Synthesis and Fluorination of Diaryliodonium Salts

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By

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Ahmed Abudken

The introduction of a fluorine atom into pharmaceutical compounds helps to change pharmacokinetic properties such as lipophilicity, pK_a/pK_b, metabolic stability and conformation. Many pharmaceutical molecules contain aromatic rings, so finding ways to fluorinate aryl moieties is crucial. Recently, hypervalent iodine(III) compounds showed great promise in a variety of transformations. More specifically, diaryliodonium salts are used widely in the fluorination of aromatic compounds because they are excellent leaving groups with high electrophilic properties which facilitate the fluorination of aryl moieties.

In chapter two a series of novel unsymmetrical diaryliodonium salts are reported which were synthesized in high yields under mild reaction conditions. The protocol was achieved through reaction of fluoroiodane **1.22** with an activated aromatic under acidic conditions. Generally, the new salts contain a sidearm with a hydroxyl group and two methyl groups. The fluoroiodane **1.22**, which has two methyl groups, used in this chapter was prepared via a multi-stage reaction pathway which gave high yields in each step following Stuart's protocol.

In chapter three, a new cyclic hypervalent iodine(III) reagent **3.5** is reported which was prepared by a five step synthesis. The new reagent **3.5** contained a methyl and phenyl group in the sidearm instead of two methyl groups which are in the orginal fluoriodane reagent **1.22**. The fluoroiodane **3.5** was also reacted with a series of activated aromatics under the same conditions as in chapter 2 in order to prepare a new class of unsymmetrical diaryliodonium salts. Generally, it was found that **3.5** was more reactive than **1.22** in terms of yields. In addition, when **3.5** was used, the diaryliodonium salt dehydrated easily in the presence of triflic acid to form an alkene sidearm.

In chapter four the new salts were fluorinated with KF in DMF in the presence or absence of a copper catalyst. Interestingly, the fluorination of diaryliodonium salts having a hydroxy group in the sidearm was unsuccessful due to the strong interaction between the oxygen atom of the hydroxyl group with the iodine(III) centre. However, moderate to high yields of the desired fluorinated products were obtained in the fluorination of the diaryliodonium salt which contained an alkene sidearm.

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Statement

This work is based on work conducted by the author in the department of chemistry at the University of Leicester, during the period between July 2015 and June 2018. The work has not been submitted, and is not presently being submitted, for any other degree at this or any other university. All experimental work described in this thesis is original unless otherwise acknowledged in the text or by references.

Signed: Date: / /

Ahmed M. Abudken

Contents

Abbreviations

1,2-DCE	1,2-Dchloroethane
^{18}F-DOPA	^{18}F-fluorodopamine
18-C-6	18-crown-6 ether
Å	Angstroms
Ar	Aryl
ASAP	Atmospheric Solid Analysis Probe
br	broad peak
Bu	Butyl
d	doublet
DCM	Dichloromethane
dd	doublet of doublets
DIPEA	N,N-diisopropyl ethylamine
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl sulfoxide
dt	doublet of triplets
EAS	Electrophilic aromatic substitution
EDG	Electron donating groups
eq.	equivalents
ESI	Electrospray Ionization
Et_2O	Diethyl ether
FAB	Fast Atom Bombardment
F-TEDA	Selectofluor
g	gram
GC	Gas Chromatography

h	hour
HFIP	Hexafluoro-2-propanol
Hz	Hertz
iPr	isopropyl
j	Coupling Constant
m-CPBA	meta-Chloroperoxybenzoic acid
Me	Methyl
MeCN	acetonitrile
MeOH	Methanol
mp	Melting point
Ms	Mass spectroscopy
NMR	Nuclear Magnetic Resonance
mol	moles
MOMCl	Methyl Chloromethyl ether
MS	Mass Spectrometry
m/z	mass/charge ratio
NBS	N-Bromosuccinimide
OAc	acetate
ºC	degrees centigrade
OH	hydroxy
PET	Positron Emission Tomography
Ph	Phenyl
ppm	parts per million
q	quartet
RT	Room temperature
s	singlet
t	triplet

td	triplet of doublets
TBAF	Tetra-n-butylammonium fluoride
TEMPO	2,2,6,6,-tetramethylpiperidine
TFA	Trifluoroacetic acid
TfOH	Triflic acid
THF	tetrahydrofuran
TFE	trifluoroethanol
TMP	Trimethoxyphenyl
TREAT-HF	Hydrogen fluoride trimethylamine ($Et_3N.3HF$)
TsOH	*p*-Toluenesulfonic acid
α	alpha
β	beta
δ	delta (NMR chemical shift)
μ	mu

