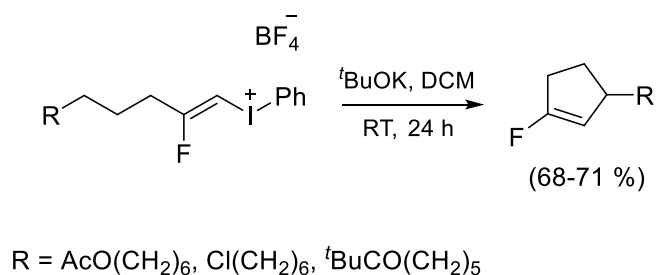
Scheme 4.6 Applications of fluoroalkenylidonium salts

The preparation of (*E*)- and (*Z*)-fluoroalkenylboronates from corresponding fluoroalkenylidonium salts with di(*p*-fluorophenoxy)alkylboranes was reported by Guan who successfully used the fluorinated boronates for the synthesis of pinacol esters, widely used in Suzuki-Miyaura coupling reactions (**Scheme 4.7**).¹⁴⁷



Scheme 4.7 Synthesis of pinacol esters from fluorovinylidonium salts

Yoshida and co-workers showed that strong base induced deprotonation of vinylidonium salts generated alkylidenecarbenes by α -elimination. The alkylidenecarbenes underwent 1,5- carbon-hydrogen insertion to generate substituted cyclopentenes. Following Yoshida's proposed method, Guan and co-workers demonstrated that fluorocyclopentenes could be obtained in the reaction between (*Z*)-(2-fluoroalkenyl)iodonium salts and potassium *tert*butoxide (**Scheme 4.8**).¹⁴⁸

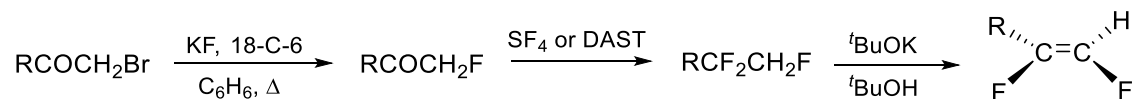


Scheme 4.8 Cyclisation reactions of fluoroalkenylidonium salts

4.1.2 Preparation of difluoroalkenes

The use of fluoroolefins as amide bond analogues has been used in the synthesis of bioactive compounds having good enzyme/receptor affinity and bioavailability.¹⁴⁹ Consequently, the ability to make fluoroalkenes stereoselectively in a straightforward

synthetic procedure would be a valuable tool, opening new frontiers in chemical biology and related science.

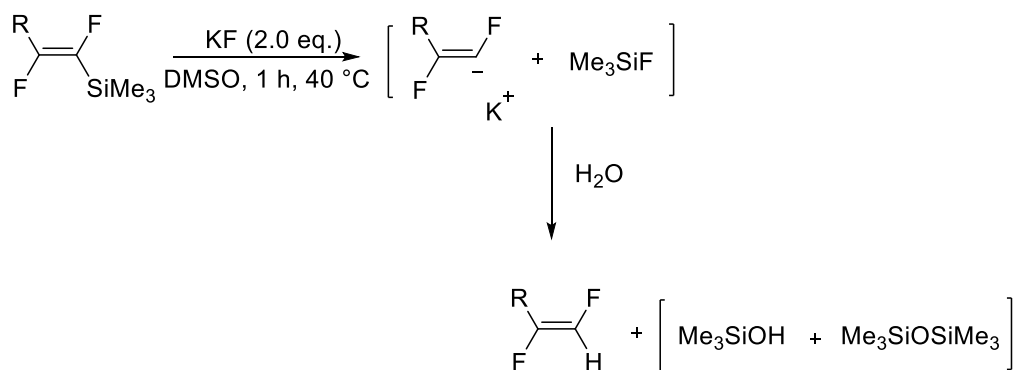


Scheme 4.9 *Synthesis of fluoroethylenes via fluoroketones*

Only a small number of reports for the preparation of difluoroalkenes are found in the literature. In 1981 Leroy reported the synthesis of 1,2-difluoroethylenes derived from fluoro-ketones (**Scheme 4.9**). The direct exchange of bromine by fluorine into bromoethyl ketones gave good yields (> 75 %) with KF used as the fluoride source which was activated by 18-crown-6. The resulting fluoroketone was reacted with either SF₄ or DAST which generated the intermediate trifluoroalkane which was then treated with base resulting in the final difluoroalkene.¹⁵⁰ Although yield efficient, the method required the use of sulfur tetrafluoride which is toxic and DAST which tends to decompose violently upon contact with water or at higher temperatures.

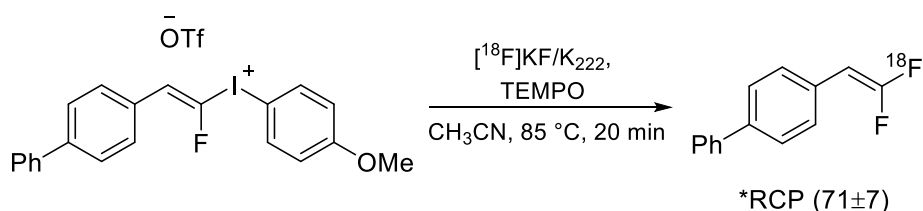
Moderai reported that fluoroalkenes can be obtained from the dehydrofluorination of fluorohydrocarbons based on the elimination of HF by KOH under anhydrous conditions, resulting in the equimolar mixture of *cis:trans* isomers in good yields >71 %. The major drawback of the method was the elimination of the highly corrosive and dangerous to use hydrogen fluoride, requiring special handling and usage precautions limiting process applications.¹⁵¹

An improved method towards making difluoroalkenes was reported by Martin *et al.* from (Z)- fluorovinylsilanes using KF as the source of fluoride which resulted in *trans* alkenes only. In their proposed mechanism, the silicon atom is attacked by the fluoride, generating a vinylic carbanion. The protonation of the carbanion is faster than the elimination of the fluoride on the β-carbon, therefore the fluoride stays in the *cis* position with respect to the metal and the overall configuration of the difluoroalkene is *trans* (**Scheme 4.10**).¹⁵²



Scheme 4.10 *Synthesis of difluoroalkenes from difluorovinylsilanes*

Although reported methods have proved their efficiency in generating the desired fluorovinyl iodonium salts in high yields and excellent selectivity >90 % (*E* / *Z*), the use and handling of toxic reagents such as hydrofluoric acid and pyridine.HF is unfavourable. Therefore, the aim of this research was to use less environmentally hazardous and dangerous to handle reagents by employing the hypervalent iodine(III) reagent **91** for the synthesis of β -fluorovinylidonium salts. After eliminating the alcohol sidearm, it was also intended to investigate the fluorination of the β -fluorovinylidonium salts to develop a new procedure for the preparation of difluoroalkenes building on the fluorination methodology developed in Chapter 3.



Scheme 4.11 ^{18}F -fluorination of fluoroalkenyl(4-methoxyphenyl)iodonium triflate
(*Radiochemical purity)

A profound use of 1,1- ^{18}F -difluorinated alkenes as enzyme inhibitors or drugs that treat disorders of the central nervous system has been reported in several review papers.¹⁵¹⁻¹⁵⁵ Therefore, the development of new radiotracers containing ^{18}F -perfluorinated functionals groups such as the geminal CF_2 is highly desirable. Recently, Tredwell *et al.* reported the synthesis of 1,1- ^{18}F -difluoroalkenes from non-carrier added ^{18}F fluoride and fluoroalkenyl(4-methoxyphenyl)iodonium triflates (**Scheme 4.11**).¹⁵⁶ A wide range

of functional groups were compatible with the precursor fluoroalkenyl(4-methoxyphenyl)iodonium triflate which did not have an effect upon the ^{18}F -fluorination.

It was found that the use of TEMPO was essential for the reaction to proceed in good radiochemical purity. Interestingly, when TEMPO was replaced by $(\text{MeCN})_4\text{CuOTf}$, the reaction did not progress which was in contrast to Sanford's reported synthesis of ^{18}F fluoroarenes.¹⁵⁷ As stated, this versatile and functional group-tolerant method can be further expanded for the synthesis of similar radiolabelled motifs with a huge potential in PET technology.¹⁵⁶⁻¹⁵⁷

4.2 Synthesis of β -fluoroalkenylidonium salts using a novel hypervalent iodine(III) reagent **91**

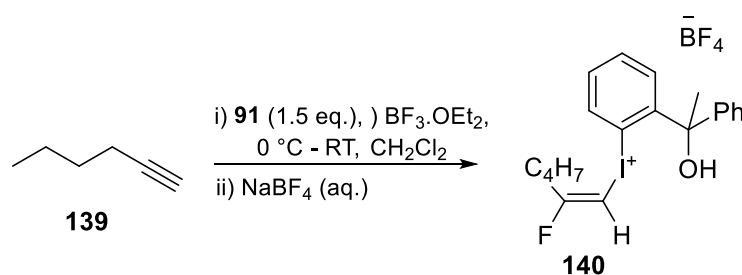


Table 4.1 Optimisation of reaction conditions with 1-hexyne

Entry	$\text{BF}_3\cdot\text{Et}_2\text{O}$ (eq.)	Time (h)	Conversion ^a (%)	Yield ^b (%)
1	1.65	2	0	0
2	3.3	2	100	57
3	3.3	3	100	62
4	4.95	3	100	53
5	3.3	4.5	100	84

^a Conversion calculated by ^1H NMR spectroscopy, refers to the consumption of the starting material

^b Isolated yield

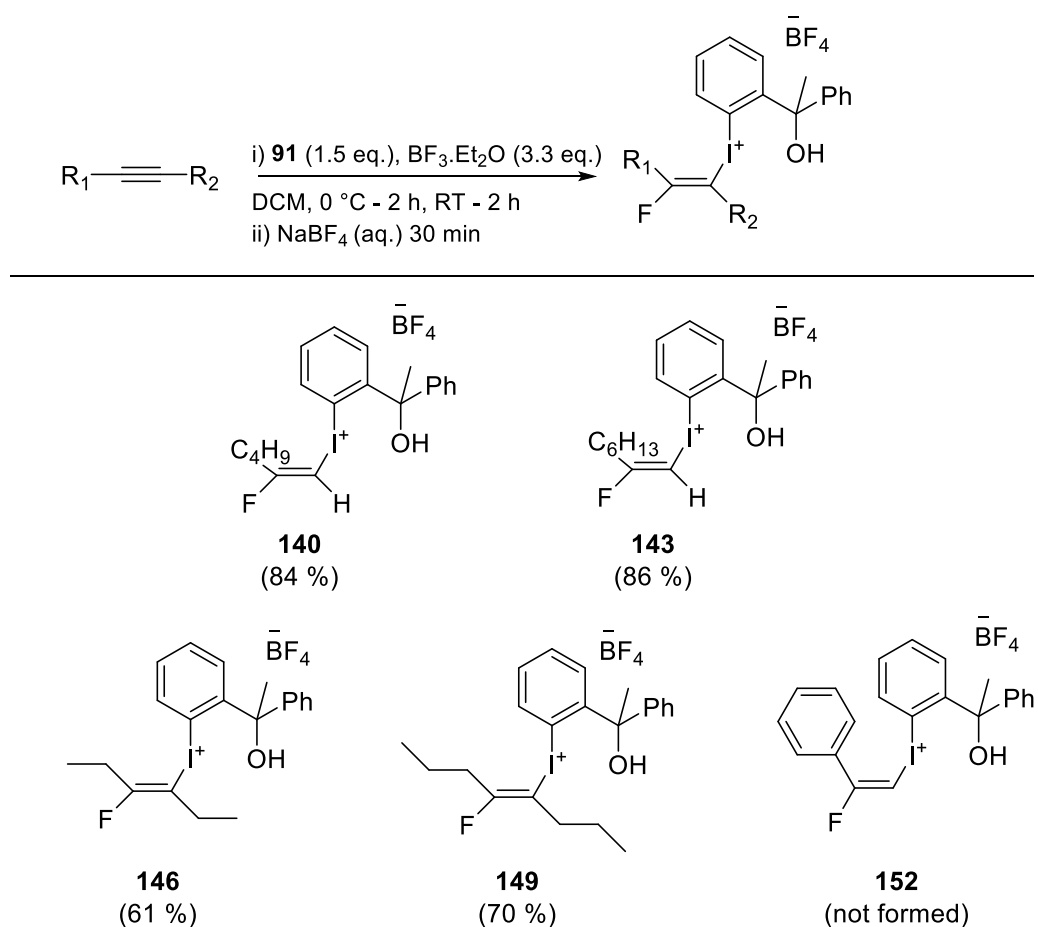
The preparation of β -fluoroalkenylidonium salts was investigated initially by reacting the fluoroiodane reagent **91** with 1-hexyne as substrate (**Table 4.1**). In entry 1, $\text{BF}_3\cdot\text{Et}_2\text{O}$ was added to a solution of reagent **91** (1.5 eq.) in dichloromethane (0 °C) and the mixture

was stirred for 10 minutes. The substrate (0.53 mmol) was added and the contents were stirred for 2 hours at room temperature. After which the saturated solution of NaBF₄ (10 mL) was added and the mixture was left to stir at room temperature for 30 min. After washing the crude product with water, the salt was washed with hexane/diethyl ether mixture (2:1). However, ¹⁹F NMR spectroscopy revealed that the desired salt was not formed as a singlet at -143.2 ppm for the fluoroiodane was observed. Also, there was no indication for the coupling between the aliphatic CH₂ and fluorine atom in the ¹H NMR spectrum.

When the amount of BF₃.Et₂O was doubled to 3.3 equivalents, a full conversion from the starting material was confirmed by ¹H and ¹⁹F NMR spectroscopy (entry 2). After washing the crude product with water and then with a hexane/diethyl ether mixture (2:1), the desired product was isolated in a good yield (57 %). However, it was noticed that the final salt was soluble in diethyl ether which resulted in product loss. When the reaction time was increased to 3 hours and chloroform was used instead of diethyl ether, a slightly higher reaction yield of 62 % was obtained (entry 3). Importantly, the substitution of diethyl ether to chloroform removed the majority of impurities in the aromatic region found in the ¹H NMR spectrum. In entry 4, a further increase in the amount of BF₃.Et₂O to 4.95 equivalents did not enhance the reaction efficiency and generated the salt in 50 % yield. Lastly, it was decided to increase the reaction time to 4.5 hours but reduce the amount of BF₃.Et₂O to 3.3 equivalents (entry 5). The ¹H NMR spectrum of the crude product indicated a full consumption of the starting material and the ¹⁹F NMR spectrum showed that there was no fluoroiodane **91** remaining as no peak at -143.2 ppm was found. In the ¹H NMR spectrum the singlet for the sidearm was shifted upfield to 2.06 ppm and there was a doublet of triplets at 2.46 and 2.51 ppm indicating coupling between the aliphatic CH₂ group and the fluorine atom with a ³J_{HF} coupling constant of 22.6 Hz. The doublet at 6.28 ppm was due to the vinylic proton which was coupled to the fluorine atom with a coupling constant of 15.7 Hz. In the ¹⁹F NMR spectrum there was a singlet at -58.6 ppm along with the tetrafluoroborate singlet at -148.5 ppm. Three doublets were found in the ¹³C NMR spectrum. The doublet at 31.6 ppm corresponded to the CH₂ group on the aliphatic chain which coupled to fluorine with a coupling constant of 24.1 Hz. The doublet for the alkenic CH group was at 76.9 ppm with a two-bond coupling constant of 44.3 Hz. The carbon directly bonded to the fluorine atom appeared at 178.0 ppm and had a large

coupling constant of 290.7 Hz. The ESI-MS showed a peak at m/z 425 corresponding to the parent cation, M^+ .

With the optimum conditions found, the other substrates were successfully prepared in good to high yields (**Scheme 4.12**). Disappointingly, the reaction employing phenylacetylene did not generate the desired product. The ^1H NMR spectrum of the crude product showed the unreacted starting material together with fluoroiodane which was observed in the ^{19}F NMR spectrum, showing a singlet at -143.2 ppm.



Scheme 4.12 Synthesis of β -fluorovinylidonium salts from fluoroiodane reagent **91**

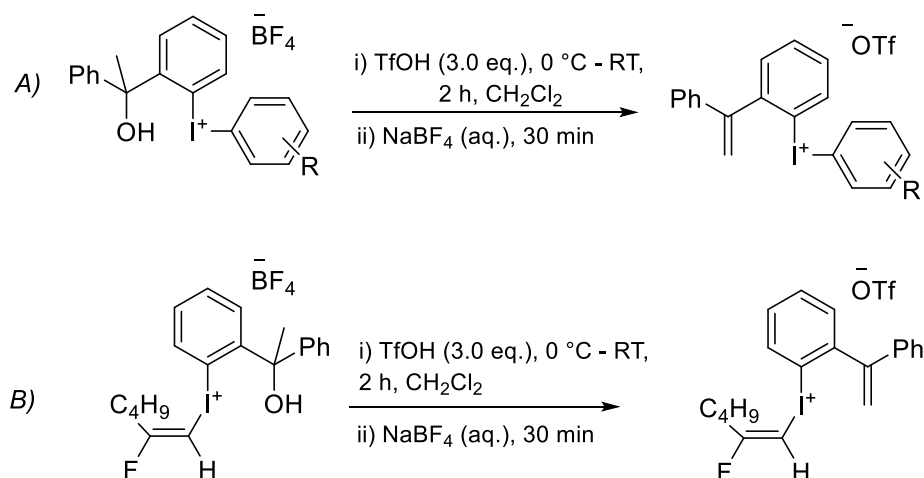
When 1-octyne was reacted using the same procedure, the salt **143** was obtained in a high 86 % yield. The reaction went to completion which was confirmed by ^1H , ^{19}F and ^{13}C NMR spectra, and the desired tetrafluoroborate salt was obtained as a brown oil. The aliphatic CH_2 protons were coupled to the fluorine atom by a three-bond coupling constant of 22.0 Hz and the alkene CH proton had a coupling constant of 15.7 Hz in the

^1H NMR spectrum. The ^{19}F NMR spectroscopy confirmed the product formation by showing a singlet at -58.8 ppm for the fluoroalkene. Three doublets were found in the ^{13}C NMR spectrum with two-bond couplings to fluorine having coupling constants of 24.1 Hz and 48.8 Hz, respectively and a large single-bond coupling constant of 290.8 Hz for C-F.

A slightly lower yield of 61 % was obtained for product **146**. However, the reaction fully went to completion which was confirmed by ^1H , ^{19}F and ^{13}C NMR spectroscopy and mass spectrometry. A doublet at 25.4 ppm in the ^{13}C NMR spectrum was coupled to the fluorine atom with a small three-bond coupling constant of 5.9 Hz and a larger two-bond coupling constant of 26.2 Hz was found for the carbon atom at 27.3 ppm. A doublet at 171.8 ppm with a coupling constant of 284.0 Hz corresponded to the C-F bond. In comparison to structures bearing terminal alkenes (**140** and **143**), the fluorine singlet was shifted further downfield to -74.2 ppm in the ^{19}F NMR spectrum. The mass spectrum confirmed the formation of the desired salt by showing the parent cation at m/z 425.

A similar reactivity pattern was observed when 4-octyne was reacted under the same reaction conditions. The salt **149** was obtained in a good 70 % yield. The ^{19}F NMR spectrum showed a singlet for the fluoroalkene at -72.9 ppm along with a singlet at -148.6 ppm for the tetrafluoroborate counteranion. A one-bond coupling constant of 284.8 Hz was observed for the doublet at 171.6 ppm for the alkene carbon atom containing fluorine in the ^{13}C NMR spectrum. The mass spectrum showed the mass of the parent cation at m/z 453.

4.3 Elimination of β -fluoroalkenyliodonium salts **140-149**



Scheme 4.13 A) Elimination of diaryliodonium and B) β -fluorovinyl iodonium salts using *TfOH*

Due to the structural similarity, the method for the elimination of the alcohol sidearm described in Chapter 3 was applied to the β -fluorovinyl iodonium salts (**Scheme 4.13**). The elimination was attempted in triflic acid (3 equivalents) at 0 °C – RT for 2 hours in dichloromethane. However, an immediate colour change from light brown to black occurred which was not observed in the previous reactions with the diaryliodonium salts. After washing the crude reaction mixture with water, the ^1H NMR spectrum revealed that the reaction was not successful. Neither the starting material **140** nor the eliminated product **141** was found and the spectrum was difficult to assign. The same pattern was observed when the amount of triflic acid was reduced to 1 equivalent, showing that triflic acid was too strong to induce the elimination of the alcohol sidearm but lead to sample decomposition instead.

Table 4.2 Elimination using $\text{BF}_3 \cdot \text{Et}_2\text{O}$

$\text{140} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{BF}_3 \cdot \text{Et}_2\text{O}} \text{141}$

Entry	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (eq.)	T (°C)	Time (h)	Conversion ^a (%)
1	5	0	3	50
2	7	RT	3	88
3	7	30	4	100

^a Conversion calculated by ^1H NMR spectroscopy, refers to the consumption of the starting material **140**.

As $\text{BF}_3 \cdot \text{Et}_2\text{O}$ is a milder Lewis acid than TfOH , it was thought that it could facilitate the elimination reaction without decomposing the starting material. Firstly, 5 equivalents of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ were added to a cooled solution (0 °C) of **140** in DCM and the resulting mixture was stirred at this temperature for 3 hours. There was no distinctive colour change upon addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ which was taken as a positive step towards the elimination reaction. Upon reaction completion, a 1:1 mixture of eliminated and non-eliminated salts was confirmed by ^1H and ^{19}F NMR spectra. The eliminated **141** had two singlet peaks at 5.48 and 6.07 ppm which indicated the formation of the alkene. However, the CH_3 singlet at 2.06 ppm was still present. Also, in the eliminated salt **141**, a singlet fluorine peak at -63.7 ppm appeared further downfield from the fluorine peak in **140** which was found at -58.6 ppm.

To reach full conversion from the starting material, the amount of Lewis acid $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was increased to 7 equivalents and the reaction was attempted for 3 hours at room temperature. A much higher 88 % conversion was obtained, but there was still some **140** present. Therefore, the reaction temperature was increased slightly above RT to see whether the elimination process can be facilitated (entry 3). The new reaction conditions using 7 equivalents of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at 30 °C for 4 hours generated the desired salt **141** in 100 % conversion. The ^1H NMR spectroscopy confirmed full consumption of **140** as there was no singlet for CH_3 group observed at 2.06 ppm. The CH_2 group for the eliminated

sidearm was found at 119.8 ppm and the quaternary carbon was identified at 137.5 ppm in the ^{13}C NMR spectrum. The ESI-MS showed a peak at m/z 407 for the parent cation M^+ of the desired salt **141**.

Table 4.3 Elimination of β -fluoroalkenyliodonium salts

(67 - 81 %)

Entry	Substrate	Product	Yield ^a (%)
1	<p>140</p>	<p>141</p>	67
2	<p>143</p>	<p>144</p>	81
3	<p>146</p>	<p>147</p>	79
4	<p>149</p>	<p>150</p>	77

^a Isolated yield

The optimised reaction conditions were applied to the other β -fluorovinylidoni-um salts (Table 4.3). When the 1-octyne based salt **143** was subject to elimination using in the

same procedure, the final product **144** was obtained in a good 81 % yield and was fully characterised by multinuclear NMR spectroscopy and mass spectrometry. The CH₂ group on the eliminated sidearm was found at 119.7 ppm and the quaternary alkene carbon was observed at 137.6 ppm in the ¹³C NMR spectrum.

The formation of the internal alkyne based salt **147** was obtained in a good 79 % yield which was proved by ¹H, ¹⁹F and ¹³C NMR spectroscopy, as well as by mass spectrometry. The disappearance of the methyl singlet at 2.07 ppm and the formation of two alkene singlets at 5.48 and 6.11 ppm in the ¹H NMR spectrum indicated that the elimination process had occurred. The quaternary carbon atom of the eliminated sidearm was found at 137.2 ppm. The M⁺ of the parent cation was found at *m/z* 407.

The elimination reaction of **149** with BF₃.Et₂O generated the desired β-fluoroalkenyliodonium salt **150** in a good 77 % yield. The formation of the salt was confirmed by ¹H NMR spectroscopy, showing the alkene singlets at 5.48 and 6.11 ppm, respectively. The singlet peak at 136.6 ppm corresponded to the quaternary alkene carbon atom and the disappearance of the peak at 77.8 ppm for the same atom in **149** was confirmed by ¹³C NMR spectroscopy. The ESI-MS gave a peak at *m/z* 435 for M⁺.

4.4 Preliminary fluorination of a β-fluorovinyliodonium salts

Table 4.4 Fluorination of **144**

Entry	Cu(OTf) ₂ (eq.)	Yield of 153 ^a (%)	Yield of 154 ^a (%)	Yield of 131 ^a (%)	Alk- F : 131
1	0.2	15	27	13	54:46

^a Determined by ¹⁹F NMR spectroscopy with internal standard, 1-fluoro-4-nitrobenzene.

Following the fluorination conditions applied to the unsymmetrical diaryliodonium salts in chapter 3, β -fluorovinylidonium tetrafluoroborate **144** was subject to a preliminary fluorination under the same reaction conditions. The substrate **144** was reacted with KF, 18-C-6 and Cu(OTf)₂ in DMF for 4 hours at 80 °C to generate 1,2-difluorooct-1-ene **153** (15 %) which was confirmed by ¹⁹F{¹H} NMR spectroscopy, showing two doublets at -159.8 ppm and -183.2 ppm with a ³J_{FF} coupling constant of 127 Hz. The selectivity over fluoroalkene **131**, which was formed in 13 % yield, was 54:46 (**153**:**131**). Despite low reactivity towards fluorination, no unreacted starting material was found as no peak at -63.2 ppm was observed in the ¹⁹F NMR spectrum.

Interestingly, the reaction also generated (*E*)-2-fluoro-1-iodooct-1-ene **154** (27 %) which presumably was formed after fluorination of the aromatic moiety. The triplet of doublets at -82.4 ppm in the ¹⁹F NMR spectrum corresponded to the fluorine atom with ³J_{HF} coupling constants of 23.1 Hz and 18.6 Hz which was in agreement with the literature.¹⁵⁷ The proton decoupled ¹⁹F{¹H} NMR spectrum was consistent with the proposed structure as only a singlet at -82.4 ppm was observed.

4.5 Conclusions

A small series of β -fluorovinylidonium salts containing an alcohol sidearm were prepared using fluoroiodane **91** and commercially available alkyne substrates in the presence BF₃.Et₂O (3.3 eq.). The addition of excess BF₃.Et₂O (7.0 eq.) induced the elimination reaction resulting in the formation of β -fluorovinylidonium salts containing a styrene sidearm. Four salts were prepared successfully in good yields (67-81 %). The stereochemistry of the β -fluorovinylidonium salts formed from terminal alkyne substrates (**141** and **144**) was determined by ¹H NMR spectroscopy. The vinylic proton appeared at 6.28 ppm and was coupled to the fluorine atom (15.7 Hz). The β -fluorovinylidonium salts made from internal alkyne substrates **147** and **150** successfully generated the desired products which were fully characterised by multinuclear NMR spectroscopy and mass spectrometry. The preliminary fluorination of **144** was attempted in the presence of 0.2 eq. of Cu(OTf)₂ at 80 °C for 4 hours and resulted in the formation of 1,2-difluorooct-1-ene **153** in a low 15 % yield along with 13 % of **131** and 27 % of (*E*)-2-fluoro-1-iodooct-1-ene **154**. If more time was available, I would like to have studied this reaction further to see if an efficient method could be developed to access difluoroalkenes or fluoroiodoalkenes solely.

Chapter 5

Experimental



5.1 General Information

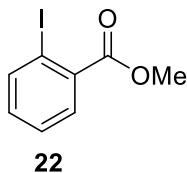
Starting materials were used as received from SigmaAldrich, Apollo Scientific, Alfa Aesar, Fluorochem, Acros Organics and Manchester Organics and were used without further purification unless otherwise stated. Solvents were distilled under nitrogen from appropriate drying agents. Dichloromethane (DCM) was distilled prior to use from calcium hydride (CaH_2). Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium in the presence of benzophenone.

^1H , ^{19}F and ^{13}C NMR spectra were recorded on Bruker AV 500 and Bruker DRX 400 spectrometers at ambient temperatures. They were referenced to external SiMe_4 (^1H), 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. Spectral data is reported as follows: chemical shift, integration, multiplicity with the following abbreviations for the observed peaks: (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet), coupling constant(s) and assignment.

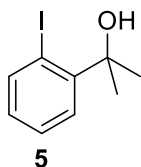
Concentrated refers to removal of solvent under reduced pressure on a rotary evaporator. Column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh). Analytical thin-layer chromatography (TLC) was carried out on silica gel F254/366 60 Å plates with visualisation using UV light (254 nm) and KMnO_4 stain was used for visualising TLC plates where necessary. Melting points (mp) were determined by using a Gallenkamp melting point apparatus (model MFB-595). Electrospray mass spectrometry (ESI-MS) was recorded using a micromass Quattro LC mass spectrometer with methanol (MeOH) as matrix. Atmospheric Solids Analysis Probe (ASAP) mass spectra were recorded on a Xevo QToF mass spectrometer (Waters). X-ray crystallography data were collected on a Bruker Apex SMART 2000 diffractometer using graphite monochromated $\text{Mo-K}\alpha$ radiation ($\lambda = 0.71073$ Å).

5.2 Experimental for Chapter 2

5.2.1 Preparation of 1-fluoro-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole **7**



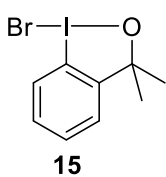
A solution of 2-iodobenzoic acid **1** (25.00 g, 100.8 mmol) in MeOH (150 mL) was cooled to 0 °C before thionyl chloride (13 mL, 151.2 mmol) was added dropwise over 30 min. The resulting colourless solution was refluxed at 70 °C for 19 h. After concentrating the reaction mixture on a rotary evaporator to give a pale yellow oil, it was dissolved in ethyl acetate (50 mL) and washed with brine (3 x 50 mL). The organic layer was then dried (MgSO₄) and concentrated under reduced pressure to give methyl-2-iodobenzoate **22** as a pale-yellow oil (23.10 g, 92 %). The characterisation data was in agreement with the literature.⁹⁶ δ_{H} (CDCl₃, 400 MHz) 3.94 (3H, s, OCH₃), 7.16 (1H, t, $^3J_{\text{HH}} = 7.5$ Hz, ArH), 7.41 (1H, t, $^3J_{\text{HH}} = 7.5$ Hz, ArH), 7.80 (1H, d, $^3J_{\text{HH}} = 7.5$ Hz, ArH), 8.00 (1H, d, $^3J_{\text{HH}} = 7.5$ Hz, ArH). δ_{C} (CDCl₃, 100 MHz) 52.6 (CH₃), 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⁺, C₈H₈IO₂ requires 262.9569, 100 %), 230.9304 ((M – OCH₃)⁺, 99%).



A dry, 3 necked round bottomed flask (250 mL), equipped with a reflux condenser, dropping funnel and a nitrogen supply, was charged with Mg turnings (4.2 g, 175 mmol). Dry diethyl ether (10 mL) was added to the flask whilst the solution of methyl iodide (7.8 mL, 125 mmol) in dry diethyl ether (10 mL) was added to the dropping funnel. The solution in the dropping funnel was added to the flask dropwise. The initiation of the reaction was observed immediately after the addition of the methyl iodide. The flask was diluted with more diethyl ether (14.5 mL) and the dropwise addition of methyl iodide was continued 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 3 necked round bottomed flask (250 mL) was equipped with a dropping funnel, reflux condenser, evacuated and back-filled with nitrogen. The methylmagnesium iodide solution was transferred by cannula. The excess magnesium turnings were rinsed with dry diethyl ether (10 mL) and transferred to the new flask. The solution of methylmagnesium iodide was cooled to 0 °C and a solution of methyl-2-iodobenzoate (15 g, 57.3 mmol) in dry diethyl ether (8 mL)

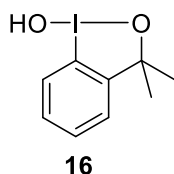
was added to a dropping funnel. The methyl-2-iodobenzoate **22** solution was added dropwise to the solution of methylmagnesium iodide over 10 min. The dropping funnel was rinsed with more dry diethyl ether (6 mL). The solution was stirred and allowed to warm to room temperature for 18 hours.

After this time, TLC analysis confirmed complete consumption of the starting material and the mixture was poured into an ice cold saturated solution of ammonium chloride (50 mL). Water (60 mL) was added and the mixture was stirred until all of the solids had dissolved. After filtration through celite, the organic layer was separated and the aqueous layer was extracted with diethyl ether (4 x 50 mL). The organic layers were combined, dried over K₂CO₃ and concentrated under reduced pressure to give a brown oil (10.1 g). Purification by flash chromatography (5% EtOAc in hexane) gave 2-(2-iodophenyl)propan-2-ol **5** as a yellow oil (8.5 g, 57 %). The characterisation data was in agreement with the literature.⁹⁶ δ_{H} (CDCl₃, 400 MHz) 1.64 (6H, s, CH₃), 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} = 7.5 Hz, ⁴J_{HH} = 2.0 Hz, ArH), 7.83 (1H, dd, ³J_{HH} = 7.8 Hz, ⁴J_{HH} 1.4 Hz, ArH). δ_{C} (CDCl₃, 100 MHz) 28.5 (CH₃), 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⁺, C₉H₁₁IO requires 261.98519, 30%), 247 ((M-CH₃)⁺, 100%).

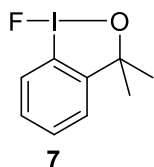


A solution of 2-(2-iodophenyl) propan-2-ol **5** (7.4 g, 28 mmol) in CHCl₃ (74 mL) was prepared in a round bottomed flask. To this was added NBS (4.9 g, 28 mmol) in three portions. The yellow suspension was stirred at room temperature overnight. After transferring the clear yellow solution to a separating funnel, the organic layer was washed with water (3 x 30 mL) and brine (30 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure to give a yellow solid which was re-crystallized from ethyl acetate to give 1-bromo-3,3-dimethyl-1,3-dihydro-λ³-benzo[d][1,2]iodoxole **15** as yellow crystals (6.05 g, 82 %). The characterisation data was in agreement with the literature.⁹⁷ m.p. 126 – 129 °C (lit.,⁹⁷ 126 – 128 °C) δ_{H} (CDCl₃, 400 MHz) 1.49 (6H, s, CH₃), 7.13 – 7.15 (1H, m, ArH), 7.44-7.50 (2H, m, ArH), 7.98-8.01 (1H, m, ArH). δ_{C} (CDCl₃, 100 MHz) 29.2 (CH₃), 84.2 (C), 112.0 (CI), 125.9 (CH), 129.3 (CH), 130.4 (CH), 131.1 (CH), 149.8 (C).

m/z (EI) 327/325 ($M - CH_3$)⁺, 261 ($M - Br$)⁺. (ASAP) 339.8959 (M^+ , $C_9H_{10}^{79}BrIO$ requires 339.8960), 341.8939 (M^+ , $C_9H_{10}^{81}BrIO$ requires 341.8938).

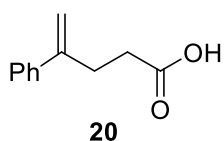


A solution of 1-bromo-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole **15** (6.05 g, 18.8 mmol) in dry dichloromethane (74 mL) was added to an aqueous solution of KOH (2.11 g, 37.6 mmol). The mixture was then stirred for 2 hours at RT. After separating the organic layer, the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were then dried over $MgSO_4$ and concentrated under reduced pressure to give the desired compound as a pale pink solid (3.8 g, 63 %). The characterisation data was in agreement with the literature.⁵⁶ m.p. 139 - 141 °C (lit.,⁵⁶ 126 - 128 °C). δ_H ($CDCl_3$, 400 MHz) 1.42 (6H, s, CH_3), 7.21 (1H, d, $^3J_{HH} = 7.2$ 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), 7.75 (1H, d, $^3J_{HH} = 7.8$ Hz, ArH). δ_C ($CDCl_3$, 100 MHz) 30.1 (CH_3), 80.3 (C), 115.4 (CI), 126.3 (CH), 126.8 (CH), 129.3 (CH), 129.9 (CH), 149.6 (C). m/z (ES) 278.9880 (MH^+ , $C_9H_{12}IO_2$ requires 278.9882).



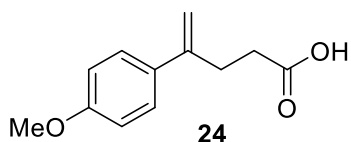
To a solution of 1-hydroxy-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole **16** (3.3 g, 11.8 mmol) in dichloromethane (150 mL) was added $Et_3N \cdot 3HF$ (2.3 mL, 14.3 mmol) and the reaction mixture was stirred at room temperature for 4 hours. After adding water (150 mL) the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 100 mL) and the organic extracts were combined and concentrated under reduced pressure to give a pale yellow solid. Residual water was removed by co-evaporating the azeotropic mixture with toluene (3 x 20 mL) to give a pale yellow crystalline solid (3.2 g, 96 %). The characterisation data was in agreement with the literature.⁵⁶ m.p. 83-85 °C (lit.,⁵⁶ 82 - 84 °C). δ_H ($CDCl_3$, 400 MHz) 1.45 (6H, s, CH_3), 7.15 (1H, dd, $^3J_{HH} = 7.5$ Hz, $^4J_{HH} = 1.2$ Hz, ArH), 7.47 (1H, td, $^3J_{HH} = 8.3$ Hz, $^4J_{HH} = 1.0$ Hz, ArH), 7.55 (1H, td, $^3J_{HH} = 8.3$ Hz, $^4J_{HH} = 1.4$ Hz, ArH), 7.78 (1H, dd, $^3J_{HH} = 8.1$ Hz, $^4J_{HH} = 0.9$ Hz, ArH). δ_F ($CDCl_3$, 376 MHz) -143.1 (s). δ_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) 280.9847 (MH^+ , $C_9H_{11}FIO$ requires 280.9839), 260.9775 ($M - F^+$), 245.9562 ($M - F - CH_3$)⁺.

5.3 Preparation of the starting materials for the fluorocyclisation reactions (Scheme 2.8)

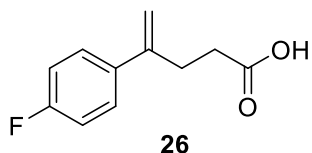


To a suspension of methyltriphenylphosphonium bromide (13.0 g, 36.5 mmol) in THF (67 mL) was added sodium *tert*-butoxide (7.0 g, 73 mmol) at 0 °C. The mixture was then stirred for 1 hour before 3-benzoylpropionic acid (5.0 g, 28.1 mmol) was added to the reaction mixture at 0 °C. The mixture was allowed to warm to room temperature whilst stirring for 18 hours. After concentrating the reaction mixture under reduced pressure, dichloromethane (100 mL) and 1M NaOH (170 mL) were added. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The aqueous layer was then acidified to pH *ca.* 2 using 12 M HCl (12 M) and the product was extracted into DCM (3 x 50 mL), dried over MgSO₄ and concentrated under reduced pressure to give 4-phenyl-4-pentenoic acid as a white solid (4.58 g, 93 %). The characterisation data was in agreement with the literature.⁶⁰ m.p. 92 – 95 °C (lit.,⁶⁰ 92 – 93 °C). δ_{H} (CDCl₃, 400 MHz) 2.53 (2H, t, $^3J_{\text{HH}} = 7.4$ Hz, CH₂), 2.85 (2H, t, $^3J_{\text{HH}} = 7.4$ Hz, CH₂), 5.11 (s, 1H, *HH*=C), 5.32 (s, 1H, *HH*=C), 7.25-7.41 (5H, m, ArH), 10.7 (1H, br s, COOH). δ_{C} (CDCl₃, 100 MHz) 30.1 (CH₂), 32.9 (CH₂), 112.9 (CH₂), 126.1 (CH), 127.7 (CH), 128.4 (CH), 140.4 (C), 146.5 (C), 179.4 (CO). *m/z* (ASAP) 177.0917 (MH⁺ C₁₁H₁₃O₂ requires 177.0916).

The other substrates for the fluorocyclisation reactions were prepared using the same method.

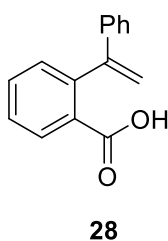


The reaction mixture was stirred at room temperature for 18 hours. The crude product was purified by column chromatography (50 % EtOAc in petroleum ether 40 – 60) and re-crystallised from chloroform to give 4-(4-methoxyphenyl)pent-4-enoic acid **24** as a white solid (0.16 g, 17 %). The characterisation data was in agreement with the literature.⁶⁰ m.p. 143 – 145 °C (lit.,⁶⁰ 145 – 146 °C). δ_{H} (CDCl₃, 400 MHz) 2.53 (2H, t, $^3J_{\text{HH}} = 7.4$ Hz, CH₂), 2.82 (2H, t, $^3J_{\text{HH}} = 7.4$ Hz, CH₂), 3.82 (3H, s, OCH₃), 5.01 (s, 1H, *HH*=C), 5.25 (s, 1H, *HH*=C), 6.87 (2H, d, $^3J_{\text{HH}} = 9.2$ Hz, ArH), 7.35 (2H, d, $^3J_{\text{HH}} = 9.2$ Hz, ArH), 10.45 (1H, br s, COOH). δ_{C} (CDCl₃, 100 MHz) 29.8 (CH₂), 33.1 (CH₂), 55.0 (OCH₃), 110.7 (CH₂), 113.7 (CH), 127.1 (CH), 132.4 (C), 145.7 (C), 158.9 (C), 174.2 (CO). *m/z* (ASAP) 207.1025 (MH⁺, C₁₂H₁₅O₃ requires 207.1021, 100%), 189.0925 ((M-OH)⁺), 161.0974 ((M-CO₂H)⁺).



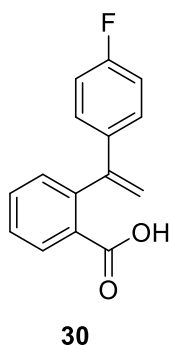
The reaction mixture was stirred at room temperature for 24 hours. The crude product was re-crystallised from ethyl acetate and petroleum ether 40 – 60 to give 4-(4-fluorophenyl)pent-4-

enoic acid **26** as a white solid (1.06 g, 53 %). The characterisation data was in agreement with the literature.⁶⁰ m.p. 85 – 87 °C (lit.,⁶⁰ 83 – 85 °C). δ_{H} (CDCl₃, 400 MHz) 2.49 (2H, t, $^3J_{\text{HH}} = 7.6$ Hz, CH₂), 2.85 (2H, t, $^3J_{\text{HH}} = 7.6$ Hz, CH₂), 5.01 (s, 1H, $\text{HH}=\text{C}$), 5.31 (s, 1H, $\text{HH}=\text{C}$), 7.01 (2H, dd, $^3J_{\text{HF}} = 8.6$ Hz, $^3J_{\text{HH}} = 8.6$ Hz, ArH), 7.35 (2H, dd, $^3J_{\text{HH}} = 9.0$ Hz, $^4J_{\text{HF}} = 5.2$ Hz, ArH), 11.20 (1H, br s, COOH). δ_{F} (CDCl₃, 376 MHz) -114.8 (s). δ_{C} (CDCl₃, 100 MHz) 30.3 (CH₂), 33.1 (CH₂), 112.7 (CH₂), 115.6 (CH, d, $^2J_{\text{CF}} = 21.1$ Hz), 127.9 (CH, d, $^3J_{\text{CF}} = 7.5$ Hz), 136.4 (C, d, $^4J_{\text{CF}} = 3.3$ Hz), 145.7 (C), 161.9 (C, d, $^1J_{\text{CF}} = 245.6$ Hz), 179.2 (CO). m/z (ASAP) 195.0819 (MH⁺, C₁₁H₁₂FO₂ requires 195.0821), 177.0703 ((M-OH)⁺), 149.0759 ((M-CO₂H)⁺), 135.0601 ((M-CO₂H-CH₂)⁺).

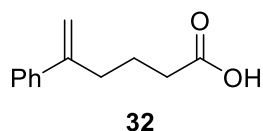


The reaction mixture was stirred at room temperature for 24 hours. The product was recrystallised from ethyl acetate and petroleum ether 40 – 60 to give 2-(1- phenylvinyl)benzoic acid **28** as a white solid (1.79 g, 39 %).

The characterisation data was in agreement with the literature.⁶⁰ mp 134 – 136 °C (lit.,⁶⁰ 130 – 131 °C). δ_{H} (CDCl₃, 400 MHz) 5.22 (1H, d, $^2J_{\text{HH}} = 0.8$ Hz, $\text{HHC}=\text{C}$), 5.67 (1H, d, $^2J_{\text{HH}} = 0.8$ Hz, $\text{HHC}=\text{C}$), 7.16-7.28 (5H, m, ArH), 7.39 (1H, dd, $^3J_{\text{HH}} = 7.4$ Hz, $^4J_{\text{HH}} = 1.2$ Hz, ArH), 7.46 (1H, td, $^3J_{\text{HH}} = 7.7$ Hz, $^4J_{\text{HH}} = 1.2$ Hz, ArH), 7.58 (1H, td, $^3J_{\text{HH}} = 7.5$ Hz, $^4J_{\text{HH}} = 1.2$ Hz, ArH), 7.93 (1H, dd, $^3J_{\text{HH}} = 7.4$ Hz, $^4J_{\text{HH}} = 1.2$ Hz, ArH), 11.12 (1H, br s, COOH) δ_{C} (CDCl₃, 100 MHz) 114.2 (CH₂), 126.6 (CH), 127.3 (CH), 127.6 (CH), 128.1 (CH), 129.5 (C), 131.1 (CH), 131.7 (CH), 132.7 (CH), 141.2 (C), 143.8 (C), 149.9 (C), 172.0 (C=O). m/z (ASAP) 225.0918 (MH⁺, C₁₅H₁₃O₂ requires 225.0916), 207.0807 ((M-OH)⁺).

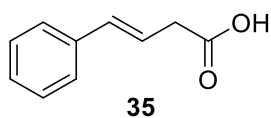


The reaction mixture was stirred at room temperature for 48 hours, giving the desired product as a white solid (1.01 g, 53 %). No purification was required. The characterisation data was in agreement with the literature.⁶⁰ m.p. 144 – 147 °C (lit.,⁶⁰ 143 – 145 °C). δ_{H} (CDCl₃, 400 MHz) 5.18 (1H, s, *HHC*=), 5.61 (1H, s, *HHC*=), 6.91 (2H, dd, $^3J_{\text{HH}} = 8.7$ Hz, ArH), 7.14 (2H, dd, $^3J_{\text{HH}} = 8.7$ Hz, $^4J_{\text{HF}} = 5.2$ Hz, ArH), 7.35 (1H, dd, $^3J_{\text{HH}} = 7.7$ Hz, $^4J_{\text{HH}} = 1.2$ Hz, ArH), 7.43 (1H, td, $^3J_{\text{HH}} = 7.5$ Hz, $^4J_{\text{HH}} = 1.2$ Hz, ArH), 7.53 (1H, td, $^3J_{\text{HH}} = 7.4$ Hz, $^4J_{\text{HH}} = 1.2$ Hz, ArH), 7.94 (1H, dd, $^3J_{\text{HH}} = 7.4$ Hz, $^4J_{\text{HH}} = 1.3$ Hz, ArH), 10.31 (1H, br s, COOH). δ_{F} (CDCl₃, 376 MHz) -114.9 (s). δ_{C} (CDCl₃, 100 MHz) 114.2 (CH₂), 114.6 (CH, d, $^2J_{\text{CF}} = 20.4$ Hz), 127.6 (CH), 128.2 (CH, d, $^3J_{\text{CF}} = 8.3$ Hz), 129.4 (C), 130.8 (CH), 131.2 (CH), 132.4 (CH), 137.3 (C, d, $^4J_{\text{CF}} = 2.8$ Hz), 143.2 (C), 148.9 (C), 162.3 (C, d, $^1J_{\text{CF}} = 243.7$ Hz), 172.4 (CO). *m/z* (ASAP) 243.0818 (MH⁺, C₁₅H₁₂FO₂ requires 243.0821), 225.061 ((M-OH)⁺).



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 **32** as a white solid (3.56 g, 72%). The characterisation data was in agreement with the literature.⁶⁰ mp 47 – 48 °C (lit.,⁶⁰ 44 °C). δ_{H} (CDCl₃, 400 MHz) 1.72 (2H, quintet, $^3J_{\text{HH}} = 7.5$ Hz, CH₂), 2.30 (2H, t, $^3J_{\text{HH}} = 7.5$ Hz, CH₂), 2.49 (2H, t, $^3J_{\text{HH}} = 7.5$ Hz, CH₂), 5.00 (1H, d, $^2J_{\text{HH}} = 1.3$ Hz, C=CH₂), 5.23 (1H, d, $^2J_{\text{HH}} = 1.3$ Hz, C=CH₂), 7.18 (1H, t, $^3J_{\text{HH}} = 7.0$ Hz, ArH), 7.24 (2H, t, $^3J_{\text{HH}} = 7.0$ Hz, ArH), 7.31 (2H, d, $^3J_{\text{HH}} = 7.0$ Hz, ArH), 11.05 (1H, br s, COOH). δ_{C} (CDCl₃, 100 MHz) 23.0 (CH₂), 33.3 (CH₂), 34.5 (CH₂), 113.1 (CH₂), 126.1 (CH), 127.5 (CH), 128.4 (CH), 140.8 (C), 147.4 (C), 179.9 (CO). *m/z* (ASAP) 191.1066 (MH⁺, C₁₂H₁₅O₂ requires 224 191.1072), 173.0945 ((M-OH)⁺).

5.3.1 Preparation of (*E*)-4-phenylbut-3-enoic acid (Scheme 2.9)

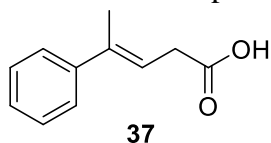


A solution of phenylacetaldehyde (5.62 mL, 64 mmol) and malonic acid (5.00 g, 48.0 mmol) in pyridine (3.87 mL, 48.0 mmol) was refluxed for 20 hours at 95 °C. After this time, the reaction mixture was cooled to room temperature and dissolved in Et₂O (200 mL). After

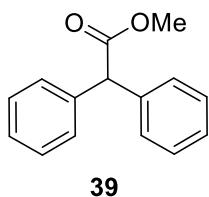
extracting the product into aqueous NaOH (1 M) solution (3 x 125 mL), the combined aqueous layers were acidified to pH = 1 with conc. H₂SO₄. After further extraction using Et₂O (3 x 125 mL), the organic layers were combined, dried over MgSO₄ and concentrated under reduced pressure to yield the crude product as a pale yellow solid (4.8 g). The crude product was purified by column chromatography using 80% ethyl acetate in petroleum ether (40-60) and re-crystallised from toluene:hexane (1:10) which yielded (*E*)-4-phenylbut-3-enoic acid **35** (3.4 g, 44 %) as white needles. The characterisation data was in agreement with the literature.^{100, 102} m.p. 81-85 °C (lit.,¹⁰⁰⁻¹⁰² 81-83 °C). δ_{H} (CDCl₃, 400 MHz) 3.36 (2H, dd, $^3J_{\text{HH}} = 7.1$ Hz, $^4J_{\text{HH}} = 1.4$ Hz, CH₂), 6.28 (1H, d, $^3J_{\text{HH}} = 15.8$ Hz, CH=CH ArH), 6.48 (1H, dt, $^3J_{\text{HH}} = 15.2$ Hz, $^3J_{\text{HH}} = 7.1$ Hz, CH=CH), 7.19 (1H, m, ArH), 7.27-7.33 (2H, m, ArH), 7.37-7.39 (2H, m, ArH), 12.32 (1H, br s, OH). δ_{C} (CDCl₃, 100 MHz) 37.8 (CH₂), 120.8 (CH), 126.3 (ArCH), 127.7, (ArCH), 128.6 (ArCH), 134.0 (CH), 136.4 (C), 174.0 (C=O). m/z (ASAP) 163.0922 ((M-H⁺), C₁₀H₁₁O₂ requires 162.0920).

5.3.2 Preparation of (*E*)-4-phenylpent-3-enoic acid (Scheme 2.10)

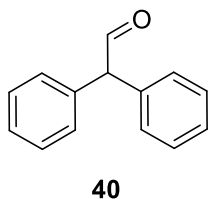
A mixture of 2-phenylpropanal (5.00 g, 37.3 mmol), triethylamine (7.8 mL, 60 mmol) and malonic acid (3.9 g, 37.0 mmol) was refluxed overnight. After cooling to room temperature, diethyl ether was added (15 mL) and the mixture was acidified by the addition of an aqueous solution (20 mL) of 1M HCl (pH 1). The aqueous phase was extracted with diethyl ether (15 mL) followed by the addition of an aqueous solution (20 mL) of 1 M NaOH (pH 10). After extraction with diethyl ether (3 x 10 mL), the aqueous phase was acidified by addition of an aqueous solution (20 mL) 1 M HCl (pH 1) and extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by recrystallization from ethyl acetate and petroleum ether (40 – 60) to give (*E*)-4-phenylpent-3-enoic acid **37** as white needles (2.5 g, 38 %). The characterisation was in agreement with the literature.¹⁰¹ m.p. 73 – 75 °C (lit.,¹⁰¹ 75 °C). δ_{H} (CDCl₃, 400 MHz) 2.07 (3H, d, $^4J_{\text{HH}} = 1.1$ Hz, CH₃), 3.29 (2H, d, $^3J_{\text{HH}} = 7.1$ Hz, CH₂), 5.97 (1H, t, $^3J_{\text{HH}} = 7.9$ Hz, CHCH₂), 7.26 – 7.41 (5H, m, ArH), 12.35 (1H, br s, OH). δ_{C} (CDCl₃, 125 MHz) 16.3 (CH₃), 34.0 (CH₂), 118.4 (CH), 125.8 (CH), 127.2 (CH), 128.3 (CH), 138.8 (C), 142.92 (C), 177.5 (C=O). m/z (ASAP) 177.0919 (M⁺, C₁₁H₁₂O₂ requires 176.0916).



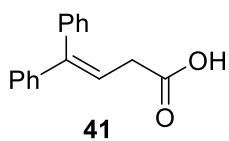
5.3.3 Preparation of 4,4-diphenylbut-3-enoic acid **41** (Scheme 2.11)



A solution of 2,2-diphenylacetic acid **38** (5.00 g, 23.6 mmol) in MeOH (35 mL) was cooled to 0 °C before thionyl chloride (2.6 mL, 36.0 mmol) was added dropwise over 30 min. The resulting colourless solution was refluxed at 75 °C for 19 hours. After concentrating the reaction mixture on a rotary evaporator to give a pale yellow oil, it was dissolved in ethyl acetate (30 mL) and washed with brine (3 x 20 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure to give methyl-2,2-diphenylacetate **39** as a pale yellow oil (4.8 g, 91 %). The characterisation was in agreement with the literature.¹⁰² δ_{H} (CDCl₃, 400 MHz) 3.72 (3H, s, OCH₃), 5.01 (1H, s, CH), 7.24-7.31 (10H, m, ArH). δ_{C} (CDCl₃, 125 MHz) 52.3 (CH₃), 57.4 (CH), 127.3 (CH), 128.5 (CH), 128.9 (CH), 138.6 (C), 173.2 (C=O). m/z (ASAP) 227.1072 (M⁺, C₁₅H₁₅O₂ requires 227.166).



To a solution of the methyl-2,2-diphenylacetate **39** (3.00 g, 13.3 mmol) in CH₂Cl₂ was added DIBAL-H (15.3 mL, 92.3 mmol) dropwise at -78 °C. The reaction mixture was stirred for 2 hours before being quenched with H₂O (0.6 mL), an aqueous solution of NaOH (0.6 mL) and H₂O (2 mL). The quenched slurry was allowed to warm up to room temperature and stirred for a further 30 min. After this time, it was filtered through celite washed with DCM (3 x 30 mL) and brine (2 x 20 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give 2,2-diphenylacetaldehyde **40** (2.45 g, 94 %) as a pale yellow oil. No further purification was required. The characterisation was in agreement with the literature.¹⁰² δ_{H} (CDCl₃, 400 MHz) 4.86 (1H, s, CH), 7.11-7.38 (10H, m, ArH), 9.90 (1H, s, CH=O). δ_{C} (CDCl₃, 125 MHz) 64.0 (CH), 127.5 (CH), 128.9 (CH), 129.1 (CH), 136.2 (C), 198.4 (C=O). m/z (ASAP) 197.0966 (M⁺, C₁₄H₁₃O requires 197.0966).