Chapter One: Introduction

1.1 Fluorine in medicinal chemistry

Fluorine chemistry began in the 19th century, and now plays a vital role in the pharmaceutical[1] agrochemical[2] and materials industries,[3] as well as in the generation of radiotracers for positron emission tomography (PET).[4] For this reason, there is considerable interest in finding new and more efficient routes to introduce fluorine into organic molecules.

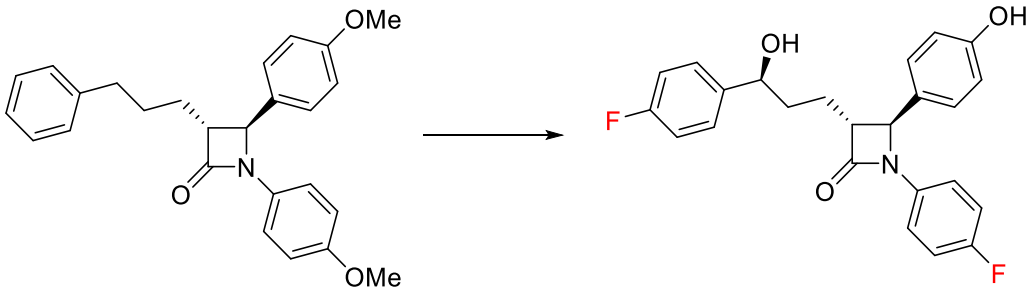
The importance of fluorine in the pharmaceutical industry is demonstrated by the fact that 25-30 % of drugs have at least one fluorine atom. The presence of fluorine can influence the pharmacological properties of a molecule, such as an increase or a decrease of its lipophilicity and pKa, as well as the potential to prevent metabolic oxidation pathways.[5]

Changing the pKa of a molecule can strongly modify the binding affinity and the pharmacokinetic properties of a pharmaceutical by affecting the absorption process. This is of importance to orally administered drugs as intravenously administered drugs have a bioavailability (the percentage of the dose reaching the circulatory system) of 100% as they are injected straight into the circulatory system. Orally administered drugs have to pass through the stomach before reaching the blood stream, which means they come into contact with the acidic conditions in the stomach (~pH 1.5-3.5). In order for the drug to have a useful bioavailability, it must resist the physiological pH in the stomach long enough for a sufficient dose to transfer. Thus, the ability to modulate the acidity or basicity of a molecule is a vital property and can be achieved by the inclusion of organofluorine bonds.[6]

Lipophilicity is expressed as a partition coefficient (log P) between octanol and water. For a drug molecule to pass through a cell membrane, lipophilicity must be such that it can pass into the lipid core but not become trapped in it. The Lipinski ‘‘rule-of-5’’, a set of empirical rules used as a guide to predicting good drug candidates, states that a log P > 5 will give poor absorption.[7] However, excess lipophilicity is a common cause of poor solubility, leading to erratic and incomplete absorption following oral administration. Substitution of a fluorine containing moiety, such as a CF_3 group, into a drug candidate molecule will increase the lipophilicity in such a way that the drug can permeate membranes, such as the blood/brain barrier, providing it meets the size requirements.[8]

However, lipophilicity is not always increased by the presence of fluorine. Fluorination of saturated alkyl groups/chains will decrease lipophilicity due to the strong electron withdrawing effects whilst it is increased in aromatic compounds as a result of efficient orbital overlap between the 2s and 2p orbitals on the fluorine with neighbouring carbon atoms. This reduces polarizability of the C-F bond thereby increasing the lipophilicity of a molecule.[6] The ability to modify the lipophilicity of a molecule by adding fluorine to the molecules is being utilised in many drugs such as leukotriene receptor inhibitors. These drugs help reduce bronchoconstriction for asthma sufferers and have been found to have a 10 fold increase in potency when fluoro amide substituents were added.[9]