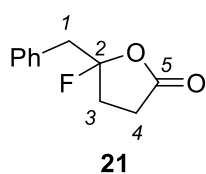
A mixture of 2,2-diphenylacetaldehyde **40** (2.45 g, 12.5 mmol), triethylamine (2.6 mL, 18.8 mmol) and malonic acid (1.3 g, 12.5 mmol) was refluxed for 20 hours. After cooling to room temperature, diethyl ether was added (15 mL) and the mixture was acidified by the addition of an

aqueous solution (20 mL) of 1M HCl (pH 1). The aqueous phase was extracted with diethyl ether (15 mL) followed by the addition of an aqueous solution (20 mL) of 1 M NaOH (pH 10). After extraction with diethyl ether (3 x 10 mL), the aqueous phase was acidified by addition of an aqueous solution (20 mL) 1 M HCl (pH 1) and extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by recrystallization from ethyl acetate and petroleum ether (40 – 60) to give 4,4-diphenyl-3-butenic acid **41** as white needles (1.5 g, 52 %). The characterisation was in agreement with the literature.¹⁰² m.p. 73 – 75 °C (lit.,¹⁰² 75 °C). δ_{H} (CDCl₃, 400 MHz) 3.21 (2H, d, $^3J_{\text{HH}} = 7.4$ Hz, CH₂), 7.23 (1H, t, $^3J_{\text{HH}} = 7.4$ Hz, CHCH₂), 7.14-7.45 (10H, m, ArH). δ_{C} (CDCl₃, 125 MHz) 34.9 (CH₂), 119.5 (CH), 127.4 (CH), 127.5 (CH), 128.2 (CH), 128.5 (CH), 129.7 (CH), 139.0 (C), 141.7 (C), 145.3 (C), 176.6 (C=O). m/z (ASAP) 238.0986 (M⁺, C₁₆H₁₄O₂ requires 238.09992).

5.3.4 Procedures for the fluorocyclisations

5.3.5 Preparation of 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one **21**

(Table 2.1, entry 1)



AgBF₄ (0.19 g, 1.02 mmol) and powdered 4Å molecular sieves (0.15 g) were added to a small Schlenk flask in the glove box. 1-Fluoro-3,3-dimethyl-1,3-dihydro- λ_3 -benzo[d][1,2]iodoxole **7** (0.43 g, 1.5 mmol), 4-phenylpent-4-enoic acid **20** (0.18 g, 1.02 mmol) and dry dichloromethane (0.5 mL) were added to the flask and the contents were stirred at 40 °C for 1 hour. After cooling to room temperature, the reaction mixture was concentrated on a rotary evaporator. The crude product was purified by column chromatography (15% EtOAc in petroleum ether 40-60) to give 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one as a pale yellow oil (0.183 g, 91%). The product was visualised on the TLC plate using a KMnO₄ stain. The characterisation data was in agreement with the literature.⁶⁰ δ_{H} (CDCl₃, 400 MHz) 2.15-2.30 (2H, m, H₃, H_{3'}), 2.42 (1H, ddd, $^2J_{\text{HH}} = 17.8$ Hz, $^3J_{\text{HH}} = 8.7$ Hz, $^3J_{\text{HH}} = 3.1$ Hz, H₄), 2.74 (1H, ddd, $^2J_{\text{HH}} = 17.8$ Hz, $^3J_{\text{HH}} = 10.5$ Hz, $^3J_{\text{HH}} = 9.3$ Hz, H_{4'}), 3.29 (2H, d, $^3J_{\text{HF}} = 14.7$ Hz, H₁, H_{1'}), 7.28 – 7.36 (5H, m, ArH). δ_{F} (CDCl₃, 376 MHz) -97.0 (1F, s). δ_{C} (CDCl₃, 100 MHz) 26.9 (CH₂), 30.7 (CH₂, d, $^2J_{\text{CF}} = 28$ Hz), 42.6 (d, $^2J_{\text{CF}} =$

28.0 Hz, CH₂), 118.01 (d, ¹J_{CF} = 229.0 Hz, C), 127.6 (CH), 128.4 (CH), 130.3 (CH), 133.01 (C), 174.6 (CO). *m/z* (ASAP) 195.0822 (MH⁺, C₁₁H₁₂FO₂ requires 195.0821), 175.0722 ((M-F)⁺).

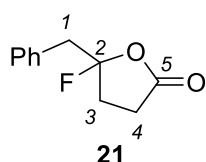
5.3.6 General Procedure for Tables 2.2 and 2.3

The same procedure for the preparation of **28** (Table 1 above) was applied to the fluorocyclisation of 4-phenyl-4-pentenoic acid (0.18 g, 1.02 mmol) using either [Cu(MeCN)₄]PF₆ or [Cu(MeCN)₄]BF₄, the fluoroiodane reagent (0.43 g, 1.5 mmol), 4Å molecular sieves (0.15 g) and dry dichloromethane (0.5 mL). The reaction time and temperature was varied as reported in Table 2.

5.3.7 General Procedure for Scheme 2.13

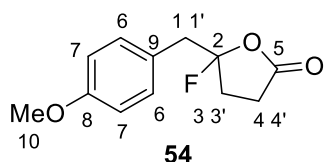
[Cu(MeCN)₄]BF₄ (0.031 g, 0.1 mmol) and powdered 4Å molecular sieves (0.15 g) were added to a small Schlenk flask in the glove box. 1-Fluoro-3,3-dimethyl-1,3-dihydro-λ³-benzo[d][1,2]iodoxole (0.43g, 1.5 mmol) **7**, substrate (1.02 mmol) and dry dichloromethane (0.5 mL) were added to the flask and the contents were 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.

5.3.8 Characterisation data for the fluorocyclised products in Scheme 2.13



The crude product was purified by column chromatography (15% EtOAc in petroleum ether 40-60) to give 5-benzyl-5-fluorodihydrofuran-2-(3*H*)-one as a pale yellow oil (0.145 g, 76%).

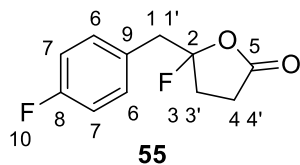
The product was visualised on the TLC plate using a KMnO₄ stain. The characterisation data was in agreement with the literature.⁶⁰



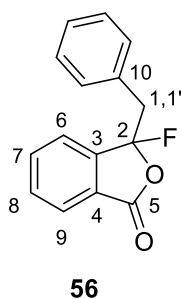
The crude product was purified by column chromatography (15% EtOAc in petroleum ether 40-60) to give 5-fluoro-5-(4-methoxybenzyl)dihydrofuran-2(3*H*)-one **54** as a pale yellow oil (0.146 g, 64%). The characterisation was in agreement

with the literature.⁶⁰ δ_H (CDCl₃, 400 MHz) 2.16-2.28 (2H, m, H₃ and H_{3'}), 2.43 (1H, m, H₄), 2.76 (1H, ddd, ²J_{HH} = 18.0 Hz, ³J_{HH} = 10.5 Hz, ³J_{HH} = 9.6 Hz, H_{4'}), 3.24 (2H, d, ³J_{HF} = 14.1 Hz, H₁ and H_{1'}), 3.80 (3H, s, OCH₃), 6.85 (2H, d, ³J_{HH} = 8.4 Hz, ArH), 7.20 (2H, d, ³J_{HH} = 8.4 Hz, ArH). δ_F (CDCl₃, 376 MHz) -97.4 (s). δ_C (CDCl₃, 100 MHz) 26.9 (CH₂), 30.6 (CH₂, d, ²J_{CF} = 28.5 Hz), 43.8 (CH₂, d, ²J_{CF} = 29.2 Hz), 55.8 (OCH₃) 114.1 (CH),

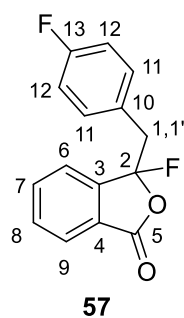
119.6 (CH), 130.2 (C, d, $^1J_{\text{CF}} = 233.3$ Hz), 143.3 (C, d, $^3J_{\text{CF}} = 6.5$ Hz), 157.8 (C), 176.0 (CO). m/z (ASAP) 205.0863 ((M-F) $^+$, $\text{C}_{12}\text{H}_{13}\text{O}_3$ requires 205.0865, 100%).



The crude product was purified by column chromatography (15 % EtOAc in petroleum ether 40-60) to give 5-fluoro-5-(4-fluorobenzyl)dihydrofuran-2(3H)-one **55** as a yellow oil (0.156 g, 72 %). The characterisation was in agreement with the literature.⁶⁰ δ_{H} (CDCl_3 , 400 MHz) 2.12- 2.39 (2H, m, H_3 and $\text{H}_{3'}$), 2.39 – 2.47 (1H, m, H_4), 2.76 (1H, ddd, $^2J_{\text{HH}} = 18.3$ Hz, $^3J_{\text{HH}} = 10.8$ Hz, $^3J_{\text{HH}} = 9.7$ Hz, $\text{H}_{4'}$), 3.28 (2H, d, $^3J_{\text{HF}} = 14.4$ Hz, H_1 and $\text{H}_{1'}$), 6.98 (2H, dd, $^3J_{\text{HF}} = 8.5$ Hz, $^3J_{\text{HH}} = 8.7$ Hz, ArH), 7.28 (2H, dd, $^3J_{\text{HH}} = 8.7$ Hz, $^3J_{\text{HF}} = 5.5$ Hz, ArH). δ_{F} (CDCl_3 , 376 MHz) - 97.8 (1F, s, CF), -114.9 (1F, s, ArF). δ_{C} (CDCl_3 , 100 MHz) 30.1 (CH_2), 30.6 (CH_2 , d, $^2J_{\text{CF}} = 28.7$ Hz), 42.4 (CH_2 , d, $^2J_{\text{CF}} = 27.5$ Hz), 115.5 (CH, d, $^2J_{\text{CF}} = 23.1$), 119.2 (C, d, $^1J_{\text{CF}} = 232.5$), 128.2 (C), 131.3 (CH, d, $^3J_{\text{CF}} = 8.0$ Hz), 162.5 (C, d, $^1J_{\text{CF}} = 246.2$ Hz), 175.1 (CO). m/z (ASAP) 193.0660 ((M-F) $^+$, $\text{C}_{11}\text{H}_{10}\text{FO}_2$ requires 193.0665, 100%).

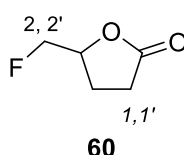


The crude product was purified by column chromatography (10 % EtOAc in petroleum ether 40 – 60) to give 3-benzyl-3-fluoroisobenzofuran-1(3H)-one **56** as a pale yellow oil (0.192 g, 78 %). The characterisation was in agreement with the literature.⁶⁰ δ_{H} (CDCl_3 , 400 MHz) 3.49 (1H, dd, $^2J_{\text{HH}} = 14.1$ Hz, $^3J_{\text{HF}} = 14.0$ Hz, H_1), 3.61 (1H, dd, $^2J_{\text{HH}} = 14.2$ Hz, $^3J_{\text{HF}} = 12.1$ Hz, $\text{H}_{1'}$), 7.20-7.28 (5H, m, PhH), 7.32 (1H, d, $^3J_{\text{HH}} = 7.3$ Hz, ArH), 7.61 (1H, t, $^3J_{\text{HH}} = 7.5$ Hz, ArH), 7.72 (1H, t, $^3J_{\text{HH}} = 7.5$ Hz, ArH), 7.80 (1H, d, $^3J_{\text{HH}} = 7.5$ Hz, ArH). δ_{F} (CDCl_3 , 376 MHz) -100.7 (s). δ_{C} (CDCl_3 , 100 MHz) 40.6 (CH_2 , d, $^2J_{\text{CF}} = 28.4$ Hz), 113.4 (C, d, $^1J_{\text{CF}} = 233.5$ Hz), 121.9 (CH), 124.2 (CH), 125.1 (C), 126.2 (CH), 126.5 (CH), 129.1 (CH), 129.8 (CH), 130.5 (C, d, $^3J_{\text{CF}} = 4.7$ Hz), 133.2 (CH), 143.1 (C, d, $^2J_{\text{CF}} = 21.3$ Hz), 164.7 (CO). m/z (ASAP) 223.0754 ((M-F) $^+$, $\text{C}_{15}\text{H}_{11}\text{O}_2$ requires 223.0754), 195.0813 ((M-F-CO) $^+$).



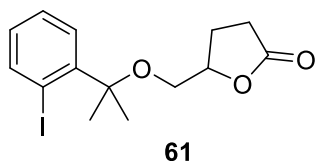
The crude product was purified by column chromatography (15 % EtOAc in petroleum ether 40–60) to give 3-fluoro-3-fluoroisobenzofuran-1(3*H*)-one **57** as a white solid (0.138 g, 52 %). The characterisation was in agreement with the literature.⁶⁰ m.p. 68 – 70 °C (lit.,⁶⁰ m.p. 69 – 71 °C). δ_{H} (CDCl₃, 400 MHz) 3.49 (1H, dd, $^2J_{\text{HH}} = 14.4$ Hz, $^3J_{\text{HF}} = 14.2$ Hz, H₁), 3.59 (1H, dd, $^2J_{\text{HH}} = 14.3$ Hz, $^3J_{\text{HF}} = 12.5$ Hz, H_{1'}), 6.94 (2H, t, $^3J_{\text{HH}} = 8.5$ Hz, ArH), 7.20 (2H, dd, $^3J_{\text{HH}} = 8.3$ Hz, $^4J_{\text{HF}} = 5.5$ Hz, ArH), 7.40 (1H, d, $^3J_{\text{HH}} = 7.5$ Hz, ArH), 7.62 (1H, t, $^3J_{\text{HH}} = 7.4$ Hz, ArH), 7.73 (1H, t, $^3J_{\text{HH}} = 7.5$ Hz, ArH), 7.85 (1H, d, $^3J_{\text{HH}} = 7.5$ Hz, ArH). δ_{F} (CDCl₃, 376 MHz) -101.0 (1F, s, CF), -114.6 (1F, s, ArF). δ_{C} (CDCl₃, 100 MHz) 41.4 (CH₂, d, $^2J_{\text{CF}} = 39.8$ Hz), 115.2 (CF, d, $^1J_{\text{CF}} = 233.7$ Hz), 115.8 (CH, d, $^2J_{\text{CF}} = 22.3$), 123.2 (CH), 124.1 (CH), 125.6 (CH), 126.4 (C, d, $^3J_{\text{CF}} = 1.2$ Hz), 128.2 (C, dd, $^3J_{\text{CF}} = 5.5$ Hz, $^4J_{\text{CF}} = 3.5$ Hz), 131.9 (CH, d, $^3J_{\text{CF}} = 2.6$ Hz), 132.6 (CH, d, $^3J_{\text{CF}} = 8.1$ Hz), 144.8 (C, d, $^2J_{\text{CF}} = 21.3$ Hz), 162.5 (CF, d, $^1J_{\text{CF}} = 247.2$ Hz), 166.4 (CO, d, $^3J_{\text{CF}} = 2.2$ Hz). *m/z* (ASAP) 241.0674 ((M-F)⁺, C₁₅H₁₀FO₂ requires 241.0665, 100 %), 213.0698 ((M-F-CO)⁺).

5.4 Preparation of 5-(fluoromethyl)dihydrofuran-2-(3*H*)-one (Table 2.5, Entry 6)



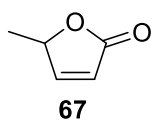
[Cu(MeCN)₄]⁺BF₄⁻ (0.065 g, 0.20 mmol) and 4 Å molecular sieves (0.18 g) were charged to a small Schlenk flask in the glove box. To this was added 1-fluoro-3,3-dimethyl-1,3-dihydro- λ^3 -benzo-[d][1,2]-iodoxole (0.43 g, 1.5 mmol), 4-pentenoic acid (0.102 g, 1.02 mmol) and dry dichloromethane (0.5 mL). The flask was sealed and the contents stirred at 40 °C for the stated temperature and time. After this time, the reaction mixture was cooled down to room temperature and concentrated on a rotary evaporator. The crude product was purified by column chromatography (100 % DCM) to give 5-(fluoromethyl)dihydrofuran-2-(3*H*)-one as a pale yellow oil (0.066 g, 55 %). The characterisation was in agreement with the literature.⁹⁵ δ_{H} (CDCl₃, 400 MHz) 2.10-2.25 (1H, m, CH₁H_{1'}), 2.35-2.42 (1H, m, CH₁H_{1'}), 2.50-2.69 (2H, m, CH₂), 4.38 (1H, ddd, $^2J_{\text{HF}} = 47.9$ Hz, $^2J_{\text{HH}} = 10.4$ Hz, $^3J_{\text{HH}} = 2.4$ Hz, CH₂H_{2'}F), 4.57 (1H, ddd, $^2J_{\text{HF}} = 47.9$ Hz, $^2J_{\text{HH}} = 10.4$ Hz, $^3J_{\text{HH}} = 3.6$ Hz, CH₂H_{2'}F), 4.60-4.68 (1H, m, OCH). δ_{F} (CDCl₃, 376 MHz) -232.6 (s). δ_{C} (CDCl₃, 100 MHz) 22.7 (d, $^3J_{\text{CF}} = 5.0$ Hz, CH₂), 28.1 (CH₂), 82.6 (d, $^2J_{\text{CF}} =$

20.2 Hz, CH), 84.5 (d, $^1J_{\text{CF}} = 174.3$ Hz, CH_2F), 176.5 (C=O). m/z (ASAP) 118.0121 (M^+ , $\text{C}_5\text{H}_7\text{FO}_2$ requires 118.0120).



The by-product was obtained after column chromatography (100 % DCM) as a pale yellow oil (0.033 g, 9 %). δ_{H} (CDCl_3 , 400 MHz) 1.69 (6H, s, CH_3), 2.31-2.38 (2H, m, CH_2), 2.48-2.51 (1H, m, CH_2), 2.69-2.72 (1H, m, CH_2), 3.31-3.42 (2H, m, CH_2), 4.69-4.73 (1H, m, CH), 6.92 (1H, td, $^3J_{\text{HH}} = 7.7$ Hz, 2.1 Hz, ArH), 7.32-7.39 (2H, m, ArH), 8.01 (1H, dd, $^3J_{\text{HH}} = 7.7$ Hz, $^4J_{\text{HH}} = 1.3$ Hz, ArH). δ_{C} (CDCl_3 , 125 MHz) 24.4 (CH_2), 26.7 (CH_3), 27.30 (CH_3), 28.53 (CH_2), 64.49 (CH_2), 77.8 (CH), 93.5 (C), 128.1 (CH), 128.2 (CH), 129.0 (CH), 143.4 (CH), 144.6 (C), 177.6 (C=O). m/z (ASAP) 383.0121 ($(\text{M}+\text{Na})^+$, $\text{C}_{14}\text{H}_{17}\text{IO}_3\text{Na}$ requires 383.0120).

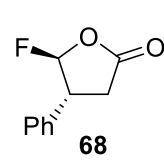
5.4.1 Preparation of 5-methylfuran-2(5H)-one (Table 2.6, Entry 5)

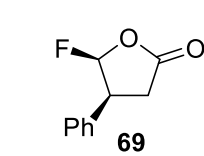


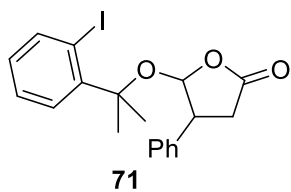
[Cu(MeCN) $_4$] BF_4 (0.065 g, 0.20 mmol) and powdered 4 Å molecular sieves (0.18 g) were charged to a small Schlenk flask in a glove box. To this was added 1-fluoro-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole (0.43 g, 1.5 mmol), 3-pentenoic acid (0.10 g, 1.02 mmol) and dry dichloromethane (0.5 mL). The flask was sealed and the contents were stirred at 40 °C for 20 hours. After this time, the reaction mixture was cooled down to room temperature and concentrated on a rotary evaporator. The crude product was purified by column chromatography (CH_2Cl_2) to give 5-methylfuran-2(5H)-one as a yellow oil (0.067 g, 69 %). The characterisation was in agreement with the literature.⁹⁵ δ_{H} (CDCl_3 , 400 MHz) 1.42 (3H, d, $^3J_{\text{HH}} = 6.9$ Hz, CH_3), 5.09-5.11 (1H, m, CHO), 6.03 (1H, dd, $^3J_{\text{HH}} = 5.6$ Hz, $^4J_{\text{HH}} = 1.9$ Hz, CH), 7.36 (1H, d, $^3J_{\text{HH}} = 5.7$ Hz, CH). δ_{C} (CDCl_3 , 100 MHz) 20.9 (CH_3), 79.7 (CH), 122.3 (CH), 158.6 (CH), 175.2 (C=O). m/z (ASAP) 97.0308 ($(\text{M}-\text{H})^+$, $\text{C}_5\text{H}_5\text{O}_2$ requires 97.0305).

5.4.2 Preparation of 5-fluoro-4-phenyldihydrofuran-2(3*H*)-one (Table 2.7, Entry 1)

AgBF₄ (0.18 g, 0.93 mmol) and powdered 4Å molecular sieves (0.11 g) were added to a small Schlenk flask in the glove box. 1-Fluoro-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole (0.38 g, 1.36 mmol) and (*E*)-4-phenylbut-3-enoic acid (0.15 g, 0.93 mmol) in dry dichloromethane (0.7 mL) were added to the flask and the contents were stirred at 40 °C for four hours, yielding 5-fluoro-4-phenyldihydrofuran-2(3*H*)-one as a 1.9:1 mixture of *anti*:-*syn*-diastereomers which were purified by column chromatography (CH₂Cl₂).

 (4*R*,5*R*)/(4*S*,5*S*)-5-Fluoro-4-phenyldihydrofuran-2(3*H*)-one was obtained as a yellow oil (0.053 g, 32 %). δ_{H} (CDCl₃, 400 MHz) 2.59 (1H, dd, $^2J_{\text{HH}} = 18.3$ Hz, $^3J_{\text{HH}} = 2.2$ Hz, COCH_AH_B), 3.15 (1H, dd, $^2J_{\text{HH}} = 18.2$ Hz, $^3J_{\text{HH}} = 9.3$ Hz, COCH_AH_B), 3.76 (1H, m, CHPh), 5.98 (1H, d, $^2J_{\text{HF}} = 61.0$ Hz, CHF), 7.10-7.49 (5H, m, ArH). $^1\text{H}\{^{19}\text{F}\}$ (CDCl₃, 400 MHz) 2.59 (1H, dd, $^2J_{\text{HH}} = 18.3$ Hz, $^3J_{\text{HH}} = 2.2$ Hz, COCH_AH_B), 3.15 (1H, dd, $^2J_{\text{HH}} = 18.2$ Hz, $^3J_{\text{HH}} = 9.3$ Hz, COCH_AH_B), 3.76 (1H, dd, $^3J_{\text{HH}} = 9.2$ Hz, $^3J_{\text{HH}} = 2.0$ Hz, CHPh), 6.01 (1H, s, CHF), 7.10-7.49 (5H, m, ArH). δ_{F} (CDCl₃, 376 MHz) -114.9 (s). δ_{C} (CDCl₃, 125 MHz) 32.9 (CH₂), 46.8 (d, $^2J_{\text{CF}} = 23.8$ Hz, CH), 114.1 (d, $^1J_{\text{CF}} = 233.8$ Hz, CH), 126.6 (CH), 128.3 (CH), 129.5 (CH) 131.8 (C), 176.4 (CO); m/z (ASAP) 161.0610 ((M-F)⁺, C₁₀H₉O₂ requires 161.0603).

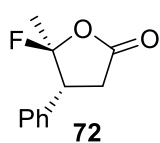
 ((4*S*,5*R*)/(4*R*,5*S*))-5-Fluoro-4-phenyldihydrofuran-2(3*H*)-one was obtained as a yellow oil (0.021 g, 13 %). δ_{H} (CDCl₃, 400 MHz) 2.87 (1H, dd, $^2J_{\text{HH}} = 17.4$ Hz, $^3J_{\text{HH}} = 8.6$ Hz, COCH_AH_B), 3.06 (1H, dd, $^2J_{\text{HH}} = 17.4$ Hz, $^3J_{\text{HH}} = 12.2$ Hz, COCH_AH_B), 3.79 (1H, m, CHPh), 6.10 (1H, dd, $^2J_{\text{HF}} = 61.3$ Hz, $^3J_{\text{HH}} = 3.9$ Hz, CHF), 7.10-7.49 (5H, m, ArH); $^1\text{H}\{^{19}\text{F}\}$ (CDCl₃, 400 MHz) 2.89 (1H, dd, $^2J_{\text{HH}} = 17.4$ Hz, $^3J_{\text{HH}} = 8.6$ Hz, COCH_AH_B), 3.06 (1H, dd, $^2J_{\text{HH}} = 17.4$ Hz, $^3J_{\text{HH}} = 12.2$ Hz, COCH_AH_B), 3.79 (1H, ddd, $^3J_{\text{HH}} = 12.3$ Hz, $^3J_{\text{HH}} = 8.7$ Hz, $^3J_{\text{HH}} = 3.9$ Hz, CHPh), 6.18 (1H, d, $^3J_{\text{HH}} = 4.0$ Hz, CHF), 7.10-7.49 (5H, m, ArH); δ_{F} (CDCl₃, 376 MHz) -134.2 (s); δ_{C} (CDCl₃, 125 MHz) 32.3 (CH₂), 47.2 (d, $^2J_{\text{CF}} = 22.1$ Hz, CH), 113.9 (d, $^1J_{\text{CF}} = 233.8$ Hz, CH), 126.6 (CH), 128.4 (CH), 129.5 (CH), 131.8 (C), 176.4 (CO); m/z (ASAP) 161.0610 ((M-F)⁺, C₁₀H₉O₂ requires 161.0603).



The by-product 5-((2-(2-iodophenyl)-propan-2-yl)oxy)-4-phenyl-dihydrofuran-2(3H)-one **71** was obtained as a colourless oil (0.043 g, 11%). δ_{H} (CDCl_3 , 400 MHz) 1.56 (3H, s, CH_3), 1.61 (3H, s, CH_3), 2.57 (1H, dd, $^2J_{\text{HH}} = 17.8$ Hz, $^3J_{\text{HH}} = 2.8$ Hz, CH_ACH_B), 3.27 (1H, dd, $^2J_{\text{HH}} = 17.8$ Hz, $^3J_{\text{HH}} = 9.1$ Hz, CH_ACH_B), 3.95 (1H, dd, $^3J_{\text{HH}} = 7.2$ Hz, $^3J_{\text{HH}} = 2.4$ Hz, CHPh), 5.35 (1H, d, $^3J_{\text{HH}} = 1.4$ Hz, OCHO), 6.92 (1H, td, $^3J_{\text{HH}} = 7.5$ Hz, $^4J_{\text{HH}} = 2.4$ Hz, ArH), 7.12 (1H, m, ArH), 7.28 (1H, td, $^3J_{\text{HH}} = 7.4$ Hz, $^4J_{\text{HH}} = 1.2$ Hz, ArH), 7.32-7.42 (4H, m, ArH), 7.48 (1H, m, ArH), 8.01 (1H, dd, $^3J_{\text{HH}} = 7.5$ Hz, $^4J_{\text{HH}} = 1.3$ Hz, ArH). δ_{C} (CDCl_3 , 100 MHz) 28.4 (CH_3), 28.5 (CH_3), 32.9 (CH_2), 34.5 (CH), 80.6 (C), 93.9 (C-I), 105.3 (CH), 128.08-129.50 (ArCH's), 144.2 (C), 157.3 (C), 175.6 (C=O); m/z (ASAP) 422.0556 (M^+ , $\text{C}_{19}\text{H}_{19}\text{IO}_3$ requires 422.0563).

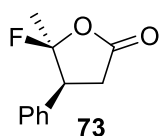
5.4.3 Preparation of 5-fluoro-5-methyl-4-phenyldihydrofuran-2-(3H)-one (Table 2.8, Entry 1)

AgBF_4 (0.17 g, 0.85 mmol) and powdered 4Å molecular sieves (0.11 g) were added to a small Schlenk flask in the glove box. 1-Fluoro-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole (0.36 g, 1.27 mmol) and (*E*)-4-phenylpent-3-enoic acid (0.15 g, 0.85 mmol) in dry dichloromethane (0.7 mL) were added to the flask and the contents were stirred at 40 °C for four hours, yielding 5-fluoro-5-methyl-4-phenyldihydrofuran-2-(3H)-one as a 1:2.2 mixture of *anti*:-*syn*-diastereomers which were purified by column chromatography (CH_2Cl_2).



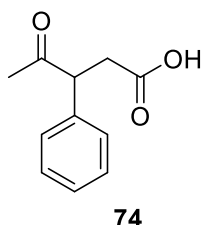
(4*R*,5*R*)/(4*S*,5*S*)-5-Fluoro-5-methyl-4-phenyl-dihydrofuran-2-(3H)-one was obtained as a yellow oil (0.04 g, 24 %). δ_{H} (CDCl_3 , 400 MHz) 1.37 (3H, d, $^3J_{\text{HF}} = 18.9$ Hz, CH_3), 2.72 (1H, dd, $^2J_{\text{HH}} = 18.1$ Hz, $^3J_{\text{HH}} = 1.6$ Hz, COCH_AH_B), 3.31 (1H, dd, $^2J_{\text{HH}} = 18.0$ Hz, $^3J_{\text{HH}} = 8.8$ Hz, COCH_AH_B), 3.72 (1H, ddd, $^3J_{\text{HF}} = 10.3$ Hz, $^3J_{\text{HH}} = 8.7$ Hz, $^3J_{\text{HH}} = 1.6$ Hz, CHPh), 7.14 (2H, dd, $^3J_{\text{HH}} = 7.6$ Hz, $^4J_{\text{HH}} = 1.7$ Hz, ArH), 7.33-7.35 (3H, m, ArH). $^1\text{H}\{^{19}\text{F}\}$ NMR (CDCl_3 , 400 MHz) 1.29 (3H, s, CH_3), 2.64 (1H, dd, $^2J_{\text{HH}} = 18.0$ Hz, $^3J_{\text{HH}} = 1.6$ Hz, COCH_AH_B), 3.24 (1H, dd, $^2J_{\text{HH}} = 18.0$ Hz, $^3J_{\text{HH}} = 8.8$ Hz, COCH_AH_B), 3.66 (1H, dd, $^3J_{\text{HH}} = 8.7$ Hz, $^3J_{\text{HH}} = 1.5$ Hz, CHPh), 7.14 (2H, dd, $^3J_{\text{HH}} = 7.6$ Hz, $^4J_{\text{HH}} = 1.7$ Hz, ArH), 7.33-7.35 (3H, m, ArH). δ_{F} (CDCl_3 , 376 MHz) -86.3 (s). δ_{C} (CDCl_3 , 125 MHz) 20.9 (d, $^2J_{\text{CF}} = 35.5$ Hz, CH_3), 35.0 (CH_2), 50.2 (d,

$^2J_{\text{CF}} = 28.7$ Hz, CH), 120.9 (d, $^1J_{\text{CF}} = 228.6$ Hz, C), 127.3 (CH), 128.4 (CH), 129.4 (CH), 137.8 (C), 175.1 (CO); m/z (ASAP) 195.0814 (MH^+ , $\text{C}_{11}\text{H}_{12}\text{FO}_2$ requires 195.0821).



(4*S*,5*R*)/(4*R*,5*S*)-5-Fluoro-5-methyl-4-phenyl-dihydrofuran-2-(3*H*)-one was obtained as a white solid (0.125 g, 40 %). Crystals suitable for X-ray crystallography were grown by slow diffusion from DCM : hexane (1:3). m.p. 53 – 55 °C. δ_{H} (CDCl_3 , 400 MHz) 1.69 (3H, d, $^3J_{\text{HF}} = 17.8$ Hz, CH_3), 2.87 (1H, dd, $^2J_{\text{HH}} = 17.5$ Hz, $^3J_{\text{HH}} = 8.5$ Hz, $\text{COCH}_\text{A}\text{H}_\text{B}$), 3.13 (1H, dd, $^2J_{\text{HH}} = 17.4$ Hz, $^3J_{\text{HH}} = 12.4$ Hz, $\text{COCH}_\text{A}\text{H}_\text{B}$), 3.55 (1H, ddd, $^3J_{\text{HF}} = 20.7$ Hz, $^3J_{\text{HH}} = 12.4$ Hz, $^3J_{\text{HH}} = 8.3$ Hz, CHPh), 7.32 – 7.42 (5H, m, ArH). $^1\text{H}\{^1\text{F}\}$ (CDCl_3 , 400 MHz) 1.69 (3H, s, CH_3), 2.87 (1H, dd, $^2J_{\text{HH}} = 17.5$ Hz, $^3J_{\text{HH}} = 8.3$ Hz, $\text{COCH}_\text{A}\text{H}_\text{B}$), 3.14 (1H, dd, $^2J_{\text{HH}} = 17.5$ Hz, $^3J_{\text{HH}} = 12.4$ Hz, $\text{COCH}_\text{A}\text{H}_\text{B}$), 3.56 (1H, dd, $^3J_{\text{HH}} = 12.4$ Hz, $^3J_{\text{HH}} = 8.4$ Hz, CHPh), 7.32 – 7.42 (5H, m, ArH). δ_{F} (CDCl_3 , 376 MHz) -107.7 (s). δ_{C} (CDCl_3 , 125 MHz) 21.3 (d, $^2J_{\text{CF}} = 28.8$ Hz, CH_3), 33.5 (CH_2), 50.7 (d, $^2J_{\text{CF}} = 23.8$ Hz, CH), 117.9 (d, $^1J_{\text{CF}} = 231.3$ Hz, C), 128.5 (CH), 128.8 (CH), 128.9 (CH), 133.0 (C), 173.5 (CO). m/z (ASAP) 195.0814 (MH^+ , $\text{C}_{11}\text{H}_{12}\text{FO}_2$ requires 195.0821).

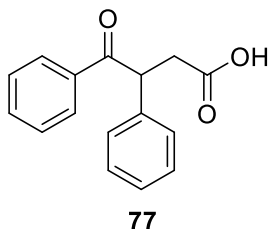
5.4.4 Preparation of 4-oxo-3-phenylpentanoic acid (Table 2.10, Entry 2)



A small Schlenk flask was charged with AgBF_4 (0.17 g, 0.87 mmol) in a glove box. 1-Fluoro-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole (0.36 g, 1.27 mmol), (*E*)-4-phenylpent-3-enoic acid (0.15 g, 0.85 mmol) and dry dichloromethane (0.7 mL) were added to the flask. The flask was then sealed and the contents were stirred at 40 °C for one hour. After cooling the reaction mixture to room temperature, it was concentrated on a rotary evaporator to give the crude product which was purified by column chromatography (100 % DCM) to give 4-oxo-3-phenylpentanoic acid **74** as a yellow solid (0.10 g, 65%). Crystals suitable for X-ray crystallography were grown by slow diffusion from DCM : hexane (1:3). m.p. 98 – 100 °C. δ_{H} (CDCl_3 , 400 MHz) 2.10 (3H, s, CH_3), 2.59 (1H, dd, $^2J_{\text{HH}} = 17.4$ Hz, $^3J_{\text{HH}} = 4.9$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.28 (1H, dd, $^2J_{\text{HH}} = 17.4$ Hz, $^3J_{\text{HH}} = 9.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}$), 4.16 (1H, dd, $^3J_{\text{HH}} = 8.1$ Hz, $^3J_{\text{HH}} = 4.8$ Hz, CHPh), 7.22 (2H, dd, $^3J_{\text{HH}} = 6.9$ Hz, $^4J_{\text{HH}} = 1.6$ Hz, ArH), 7.26-7.36 (3H, m, ArH). δ_{C} (CDCl_3 , 125 MHz) 28.8 (CH_3), 36.6 (CH_2), 54.6 (CH), 127.9 (CH), 128.2 (CH), 129.3 (CH), 127.1

(C), 177.4 (CO), 206.6 (CO) m/z (ASAP) 175.0759 ((M-OH)⁺, C₁₁H₁₁O₂ requires 175.0759).

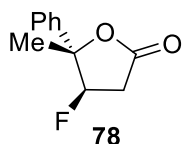
5.4.5 Preparation of 4-oxo-3,4-diphenylbutanoic acid (Scheme 2.17)



A small Schlenk flask was charged with AgBF₄ (0.12 g, 0.62 mmol) in a glove box. 1-Fluoro-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole (0.26 g, 0.92 mmol), 4,4-diphenylbut-3-enoic acid (0.15 g, 0.62 mmol) and dry dichloromethane (0.7 mL) were added to the flask. The flask was then sealed and the contents were stirred at 60 °C for 20 hours. After cooling the reaction mixture to room temperature, it was concentrated on a rotary evaporator to give the crude product which purified by column chromatography (CH₂Cl₂) to give 4-oxo-3,4-diphenylbutanoic acid **77** as a white solid (0.120 g, 75%). Crystals suitable for X-ray crystallography were grown by slow diffusion from DCM : hexane (1:3). δ_H (CDCl₃, 400 MHz) 2.75 (1H, dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 4.8 Hz, CH_AH_B), 3.41 (1H, dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 9.8 Hz, CH_AH_B), 5.05 (1H, dd, $^3J_{HH}$ = 9.7 Hz, 4.8 Hz, CH), 7.15-7.61 (8H, m, ArH), 7.94 (2H, m, ArH). δ_C (CDCl₃, 125 MHz) 30.9 (CH₂), 49.4 (CH), 127.1 (CH), 127.6 (CH), 128.1 (CH), 128.7 (CH), 128.9 (CH), 129.5 (CH), 133.6 (C), 137.9 (C), 171.2 (C=O), 198.3 (C=O). m/z (ASAP) 237.0921 ((M-OH)⁺, C₁₆H₁₃O₂ requires 237.0916).

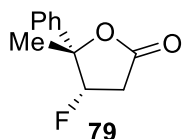
5.4.6 Preparation of 4-fluoro-5-methyl-5-phenyl-dihydrofuran-2-one (Scheme 2.18)

Selectfluor (0.46 g, 1.29 mmol), (*E*)-4-phenylpent-3-enoic acid (0.15 g, 0.85 mmol) and dry acetonitrile (10 mL) were charged to a small Schlenk flask. The reaction mixture was stirred at room temperature for 20 hours. After removing the solvent under reduced pressure, the residue was dissolved in diethyl ether (15 mL) and a solution of 10% NaHCO₃ (15 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure yielding the crude product as a 1:6:1 mixture of *syn*-.*anti*-diastereomers which were purified by column chromatography (CH₂Cl₂).

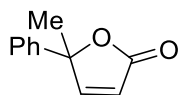


(4*R*,5*S*)/(4*S*,5*R*)-4-Fluoro-5-methyl-5-phenyl-dihydrofuran-2-one was obtained as a white solid (0.069 g, 42%). The characterisation was in agreement with the literature.¹⁰⁵ Crystals suitable for X-ray crystallography were grown by slow diffusion from DCM : hexane (1:3).

(lit.,¹⁰⁵ m.p. 49 – 52 °C). δ_{H} (CDCl₃, 400 MHz) 1.79 (3H, d, $^4J_{\text{HF}} = 3.7$ Hz, CH₃), 2.66-2.91 (2H, m, CH₂), 5.16-5.31 (1H, ddd, $^2J_{\text{HF}} = 52.5$ Hz, $^3J_{\text{HH}} = 5.4$ Hz, $^3J_{\text{HH}} = 2.9$ Hz, CHF), 7.35 (2H, d, $^3J_{\text{HH}} = 6.2$ Hz, ArH), 7.39-7.43 (3H, m, ArH). δ_{F} (CDCl₃, 376 MHz) -182.1 (s). δ_{C} (CDCl₃, 125 MHz) 22.7 (d, $^3J_{\text{CF}} = 10.0$ Hz, CH₃), 35.8 (d, $^2J_{\text{CF}} = 23.8$ Hz, CH₂), 89.7 (d, $^2J_{\text{CF}} = 21.3$ Hz, C), 94.4 (d, $^1J_{\text{CF}} = 190.0$ Hz, CH), 124.3 (CH), 128.5 (CH), 129.1 (CH), 140.7 (d, $^3J_{\text{CF}} = 5.0$ Hz, C), 173.5 (CO). m/z (ASAP) 175.0751 ((M-F)⁺, C₁₁H₁₁O₂ requires 175.0759).

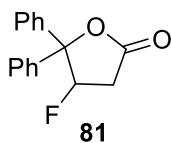


(4*S*,5*S*)/(4*R*,5*R*)-4-Fluoro-5-methyl-5-phenyl-dihydrofuran-2-one was obtained as a colourless oil (0.045 g, 27%). The characterisation was in agreement with the literature.¹⁰⁵ δ_{H} (CDCl₃, 400 MHz) 1.62 (3H, s, CH₃), 2.82 (1H, dd, $^3J_{\text{HF}} = 22.5$ Hz, $^2J_{\text{HH}} = 18.6$ Hz, CH_AH_B), 3.11 (1H, ddd, $^3J_{\text{HF}} = 22.3$ Hz, $^2J_{\text{HH}} = 18.6$ Hz, $^3J_{\text{HH}} = 5.0$ Hz, CH_AH_B), 5.22 (1H, dd, $^2J_{\text{HF}} = 52.8$ Hz, $^3J_{\text{HH}} = 5.0$ Hz, CHF), 7.30-7.34 (5H, m, ArH). δ_{F} (CDCl₃, 376 MHz) -176.1 (s). δ_{C} (CDCl₃, 125 MHz) 26.4 (d, $^3J_{\text{CF}} = 3.8$ Hz, CH₃), 36.3 (d, $^2J_{\text{CF}} = 26.3$ Hz, CH₂), 89.6 (d, $^2J_{\text{CF}} = 21.1$ Hz, C), 93.6 (d, $^1J_{\text{CF}} = 187.5$ Hz, CH), 124.3 (CH), 125.1 (CH), 128.4 (CH), 137.4 (d, $^3J_{\text{CF}} = 4.4$ Hz, C), 172.7 (CO). m/z (ASAP) 175.0751 ((M-F)⁺, C₁₁H₁₁O₂ requires 175.0759).



5-Methyl-5-phenylfuran-2-(5*H*)-one (0.008 g, 5%) was isolated together with *anti* as a white solid. The characterisation data was in agreement with the literature.¹⁰⁸ δ_{H} (CDCl₃, 400 MHz) 1.86 (3H, s, CH₃), 5.98 (1H, d, $^3J_{\text{HH}} = 5.6$ Hz, CH), 7.30-7.43 (5H, m, ArH), 7.59 (1H, d, $^3J_{\text{HH}} = 5.6$ Hz, CH); δ_{C} (CDCl₃, 125 MHz) 29.7 (CH₃), 88.7 (C), 119.4 (CH), 124.8 (CH), 128.4 (CH), 128.8 (CH), 139.1 (C), 160.4 (CH), 172.7 (CO). m/z (ASAP) 175.0715 (MH⁺, C₁₁H₁₁O₂ requires 175.0722).

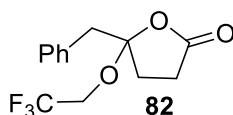
5.4.7 Preparation of 4-fluoro-5,5-diphenyldihydrofuran-2(3*H*)-one (Scheme 2.19)



Selectfluor (0.33 g, 0.94 mmol), 4,4-diphenylbut-3-enoic acid (0.15 g, 0.62 mmol) and dry acetonitrile (10 mL) were charged to a small Schlenk flask. The reaction mixture was stirred at room temperature for 20 hours.

After removing the solvent under reduced pressure, the residue was dissolved in diethyl ether (15 mL) and a solution of 10% NaHCO₃ (15 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (CH₂Cl₂), yielding of the pale yellow solid (0.114 g, 67 %). δ_{H} (CDCl₃, 400 MHz) 2.78-2.89 (2H, m, CH₂), 5.85 (1H, ddd, $^2J_{\text{HF}} = 46.7$ Hz, $^3J_{\text{HH}} = 3.7$ Hz, 1.6 Hz, CH), 7.28-7.50 (10H, m, CH). δ_{F} (CDCl₃, 376 MHz) -180.5 (1F, s). δ_{C} (CDCl₃, 125 MHz) 36.4 (d, $^2J_{\text{CF}} = 25.0$ Hz, CH₂), 91.9 (d, $^1J_{\text{CF}} = 184.1$ Hz, CH), 125.3 (CH), 126.2 (CH), 128.4 (CH), 128.8 (CH), 129.1 (CH), 129.7 (CH), 137.6 (C), 139.7 (C), 141.4 (C), 172.8 (C=O). m/z (ASAP) 257.0977 (MH⁺, C₁₆H₁₄O₂F requires 257.0978).

5.4.8 Preparation of 5-benzyl-5-(2,2,2-trifluoroethoxy)dihydrofuran-2(3*H*)-one (Scheme 2.20)



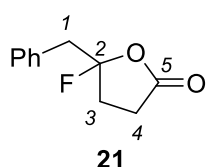
A small Schlenk flask was charged with powdered 4 Å molecular sieves (0.11 g), 1-fluoro-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]-iodoxole (0.38 g, 1.36 mmol), 4-phenyl-4-pentenoic acid (0.15 g, 0.85 mmol) and trifluoroethanol (3 mL). The flask was then sealed and the contents were stirred at 40 °C for one hour. After cooling the reaction mixture to room temperature, it was concentrated on a rotary evaporator to give the crude product which was analysed by ¹H and ¹⁹F NMR spectroscopy. The crude product was purified by column chromatography (100 % CH₂Cl₂), yielding 5-benzyl-5-(2,2,2-trifluoroethoxy)dihydrofuran-2(3*H*)-one (0.175 g, 75 %) as a colourless oil. δ_{H} (CDCl₃, 400 MHz) 2.15-2.27 (3H, m, CH₂), 2.61-2.69 (1H, ddd, $^2J_{\text{HH}} = 17.8$ Hz, $^3J_{\text{HH}} = 7.8$ Hz, CH₂), 3.09-3.13 (1H, d, $^2J_{\text{HH}} = 14.3$ Hz, HCHPh), 3.24-3.28 (1H, d, $^2J_{\text{HH}} = 14.3$ Hz, HCHPh), 4.03-4.12 (2H, q, $^3J_{\text{CF}} = 15.8$ Hz, CH₂CF₃), 7.23-7.26 (2H, dd, $^3J_{\text{HH}} = 7.9$ Hz, $^3J_{\text{HH}} = 1.4$ Hz, ArH), 7.29-7.33 (3H, m, ArH). δ_{F} (CDCl₃, 376 MHz) -74.4 (3F, s, CF₃).

δ_C (CDCl₃, 125 MHz) 27.9 (CH₂), 32.3 (CH₂), 41.4 (CH₂), 60.8 (q, $^2J_{CF}$ = 71.4 Hz, CH₂), 109.7 (C), 123.5 (q, $^1J_{CF}$ = 276.7 Hz, CF₃), 124.9 (CH), 127.6 (CH), 130.2 (CH), 133.6 (C), 175.2 (C=O). m/z 275.0922 (MH⁺, C₁₃H₁₃F₃O₂ requires 275.0921).

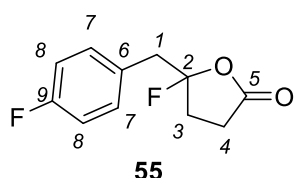
5.4.9 General procedure for the intramolecular fluorocyclisations in HFIP (Table 2.13)

A small Schlenk flask was charged with powdered 4 Å molecular sieves (0.11 g), 1-fluoro-3,3-dimethyl-1,3-dihydro- λ^3 -benzo[d][1,2]iodoxole (0.38 g, 1.36 mmol), substrate (0.9 mmol) and hexafluoroisopropanol (3 mL). The flask was then sealed and the contents were stirred at 40 °C for either one hour (entries 1-5 and 8) or four hours (entries 6-7). After cooling the reaction mixture to room temperature, it was concentrated on a rotary evaporator to give the crude product which was analysed by ¹H and ¹⁹F NMR spectroscopy. The crude product was purified by column chromatography (CH₂Cl₂).

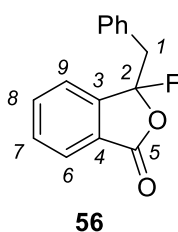
5.5 Characterisation for products in Table 2.13



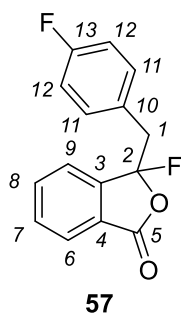
Entry 1: Following the general procedure for Table 2.13, the 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one was obtained as a colourless oil (0.139 g, 84%). The characterisation data was in agreement with the literature.⁶⁰



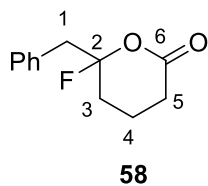
Entry 2: Following the general procedure for Table 2.13, the 5-fluoro-5-(4-fluorobenzyl)-dihydrofuran-2(3*H*)-one was obtained as a colourless oil (0.130 g, 80%). The characterisation data was in agreement with the literature.⁶⁰



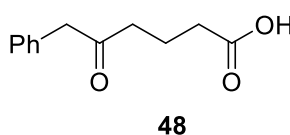
Entry 3: Following the general procedure for Table 2.13, the 3-benzyl-3-fluoroisobenzofuran-1(3*H*)-one was obtained as a colourless oil (0.129 g, 79%). The characterisation data was in agreement with the literature.⁶⁰



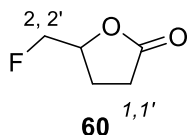
Entry 4: Following the general procedure for Table 2.13, the 3-fluoro-3-(4-fluorobenzyl)isobenzofuran-1(3*H*)-one was obtained as a white solid (0.131 g, 81%). The characterisation data was in agreement with the literature.⁶⁰



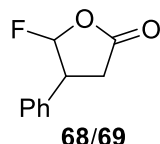
Entry 5: Following the general procedure for Table 2.13, the 6-benzyl-6-fluorotetrahydro-2*H*-pyran-2-one was obtained as a colourless oil (0.109 g, 66%). The characterisation data was in agreement with the literature.⁶⁰ δ_{H} (CDCl_3 , 400 MHz) 1.63 – 1.82 (2H, m, H_3 and H_4), 1.96 – 2.11 (2H, m, H_3' and H_4'), 2.35 – 2.45 (1H, m, H_5), 2.69 (1H, dm, H_5'), 3.20 (2H, d, $^3J_{\text{HF}} = 14.8$ Hz, H_1 and H_1'), 7.26 – 7.34 (5H, m, ArH). δ_{F} (CDCl_3 , 376 MHz) -96.7 (s). δ_{C} (CDCl_3 , 100 MHz) 14.8 (d, $^3J_{\text{CF}} = 3.2$ Hz, CH_2), 28.8 (d, $^2J_{\text{CF}} = 26.9$ Hz, CH_2), 29.1 (CH_2), 45.2 (d, $^2J_{\text{CF}} = 26.7$ Hz, CH_2), 115.5 (d, $^1J_{\text{CF}} = 228.0$ Hz, C), 127.4 (CH), 128.5 (CH), 130.5 (CH), 133.5 (d, $^3J_{\text{CF}} = 5.5$ Hz, C), 168.8 (CO). m/z (ASAP) 189.0923 ((M-F)⁺. $\text{C}_{12}\text{H}_{13}\text{O}_2$ requires 189.0916, 5%), 161.0948 ((PhCH₂COCH₂CH₂CH₂)⁺, 100%).



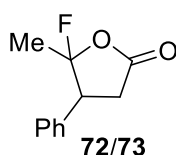
The by-product 5-oxo-6-phenylhexanoic acid was obtained after 6-benzyl-6-fluorotetrahydro-2*H*-pyran-2-one decomposed in CDCl_3 over several hours. The characterisation data was in agreement with the literature.⁶⁰ m.p. 42 – 44 °C. δ_{H} (CDCl_3 , 400 MHz) 1.79 (2H, quintet, $^3J_{\text{HH}} = 7.4$ Hz, CH_2), 2.26 (2H, t, $^3J_{\text{HH}} = 7.4$ Hz, CH_2), 2.47 (2H, t, $^3J_{\text{HH}} = 7.4$ Hz, CH_2), 3.61 (2H, s, CH_2), 7.12 (2H, d, $^3J_{\text{HH}} = 7.3$ Hz, ArH), 7.19 (1H, t, $^3J_{\text{HH}} = 7.3$ Hz, ArH), 7.25 (2H, t, $^3J_{\text{HH}} = 7.3$ Hz, ArH), 10.38 (1H, br s, COOH); δ_{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)⁺. $\text{C}_{12}\text{H}_{13}\text{O}_2$ requires 189.0916, 55%), 175.0752 (75%), 161.0941 ((M-CO₂H)⁺, 60%).



Entry 6: Following the general procedure for Table 2.13, the 5-(fluoromethyl)dihydrofuran-2(3*H*)-one was obtained as a yellow oil (0.145 g, 82%). The characterisation data was in agreement with the literature.⁹⁵



Entry 7: Following the general procedure for Table 2.13, the 5-fluoro-4-phenyldihydrofuran-2(3*H*)-one was obtained as a mixture of *anti-syn*-diastereomers (0.059 g, 36%).

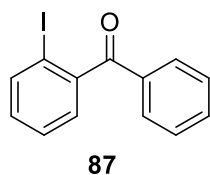


Entry 8: Following the general procedure for Table 2.13, the 5-fluoro-5-methyl-4-phenyldihydrofuran-2(3*H*)-one was obtained as a 2.2:1 mixture of *anti-syn*-diastereomers (0.142 g, 86%).

5.6 Experimental for Chapter 3

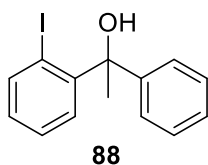
5.6.1 Preparation of 1-fluoro-3-methyl-3-phenyl-1,3-dihydro- λ^3 -benzo[d][1,2]

iodoxole 91

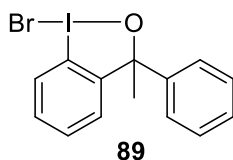


A three-neck flask, equipped with an addition funnel and a magnetic stirrer, was charged with *p*-toluenesulfonic acid (21.74 g, 0.114 mol) dissolved in acetonitrile (140 mL). 2-Aminobenzophenone (7.50 g, 0.038 mol) was added to the solution and the reaction mixture was cooled to 0 °C. Potassium iodide (16.48 g, 0.099 mol) and sodium nitrite (5.49 g, 0.080 mol) were dissolved in water (120 mL) and the solution was added dropwise to the reaction mixture over 30 minutes. After the addition was complete, the reaction mixture was warmed to room temperature and left to stir overnight. A saturated solution of sodium hydrogen carbonate (75 mL) was added to the reaction mixture until the aqueous layer was no longer acidic. A saturated solution of sodium thiosulfate (50 mL) was then added to the reaction mixture resulting in the formation of a biphasic solution. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 x 60 mL). The organic phases were combined, dried over magnesium sulphate and filtered into a round

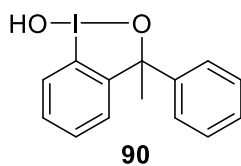
bottom flask. The organic phase was concentrated *in vacuo* affording the pure product as a yellow oil (9.5 g, 81 %). δ_{H} (CDCl_3 , 400 MHz) 7.18 (1H, td, $^3J_{\text{HH}} = 7.8$ Hz, $^4J_{\text{HH}} = 1.6$ Hz, ArH), 7.30 (1H, dd, $^3J_{\text{HH}} = 7.7$ Hz, $^4J = 1.5$ Hz, ArH), 7.43 - 7.49 (3H, m, ArH), 7.60 (1H, t, $^3J_{\text{HH}} = 7.5$ Hz, ArH), 7.81 (2H, d, $^3J_{\text{HH}} = 7.2$ Hz, ArH), 7.93 (1H, d, $^3J_{\text{HH}} = 8.0$ Hz, ArH). δ_{C} (CDCl_3 , 125 MHz) 92.2 (CI), 127.6 (CH), 128.3 (CH), 128.8 (CH), 130.2 (CH), 131.2 (CH), 133.7 (CH), 135.8 (C), 139.6 (CH), 144.4 (C), 197.5 (CO). m/z (ESI) 308.9777 (MH^+ , $\text{C}_{13}\text{H}_{10}\text{IO}$ requires 308.9776).