The replacement of a C-H bond by a C-F bond prevents metabolism by the liver cytochrome P450 monooxygenase. This important group of enzymes account for 75 % of metabolism and reduce the biological half-life of a drug and facilitate excretion. There are several examples that provide evidence that the replacement of a C-H with a C-F bond increases metabolic stability, such as Ezetimibe a cholesterol absorption inhibitor.[10] The strategic incorporation of fluorine was used to block sites of metabolism (Figure 1.1). Introduction of fluorine atoms prevent oxidation of the phenyl rings to phenol.[11] The increased metabolic stability from the incorporation of two fluorine atoms was a vital component in producing a 55 fold increase in potency for this cholesterol inhibitor.[12]



1.1 **1.2**

***Figure 1.1**: Development of Ezetimibe by blocking sites of metabolism with fluorine*

The fluorination of steroids has been valuable, especially in the anti-inflammatory field. For example, Dexamethasone **1.3** and Triamcinolone **1.4** (Figure 1.2) have been shown to be more effective than cortisol and cortisone in the treatment of rheumatoid arthritis. These 9α- fluorosteroids have displayed higher anti-inflammatory action with less sodium retention.[13]

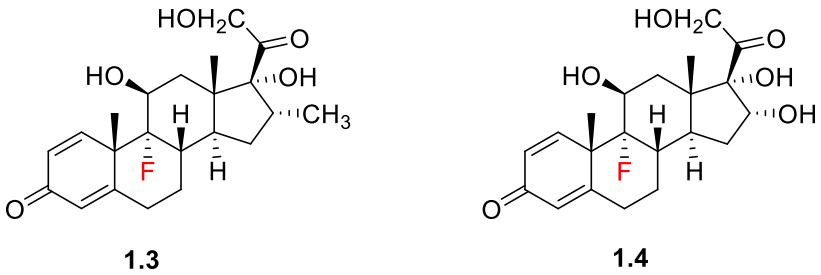
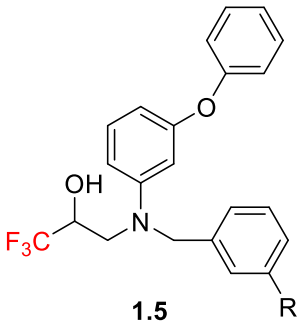


***Figure 1.2**: Dexamethasone **1.3** and Triamcinolone **1.4** structures*

A fluorine substituent can also lead to a change in the preferred molecular conformation, which can be explained by the size and electronegativity of fluorine. Therefore, the effect of fluorine substitution on molecular conformation is quite subtle and sometimes difficult to predict. However, based on the van der Waals radius of 1.47 Å for fluorine, the volume of a trifluoromethyl group is roughly twice that of a methyl group. The cholesteryl ester protein **1.5** is involved in coronary heart disease, playing a vital role in the transfer of cholesteryl ester from high to low density lipoprotein. When the R group was changed from a non-fluorinated ethoxy group to a tetrafluoroethyl group (Figure 1.3), an 8 fold increase in potency was observed.[6]



1.5

R = OCH_2CH_2H

R = OCF_2CF_2H

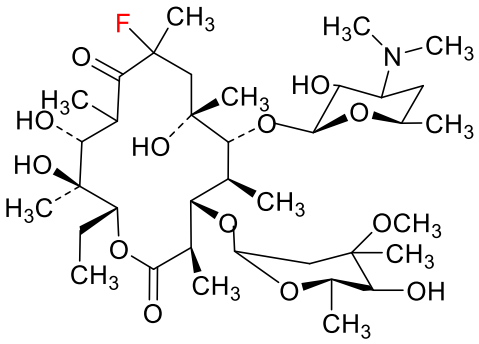
Figure 1.3**: Cholesteryl ester transfer protein inhibitor **1.5

The benefits of fluorine chemistry are nowadays well established and provides opportunities in drug design. In the 1970s there were only about 2 % of fluorine-containing drugs on the market, while the current number has grown to more than 25 %.[14] Recent survey showed that there are several fluorine containing drugs are among the most-prescribed and profitable in the U.S. pharmaceutical market.[5] Some examples of popular fluorinated drugs are shown in Figure 1.4.