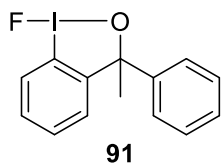
An oven dried three-necked flask, equipped with an addition funnel, reflux condenser, N_2 inlet and a magnetic stirrer, was charged with magnesium turnings (2.64 g, 0.11 mol) and dry diethyl ether (15 mL). Iodomethane (4.7 mL, 0.078 mol) and dry diethyl ether (15 mL) were added to the addition funnel and the resulting solution was added dropwise over 15 min to the flask containing the magnesium turnings and stirred vigorously for 1 hour. The reaction mixture was transferred to the new three-necked flask *via* cannula and the Grignard solution was cooled to 0 °C with stirring. The 2-iodobenzophenone (9.00 g, 0.032 mol) in dry diethyl ether (20 mL) was added dropwise over 15 minutes and the reaction mixture was left to stir overnight at room temperature. The reaction mixture was cooled to 0 °C before a saturated solution of ammonium chloride (60 mL) was added slowly followed by water (50 mL). The reaction mixture was stirred for 20 minutes, and then filtered through Celite. The filtrate was transferred to a separating funnel, the organic phase was separated and the aqueous phase was extracted with diethyl ether (3 x 60 mL). The organic phases were combined, dried over magnesium sulphate and concentrated *in vacuo* to afford the pure product **88** as a yellow oil (8.98 g, 95 %). δ_{H} (CDCl_3 , 400 MHz) 1.98 (3H, s, CH_3) 3.24 (1H, br. s, OH), 6.96 (1H, td, $^3J_{\text{HH}} = 7.5$ Hz, $^4J_{\text{HH}} = 1.7$ Hz, ArH), 7.20 - 7.33 (5H, m, ArH), 7.45 (1H, td, $^3J_{\text{HH}} = 7.6$ Hz, $^4J_{\text{HH}} = 1.4$ Hz, ArH), 7.80 (1H, d, $^3J_{\text{HH}} = 7.6$ Hz, ArH), 7.89 (1H, d, $^3J_{\text{HH}} = 7.5$ Hz, ArH). δ_{C} (CDCl_3 , 125 MHz) 30.7 (CH_3), 78.2 (C), 96.6 (CI), 126.2 (CH), 127.0 (CH), 128.1 (CH), 128.2 (CH x 2), 129.2 (CH), 142.4 (CH), 147.1 (C), 147.5 (C). m/z (ASAP): 322.9940 (M-H^+ , $\text{C}_{14}\text{H}_{12}\text{IO}$ requires 322.9933, 100 %).



2-Iodophenyl-1-phenylethan-1-ol **88** (8.50 g, 0.026 mol) and chloroform (100 mL) were added to a round-bottom flask. *N*-Bromosuccinimide (7.11 g, 0.041 mol) was then added in three portions and stirred overnight at room temperature. After this time, the clear yellow solution was transferred to a separating funnel and the organic phase was washed with water (4 x 50 mL) and brine (3 x 30 mL). The combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure to give a yellow solid which was re-crystallised from ethyl acetate to give 1-bromo-3-methyl-3-phenyl-1,3-dihydro- λ^3 -benzoiodoxole **89** as yellow crystals (9.68 g, 97 %). m.p. 115-117 °C. δ_{H} (CDCl₃, 400 MHz) 1.88 (3H, s, CH₃), 7.15 - 7.20 (1H, m, ArH), 7.26 - 7.34 (2H, m, ArH), 7.48 - 7.60 (5H, m, ArH), 7.98 - 8.10 (1H, m, ArH). δ_{C} (CDCl₃, 125 MHz) 29.3 (CH₃), 87.1 (C), 113.9 (CI), 125.9 (CH), 126.5 (CH), 127.9 (CH), 128.20 (CH), 128.4 (CH), 129.5 (CH), 130.7 (CH), 142.3 (C), 144.4 (C). m/z (ASAP): 402.9191 (MH⁺, C₁₄H₁₃⁷⁹BrIO, requires 402.9195, 100 %).



A solution of 1-bromo-3-methyl-3-phenyl-1,3-dihydro- λ^3 -benzoiodoxole **89** (9.00 g, 0.022 mmol) in dichloromethane (90 mL) was added to an aqueous solution (85 mL) of potassium hydroxide (2.13 g, 0.038 mol). The mixture was stirred vigorously at room temperature for 2 hours. After this time, the organic layer was separated and the aqueous layer was extracted with dichloromethane (4 x 50 mL). The combined organic extracts were dried over magnesium sulphate, filtered and concentrated under reduced pressure to give the desired compound **3.5** as a red solid (6.99 g, 92 %). δ_{H} (CDCl₃, 400 MHz) 1.85 (3H, s, CH₃), 7.15 - 7.32 (3H, m, ArH), 7.39 (3H, dd, ³*J*_{HH} = 7.3 Hz, ⁴*J*_{HH} = 1.3 Hz, ArH), 7.45 - 7.61 (2H, m, ArH), 7.82 - 7.86 (1H, m, ArH). δ_{C} (CDCl₃, 125 MHz) 30.5 (CH₃) 84.8 (C), 115.5 (CI), 127.3 (CH), 128.4 (CH), 128.8 (CH), 129.2 (CH), 129.6 (CH), 131.1 (CH), 131.4 (CH), 147.5 (C), 149.2 (C). m/z (ESI): 341.0053 (MH⁺, C₁₄H₁₄IO₂ requires 341.0039, 100 %).



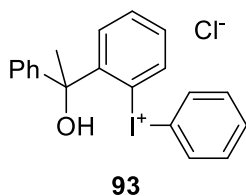
To a solution of 1-hydro-3-methyl-3-phenyl-1,3-dihydro- λ^3 -benziodoxole **90** (6.50 g, 0.019 mol) in dichloromethane (200 mL) was added Et₃N.3HF (6.5 mL, 0.039 mol) and the reaction mixture was stirred at room temperature for 4 hours. After adding water (3 x 80 mL), the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 80 mL) and the organic extracts were combined and concentrated under reduced pressure to give a dark red solid. Residual water was removed by co-evaporating the azeotropic mixture with toluene (3 x 20 mL) to give a red crystalline solid **91** (6.23 g, 95 %). δ_{H} (CDCl₃, 400 MHz) 1.86 (3H, s, CH₃), 7.25 - 7.36 (6H, m, ArH), 7.44 - 7.50 (1H, m, ArH), 7.57 (1H, t, ³J_{HH} = 7.8 Hz, ArH), 7.79 (1H, d, ³J_{HH} = 8.4 Hz, ArH). δ_{C} (CDCl₃, 125 MHz) 28.0 (CH₃) 86.7 (C), 116.7 (CI), 125.8 (CH), 126.7 (CH), 127.3 (CH), 127.4 (CH), 127.7 (CH), 129.3 (CH), 129.5 (CH), 143.5 (C), 145.6 (C). δ_{F} (CDCl₃, 376 MHz) -143.2 (1F, s). *m/z* (ESI): 322.9944 ((M-F)⁺, C₁₄H₁₂IO requires 322.9933, 100 %).

5.6.2 General procedure for the preparation of the Grignard reagents (1M in THF)

Bromobenzene (1.04 mL, 0.01 mol) was added to magnesium turnings (0.29 g, 0.012 mol) stirring in THF (10 mL) at room temperature under an atmosphere of nitrogen. The dropwise addition of bromobenzene was maintained over 10 min to ensure a gentle reflux. Once the addition was complete, the reaction mixture was refluxed for a further 2 hours. After cooling to room temperature, the solution of the Grignard reagent **92** was transferred by cannula to a Schlenk flask and stored under nitrogen.

The Grignard reagents **94** (from 3-bromotoluene), **96** (from 4-bromotoluene), **98** (from 4-bromofluorobenzene), **100** (from 3-bromofluorobenzene), **102** (from 3-trifluoromethylbromobenzene), **104** (from 4-trifluoromethylbromobenzene) and **106** (from 2-trifluoromethylbromobenzene) were prepared following the same experimental procedure.

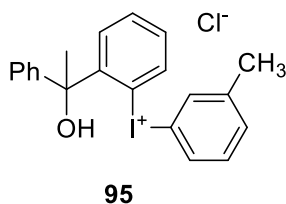
5.6.3 General procedure for Method A Table 3.1



A solution of 1-fluoro-3-methyl-3-phenyl-1,3-dihydro-1,3-benzo[d]-[1,2]iodaoxole (0.36 g, 1.05 mmol) in DCM (2 mL) was cooled to 0 °C before the Grignard reagent **92** (0.60 mL, 0.60 mmol) was added. The reaction mixture was allowed to warm to room temperature and left to stir for 4 hours. After this time, concentrated hydrochloric acid HCl (2 mL, 66 mmol) was added to quench the unreacted Grignard reagent and the solution was left to stir for 1 hour. The clear yellow solution was diluted with DCM (10 mL) and washed with water (3 x 5 mL). The aqueous layer was extracted with DCM (3 x 5 mL) and the organic extracts were combined, dried over MgSO₄ and concentrated under reduced pressure to give a pale yellow solid. The crude product was washed with hexane (3 x 5 mL) and then stirred in ice-cold diethyl ether (3 x 20 mL) for 15 min with each wash, generating (2-(1-hydroxy-1-phenylethyl)phenyl)(phenyl)iodonium chloride **93** as a white solid (0.183 g, 71 %). m.p. 153-159 °C. δ_{H} (CDCl₃, 400 MHz) 2.09 (3H, s, CH₃), 6.26 (1H, br s, OH), 6.92 (1H, d, $^3J_{\text{HH}}$ = 8.7 Hz, ArH), 7.23 (1H, m, ArH), 7.33-7.43 (5H, m, ArH), 7.48 (2H, m, ArH), 7.56 (2H, t, $^3J_{\text{HH}}$ = 7.6 Hz, ArH), 7.74 (1H, t, $^3J_{\text{HH}}$ = 7.8 Hz, ArH), 7.92 (2H, dd, $^3J_{\text{HH}}$ = 8.1 Hz, $^4J_{\text{HH}}$ = 1.1 Hz, ArH). δ_{C} (CDCl₃, 100 MHz): 29.9 (CH₃), 78.0 (C), 110.0 (CI), 110.3 (CI), 126.2 (CH), 128.2 (CH), 128.7 (CH), 129.3 (CH), 130.6 (CH), 131.0 (CH), 131.1 (CH), 132.5 (CH), 133.7 (CH), 138.0 (CH), 143.7 (C), 145.5 (C). m/z (ESI⁺) 401.0205 ([M-Cl]⁺, C₂₀H₁₈IO requires 401.0196). m/z (ESI⁻) 35/37 (Cl⁻).

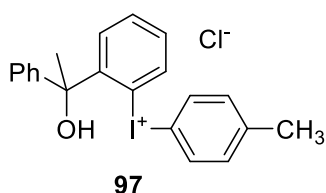
Products **95**, **97**, **99**, **101**, **103**, **105** and **107** were prepared following the same experimental procedure as reported for **93**, using 1-fluoro-3-methyl-3-phenyl-1,3-dihydro-1,3-benzo[d]-[1,2]iodaoxole **91** (0.36 g, 1.05 mmol) in DCM (2 mL) and the required amounts of **94**, **96**, **98**, **100**, **102**, **104**, **106** (0.60 mmol).

(2-(1-Hydroxy-1-phenylethyl)-phenyl)-(m-tolyl)iodonium chloride **95** was obtained as a

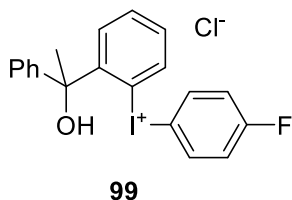


white solid (0.247 g, 93 %). m.p. 145-152 °C. δ_{H} (CDCl₃, 400 MHz) 2.17 (3H, s, CH₃), 2.36 (3H, s, CH₃), 6.87 (1H, d, $^3J_{\text{HH}}$ = 7.9 Hz, ArH), 7.06 (1H, t, $^3J_{\text{HH}}$ = 7.4 Hz, ArH), 7.14 (1H, d, $^3J_{\text{HH}}$ = 7.5 Hz, ArH), 7.18-7.24 (5H, m, ArH), 7.36-7.41 (2H,

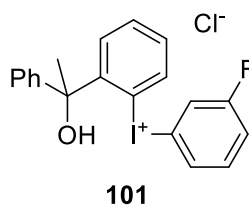
m, ArH), 7.46 (1H, d, $^3J_{\text{HH}} = 7.4$ Hz, ArH), 7.67 (2H, dd, $^3J_{\text{HH}} = 7.6$ Hz, $^4J_{\text{HH}} = 1.2$ Hz, ArH). δ_{C} (CDCl₃, 125MHz) 21.4 (CH₃), 31.5 (CH₃), 78.0 (C), 114.8 (CI), 116.1 (CI), 126.2 (CH), 126.4 (CH), 127.2 (CH), 127.5 (CH), 128.4 (CH), 129.9 (CH), 130.9 (CH), 131.4 (CH), 133.1 (CH), 134.6 (CH), 135.8 (CH), 143.9 (C), 145.1 (C), 145.5 (C). m/z (ESI) 415.0509 [M-Cl]⁺, C₂₁H₂₀IO requires 415.0508).



(2-(1-Hydroxy-1-phenylethyl)phenyl)-(p-tolyl)iodonium chloride **97** was obtained as a white solid (0.181 g, 68 %). m.p. 145-152 °C. δ_{H} (CDCl₃, 400 MHz) 2.04 (3H, s, CH₃), 2.46 (3H, s, CH₃), 6.15 (1H, br. s, OH), 6.88 (1H, d, $^3J_{\text{HH}} = 8.4$ Hz, ArH), 7.19 (1H, td, $^3J_{\text{HH}} = 8.5$ Hz, $^4J_{\text{HH}} = 2.2$ Hz, ArH), 7.26-7.35 (5H, m, ArH), 7.37-7.45 (4H, m, ArH), 7.68 (2H, dd, $^3J_{\text{HH}} = 8.2$ Hz, $^4J_{\text{HH}} = 2.1$ Hz, ArH). δ_{C} (CDCl₃, 125 MHz) 21.8 (CH₃), 29.9 (CH₃), 77.9 (C), 106.2 (CI), 110.5 (CI), 126.2 (CH), 128.2 (CH), 129.0 (CH), 129.9 (CH), 130.5 (CH), 131.0 (CH), 131.1 (CH), 133.4 (CH), 137.8 (CH), 143.9 (C), 145.1 (C), 145.3 (C). m/z (ESI) 415.0509 ([M-Cl]⁺, C₂₁H₂₀IO requires 415.0508).

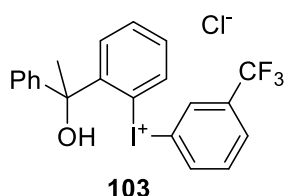


(4-Fluorophenyl)-(2-(1-hydroxy-1-phenylethyl)-phenyl) iodonium chloride **99** was obtained as a white solid (0.228 g, 85 %). m.p. 153-159 °C. δ_{H} (CDCl₃, 400 MHz) 2.04 (3H, s, CH₃), 6.20 (1H, br. s, OH), 7.03 (1H, d, $^3J_{\text{HH}} = 8.1$ Hz, ArH), 7.21-7.30 (3H, m, ArH), 7.29-7.36 (5H, m, ArH), 7.48 (2H, m, ArH), 8.04 (2H, dd, $^3J_{\text{HF}} = 9.5$ Hz, $^3J_{\text{HH}} = 7.8$ Hz, ArH). δ_{F} (CDCl₃, 376.5 MHz) -107.1 (1F, s, ArF). δ_{C} (CDCl₃, 125 MHz) 37.8 (CH₃), 77.8 (C), 106.8 (CI), 106.9 (CI), 119.2 (CH), 119.5 (d, $^2J_{\text{CF}} = 22.1$ Hz, CH), 128.9 (CH), 129.1 (CH), 131.6 (CH), 132.0 (CH), 133.1 (CH), 136.9 (CH), 138.1 (d, $^3J_{\text{CF}} = 10.1$ Hz, CH), 145.2 (C), 148.3 (C), 164.7 (d, $^1J_{\text{CF}} = 256.5$ Hz, C). m/z (ESI) 419.0319 ([M-Cl]⁺, C₂₀H₁₇IOF requires 419.0308).

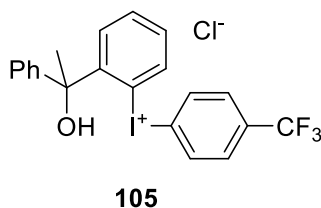


(3-Fluorophenyl)(2-(1-hydroxy-1-phenylethyl)-phenyl)iodonium chloride **101** was obtained as a white solid (0.188 g, 70 %). m.p. 154-159 °C. δ_{H} (CDCl₃, 400 MHz) 2.15 (3H, s, CH₃), 6.89 (1H, dd, $^3J_{\text{HH}} = 8.3$ Hz, $^4J_{\text{HH}} = 1.2$ Hz, ArH), 7.09-7.16 (2H, td, $^3J_{\text{HH}} = 8.2$ Hz, $^4J_{\text{HH}} = 1.7$ Hz, ArH), 7.22-7.36 (3H, m, ArH), 7.42-7.50 (4H, m, ArH), 7.88 (2H, m, ArH), 7.95 (1H, dd, $^3J_{\text{HH}} = 8.5$ Hz, $^4J_{\text{HH}} = 1.4$ Hz, ArH). δ_{F} (CDCl₃,

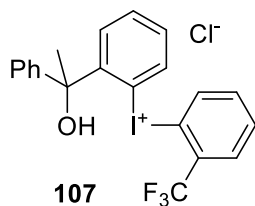
376.5 MHz) -106.2 (1F, s, ArF). δ_{C} (CDCl₃, 100 MHz) 36.4 (CH₃), 78.4 (C), 109.8 (CI), 110.4 (CI), 112.7 (d, $^2J_{\text{CF}}$ = 22.1 Hz, CH), 114.2 (d, $^2J_{\text{CF}}$ = 20.1 Hz, CH), 121.4 (CH), 126.9 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH), 128.9 (CH), 129.9 (d, $^3J_{\text{CF}}$ = 8.0 Hz, CH), 130.7 (CH), 139.5 (CH), 147.3 (C), 151.6 (C), 162.9 (d, $^1J_{\text{CF}}$ = 244.5 Hz, C). m/z (ESI) 419.0322 ([M-Cl]⁺, C₂₀H₁₇IOF requires 419.0308).



(2-(1-Hydroxy-1-phenylethyl)-phenyl)-(3-(trifluoromethyl)-phenyl)iodonium chloride **103** was obtained as a white solid (0.259 g, 87 %). m.p. 153-161 °C. δ_{H} (CDCl₃, 400 MHz) 2.04 (3H, s, CH₃), 6.78 (1H, d, $^3J_{\text{HH}}$ = 8.4 Hz, ArH), 7.25-7.37 (6H, m, ArH), 7.41-7.48 (2H, m, ArH), 7.69 (1H, t, $^3J_{\text{HH}}$ = 7.8 Hz, ArH), 7.97 (1H, d, $^3J_{\text{HH}}$ = 7.9 Hz, ArH), 8.05 (1H, s, ArH), 8.16 (1H, d, $^3J_{\text{HH}}$ = 7.5 Hz, ArH). δ_{F} (CDCl₃, 376.5 MHz) -64.25 (3F, s, CF₃). δ_{C} (CDCl₃, 125 MHz) 29.9 (CH₃), 79.9 (C), 110.8 (CI), 110.9 (CI), 122.3 (q, $^1J_{\text{CF}}$ = 264.6 Hz, CF₃), 126.1 (CH x 2), 126.4 (CH), 126.9 (CH), 127.2 (CH x 2), 128.5 (CH), 129.2 (CH), 130.7 (q, $^3J_{\text{CF}}$ = 8.0 Hz, CH), 131.9 (CH), 138.6 (q, $^2J_{\text{CF}}$ = 24.1 Hz, C), 141.2 (CH), 143.5 (C), 145.6 (C). m/z (ESI) 469.0283 ([M-Cl]⁺, C₂₁H₁₇OF₃I requires 469.0276).

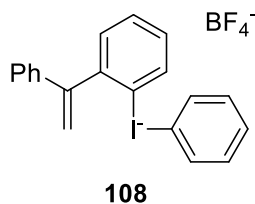


(2-(Hydroxy-1-phenyl)-phenyl)(4-(trifluoromethyl)-phenyl)iodonium chloride **105** was obtained as a white solid (0.274 g, 92 %). m.p. 155-162 °C. δ_{H} (CDCl₃, 400 MHz) 2.00 (3H, s, CH₃), 6.93 (1H, d, $^3J_{\text{HH}}$ = 8.8 Hz, ArH), 7.12 (1H, m, ArH), 7.17-7.27 (3H, m, ArH), 7.28-7.32 (2H, m, ArH), 7.35-7.42 (2H, m, ArH), 7.78 (2H, d, $^3J_{\text{HH}}$ = 8.2 Hz, ArH), 8.07 (2H, d, $^3J_{\text{HH}}$ = 8.0 Hz, ArH). δ_{F} (CDCl₃, 376.5 MHz) -64.61 (3F, s, CF₃). δ_{C} (CDCl₃, 125 MHz) 22.9 (CH₃), 78.3 (C), 110.6 (CI), 114.3 (CI), 122.0 (q, $^1J_{\text{CF}}$ = 273.6 Hz, CF₃), 124.8 (CH x 2), 128.3 (CH x 2), 129.3 (CH), 129.5 (CH), 130.2 (q, $^3J_{\text{CF}}$ = 10.1 Hz, CH), 134.1 (q, $^2J_{\text{CF}}$ = 32.2 Hz, C), 137.4 (CH x 2), 142.6 (C), 144.7 (C). m/z (ESI) 469.0277 ([M-Cl]⁺, C₂₁H₁₇OF₃I requires 469.0276).



(2-(1-Hydroxy-1-phenylethyl)phenyl)(2-(trifluoromethyl)-phenyl)iodonium chloride **107** was obtained as a white solid (0.244 g, 82 %). m.p. 150-155 °C. δ_{H} (CDCl_3 , 400 MHz) 2.12 (3H, s, CH_3), 4.89 (1H, br. s, OH), 6.76-6.69 (1H, dd, $^3J_{\text{HH}} = 8.4$ Hz, $^4J_{\text{HH}} = 0.8$ Hz, ArH), 7.19-7.23 (1H, td, $^3J_{\text{HH}} = 8.5$ Hz, $^4J_{\text{HH}} = 2.1$ Hz, ArH), 7.36-7.38 (4H, m, ArH), 7.44-7.51 (3H, m, ArH), 7.74-7.79 (2H, ddd, $^3J_{\text{HH}} = 9.4$ Hz, 7.8 Hz, $^4J_{\text{HH}} = 1.7$ Hz, ArH), 7.91-7.94 (1H, m, ArH), 7.97-7.99 (1H, dd, $^3J_{\text{HH}} = 7.8$ Hz, $^4J_{\text{HH}} = 1.6$ Hz, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -60.33 (3F, s, CF_3). δ_{C} (CDCl_3 , 125 MHz) 20.6 (CH_3), 79.2 (C), 108.5 (CI), 115.5 (CI), 122.1 (q, $^1J_{\text{CF}} = 274.6$ Hz, CF_3), 127.3 (CH x 2), 129.4 (CH x 2), 126.6 (CH), 132.2 (CH), 132.9 (CH), 133.7 (CH), 134.2 (d, $^2J_{\text{CF}} = 34.2$ Hz, C), 135.3 (CH), 135.8 (CH), 140.9 (CH), 144.7 (C), 148.7 (C). m/z (ESI) 469.0283 [$[\text{M}-\text{Cl}]^+$], $\text{C}_{21}\text{H}_{17}\text{OF}_3\text{I}$ requires 469.0276).

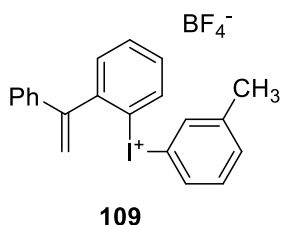
5.6.4 General Procedure for Table 3.2



A solution of (2-(1-hydroxy-1-phenylethyl)phenyl)(phenyl)iodonium chloride **93** (0.354 g, 0.81 mmol) in DCM (10 mL) was cooled to 0 °C before triflic acid (0.22 mL, 2.44 mmol) was added. The resulting dark brown solution was stirred at 0 °C for 2 hours after which DCM (10 mL) was added and the solution was washed with water (3 x 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over MgSO_4 and concentrated under reduced pressure generating a thick brown oil which was washed with hot hexane (3 x 10 mL) and cold diethyl ether (3 x 20 mL), giving the product as a white powder (0.39 g, 87 %). The salt was then dissolved in MeOH (8 mL): H_2O (8 mL) homogenous mixture to which NaBF_4 (8.0 g, 73 mmol, 100 eq.) was added and the mixture was stirred at 40 °C for 4 hours. After this time, DCM (10 mL) was added and the solution was washed with water (3 x 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over MgSO_4 and concentrated under reduced pressure, yielding phenyl(2-(1-phenylvinyl)phenyl)iodonium-tetrafluoroborate **108** as a white solid (0.309 g, 87 %). m.p. 156-161 °C. δ_{H} (400 MHz) (CDCl_3 , 400 MHz) 5.40 (1H, d, $^2J_{\text{HH}} = 1.7$ Hz, $\text{C}=\text{CH}_2$), 6.05

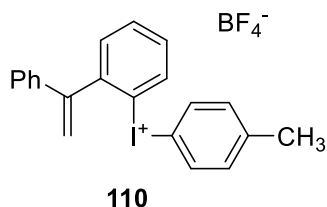
(1H, d, $^2J_{\text{HH}} = 1.7$ Hz, C=CH₂), 7.06 (2H, dd, $^3J_{\text{HH}} = 7.9$ Hz, $^4J_{\text{HH}} = 1.0$ Hz, ArH), 7.18-7.26 (5H, m, ArH), 7.35 (1H, m, ArH), 7.41-7.47 (2H, m, ArH), 7.53-7.60 (3H, m, ArH), 7.86 (1H, dd, $^3J_{\text{HH}} = 8.1$ Hz, $^4J_{\text{HH}} = 1.2$ Hz, ArH). δ_{F} (CDCl₃, 376.5 MHz) -148.9 (4F, s, BF₄). δ_{C} (CDCl₃, 125 MHz) 112.4 (CI), 116.1 (CI), 119.9 (CH₂), 127.1 (CH), 129.4 (CH), 129.5 (CH), 131.9 (CH), 132.4 (CH), 132.9 (CH), 133.2 (CH), 133.7 (CH), 135.6 (CH), 135.9 (CH), 137.7 (C), 145.4 (C), 148.5 (C). m/z (ESI) 383.0304 (M⁺, C₂₀H₁₆I requires 383.0297).

Products **109-115** were prepared following the same experimental procedure as reported for the preparation of **108**, from substrates **95**, **97**, **99**, **101**, **103**, **105** and **107** using the required amount of triflic acid (3 eq.) and NaBF₄ (aq.) (100 eq.), (**Table 3.2**).



(2-(1-Phenylvinyl)phenyl)(m-tolyl)iodonium-tetrafluoroborate **109** was obtained from **95** (0.247 g) as a white solid (0.180 g, 68 %). Crystals suitable for X-ray crystallography were grown by slow diffusion from DCM : hexane (1:3). m.p. 153-158 °C. δ_{H} (CDCl₃, 400 MHz CDCl₃) 2.29 (3H, s, CH₃), 5.45 (1H, d, $^2J_{\text{HH}} =$

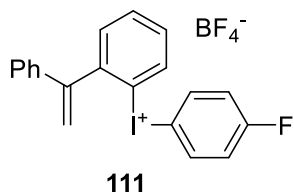
1.5 Hz, C=CH₂), 6.05 (1H, d, $^2J_{\text{HH}} = 1.5$ Hz, C=CH₂), 7.18 (2H, dd, $^3J_{\text{HH}} = 7.8$ Hz, $^4J_{\text{HH}} = 1.8$ Hz, ArH), 7.21-7.26 (1H, t, $^3J_{\text{HH}} = 7.8$ Hz, ArH), 7.31-7.38 (4H, m, ArH), 7.42-7.47 (2H, m, ArH), 7.51 (2H, m, ArH), 7.67 (1H, td, $^3J_{\text{HH}} = 8.0$ Hz, $^4J_{\text{HH}} = 1.1$ Hz, ArH), 7.92 (1H, dd, $^3J_{\text{HH}} = 8.2$ Hz, $^4J_{\text{HH}} = 1.0$, ArH). δ_{F} (CDCl₃, 376.5 MHz) -147.2 (4F, s, BF₄). δ_{C} (CDCl₃, 125 MHz) 21.3 (CH₃), 112.2 (CI), 116.2 (CI), 119.9 (CH₂), 127.1 (CH), 129.3 (CH), 130.6 (CH), 130.8 (CH), 131.7 (CH), 131.9 (CH), 132.2 (CH), 132.6 (CH), 133.1 (CH), 133.8 (CH), 134.1 (CH), 138.4 (C), 143.3 (C), 145.3 (C), 148.5 (C). m/z (ESI) 397.0768 (M⁺, C₂₁H₁₈I requires 397.0766).