Erythromycin is an antibiotic drug which is used widely to treat patients who have penicillin allergies. However, this antibiotic is inappropriate for the treatment of gastritis caused by Helicobacter pylori infection, because Erythromycin is affected and decomposes under the acidic conditions in the stomach.[6] Flurithromycin **1.6** (Figure 1.4 a), a fluorinated analogue of Erythromycin, was produced by adding a fluorine atom alpha to the ketone functionality resulted in better bioavailability, longer biological half-life and higher tissue concentrations *in vivo*.[15]

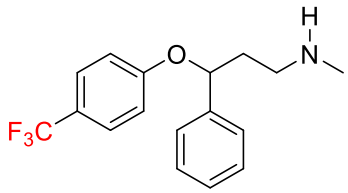
The antidepressant Fluoxetine (Prozac) **1.7** (Figure 1.4 b) is another important drug used successfully in the treatment of bulimia disease and obsessive-compulsive disorder (OCD). Recent studies displayed that depression is caused by low levels of serotonin (5-HT). Fluoxetine **1.7** acts by selectively inhibiting the reuptake of serotonin, allowing the neurotransmitter to activate specific receptors. Significantly, the presence of a trifluoromethyl group in the *para* position of the phenolic ring increased the activity

toward inhibiting serotonin uptake by 6-fold, in comparison with the non-fluorinated compound.[16]



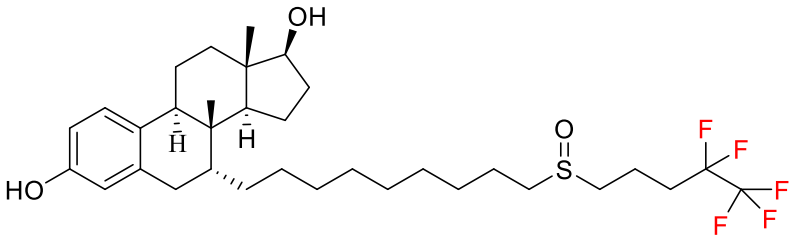
1.6

a) Flurithromycin



1.7

b) Fluoxetine (Prozac)



1.8

c) Faslodex

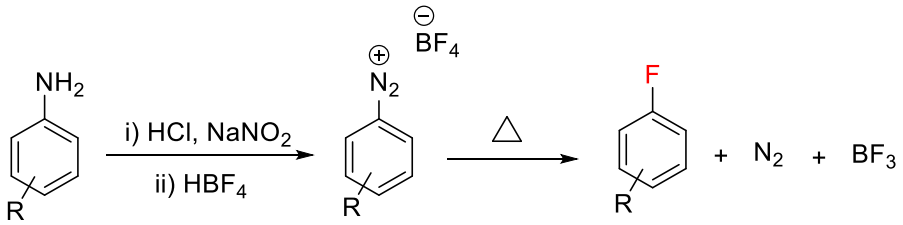
***Figure 1.4**: Popular fluorinated drugs*

The drug Tamoxifen has been used for the treatment of hormone-dependent breast cancer successfully since the 1970s. Tamoxifen is an oestrogen antagonist in breast tissue, but it acts as an oestrogen agonist in the endometrium and bones. Consequently, reductions in oestrogen due to Tamoxifen might lead to an increased risk of, for example, endometrial cancer which is considered the main side effect of this drug. Faslodex **1.8** (Figure 1.4 c) is a pentafluorinated 7α-alkylsulfinyl analogue of 17β-oestradiol that has been developed to avoid the side effects of Tamoxifen. The new drug works as an antagonist oestrogen receptor without any negative side effects.[17]

1.2 Current techniques for the fluorination of aromatic compounds.

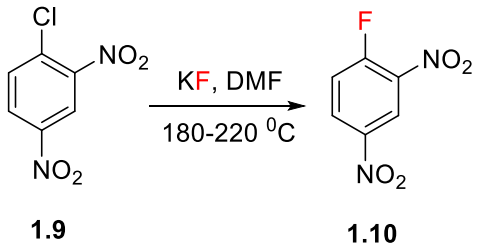
The characteristics of the fluorine atom, its size and unique electronic properties, provide peculiar biological properties to aromatic fluorides. The main problem is that it is very difficult to synthesis the Ar-F bond efficiently and in high yields.[18] In 1927, Balz and Schiemann introduced the first nucleophilic fluorination of aromatics by thermal decomposition of aryl diazonium tetrafluoroborate salts.[19]

This method, which was used in industry, involved the conversion of primary aromatic amines into their diazonium salts (Scheme 1.1) followed by the controlled decomposition of this salt by heat to yield Ar-F with nitrogen and boron trifluoride (toxic) as the side-products. [19] However, this reaction needs harsh conditions such as high temperature along with the need to isolate potentially explosive diazonium salts.[20]



***Scheme 1.1**: Fluorination of aromatic compound through diazotisation reaction.*

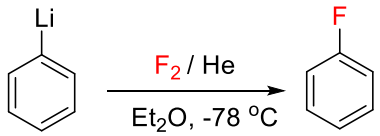
Halogen-exchange reaction (Halex) was also very important technique to introduce a fluorine atom on an aromatic compound. This reaction is used on an industrial scale to produce many fluoroaromatic compound such as 2,4-difluoroaniline and 2,6-difluorobenzonitrile.[21] In this reaction, halogens (mostly chlorine arenes) that are activated towards nucleophilic substitution by electron-deficient groups are exchanged against fluoride at high temperature (> 200 ^{0}C) to produce the corresponding fluoroaromatics in moderate to good yields (Scheme 1.2).[22] However, the substrate scope of this reaction was limited due to the need for strong electron-deficient group on the starting materials.



1.9 **1.10**

Scheme 1.2*: *the halogenation exchange of 2,4-dinitrochlorobenzene

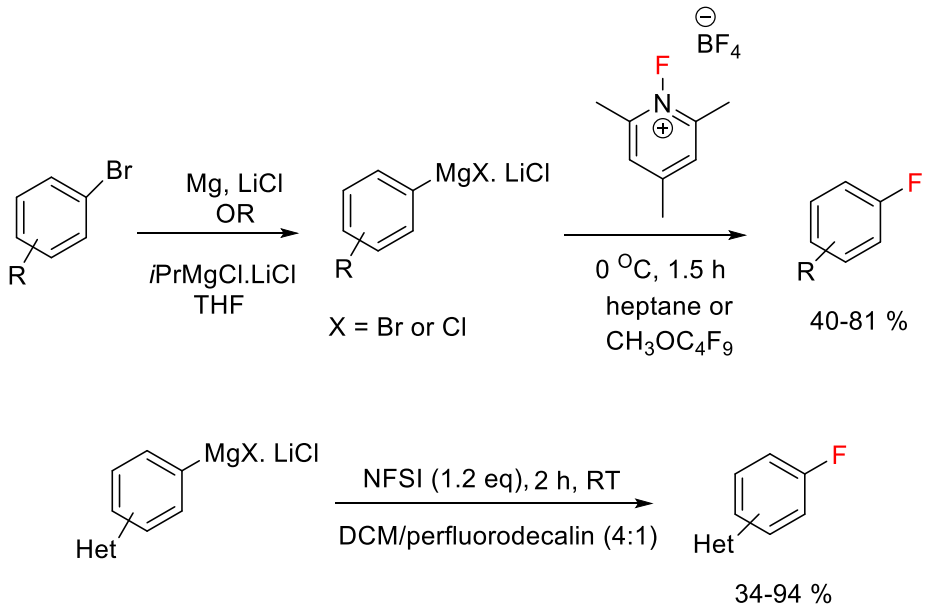
The development of many other routes to aryl fluorides have been made. Transition-metal organometallic compounds can be fluorinated electrophilically to afford aryl fluorides. Aryl metal reagents such as Aryl- Sn,[23] -Hg,[24] -Ge,[25] -Si,[26] and -Pb [27], can easily react with fluorine gas, XeF_2, hypofluorites, and fluoroxysulfates to produce fluorinated arenes. However, the substrate scope here is limited and selectivity to the fluorinated products is poor, due to the high reactivity of the reagents, which are major drawbacks to these routes. In contrast, reagents with highly electropositive metals such as lithium can react with less reactive electrophilic fluorinating reagents, such as F_2 gas (diluted with helium) to afford fluorinated arenes (Scheme 1.3).[28]