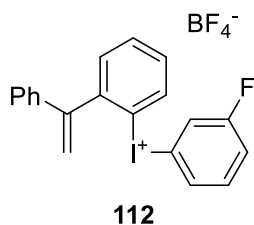
(2-(1-Phenylvinyl)phenyl)(p-tolyl)iodonium tetrafluoroborate **110** was obtained from **97** (0.181 g) as a white solid (0.153 g, 79 %). m.p. 149-156 °C. δ_{H} (CDCl₃, 400 MHz,) 2.37 (3H, s, CH₃), 5.43 (1H, d, $^2J_{\text{HH}} = 1.7$ Hz, C=CH₂), 6.06 (1H, d, $^2J_{\text{HH}} = 1.7$ Hz, C=CH₂), 7.11-7.18 (4H, m, ArH),

7.31-7.38 (3H, m, ArH), 7.42 (1H, td, $^3J_{\text{HH}} = 7.9$ Hz, $^4J_{\text{HH}} = 1.4$ Hz, ArH), 7.52 (1H, dd, $^3J_{\text{HH}} = 7.6$ Hz, $^4J_{\text{HH}} = 1.8$ Hz, ArH), 7.54-7.57 (2H, dd, $^3J_{\text{HH}} = 7.5$ Hz, $^4J_{\text{HH}} = 1.2$ Hz, ArH), 7.64 (1H, td, $^3J_{\text{HH}} = 7.8$ Hz, $^4J_{\text{HH}} = 1.0$ Hz, ArH), 7.92 (1H, dd, $^3J_{\text{HH}} = 8.2$ Hz, $^4J_{\text{HH}} = 1.0$, ArH). δ_{F} (CDCl₃, 376.5 MHz) -147.6 (4F, s, BF₄). δ_{C} (CDCl₃, 125 MHz): 21.4

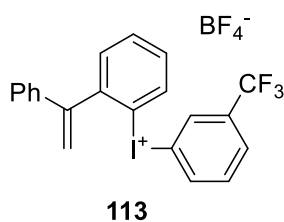
(CH₃), 109.6 (CI), 115.9 (CI), 119.7 (CH₂), 127.1 (CH), 129.3 (CH), 131.6 (CH), 132.1 (CH), 132.8 (CH), 132.9 (CH), 133.8 (CH), 135.6 (CH), 135.7 (CH), 143.9 (C), 145.1 (C), 148.5 (C). *m/z* (ESI) 397.0768 (M⁺, C₂₁H₁₈I requires 397.0766).



(4-Fluorophenyl)-(2-(1-phenylvinyl)phenyl)iodonium-tetrafluoroborate **111** was obtained from **99** (0.228 g) as a white solid (0.214 g, 72 %). Crystals suitable for X-ray crystallography were grown by slow diffusion from DCM:hexane (1:3). m.p. 152-159 °C. δ_{H} (CDCl₃, 400 MHz) 5.43 (1H, d, $^2J_{\text{HH}} = 1.4$ Hz, C=CH₂), 5.96 (1H, d, $^2J_{\text{HH}} = 1.4$ Hz, C=CH₂), 6.84 (2H, td, $^3J_{\text{HF}} = 8.1$ Hz $^4J_{\text{HH}} = 1.2$ Hz, ArH), 7.19-7.28 (2H, dd, $^3J_{\text{HH}} = 7.8$ Hz, $^4J_{\text{HH}} = 1.8$ Hz, ArH), 7.32-7.38 (3H, m, ArH), 7.56 (2H, m, ArH), 7.60-7.68 (3H, m, ArH), 8.22 (1H, dd, $^3J_{\text{HH}} = 7.0$ Hz, $^4J_{\text{HH}} = 1.0$ Hz, ArH). δ_{F} (CDCl₃, 376.5 MHz) -107.1 (1F, s, ArF), -147.3 (4F, s, BF₄). δ_{C} (CDCl₃, 125 MHz) 105.5 (CI), 116.7 (CI), 119.6 (d, $^2J_{\text{CF}} = 23.1$ Hz, CH), 119.9 (CH₂), 127.1 (CH), 129.3 (CH x 2), 131.9 (CH), 132.2 (CH), 133.3 (CH), 136.5 (CH), 137.8 (C), 138.3 (d, $^3J_{\text{CF}} = 9.1$ Hz, CH), 145.3 (C), 148.3 (C), 165.0 (d, $^1J_{\text{CF}} = 257.5$ Hz, CF). *m/z* (ESI) 401.0202 (M⁺, C₂₀H₁₅IF requires 401.0202).

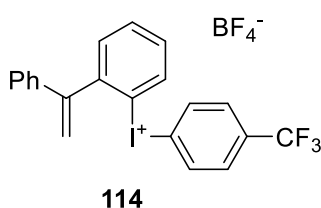


(3-Fluorophenyl)-(2-(1-phenylvinyl)phenyl)iodonium-tetrafluoroborate **112** was obtained from **101** (0.188 g) as a white solid (0.098 g, 49 %). Crystals suitable for X-ray crystallography were grown by slow diffusion from DCM:hexane (1:3). m.p. 155-163 °C. δ_{H} (CDCl₃, 400 MHz) 5.45 (1H, d, $^2J_{\text{HH}} = 1.7$ Hz, C=CH₂), 6.07 (1H, d, $^2J_{\text{HH}} = 1.7$ Hz, C=CH₂), 7.15 (2H, dd, $^3J_{\text{HH}} = 7.8$ Hz, $^4J_{\text{HH}} = 1.5$ Hz, ArH), 7.23 (1H, td, $^3J_{\text{HH}} = 7.9$ Hz, $^4J_{\text{HH}} = 1.4$ Hz, ArH), 7.29-7.38 (5H, m, ArH), 7.52-7.59 (3H, m, ArH), 7.71 (1H, t, $^3J_{\text{HH}} = 7.4$ Hz, ArH), 8.20 (1H, dd, $^3J_{\text{HH}} = 8.2$ Hz, $^4J_{\text{HH}} = 1.0$ Hz, ArH). δ_{F} (CDCl₃, 376.5 MHz) -106.2 (1F, s, ArF), -148.9 (4F, s, BF₄). δ_{C} (CDCl₃, 125 MHz) 111.6 (CI), 116.9 (CI), 119.9 (CH₂), 120.1 (d, $^2J_{\text{CF}} = 20.7$ Hz, CH), 122.7 (d, $^2J_{\text{CF}} = 25.2$ Hz, CH), 127.1 (CH), 129.2 (CH), 129.3 (CH), 131.3 (CH), 131.9 (CH), 132.3 (CH), 133.1 (CH), 133.5 (CH), 136.9 (CH), 137.8 (C), 145.6 (C), 148.3 (C), 162.5 (d, $^1J_{\text{CF}} = 256.3$ Hz, CF). *m/z* (ESI) 401.0210 (M⁺, C₂₀H₁₅IF requires 401.0202).



(2-(1-Phenylvinyl)phenyl)-(3-(trifluoromethyl)phenyl)-
iodonium-tetrafluoroborate **113** was obtained from **103** (0.259 g)
as a white solid (0.204 g, 74 %). Crystals suitable for X-ray
crystallography were grown by slow diffusion from
DCM:hexane (1:3). m.p. 161-165 °C. δ_{H} (400 MHz, CDCl_3) 5.42

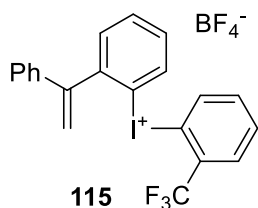
(1H, d, $^2J_{\text{HH}} = 1.6$ Hz, $\text{C}=\text{CH}_2$), 6.04 (1H, d, $^2J_{\text{HH}} = 1.6$ Hz, $\text{C}=\text{CH}_2$), 7.06 (2H, dd, $^3J_{\text{HH}} = 7.8$ Hz, $^4J_{\text{HH}} = 1.1$ Hz, ArH), 7.19-7.28 (3H, m, ArH), 7.41 (1H, t, $^3J_{\text{HH}} = 8.0$ Hz, ArH), 7.46-7.53 (2H, m, ArH), 7.67-7.73 (3H, m, ArH), 7.97 (1H, d, $^3J_{\text{HH}} = 8.2$ Hz, ArH), 8.28 (1H, d, $^3J_{\text{HH}} = 8.2$ Hz, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -64.25 (3F, s, CF_3), -145.8 (4F, s, BF_4). δ_{C} (CDCl_3 , 125 MHz) 112.4 (CI), 116.9 (CI), 119.9 (CH_2), 122.3 (q, $^1J_{\text{CF}} = 273.7$ Hz, CF_3), 126.8 (CH), 129.1 (CH), 129.2 (CH), 131.7 (CH), 131.9 (CH), 132.3 (CH), 132.4 (CH), 133.5 (q, $^2J_{\text{CF}} = 34.2$ Hz, C), 133.6 (CH), 137.5 (CH), 137.6 (C), 138.8 (CH), 145.6 (C), 148.1 (C). m/z (ESI) 451.0272 (M^+ , $\text{C}_{21}\text{H}_{15}\text{IF}_3$ requires 451.0276).



(2-(1-Phenylvinyl)phenyl)-(4-(trifluoromethyl)phenyl)-
iodonium-tetrafluoroborate **114** was obtained from **105**
(0.274 g) as a white solid (0.254 g, 87 %). m.p. 160-166 °C.
 δ_{H} (400 MHz, CDCl_3) 5.40 (1H, d, $^2J_{\text{HH}} = 1.5$ Hz, $\text{C}=\text{CH}_2$),

6.04 (1H, d, $^2J_{\text{HH}} = 1.5$ Hz, $\text{C}=\text{CH}_2$), 7.01 (2H, dd, $^3J_{\text{HH}} = 7.2$ Hz, $^4J_{\text{HH}} = 1.4$ Hz, ArH), 7.15-7.26 (3H, m, ArH), 7.38-7.50 (4H, m, ArH), 7.68 (1H, td, $^3J_{\text{HH}} = 7.3$ Hz, $^4J_{\text{HH}} = 1.0$ Hz, ArH), 7.71 (2H, d, $^3J_{\text{HH}} = 8.4$ Hz, ArH), 8.30 (1H, d, $^3J_{\text{HH}} = 8.4$ Hz, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -64.61 (3F, s, CF_3), -145.4 (4F, s, BF_4). δ_{C} (CDCl_3 , 125 MHz) 114.6 (CI), 115.6 (CI), 118.9 (CH_2), 123.3 (q, $^1J_{\text{CF}} = 258.5$ Hz, CF_3), 125.8 (CH), 127.3 (CH), 128.0 (CH x 2), 130.8 (CH), 131.2 (CH), 132.6 (CH), 133.1 (q, $^2J_{\text{CF}} = 33.2$ Hz, C), 134.6 (C), 134.7 (CH), 136.7 (q, $^3J_{\text{CF}} = 14.1$ Hz, CH), 144.7 (C), 147.1 (C). m/z (ESI) 451.0271 (M^+ , $\text{C}_{21}\text{H}_{15}\text{IF}_3$, requires 451.0276).

(2-(1-Phenylvinyl)phenyl)-(3-(trifluoromethyl)phenyl)iodonium- tetrafluoroborate **115**



was obtained from **107** (0.244 g) as a white solid (0.192 g, 70 %).
m.p. 162-165 °C. δ_{H} (400 MHz, CDCl_3) 5.94 (1H, d, $^2J_{\text{HH}} = 1.6$
Hz, $\text{C}=\text{CH}_2$), 6.11 (1H, d, $^2J_{\text{HH}} = 1.7$ Hz, $\text{C}=\text{CH}_2$), 7.14 (2H, dd,
 $^3J_{\text{HH}} = 7.7$ Hz, $^4J_{\text{HH}} = 1.5$ Hz, ArH), 7.29-7.32 (3H, m, ArH), 7.41-

7.45 (1H, m, ArH), 7.47-7.49 (1H, dd, $^3J_{\text{HH}} = 7.6$ Hz, $^4J_{\text{HH}} = 1.8$ Hz, ArH), 7.51-7.54 (1H, td, $^3J_{\text{HH}} = 9.3$ Hz, $^4J_{\text{HH}} = 1.3$ Hz, ArH), 7.97 (1H, td, $^3J_{\text{HH}} = 8.5$ Hz, $^4J_{\text{HH}} = 1.0$ Hz, ArH), 7.71-7.79 (3H, m, ArH), 8.12 (1H, d, $^3J_{\text{HH}} = 8.0$ Hz, ArH). δ_{F} (CDCl₃, 376.5 MHz) -59.4 (3F, s, CF₃), -148.1 (4F, s, BF₄). δ_{C} (CDCl₃, 125 MHz) 109.8 (CI), 111.6 (CI), 119.7 (CH₂), 122.2 (q, $^1J_{\text{CF}} = 273.1$ Hz, CF₃), 126.1 (q, $^2J_{\text{CF}} = 36.2$ Hz, C), 127.1 (CH x 2), 128.9 (CH), 129.2 (CH), 129.4 (CH), 131.7 (CH), 132.3 (CH), 133.2 (q, $^3J_{\text{CF}} = 25.9$ Hz, CH), 135.3 (CH), 135.7 (CH), 137.4 (C), 140.4 (CH), 144.9 (C), 148.5 (C). m/z (ESI) 451.0272 (M⁺, C₂₁H₁₅IF₃, requires 451.0276).

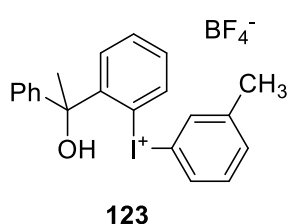
5.6.5 Method B for Scheme 3.20

A solution of 1-fluoro-3-methyl-3-phenyl-1,3-dihydro-1H-benzo[d][1,2]iodaoxole (0.36 g, 1.05 mmol, 1.75 eq.) in DCM (2 mL) was cooled to 0 °C before the required amount of Grignard reagent (**92**, **94**, **96**, **98**, **100**, **102**, **104**, **106**, 0.60 mmol) was added. The reaction mixture was allowed to warm to room temperature and left to stir for 4 hours. After this time, the solution was cooled to 0 °C before triflic acid (0.32 mL, 3.6 mmol) was added to the solution and it was left to stir at 0 °C for 1 hour. Warming up to room temperature for another hour resulted in the formation of a thick, jelly substance which was washed with water (3 x 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The product was washed with hot hexane (3 x 10 mL) and cold diethyl ether (3 x 20 mL). Finally, the salt was dissolved in a MeOH (8 mL):H₂O (8 mL) homogenous mixture to which NaBF₄ (100 eq.) was added and the mixture was stirred at 40 °C for 4 hours. After this time, DCM (10 mL) was added and the solution was washed with water (3 x 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure, yielding the desired product as a white powder.

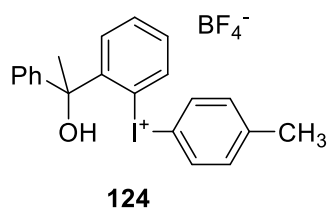
5.6.6 Method C for Table 3.4

The solution of the arylboronic acid (0.72 mmol) in DCM (9 mL) was cooled to 0 °C before BF₃.Et₂O (0.79 mmol) was added and the mixture was stirred for 10 minutes. The fluoroiodane (0.76 mmol) in DCM (2 mL) was added to the reaction mixture which was

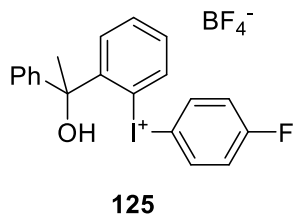
stirred for 2 hours at 0 °C. After this time, a saturated aqueous NaBF₄ (20 mL) was added and the mixture was stirred vigorously for 30 minutes. The clear yellow solution was diluted with DCM (10 mL) and washed with water (3 x 5 mL). The aqueous layer was extracted with DCM (3 x 5 mL) and the organic extracts were combined, dried over MgSO₄ and concentrated under reduced pressure to give a dark yellow solid. The crude mixture was washed with hexane (3 x 5 mL) and then stirred in ice-cold diethyl ether (3 x 10 mL) for 15 min with each wash, generating the pure product (**Table 3.4**).



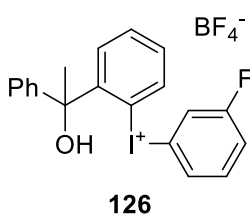
(2-(1-Hydroxy-1-phenylethyl)phenyl)(m-tolyl)iodonium-tetrafluoroborate **123** was obtained as a white solid (0.283 g, 79 %). m.p. 145-152 °C. δ_H (CDCl₃, 400 MHz) 2.17 (3H, s, CH₃), 2.36 (3H, s, CH₃), 6.87 (1H, d, $^3J_{HH}$ = 7.9 Hz, ArH), 7.06 (1H, t, $^3J_{HH}$ = 7.4 Hz, ArH), 7.14 (1H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.18-7.24 (5H, m, ArH), 7.36-7.41 (2H, m, ArH), 7.46 (1H, d, $^3J_{HH}$ = 7.4 Hz, ArH), 7.67 (2H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz, ArH). δ_F (CDCl₃, 376.5 MHz) -147.2 (4F, s, BF₄). δ_C (CDCl₃, 125MHz) 21.4 (CH₃), 31.5 (CH₃), 78.02 (C), 114.8 (CI), 116.1 (CI), 126.2 (CH), 126.4 (CH), 127.2 (CH), 127.5 (CH), 128.4 (CH), 129.9 (CH), 130.9 (CH), 131.4 (CH), 133.1 (CH), 134.6 (CH), 135.8 (CH), 143.9 (C), 145.1 (C), 145.5 (C). *m/z* (ESI) 415.0509 (M⁺, C₂₁H₂₀IO requires 415.0508).



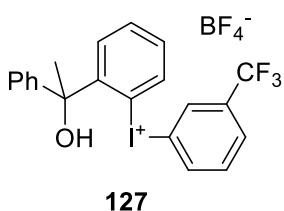
(2-(1-Hydroxy-1-phenylethyl)phenyl)(p-tolyl)iodonium-tetrafluoroborate **124** was obtained as a white solid (0.294 g, 82 %). m.p. 145-152 °C. δ_H (CDCl₃, 400 MHz) 2.04 (3H, s, CH₃), 2.46 (3H, s, CH₃), 6.15 (1H, br. s, OH), 6.88 (1H, d, $^3J_{HH}$ = 8.4 Hz, ArH), 7.19 (1H, td, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.2 Hz, ArH), 7.26-7.35 (5H, m, ArH), 7.37-7.45 (4H, m, ArH), 7.68 (2H, dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.1 Hz, ArH). δ_F (CDCl₃, 376.5 MHz) -147.6 (4F, s, BF₄). δ_C (CDCl₃, 125 MHz) 21.8 (CH₃), 29.9 (CH₃), 77.9 (C), 106.2 (CI), 110.5 (CI), 126.2 (CH), 128.2 (CH), 129.0 (CH), 129.9 (CH), 130.5 (CH), 131.0 (CH), 131.1 (CH), 133.4 (CH), 137.8 (CH), 143.9 (C), 145.1 (C), 145.3 (C). *m/z* (ESI) 415.0509 (M⁺, C₂₁H₂₀IO requires 415.0508).



(4-Fluorophenyl)(2-(1-hydroxy-1-phenylethyl)phenyl)-
 iodonium-tetrafluoroborate **125** was obtained as a white solid
 (0.281 g, 77 %). m.p. 154-159 °C. δ_{H} (CDCl₃, 400 MHz)
 2.15 (3H, s, CH₃), 6.89 (1H, dd, $^3J_{\text{HH}} = 8.3$ Hz, $^4J_{\text{HH}} = 1.2$ Hz
 ArH), 7.09-7.16 (2H, td, $^3J_{\text{HH}} = 8.2$ Hz, $^4J_{\text{HH}} = 1.7$ Hz, ArH),
 7.22-7.36 (3H, m, ArH), 7.42-7.50 (4H, m, ArH), 7.88 (2H, m, ArH), 7.95 (1H, dd, $^3J_{\text{HH}} = 8.5$ Hz, $^4J_{\text{HH}} = 1.4$ Hz, ArH). δ_{F} (CDCl₃, 376.5 MHz) -107.1 (1F, s, ArF), -147.3 (4F, s, BF₄). δ_{C} (CDCl₃, 100 MHz) 41.3 (CH₃), 77.8 (C), 106.8 (CI), 106.9 (CI), 119.2 (CH), 119.5 (d, $^2J_{\text{CF}} = 22.1$ Hz, CH), 128.9 (CH), 129.1 (CH), 131.6 (CH), 132.0 (CH), 133.1 (CH), 136.9 (CH), 137.9 (C), 138.1 (d, $^3J_{\text{CF}} = 10.1$ Hz, CH), 145.2 (C), 148.3 (C), 164.7 (d, $^1J_{\text{CF}} = 256.5$ Hz, C). m/z (ESI) 419.0322 (M⁺, C₂₀H₁₇IOF requires 419.0308).

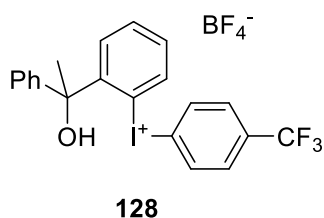


(3-Fluorophenyl)(2-(1-hydroxy-1-phenylethyl)phenyl)iodonium
 tetrafluoroborate **126** was obtained as a white solid (0.215 g, 59
 %). m.p. 154-159 °C. δ_{H} (CDCl₃, 400 MHz) 2.15 (3H, s, CH₃),
 6.89 (1H, dd, $^3J_{\text{HH}} = 8.3$ Hz, $^4J_{\text{HH}} = 1.2$ Hz ArH), 7.09-7.16 (2H,
 td, $^3J_{\text{HH}} = 8.2$ Hz, $^4J_{\text{HH}} = 1.7$ Hz, ArH), 7.22-7.36 (3H, m, ArH),
 7.42-7.50 (4H, m, ArH), 7.88 (2H, m, ArH), 7.95 (1H, dd, $^3J_{\text{HH}} = 8.5$ Hz, $^4J_{\text{HH}} = 1.4$ Hz,
 ArH). δ_{F} (CDCl₃, 376.5 MHz) -106.2 (1F, s, ArF), -148.8 (4F, s, BF₄). δ_{C} (CDCl₃, 100
 MHz) 36.4 (CH₃), 78.4 (C), 109.8 (CI), 110.4 (CI), 112.7 (d, $^2J_{\text{CF}} = 22.1$ Hz, CH), 114.2
 (d, $^2J_{\text{CF}} = 20.1$ Hz, CH), 121.4 (CH), 126.9 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH),
 128.9 (CH), 129.9 (d, $^3J_{\text{CF}} = 8.0$ Hz, CH), 130.7 (CH), 133.4 (C), 139.5 (CH), 147.3 (C),
 151.6 (C), 162.9 (d, $^1J_{\text{CF}} = 244.5$ Hz, C). m/z (ESI) 419.0322 (M⁺, C₂₀H₁₇IOF requires
 419.0308).

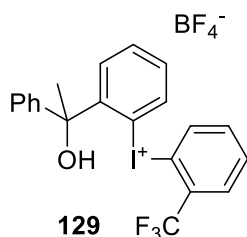


(2-(1-Hydroxy-1-phenylethyl)phenyl)(3-(trifluoromethyl)-
 (phenyl)iodonium tetrafluoroborate **127** was obtained as a white
 solid (0.305 g, 76 %). m.p. 153-161 °C. δ_{H} (CDCl₃, 400 MHz)
 2.04 (3H, s, CH₃), 6.78 (1H, d, $^3J_{\text{HH}} = 8.4$ Hz, ArH), 7.25-7.37
 (6H, m, ArH), 7.41-7.48 (2H, m, ArH), 7.69 (1H, t, $^3J_{\text{HH}} = 7.8$
 Hz, ArH), 7.97 (1H, d, $^3J_{\text{HH}} = 7.9$ Hz, ArH), 8.05 (1H, s, ArH), 8.16 (1H, d, $^3J_{\text{HH}} = 7.5$
 Hz, ArH). δ_{F} (CDCl₃, 376.5 MHz) -64.25 (3F, s, CF₃), -145.8 (4F, s, BF₄). δ_{C} (CDCl₃,
 125 MHz) 29.9 (CH₃), 79.9 (C), 110.8 (CI), 110.9 (CI), 122.3 (q, $^1J_{\text{CF}} = 264.6$ Hz, CF₃),
 126.1 (CH x 2), 126.4 (CH), 126.9 (CH), 127.2 (CH x 2), 128.5 (CH), 129.2 (CH), 130.7

(d, $^3J_{\text{CF}} = 8.0$ Hz, CH), 131.9 (CH), 138.6 (d, $^2J_{\text{CF}} = 24.1$ Hz, C), 141.2 (CH), 143.5 (C), 145.6 (C). m/z (ESI) 469.0283 (M^+ , $\text{C}_{21}\text{H}_{17}\text{OF}_3\text{I}$ requires 469.0276).



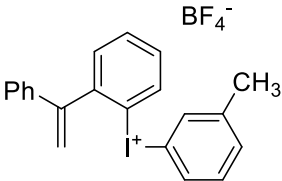
(2-(Hydroxy-1-phenyl)phenyl)-(4-(trifluoromethyl)phenyl)-iodonium-tetrafluoroborate **128** was obtained as a white solid (0.337 g, 84 %). m.p. 155-162 °C. δ_{H} (CDCl_3 , 400 MHz) 2.00 (3H, s, CH_3), 6.93 (1H, d, $^3J_{\text{HH}} = 8.8$ Hz, ArH), 7.12 (1H, m, ArH), 7.17-7.27 (3H, m, ArH), 7.28-7.32 (2H, m, ArH), 7.35-7.42 (2H, m, ArH), 7.78 (2H, d, $^3J_{\text{HH}} = 8.2$ Hz, ArH), 8.07 (2H, d, $^3J_{\text{HH}} = 8.0$ Hz, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -64.61 (3F, s, CF_3), -145.5 (4F, s, BF_4). δ_{C} (CDCl_3 , 125 MHz) 22.9 (CH_3), 78.3 (C), 110.6 (CI), 114.3 (CI), 122.0 (q, $^1J_{\text{CF}} = 273.6$ Hz, CF_3), 124.8 (CH x 2), 128.3 (CH x 2), 129.3 (CH), 129.5 (CH), 130.2 (q, $^3J_{\text{CF}} = 10.1$ Hz, CH), 134.1 (q, $^2J_{\text{CF}} = 32.2$ Hz, C), 137.4 (CH x 2), 142.6 (C), 144.7 (C). m/z (ESI) 469.0277 (M^+ , $\text{C}_{21}\text{H}_{17}\text{OF}_3\text{I}$ requires 469.0276).

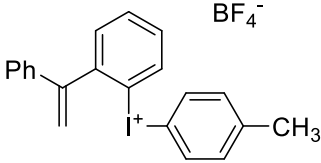


(2-(Hydroxy-1-phenyl)phenyl)-(2-(trifluoromethyl)phenyl)-iodonium-tetrafluoroborate **129** was obtained as a white solid (0.329 g, 82 %). m.p. 150-155 °C. δ_{H} (CDCl_3 , 400 MHz) 2.12 (3H, s, CH_3), 4.89 (1H, br. s, OH), 6.76-6.69 (1H, dd, $^3J_{\text{HH}} = 8.4$ Hz, $^4J_{\text{HH}} = 0.8$ Hz, ArH), 7.19-7.23 (1H, td, $^3J_{\text{HH}} = 8.5$ Hz, $^4J_{\text{HH}} = 2.1$ Hz, ArH), 7.36-7.38 (4H, m, ArH), 7.44-7.51 (3H, m, ArH), 7.74-7.79 (2H, ddd, $^3J_{\text{HH}} = 9.4$ Hz, $^4J_{\text{HH}} = 1.7$ Hz, ArH), 7.91-7.94 (1H, m, ArH), 7.97-7.99 (1H, dd, $^3J_{\text{HH}} = 7.8$ Hz, $^4J_{\text{HH}} = 1.6$ Hz, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -59.4 (3F, s, CF_3), -148.1 (4F, s, BF_4). δ_{C} (CDCl_3 , 125 MHz) 20.6 (CH_3), 79.2 (C), 108.5 (CI), 115.5 (CI), 122.1 (q, $^1J_{\text{CF}} = 274.6$ Hz, CF_3), 127.3 (CH x 2), 129.4 (CH x 2), 126.6 (CH), 132.2 (CH), 132.9 (CH), 133.7 (CH), 134.2 (q, $^2J_{\text{CF}} = 34.2$ Hz, C), 135.3 (CH), 135.8 (CH), 140.9 (CH), 144.7 (C), 148.7 (C). m/z (ESI) 469.0283 (M^+ , $\text{C}_{21}\text{H}_{17}\text{OF}_3\text{I}$ requires 469.0276).

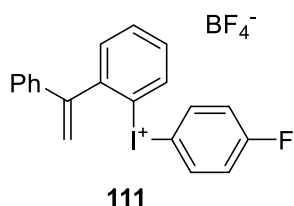
5.6.7 General Procedure for Table 3.5

The solution of the above prepared diaryliodonium salt (**123**, **124**, **125**, **126**, **127**, **128** and **129**) in DCM (10 mL) was cooled to 0 °C before triflic acid (3 eq.) was added. The resulting solution was stirred at 0 °C for 2 hours after which DCM (10 mL) was added and the solution was washed with water (3 x 5 mL). The aqueous extracts were combined and extracted with DCM (3 x 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure generating a thick brown oil which was washed with hot hexane (3 x 10 mL) and cold Et₂O (3 x 20 mL), giving the product as a white powder. The salt was then dissolved in MeOH (8 mL):H₂O (8 mL) homogenous mixture to which NaBF₄ (100 eq.) was added and the mixture was stirred at 40 °C for 4 hours. DCM (10 mL) was added and the solution was washed with water (3 x 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure to generate pure products in **Table 3.5**.

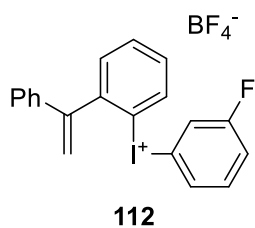

109 (2-(1-Phenylvinyl)phenyl)(m-tolyl)iodonium tetrafluoroborate **109** was obtained from **123** (0.283 g) as a white solid (0.197 g, 72 %). δ_{H} (CDCl₃, 400 MHz CDCl₃) 2.29 (3H, s, CH₃), 5.45 (1H, d, $^2J_{\text{HH}} = 1.7$ Hz, C=CH₂), 6.05 (1H, d, $^2J_{\text{HH}} = 1.7$ Hz, C=CH₂), 7.18 (2H, dd, $^3J_{\text{HH}} = 7.8$ Hz, $^4J_{\text{HH}} = 1.8$ Hz, ArH), 7.21-7.26 (1H, t, $^3J_{\text{HH}} = 7.8$ Hz, ArH), 7.31-7.38 (4H, m, ArH), 7.42-7.47 (2H, m, ArH), 7.51 (2H, m, ArH), 7.67 (1H, td, $^3J_{\text{HH}} = 8.0$ Hz, $^4J_{\text{HH}} = 1.1$ Hz, ArH), 7.92 (1H, dd, $^3J_{\text{HH}} = 8.2$ Hz, $^4J_{\text{HH}} = 1.0$, ArH). δ_{F} (CDCl₃, 376.5 MHz) -147.2 (4F, s, BF₄). δ_{C} (CDCl₃, 125 MHz) 21.3 (CH₃), 112.2 (CI), 116.2 (CI), 119.9 (CH₂), 127.1 (CH), 129.3 (CH), 130.6 (CH), 130.8 (CH), 131.7 (CH), 131.9 (CH), 132.2 (CH), 132.6 (CH), 133.1 (CH), 133.8 (CH), 134.1 (CH), 138.4 (C), 143.3 (C), 145.3 (C), 148.5 (C). m/z (ESI) 397.0768 (M⁺, C₂₁H₁₈I requires 397.0766).


110 (2-(1-Phenylvinyl)phenyl)(p-tolyl)iodonium tetrafluoroborate **110** was obtained from **124** (0.294 g), as a white solid (0.224 g, 79 %). δ_{H} (CDCl₃, 400 MHz,) 2.37 (3H, s, CH₃), 5.43 (1H, d, $^2J_{\text{HH}} = 1.7$ Hz, C=CH₂), 6.06 (1H, d, $^2J_{\text{HH}} = 1.7$ Hz, C=CH₂), 7.11-7.18 (4H, m, ArH), 7.31-7.38 (3H, m, ArH), 7.42 (1H, td, $^3J_{\text{HH}} = 7.9$ Hz, $^4J_{\text{HH}} = 1.4$ Hz, ArH), 7.52 (1H, dd, $^3J_{\text{HH}} = 7.6$ Hz,

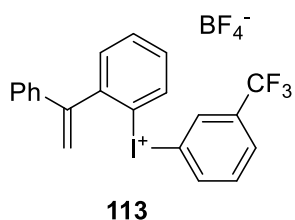
$^4J_{\text{HH}} = 1.8 \text{ Hz}$, ArH), 7.54-7.57 (2H, dd, $^3J_{\text{HH}} = 7.5 \text{ Hz}$, $^4J_{\text{HH}} = 1.2 \text{ Hz}$, ArH), 7.64 (1H, td, $^3J_{\text{HH}} = 7.8 \text{ Hz}$, $^4J_{\text{HH}} = 1.0 \text{ Hz}$, ArH), 7.92 (1H, dd, $^3J_{\text{HH}} = 8.2 \text{ Hz}$, $^4J_{\text{HH}} = 1.0$, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -147.6 (4F, s, BF_4^-). δ_{C} (CDCl_3 , 125 MHz): 21.4 (CH_3), 109.6 (CI), 115.9 (CI), 119.7 (CH_2), 127.1 (CH), 129.3 (CH), 131.6 (CH), 132.1 (CH), 132.8 (CH), 132.9 (CH), 133.8 (CH), 135.6 (CH), 135.7 (CH), 143.9 (C), 145.1 (C), 148.5 (C). m/z (ESI) 397.0768 (M^+ , $\text{C}_{21}\text{H}_{18}\text{I}$ requires 397.0766).



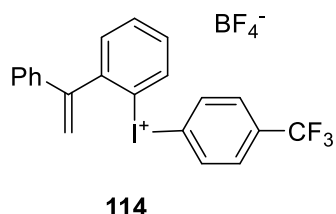
(4-Fluorophenyl)-(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **111** was obtained from **125** (0.281 g) as a white solid (0.163 g, 74 %). δ_{H} (CDCl_3 , 400 MHz) 5.43 (1H, d, $^2J_{\text{HH}} = 1.4 \text{ Hz}$, $\text{C}=\text{CH}_2$), 5.96 (1H, d, $^2J_{\text{HH}} = 1.4 \text{ Hz}$, $\text{C}=\text{CH}_2$), 6.84 (2H, td, $^3J_{\text{HF}} = 8.1 \text{ Hz}$, $^4J_{\text{HH}} = 1.2 \text{ Hz}$, ArH), 7.19-7.28 (2H, dd, $^3J_{\text{HH}} = 7.8 \text{ Hz}$, $^4J_{\text{HH}} = 1.8 \text{ Hz}$, ArH), 7.32-7.38 (3H, m, ArH), 7.56 (2H, m, ArH), 7.60-7.68 (3H, m, ArH), 8.22 (1H, dd, $^3J_{\text{HH}} = 7.0 \text{ Hz}$, $^4J_{\text{HH}} = 1.0 \text{ Hz}$, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -107.1 (1F, s, ArF), -147.3 (4F, s, BF_4^-). δ_{C} (CDCl_3 , 125 MHz) 105.5 (CI), 116.7 (CI), 119.6 (d, $^2J_{\text{CF}} = 23.1 \text{ Hz}$, CH), 119.9 (CH_2), 127.1 (CH), 129.3 (CH x 2), 131.9 (CH), 132.2 (CH), 133.3 (CH), 136.5 (CH), 137.8 (C), 138.3 (d, $^3J_{\text{CF}} = 9.1 \text{ Hz}$, CH), 145.3 (C), 148.3 (C), 165.0 (d, $^1J_{\text{CF}} = 257.5 \text{ Hz}$, CF). m/z (ESI) 401.0202 (M^+ , $\text{C}_{20}\text{H}_{15}\text{IF}$ requires 401.0202).



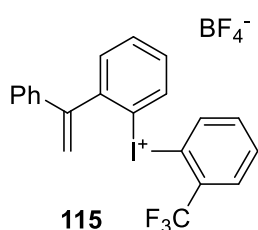
(3-Fluorophenyl)-(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **112** was obtained from **126** (0.215 g) as a white solid (0.129 g, 62 %). δ_{H} (CDCl_3 , 400 MHz) 5.45 (1H, d, $^2J_{\text{HH}} = 1.7 \text{ Hz}$, $\text{C}=\text{CH}_2$), 6.07 (1H, d, $^2J_{\text{HH}} = 1.7 \text{ Hz}$, $\text{C}=\text{CH}_2$), 7.15 (2H, dd, $^3J_{\text{HH}} = 7.8 \text{ Hz}$, $^4J_{\text{HH}} = 1.5 \text{ Hz}$, ArH), 7.23 (1H, td, $^3J_{\text{HH}} = 7.9 \text{ Hz}$, $^4J_{\text{HH}} = 1.4 \text{ Hz}$, ArH), 7.29-7.38 (5H, m, ArH), 7.52-7.59 (3H, m, ArH), 7.71 (1H, t, $^3J_{\text{HH}} = 7.4 \text{ Hz}$, ArH), 8.20 (1H, dd, $^3J_{\text{HH}} = 8.2 \text{ Hz}$, $^4J_{\text{HH}} = 1.0 \text{ Hz}$, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -106.2 (1F, s, ArF), -148.9 (4F, s, BF_4^-). δ_{C} (CDCl_3 , 125 MHz) 111.6 (CI), 116.9 (CI), 119.9 (CH_2), 120.1 (d, $^2J_{\text{CF}} = 20.7 \text{ Hz}$, CH), 122.7 (d, $^2J_{\text{CF}} = 25.2 \text{ Hz}$, CH), 127.1 (CH), 129.2 (CH), 129.3 (CH), 131.3 (CH), 131.9 (CH), 132.3 (CH), 133.1 (CH), 133.5 (CH), 136.9 (CH), 137.8 (C), 145.6 (C), 148.3 (C), 162.5 (d, $^1J_{\text{CF}} = 256.3 \text{ Hz}$, CF). m/z (ESI) 401.0210 (M^+ , $\text{C}_{20}\text{H}_{15}\text{IF}$ requires 401.0202).



(2-(1-Phenylvinyl)phenyl)-(3-(trifluoromethyl)phenyl)-iodonium tetrafluoroborate **113** was obtained from **127** (0.305 g) as a white solid (0.209 g, 72 %). δ_{H} (400 MHz, CDCl_3) 5.42 (1H, d, $^2J_{\text{HH}} = 1.6$ Hz, $\text{C}=\text{CH}_2$), 6.04 (1H, d, $^2J_{\text{HH}} = 1.6$ Hz, $\text{C}=\text{CH}_2$), 7.06 (2H, dd, $^3J_{\text{HH}} = 7.8$ Hz, $^4J_{\text{HH}} = 1.1$ Hz, ArH), 7.19-7.28 (3H, m, ArH), 7.41 (1H, t, $^3J_{\text{HH}} = 8.0$ Hz, ArH), 7.46-7.53 (2H, m, ArH), 7.67-7.73 (3H, m, ArH), 7.97 (1H, d, $^3J_{\text{HH}} = 8.2$ Hz, ArH), 8.28 (1H, d, $^3J_{\text{HH}} = 8.2$ Hz, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -64.25 (3F, s, CF_3), -145.8 (4F, s, BF_4). δ_{C} (CDCl_3 , 125 MHz) 112.4 (CI), 116.9 (CI), 119.9 (CH_2), 122.3 (q, $^1J_{\text{CF}} = 273.7$ Hz, CF_3), 126.8 (CH), 129.1 (CH), 129.2 (CH), 131.7 (CH), 131.9 (CH), 132.3 (CH), 132.4 (CH), 133.5 (q, $^2J_{\text{CF}} = 34.2$ Hz, C), 133.6 (CH), 137.5 (CH), 137.6 (C), 138.8 (CH), 145.6 (C), 148.1 (C). m/z (ESI) 451.0272 (M^+ , $\text{C}_{21}\text{H}_{15}\text{IF}_3$ requires 451.0276).



(2-(1-Phenylvinyl)phenyl)-(4-(trifluoromethyl)phenyl)-iodonium tetrafluoroborate **114** was obtained from **128** (0.337 g) as a white solid (0.225 g, 69 %). δ_{H} (400 MHz, CDCl_3) 5.40 (1H, d, $^2J_{\text{HH}} = 1.5$ Hz, $\text{C}=\text{CH}_2$), 6.04 (1H, d, $^2J_{\text{HH}} = 1.5$ Hz, $\text{C}=\text{CH}_2$), 7.01 (2H, dd, $^3J_{\text{HH}} = 7.2$ Hz, $^4J_{\text{HH}} = 1.4$ Hz, ArH), 7.15-7.26 (3H, m, ArH), 7.38-7.50 (4H, m, ArH), 7.68 (1H, td, $^3J_{\text{HH}} = 7.3$ Hz, $^4J_{\text{HH}} = 1.0$ Hz, ArH), 7.71 (2H, d, $^3J_{\text{HH}} = 8.4$ Hz, ArH), 8.30 (1H, d, $^3J_{\text{HH}} = 8.4$ Hz, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -64.61 (3F, s, CF_3), -145.4 (4F, s, BF_4). δ_{C} (CDCl_3 , 125 MHz) 114.6 (CI), 115.6 (CI), 118.9 (CH_2), 123.3 (q, $^1J_{\text{CF}} = 258.5$ Hz, CF_3), 125.8 (CH), 127.3 (CH), 128.0 (CH x 2), 130.8 (CH), 131.2 (CH), 132.6 (CH), 133.1 (q, $^2J_{\text{CF}} = 33.2$ Hz, C), 134.6 (C), 134.7 (CH), 136.7 (q, $^3J_{\text{CF}} = 14.1$ Hz, CH), 144.7 (C), 147.1 (C). m/z (ESI) 451.0271 (M^+ , $\text{C}_{21}\text{H}_{15}\text{IF}_3$, requires 451.0276).

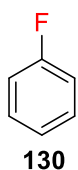


(2-(1-Phenylvinyl)phenyl)-(2-(trifluoromethyl)phenyl)iodonium tetrafluoroborate **115** was obtained from **129** (0.329 g) as a white solid (0.223 g, 70 %). δ_{H} (400 MHz, CDCl_3) 5.94 (1H, d, $^2J_{\text{HH}} = 1.6$ Hz, $\text{C}=\text{CH}_2$), 6.11 (1H, d, $^2J_{\text{HH}} = 1.7$ Hz, $\text{C}=\text{CH}_2$), 7.14 (2H, dd, $^3J_{\text{HH}} = 7.7$ Hz, $^4J_{\text{HH}} = 1.5$ Hz, ArH), 7.29-7.32 (3H, m, ArH), 7.41-7.45 (1H, m, ArH), 7.47-7.49 (1H, dd, $^3J_{\text{HH}} = 7.6$ Hz, $^4J_{\text{HH}} = 1.8$ Hz, ArH), 7.51-7.54 (1H, td, $^3J_{\text{HH}} = 9.3$ Hz, $^4J_{\text{HH}} = 1.3$ Hz, ArH), 7.97 (1H, td, $^3J_{\text{HH}} = 8.5$ Hz, $^4J_{\text{HH}} = 1.0$ Hz, ArH), 7.71-7.79 (3H, m, ArH), 8.12 (1H, d, $^3J_{\text{HH}} = 8.0$ Hz, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -59.4

(3F, s, CF₃), -148.1 (4F, s, BF₄). δ_C (CDCl₃, 125 MHz) 109.8 (CD), 111.6 (CD), 119.7 (CH₂), 122.2 (q, $^1J_{CF}$ = 273.1 Hz, CF₃), 126.1 (q, $^2J_{CF}$ = 36.2 Hz, C), 127.1 (CH x 2), 128.9 (CH), 129.2 (CH), 129.4 (CH), 131.7 (CH), 132.3 (CH), 133.2 (q, $^3J_{CF}$ = 25.9 Hz, CH), 135.3 (CH), 135.7 (CH), 137.4 (C), 140.4 (CH), 144.9 (C), 148.5 (C). m/z (ESI) 451.0272 (M⁺, C₂₁H₁₅IF₃, requires 451.0276).

5.6.8 Fluorination reactions

5.6.9 General procedure A for Table 3.6 (Entry 1)



The diaryliodonium tetrafluoroborate **108** (0.2 mmol) was charged with KF (0.21 mmol), 18-crown-6 (0.08 mmol) and Cu(OTf)₂ (0.04 mmol) into the Schlenk flask in a glove box. The contents were dissolved in anhydrous DMF (5 mL) and heated to 80 °C for 4 hours. After cooling to room temperature, 1-fluoro-3-nitrobenzene (10.6 μ l, 0.10 mmol, 0.5 eq.) was added as an internal standard. After adding DMF (5 mL), the mixture was filtered through a short silica/cotton plug and analysed by ¹⁹F NMR spectroscopy. The formation of fluorobenzene **130** (75 %) along with **131** (3 %) as a 96:4 mixture was determined by ¹⁹F NMR spectroscopy. The ¹⁹F NMR spectrum (δ_F = -113.7 ppm) was in agreement with the literature (δ_F = -114.1 ppm).¹¹⁹

5.7 General procedure B for Table 3.6 (entries 2-3)

An identical procedure to **General procedure A for Table 3.6** was attempted for diaryliodonium salt **108** in the absence of the catalyst at 80 °C for the required time.

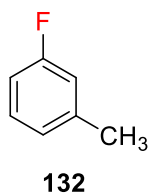
Entry 2: The formation of fluorobenzene **130** (5 %) along with **131** (12 %) as a 29:71 mixture was confirmed by ¹⁹F NMR spectroscopy.

Entry 3: The desired fluorinated compound **130** (7 %) along with **131** (13 %) was obtained as a 35:65 mixture which was confirmed by ¹⁹F NMR spectroscopy.

5.7.1 General procedure A for Table 3.7 (entries 1, 2, and 4)

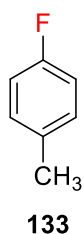
The diaryliodonium tetrafluoroborate **109** and **110** (0.2 mmol) was charged with KF (0.21 mmol), 18-crown-6 (0.08 mmol) and Cu(OTf)₂ (0.04 mmol) into the Schlenk flask in a glove box. The contents were dissolved in anhydrous DMF (5 mL) and heated to 80 °C for either 4 h or 8 h, as required. After cooling to room temperature, 1-fluoro-3-

nitrobenzene (10.6 μ l, 0.10 mmol, 0.5 eq.) was added as an internal standard. After adding DMF (5 mL), the mixture was filtered through a short silica/cotton plug and analysed by ^{19}F NMR spectroscopy.



Entry 1: The formation of *m*-fluorotoluene **132** (46 %) along with **131** (1%) as a 98:2 mixture was determined by ^{19}F NMR spectroscopy. The ^{19}F NMR spectrum ($\delta_{\text{F}} = -114.7$ ppm) was in agreement with the literature ($\delta_{\text{F}} = -115.2$ ppm).¹²¹

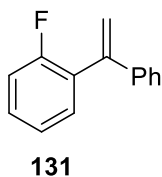
Entry 2: The desired fluorinated compound **132** (70 %) along with **131** (7 %) was obtained as a 91:9 mixture which was confirmed by ^{19}F NMR spectroscopy.



Entry 4: The desired fluorinated product **133** (71 %) along with **131** (8 %) was obtained as a 90:10 mixture which was confirmed by ^{19}F NMR spectroscopy ($\delta_{\text{F}} = -119.4$ ppm), (δ_{F} lit.¹²¹ = -119.5 ppm).

5.7.2 General procedure B for Table 3.7 (entries 3, 5)

An identical procedure to **General procedure A for Table 3.7** was performed for diaryliodonium salts **109** and **110** in the absence of the catalyst for 8 hours.



Entry 3: The compound **131** (58 %) was obtained as the only product which was confirmed by ^{19}F NMR spectroscopy showing a singlet peak ($\delta_{\text{F}} = -113.5$ ppm), (δ_{F} lit. = -113.2 ppm).¹³¹

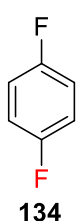
Entry 5: The compound **131** (55 %) was obtained as the only product which was confirmed by ^{19}F NMR spectroscopy.

5.7.3 General procedure A for Table 3.8 (entries 1-4 and 6-7)

The diaryliodonium tetrafluoroborate **111** and **112** (0.2 mmol) was charged with KF (0.21 mmol), 18-crown-6 (0.08 mmol) and $\text{Cu}(\text{OTf})_2$ (0.04 mmol) into the Schlenk flask in a glove box. The contents were dissolved in DMF (5 mL) and heated at the required

temperature and time. After cooling to room temperature, 1-fluoro-3-nitrobenzene (10.6 μ L, 0.10 mmol, 0.5 eq.) was added as an internal standard. After adding DMF (5 mL), the mixture was filtered through a short silica/cotton plug and analysed by ^{19}F NMR spectroscopy.

5.7.4 Characterisation data for General procedure A for **134**, Table 3.8



The formation of 1,4-difluorobenzene **134** (41 %) along with **131** (4 %) as a 91:9 mixture was determined by ^{19}F NMR spectroscopy. The ^{19}F NMR spectrum ($\delta_{\text{F}} = -119.8$ ppm) matched that of an authentic sample ($\delta_{\text{F}} = -120.01$ ppm, Alfa Aesar).

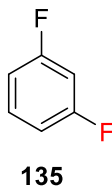
Entry 2: The desired fluorinated product **134** was obtained in (43 %) yield along with (5 %) of **131** as a 90:10 mixture.

Entry 3: The desired fluorinated product **134** was obtained in (38 %) yield along with (6 %) of **131** as a 86:19 mixture.

Entry 4: The desired fluorinated product **134** was obtained in (51 %) yield along with (2 %) of **131** as a 96:4 mixture.

5.7.5 Characterisation data for General procedure A for **135**, Table 3.8 (entries 6 and 7)

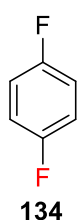
General procedure A for entry 6 was followed using **112** (98.0 mg, 0.2 mmol). The



formation of 1,3-difluorobenzene **135** (7 %) along with (3 %) of **131** as a 98:2 mixture was determined by ^{19}F NMR spectroscopy. The ^{19}F NMR spectrum was in agreement with the literature ($\delta_{\text{F}} = -110.4$ ppm), (δ_{F} lit.¹²⁰ = -110.9 ppm).

Entry 7: The desired fluorinated product **135** (15 %) was obtained along with **131** (1 %) as a 93:7 mixture.

5.7.6 Characterisation data for General Procedure B for **134**, Table 3.8 (entry 5)

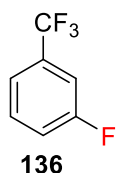


The desired fluorinated compound **134** (1 %) along with **131** (22 %) was obtained as a 50:50 mixture.

5.7.7 General procedure A for Table 3.9 (entries 1-2, 5-6 and 10)

The diaryliodonium tetrafluoroborate **113**, **114** and **115** (0.2 mmol) was charged with KF (0.21 mmol), 18-crown-6 (0.08 mmol) and Cu(OTf)₂ (0.04 mmol) into the Schlenk flask in a glove box. The contents were dissolved in anhydrous DMF (5 mL) and heated to 80 °C for the required time. After cooling to room temperature, 1-fluoro-3-nitrobenzene (10.6 µl, 0.10 mmol, 0.5 eq.) was added as an internal standard. After adding DMF (5 mL), the mixture was filtered through a short silica/cotton plug and analysed by ¹⁹F NMR spectroscopy.

5.7.8 Characterisation data for General Procedure A for **136**, Table 3.9

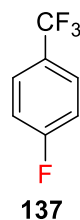


The formation of 3-fluorobenzotrifluoride **136** (35 %) along with **131** (1 %) as a 97:3 mixture was determined by ¹⁹F NMR spectroscopy. The ¹⁹F NMR spectrum was in agreement with the literature ($\delta_F = -111.1$ ppm).¹³²

Entry 2: The desired fluorinated compound **136** was obtained in (63 %) yield along with **131** (8 %) as a 89:11 mixture.

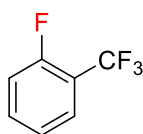
5.7.9 Characterisation data for General Procedure A for **137**, Table 3.9

The formation of 4-fluorobenzotrifluoride **137** (56 %) along with **131** (7 %) as a 89:11 mixture which was determined by ¹⁹F NMR spectroscopy. The ¹⁹F NMR spectrum was in agreement with the literature ($\delta_F = -108.4$ ppm).¹³³



Entry 6: The desired fluorinated compound **137** (51 %) along with **131** (8 %) was obtained as a 86:14 mixture.

5.8 Characterisation data for General Procedure A for 138, Table 3.9

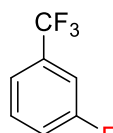


138

The formation of 2-fluorobenzotrifluoride **138** (24 %) along with **131** (2 %) as a 92:8 mixture was determined by ^{19}F NMR spectroscopy, showing the main compound peak at ($\delta_{\text{F}} = -112.5$ ppm).

5.8.1 General procedure B for Table 3.9

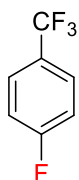
An identical procedure to **General procedure A for Table 3.9** was performed for diaryliodonium salts **113**, **114** and **115** in the absence of the catalyst at 80 °C for the required time (entries 3-4, 7-9, 11-12).



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Entry 3: The desired fluorinated product **136** was obtained in (76 %) along with **131** (13 %) as a 85:15 mixture.

Entry 4: The desired fluorinated product **136** (89 %) along with **131** (2 %) as a 98:2 mixture.



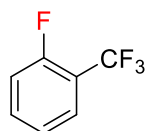
137

Entry 7: The desired fluorinated product **137** was obtained in (60 %) along with **131** (15 %) as a 80:20 mixture.

Entry 8: The desired fluorinated product **137** was obtained in (68 %) along with **131** (3 %) as a 96:4 mixture.

Entry 9: The desired fluorinated compound **137** was obtained in (84 %) as the only product.

Entry 11: The desired product 2-fluorobenzotrifluoride **138** was obtained in (60 %).



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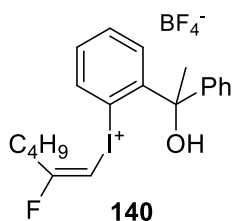
Entry 12: The desired fluorinated compound **138** was obtained in (91 %) yield along with **131** (1 %) as a 99:1 mixture.

5.9 Experimental for Chapter 4

5.9.1 General procedure for the preparation of β -Fluorovinylidonium salts (Scheme 4.12)

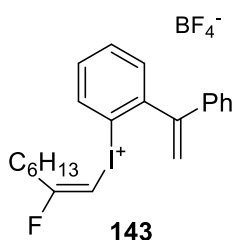
A solution of 1-fluoro-3-methyl-3-phenyl-1,3-dihydro-1,3-benzo[d][1,2]iodaoxole (0.26 g, 0.80 mmol) in DCM (2 mL) was cooled to 0 °C before $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.77 mmol) was added. After 10 min, the alkyne substrate (0.53 mmol) was added and the mixture was stirred at 0 °C for 2 hours. After warming the reaction mixture to room temperature, it was reacted for a further 2 hours. A saturated solution of NaBF_4 (10 mL) was added and the mixture was left to stir for 30 min. After this time, DCM (10 mL) was added and the solution was washed with water (3 x 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over anhydrous MgSO_4 and concentrated under reduced pressure, generating a thick brown oil which was washed with a hexane/chloroform mixture (2:1) (10 mL x 3) (2:1) to give the pure products **140**, **143**, **146**, **149**.

(*E*)-(2-Fluorohex-1-en-1-yl)-(2-(1-hydroxy-1-phenylethyl)phenyl)iodonium tetrafluoroborate **140**



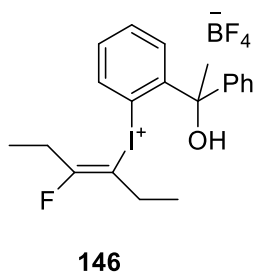
(*E*)-(2-Fluorohex-1-en-1-yl)(2-(1-hydroxy-1-phenylethyl)phenyl)iodonium tetrafluoroborate **140** was obtained as a brown oil (0.209 g, 84 %). δ_{H} (CDCl_3 , 400 MHz) 0.80 (3H, t, $^3J_{\text{HH}} = 7.3$ Hz, CH_3), 1.12 (2H, sextet, $^3J_{\text{HH}} = 7.5$ Hz, CH_2), 1.32-1.42 (2H, m, CH_2), 2.06 (3H, s, CH_3), 2.46-2.51 (2H, dt, $^3J_{\text{HF}} = 22.6$ Hz, $^3J_{\text{HH}} = 7.6$ Hz, CH_2), 6.28 (1H, d, $^3J_{\text{HF}} = 15.7$ Hz, CH), 7.29-7.33 (4H, m, ArH), 7.37-7.40 (1H, dd, $^3J_{\text{HH}} = 7.9$ Hz, $^4J_{\text{HH}} = 1.9$ Hz, ArH), 7.56-7.60 (4H, m, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -58.6 (1F, s, CF), -148.5 (4F, s, BF_4). δ_{C} (CDCl_3 , 125 MHz) 13.4 (CH_3), 21.9 (CH_2), 27.9 (CH_2), 29.8 (CH_3), 31.6 (d, $^2J_{\text{CF}} = 24.1$ Hz, CH_2), 76.9 (d, $^2J_{\text{CF}} = 44.3$ Hz, CH), 78.8 (C), 109.8 (CI), 126.0 (CH), 128.1 (CH), 128.6 (CH), 128.7 (CH), 130.3 (CH), 131.1 (CH), 131.2 (CH), 143.4 (C), 145.4 (C), 178.0 (d, $^1J_{\text{CF}} = 290.7$ Hz, CF). m/z (ESI) 425.0765 (M^+ , $\text{C}_{20}\text{H}_{23}\text{OFI}$ requires 425.0778).