1.11 42 % **1.12**

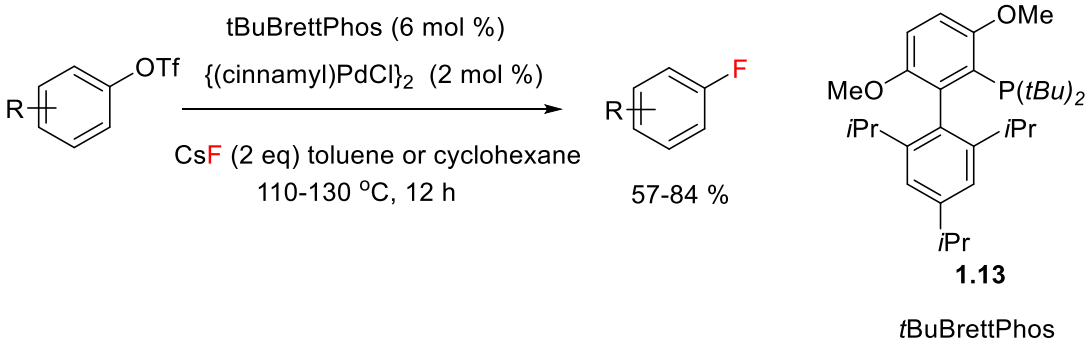
***Scheme 1.3:** Preparation of aryl fluoride from aryl lithium*

Alternatively, the reaction of Grignard reagents with N-F reagents is a good method to form Ar-F bonds with simple aryl nucleophiles (Scheme 1.4).[29] However, the basicity and nucleophilicity of the aryl magnesium reagents is a major limitation of this approach.[30]



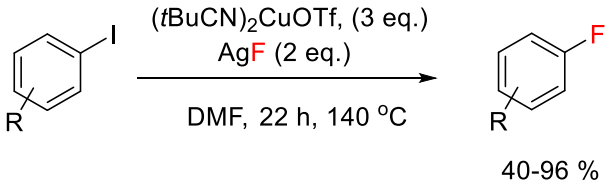
***Scheme 1.4**: Fluorination of Grignard reagents*

Transition-metal-catalysed cross-coupling with fluoride as a nucleophile has been reported. Buchwald and co-workers,[31] developed a new route for the fluorination of aryl triflates mediated by palladium catalysis (Scheme 1.5). They used the bulky monodentate phosphine ligand, ^{t}BuBrettPhos **1.13**, which is crucial for the C-F reductive elimination step in the catalytic cycle involving a mononuclear, tricoordinate palladium (II) complex.[32] This route displays a broad substrate scope in good yields (57-84 %).



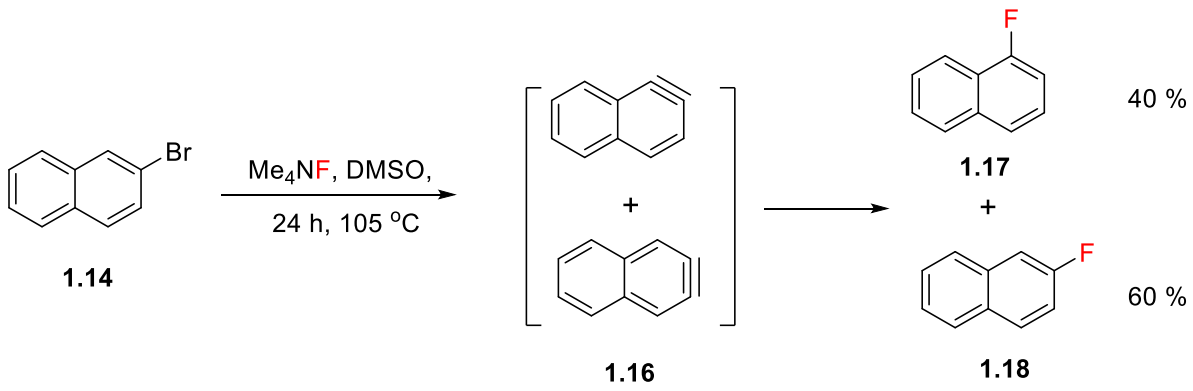
***Scheme 1.5**: Pd-catalyzed cross-coupling of aryl triflates.*

Hartwing and Fier developed a simple fluorination of aryl iodides with readily available reagents. This reaction was applied to a range of aromatic containing functional groups such as aldehyde, amide, ether, ester, and ketone as well as with some heterocyclic systems (Scheme 1.6). High yields (40-96 %) with sterically hindered aryl iodides were obtained. The proposed mechanism for this reaction includes an oxidative addition to produce a Cu(III) intermediate followed by C−F reductive elimination from an aryl-copper(III) fluoride.[33]