(*E*)-(2-Fluorooct-1-en-1-yl)(2-(1-hydroxy-1-phenylethyl)phenyl)iodonium tetrafluoroborate **143**



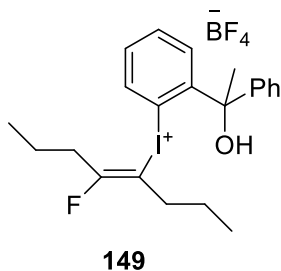
(*E*)-(2-Fluorooct-1-en-1-yl)(2-(1-hydroxy-1-phenylethyl)phenyl)iodonium tetrafluoroborate **143** was obtained as a brown oil (0.244 g, 86 %). δ_{H} (CDCl₃, 400 MHz) 0.82 (3H, t, $^3J_{\text{HH}} = 6.8$ Hz, CH₃), 1.11-1.19 (6H, m, CH₂), 1.41-1.46 (2H, m, CH₂), 2.06 (3H, s, CH₃), 2.43-2.54 (2H, dt, $^3J_{\text{HF}} = 22.0$ Hz, $^3J_{\text{HH}} = 7.5$ Hz, CH₂), 6.28 (1H, d, $^3J_{\text{HF}} = 15.7$ Hz, CH), 7.28-7.34 (5H, m, ArH), 7.36-7.38 (1H, dd, $^3J_{\text{HH}} = 7.0$ Hz, $^4J_{\text{HH}} = 1.8$ Hz, ArH), 7.50-7.57 (3H, m, ArH). δ_{F} (CDCl₃, 376.5 MHz) -58.78 (1F, s, CF), -148.6 (4F, s, BF₄). δ_{C} (CDCl₃, 125 MHz) 13.9 (CH₃), 22.3 (CH₂), 25.8 (CH₂), 28.4 (CH₂), 29.9 (CH₃), 31.3 (CH₂), 31.9 (d, $^2J_{\text{CF}} = 24.1$ Hz, CH₂), 77.9 (d, $^2J_{\text{CF}} = 48.8$ Hz, CH), 78.9 (C), 110.4 (CI), 126.1 (CH), 128.1 (CH), 128.6 (CH), 128.7 (CH), 129.2 (CH), 130.2 (CH), 131.2 (CH), 143.3 (C), 145.3 (C), 177.8 (d, $^1J_{\text{CF}} = 290.8$ Hz, CF). m/z (ESI) 453.1085 (M⁺, C₂₂H₂₇OFl, requires 453.1091).

(*E*)-(4-Fluorohex-3-en-3-yl)(2-(1-hydroxy-1-phenylethyl)phenyl)iodonium tetrafluoroborate **146**



(*E*)-(4-Fluorohex-3-en-3-yl)(2-(1-hydroxy-1-phenylethyl)phenyl)iodonium tetrafluoroborate **146** was obtained as a brown oil (0.165 g, 61 %). δ_{H} (CDCl₃, 400 MHz) 0.92 (3H, t, $^3J_{\text{HH}} = 7.4$ Hz, CH₃), 1.17 (3H, t, $^3J_{\text{HH}} = 7.5$ Hz, CH₃), 2.07 (3H, s, CH₃), 2.54-2.56 (1H, m, CH₂), 2.70-2.76 (3H, m, CH₂), 6.23 (1H, br. s, OH), 7.29-7.32 (2H, m, ArH), 7.34-7.37 (3H, m, ArH), 7.44-7.45 (2H, dd, $^3J_{\text{HH}} = 7.2$ Hz, $^4J_{\text{HH}} = 1.4$ Hz, ArH), 7.54-7.59 (2H, m, ArH). δ_{F} (CDCl₃, 376.5 MHz) -74.2 (1F, s, CF), -149.4 (4F, s, BF₄). δ_{C} (CDCl₃, 125 MHz) 10.9 (CH₃), 13.8 (CH₃), 25.4 (d, $^3J_{\text{CF}} = 5.9$ Hz, CH₂), 27.3 (d, $^2J_{\text{CF}} = 26.2$ Hz, CH₂), 30.0 (CH₃), 77.8 (C), 103.2 (d, $^2J_{\text{CF}} = 32.2$ Hz, C), 108.7 (CI), 126.1 (CH), 128.0 (CH), 128.6 (CH), 128.7 (CH), 130.5 (CH), 131.1 (CH), 131.3 (CH), 143.3 (C), 146.0 (C), 171.8 (d, $^1J_{\text{CF}} = 284.0$ Hz, CF). m/z (ESI) 425.0770 (M⁺, C₂₀H₂₃OFl, requires 425.0778).

(*E*)-(5-Fluorooct-4-en-4-yl)(2-(1-hydroxy-1-phenylethyl)phenyl)iodonium tetrafluoroborate **149**

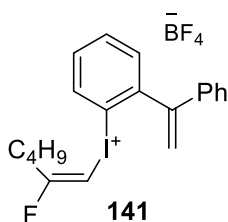


(*E*)-(5-Fluorooct-4-en-4-yl)(2-(1-hydroxy-1-phenylethyl)phenyl)iodonium tetrafluoroborate **149** was obtained as a brown oil (0.206 g, 70 %). δ_{H} (CDCl₃, 400 MHz) 0.82 (3H, t, $^3J_{\text{HH}} = 7.2$ Hz, CH₃), 0.91 (3H, t, $^3J_{\text{HH}} = 7.4$ Hz, CH₃), 1.18-1.26 (2H, m, CH₂), 1.54-1.63 (2H, m, CH₂), 2.06 (3H, s, CH₃), 2.36-2.43 (1H, m, CH₂), 2.61-2.71 (3H, m, CH₂), 7.32-7.34 (2H, m, ArH), 7.36-7.40 (4H, m, ArH), 7.43-7.46 (2H, dd, $^3J_{\text{HH}} = 7.4$ Hz, $^4J_{\text{HH}} = 1.7$ Hz, ArH), 7.58-7.60 (1H, dd, $^3J_{\text{HH}} = 7.1$ Hz, $^4J_{\text{HH}} = 1.8$ Hz, ArH). δ_{F} (CDCl₃, 376.5 MHz) -72.9 (1F, s, CF), -148.6 (4F, s, BF₄). δ_{C} (CDCl₃, 125 MHz) 12.9 (CH₃), 13.3 (CH₃), 20.1 (CH₂), 22.3 (CH₂), 29.9 (CH₃), 33.6 (d, $^3J_{\text{CF}} = 5.0$ Hz, CH₂), 35.4 (d, $^2J_{\text{CF}} = 25.3$ Hz, CH₂), 77.8 (C), 102.1 (d, $^2J_{\text{CF}} = 32.2$ Hz, C), 108.6 (CI), 126.2 (CH), 128.0 (CH), 128.5 (CH), 128.7 (CH), 130.5 (CH), 131.0 (CH), 131.3 (CH), 143.4 (C), 146.0 (C), 171.6 (d, $^1J_{\text{CF}} = 284.8$ Hz, CF). m/z (ESI) 453.1093 (M⁺, C₂₂H₂₇OFI, requires 453.1091).

5.9.2 General procedure for eliminated β -fluorovinylidonium salts (Table 4.3)

A solution of salt (0.4-0.5 mmol) **140**, **143**, **146** and **149** in dichloromethane (2 mL) was cooled to 0 °C before BF₃.Et₂O (7.0 eq.) was added and the reaction mixture was heated to 30 °C for 4 hours. The crude reaction mixture was washed with water (5 mL x 3) and the aqueous extracts were combined and extracted with dichloromethane (10 mL x 3). The combined organic layers were dried over anhydrous MgSO₄ and concentrated under reduced pressure, giving a dark yellow to brown oil which was washed with hexane (5 mL x 3), generating salts **141**, **144**, **147** and **150**.

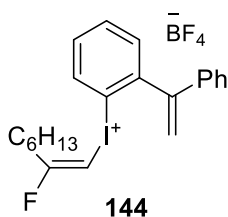
(*E*)-(2-Fluorohex-1-en-1-yl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **141**



(*E*)-(2-Fluorohex-1-en-1-yl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **141** was obtained from **140** (0.209 g) as a dark yellow oil (0.135 g, 67 %). δ_{H} (CDCl₃, 400 MHz) 0.83 (3H, t, $^3J_{\text{HH}} = 7.3$ Hz, CH₃), 1.19-1.29 (2H, m, CH₂), 1.38-1.47 (2H, m, CH₂), 2.53-2.63 (2H, dt, $^3J_{\text{HF}} = 22.0$ Hz, $^3J_{\text{HH}} = 7.4$ Hz, CH₂), 5.48 (1H, s, C=CH₂), 6.07 (1H, s, C=CH₂), 6.32 (1H, d, $^3J_{\text{HF}} = 14.3$ Hz, CH), 7.24-7.26

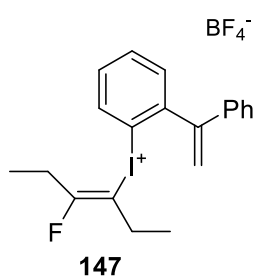
(1H, m, ArH), 7.38-7.40 (4H, m, ArH), 7.51-7.54 (2H, m, ArH), 7.67 (1H, td, $^3J_{\text{HH}} = 8.2$ Hz, 7.9 Hz, $^4J_{\text{HH}} = 1.0$ Hz, ArH), 8.02 (1H, dd, $^3J_{\text{HH}} = 7.8$ Hz, $^4J_{\text{HH}} = 0.8$ Hz, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -63.7 (1F, s, CF), -147.5 (4F, s, BF_4). δ_{C} (CDCl_3 , 125 MHz) 13.6 (CH_3), 22.0 (CH_2), 27.7 (CH_2), 31.9 (d, $^2J_{\text{CF}} = 24.1$ Hz, CH_2), 78.5 (d, $^2J_{\text{CF}} = 47.9$ Hz, CH), 116.2 (C), 119.8 (CH_2), 127.3 (CH), 129.5 (CH), 129.7 (CH), 131.9 (CH), 132.8 (CH), 132.9 (CH), 134.7 (CH), 137.5 (C), 144.7 (C), 148.9 (C), 176.5 (d, $^1J_{\text{CF}} = 287.7$ Hz, CF). m/z (ESI) 407.0675 (M^+ , $\text{C}_{20}\text{H}_{21}\text{FI}$, requires 407.0672).

(*E*)-(2-Fluorooct-1-en-1-yl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate 144



(*E*)-(2-Fluorooct-1-en-1-yl)(2-(1-phenylvinyl)phenyl) iodonium tetrafluoroborate **144** was obtained from **143** (0.244 g) as a dark yellow oil (0.190, 81 %). δ_{H} (CDCl_3 , 400 MHz) 0.86 (3H, t, $^3J_{\text{HH}} = 6.8$ Hz, CH_3), 1.17-1.21 (6H, m, CH_2), 1.56-1.67 (2H, m, CH_2), 2.52-2.61 (2H, dt, $^3J_{\text{HF}} = 22.1$ Hz, $^3J_{\text{HH}} = 7.7$ Hz, CH_2), 5.48 (1H, s, $\text{C}=\text{CH}_2$), 6.06 (1H, s, $\text{C}=\text{CH}_2$), 6.33 (1H, d, $^3J_{\text{HF}} = 14.4$ Hz, CH), 7.24-7.29 (3H, m, ArH), 7.37-7.39 (2H, m, ArH), 7.51-7.55 (2H, d, $^3J_{\text{HH}} = 7.8$, ArH), 7.64-7.68 (1H, td, $^3J_{\text{HH}} = 7.9$ Hz, $^4J_{\text{HH}} = 1.0$ Hz, ArH), 8.01-8.04 (1H, dd, $^3J_{\text{HH}} = 8.9$ Hz, $^4J_{\text{HH}} = 1.1$ Hz, ArH). δ_{F} (CDCl_3 , 376.5 MHz) -63.2 (1F, s, CF), -148.7 (4F, s, BF_4). δ_{C} (CDCl_3 , 125 MHz) 13.9 (CH_3), 22.4 (CH_2), 25.6 (CH_2), 28.6 (CH_2), 31.1 (CH_2), 32.2 (d, $^2J_{\text{CF}} = 23.1$ Hz, CH_2), 78.5 (d, $^2J_{\text{CF}} = 48.3$ Hz, CH), 115.9 (C), 119.7 (CH_2), 127.2 (CH), 129.3 (CH), 129.7 (CH), 131.9 (CH), 132.1 (CH), 132.9 (CH), 134.8 (CH), 137.6 (C), 144.7 (C), 148.8 (C), 176.3 (d, $^1J_{\text{CF}} = 287.9$ Hz, CF). m/z (ESI) 435.0980 (M^+ , $\text{C}_{22}\text{H}_{25}\text{FI}$, requires 435.0985)

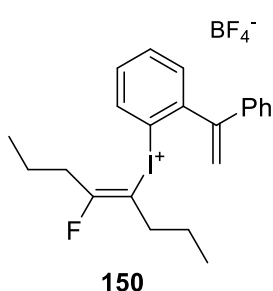
(*E*)-(4-Fluorohex-3-en-3-yl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate 147



(*E*)-(4-Fluorohex-3-en-3-yl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **147** was obtained from **146** (0.165 g) as a dark brown oil (0.126, 79 %). δ_{H} (CDCl_3 , 400 MHz) 0.98 (3H, t, $^3J_{\text{HH}} = 7.3$ Hz, CH_3), 1.12 (3H, t, $^3J_{\text{HH}} = 7.9$ Hz, CH_3), 2.57-2.64 (2H, m, CH_2), 2.67-2.78 (2H, dq, $^3J_{\text{HF}} = 22.2$ Hz, $^3J_{\text{HH}} = 7.5$ Hz, CH_2), 5.48 (1H, s, $\text{C}=\text{CH}_2$), 6.11 (1H, s, $\text{C}=\text{CH}_2$), 7.22-7.25 (2H, m, ArH), 7.39-7.41 (3H, m, ArH), 7.51-7.58 (2H, m, ArH), 7.68-7.72 (1H, td, $^3J_{\text{HH}}$

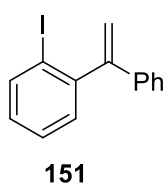
= 8.0 Hz, $^4J_{\text{HH}} = 1.1$ Hz, ArH), 7.82 (1H, dd, $^3J_{\text{HH}} = 8.2$ Hz, $^4J_{\text{HH}} = 0.9$ Hz, ArH). δ_{F} (CDCl₃, 376.5 MHz) -79.5 (1F, s, CF), -148.2 (4F, s, BF₄). δ_{C} (CDCl₃, 125 MHz) 10.5 (CH₃), 13.7 (CH₃), 25.8 (d, $^3J_{\text{CF}} = 5.1$ Hz, CH₂), 27.5 (d, $^2J_{\text{CF}} = 25.6$ Hz, CH₂), 106.7 (d, $^2J_{\text{CF}} = 32.2$ Hz, C), 113.1 (CI), 119.9 (CH₂), 127.1 (CH), 129.5 (CH), 129.9 (CH), 131.8 (CH), 132.6 (CH), 132.9 (CH), 133.4 (CH), 137.2 (C), 145.3 (C), 148.8 (C), 170.6 (d, $^1J_{\text{CF}} = 281.7$ Hz, CF). m/z (ESI) 407.0675 (M⁺, C₂₀H₂₁FI, requires 407.0672).

(*E*)-(5-Fluorooct-4-en-4-yl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **150**



(*E*)-(5-Fluorooct-4-en-4-yl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **150** was obtained from **149** (0.206 g) as a dark brown oil (0.154, 77 %). The product was isolated as a mixture with 1-iodo-2-(1-phenylvinyl)benzene **151**, therefore ^1H and ^{13}C NMR data assignments are not completely accurate since it was difficult to determine which peaks belong to the product due to overlapping peaks. δ_{H} (CDCl₃, 400 MHz) 0.98 (3H, t, $^3J_{\text{HH}} = 7.3$ Hz, CH₃), 1.12 (3H, t, $^3J_{\text{HH}} = 7.9$ Hz, CH₃), 1.41 (2H, sextet, $^3J_{\text{HH}} = 7.4$ Hz, CH₂), 1.62 (2H, sextet, $^3J_{\text{HH}} = 7.5$ Hz, CH₂), 2.57-2.64 (2H, m, CH₂), 2.67-2.78 (2H, dq, $^3J_{\text{HF}} = 22.2$ Hz, $^3J_{\text{HH}} = 7.5$ Hz, CH₂), 5.48 (1H, s, C=CH₂), 6.11 (1H, s, C=CH₂), 7.22-7.25 (2H, m, ArH), 7.39-7.41 (3H, m, ArH), 7.51-7.58 (2H, m, ArH), 7.68-7.72 (1H, td, $^3J_{\text{HH}} = 8.0$ Hz, $^4J_{\text{HH}} = 1.1$ Hz, ArH), 7.82 (1H, dd, $^3J_{\text{HH}} = 8.2$ Hz, $^4J_{\text{HH}} = 0.9$ Hz, ArH). δ_{F} (CDCl₃, 376.5 MHz) -75.9 (1F, s, CF), -147.8 (4F, s, BF₄). δ_{C} (CDCl₃, 125 MHz) 12.7 (CH₃), 13.5 (CH₃), 19.8 (CH₂), 22.0 (CH₂), 33.8 (CH₂), 35.5 (d, $^2J_{\text{CF}} = 25.2$ Hz, CH₂), 103.1 (d, $^2J_{\text{CF}} = 31.9$ Hz, C), 110.9 (CI), 119.7 (CH₂), 123.0 (CH), 127.0 (CH), 128.4 (CH), 128.9 (CH), 129.1 (CH), 129.4 (CH), 129.5 (CH), 136.6 (C), 140.1 (C), 145.4 (C), 172.2 (d, $^1J_{\text{CF}} = 281.7$ Hz, CF). m/z (ESI) 435.0980 (M⁺, C₂₂H₂₅FI, requires 435.0985).

1-Iodo-2-(1-phenylvinyl)benzene **151**



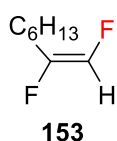
The byproduct **151** was obtained as a mixture with (*E*)-(5-fluorooct-4-en-4-yl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **150** in trace amount. δ_{H} (CDCl₃, 400 MHz) 5.16 (1H, s, C=CH₂), 5.77 (1H, s, C=CH₂), 7.18 (1H, td, $^3J_{\text{HH}} = 7.8$ Hz, $^4J_{\text{HH}} = 1.4$ Hz, ArH), 7.18-7.24 (6H, m, ArH), 7.32 (1H, t, $^3J_{\text{HH}} = 7.0$ Hz, ArH), 7.81 (1H, d, $^3J_{\text{HH}} = 8.1$ Hz, ArH). δ_{C} (CDCl₃, 125 MHz)

99.0 (CI), 117.0 (CH₂), 126.9 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH), 129.0 (CH), 130.7 (CH), 139.2 (C), 139.6 (CH), 146.6 (C), 152.6 (C). *m/z* (ASAP) 307.0023 (MH⁺, C₁₄H₁₂I, requires 306.9984).

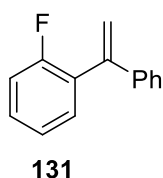
5.9.3 Procedure for Table 4.4

The β -fluorovinylidonium **144** (0.107 g, 0.2 mmol) was charged with KF (0.013 g, 0.22 mmol), 18-crown-6 (0.08 mmol) and Cu(OTf)₂ (0.011 g, 0.04 mmol) in a glove box. The contents were dissolved in DMF (5 mL) and heated to 80 °C for 4 hours (**Table 4**). After cooling to room temperature, 1-fluoro-3-nitrobenzene (10.5 μ l, 0.10 mmol, 0.5 eq.) was added as an internal standard. After adding DMF (5 mL), the mixture was filtered through a short silica/cotton plug and analysed by ¹⁹F NMR spectroscopy.

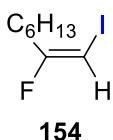
5.9.4 Characterisation Data for Table 4.4



The desired fluorinated compound **153** (15%) along with **131** (13 %) was obtained as a 54:46 mixture which was confirmed by ¹⁹F NMR spectroscopy. (δ_F = -159.9 ppm, d, ³*J*_{FF} = 126.8 Hz, 1F), (-183.3 ppm, d, ³*J*_{FF} = 127.2 Hz, 1F).



The compound **131** was obtained in (13 %) yield which was confirmed by ¹⁹F NMR spectroscopy showing a singlet peak (δ_F = -113.5 ppm), (δ_F lit. = -113.2 ppm).¹³¹



The compound **154** was obtained in (27 %) which was confirmed by ¹⁹F NMR spectroscopy. (δ_F = -82.4 ppm, td, ³*J*_{HF} = 23.1 Hz, ³*J*_{HF} = 18.6 Hz).

Appendix

Crystal Data and Structure Refinements



Table 1 *Crystal Data and Structure Refinement for 73, 74, 79, 81*

	73	74	79	81
Formula	C ₁₁ H ₁₁ FO ₂	C ₁₁ H ₁₂ O ₃	C ₁₁ H ₁₁ FO ₂	C ₁₆ H ₁₃ FO ₂
Formula weight	194.20	192.21	194.20	256.26
Crystal system	Monoclinic	Orthorhombic	Orthorhombic	Orthorhombic
Space group	P2(1)/c	Pna2(1)	P2(1)2(1)2(1)	P2(1)2(1)2(1)
Unit cell dimensions				
<i>a</i> (Å)	5.560(5)	10.1019(17)	5.605(2)	6.0608(17)
<i>b</i> (Å)	7.747(7)	9.4796(16)	7.129(3)	13.108(4)
<i>c</i> (Å)	22.119(19)	9.9375(17)	24.013(9)	15.544(4)
α (°)	90	90	90	90
β (°)	91.199(16)	90	90	90
γ (°)	90	90	90	90
<i>U</i> (Å ³)	952.4(14)	951.6(3)	959.4(6)	1234.9(6)
Temperature (K)	150(2)	150(2)	150(2)	150(2)
<i>Z</i>	4	4	4	4
<i>D_c</i> (Mg m ⁻³)	1.354	1.342	1.344	1.378
μ (Mo-K α) (mm ⁻¹)	0.105	0.097	0.104	0.100
<i>F</i> (000)	408	408	408	536
Dimensions (mm ³)	0.31 x 0.15 x 0.13	0.46 x 0.22 x 0.19	0.46 x 0.27 x 0.08	0.30 x 0.18 x 0.10
Data collection range (°)	1.84 – 26.00	2.95 – 26.00	1.70 – 25.98	2.03 – 26.00
Index ranges	-6 ≤ <i>h</i> ≤ 6 -9 ≤ <i>k</i> ≤ 9 -27 ≤ <i>l</i> ≤ 26	-12 ≤ <i>h</i> ≤ 12 -11 ≤ <i>k</i> ≤ 11 -12 ≤ <i>l</i> ≤ 12	-6 ≤ <i>h</i> ≤ 6 -8 ≤ <i>k</i> ≤ 8 -29 ≤ <i>l</i> ≤ 29	-7 ≤ <i>h</i> ≤ 7 -16 ≤ <i>k</i> ≤ 16 -19 ≤ <i>l</i> ≤ 19
Reflections	6281	6947	7366	9582
Unique reflections (<i>R</i> _{int})	1872 (0.1163)	994 (0.0715)	1877 (0.0587)	2429 (0.0735]
θ_{\max} (% complete)	26.00 (99.9)	26.00 (99.9)	25.98 (100.0)	26.00 (99.9)
Absorption correction	Empirical	Empirical	Empirical	Empirical
Max/min transmission	0.970 / 0.060	0.981 / 0.440	0.983 / 0.564	0.928 / 0.660
Data/restraints/parameters	1872 / 0 / 128	994 / 1 / 128	1877 / 0 / 128	2429 / 0 / 172
Goodness of fit on <i>F</i> ²	0.934	1.035	1.086	1.100
Final <i>R</i> indices [<i>I</i> > 2 σ (<i>I</i>)]				
<i>R</i> ₁	0.0756	0.0378	0.0478	0.0725
<i>wR</i> ₂	0.1612	0.0851	0.1044	0.1680
<i>R</i> indices (all data)				
<i>R</i> ₁	0.1177	0.0415	0.0563	0.0945
<i>wR</i> ₂	0.1789	0.0865	0.1075	0.1778
Largest diff. peak, hole (eÅ ⁻³)	0.334 and -0.324	0.204 and -0.175	0.179 and 0.142	0.589 and -0.235

Table 2 *Crystal Data and Structure Refinement for 109, 111, 112, 113*

	109	111	112	113
Formula	C ₂₁ H ₁₈ BF ₄ I	C ₂₀ H ₁₅ BF ₅ I	C ₂₀ H ₁₄ BF ₅ I	C ₂₁ H ₁₅ BF ₇ I
Formula weight	484.06	488.03	487.02	538.04
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Triclinic
Space group	P2(1)/n	P2(1)/n	P2(1)2(1)2(1)	P-1
Unit cell dimensions				
<i>a</i> (Å)	15.926(13)	14.952(9)	8.064(3)	9.080(4)
<i>b</i> (Å)	14.481(12)	7.362(4)	10.141(3)	14.623(6)
<i>c</i> (Å)	18.191(15)	18.122(11)	22.303(7)	16.153(7)
α (°)	90	90	90	98.724(7)
β (°)	110.477(15)	100.846(10)	90	90.024(7)
γ (°)	90	90	90	97.884(7)
<i>U</i> (Å ³)	3930(6)	1959(2)	1823.8(10)	2099.2(15)
Temperature (K)	150(2)	150(2)	150(2)	150(2)
<i>Z</i>	8	4	4	4
<i>D_c</i> (Mg m ⁻³)	1.636	1.681	1.774	1.702
ρ (Mo-Kα) (mm ⁻¹)	1.668	1.681	1.806	1.591
<i>F</i> (000)	1904	952	948	1048
Dimensions (mm ³)	0.33 x 0.07 x 0.05	0.47 x 0.23 x 0.21	0.47 x 0.07 x 0.04	0.48 x 0.18 x 0.05
Data collection range (°)	1.47 - 26.00	1.62– 26.00	1.83 – 26.00	1.28 - 26.00
Index ranges	-19 ≤ <i>h</i> ≤ 19 -17 ≤ <i>k</i> ≤ 17 -21 ≤ <i>l</i> ≤ 22	-18 ≤ <i>h</i> ≤ 18 -9 ≤ <i>k</i> ≤ 9 -21 ≤ <i>l</i> ≤ 22	-9 ≤ <i>h</i> ≤ 9 -12 ≤ <i>k</i> ≤ 12 -27 ≤ <i>l</i> ≤ 27	-11 ≤ <i>h</i> ≤ 11 -17 ≤ <i>k</i> ≤ 18 -19 ≤ <i>l</i> ≤ 19
Reflections	29816	14576	14407	16456
Unique reflections (<i>R</i> _{int})	7705 (0.3778)	3839 (0.1757)	3581 (0.1329)	8116 (0.0515)
θ _{max} (% complete)	26.00 (99.8)	26.00 (99.9)	26.00 (100.0)	26.00 (98.7)
Absorption correction	Empirical	Empirical	Empirical	Empirical
Max/min transmission	0.894 / 0.371	0.875 / 0.383	0.894 / 0.592	0.894 / 0.679
Data/restraints/parameters	7705 / 445 / 489	3839 / 2 / 244	3581 / 0 / 253	8116 / 24 / 541
Goodness of fit on <i>F</i> ²	0.948	1.003	0.884	0.987
<i>R</i> ₁	0.1078	0.0632	0.0596	0.0486
<i>wR</i> ₂	0.1601	0.1305	0.0865	0.1069
R indices (all data)				
<i>R</i> ₁	0.2692	0.0884	0.1013	0.0700
<i>wR</i> ₂	0.2084	0.1440	0.0972	0.1150
Largest diff. peak, hole (eÅ ⁻³)	1.368 and - 1.047	1.093 and -1.184	0.745 and -0.654	1.915 and -0.807

7.0 References

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