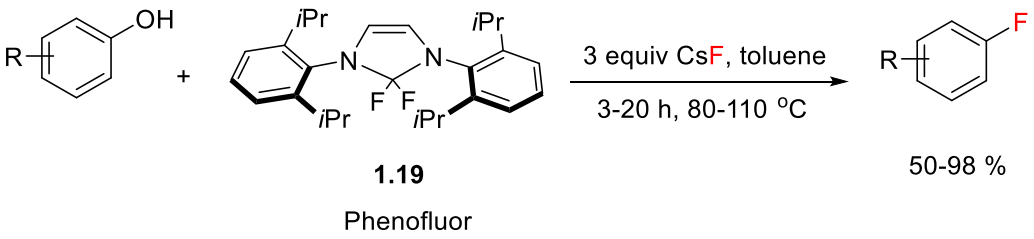
***Scheme 1.6**: Fluorination of aryl iodides.*

Aryl fluorides can also be prepared from the reaction of aryl bromides with anhydrous tetramethylammonium fluoride (Me_4NF) **1.15** in the presence of DMSO as the solvent. However, the reaction occurs through fluoride trapping of aryne intermediates **1.16**, produced from the elimination of the bromide with Me_4NF and, thus, a mixture of constitutional isomers (Scheme 1.7) is generated.[34]



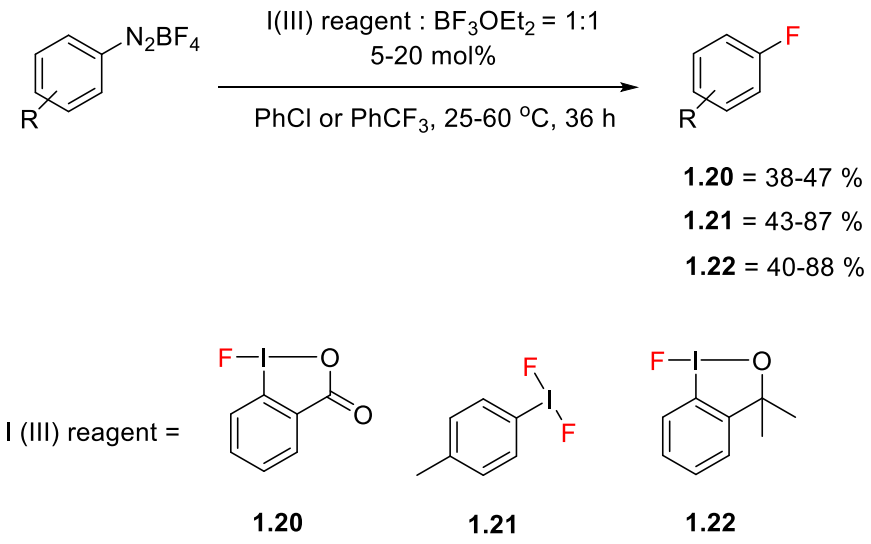
***Scheme 1.7**: Fluorination of Ar-Br via aryne intermediates.*

Ritter and co-workers have developed a route for *ipso*-deoxyfluorination of phenols by the reaction with the commercially available difluoroimidazoline reagent Pheno-Fluor **1.19** and CsF in the presence of toluene as the solvent. Electron-rich, neutral, and electron-poor aryl fluorides as well as heteroaromatic fluorides can be prepared from the corresponding phenol precursors (Scheme 1.8).[35]



***Scheme 1.8**: Deoxyfluorination of phenols with PhenoFluor.*

Recently, Hu and co-workers have developed an unprecedented hypervalent iodine(III) catalysed Balz-Schiemann reaction, where the fluorination was achieved under mild conditions (25-60 °C), and features a wide substrate scope and good functional group compatibility (Scheme 1.9).[36]



***Scheme 1.9**: Catalytic Balz-Schiemann fluorination reaction.*

1.3 Fluoroiodane

1.3.1 General introduction to hypervalent iodine reagents

Hypervalent iodine(III) reagents have been used widely in organic synthesis since the 1990s, due to their low toxicity, stability, commercial availability as well as mild reaction conditions.[37,38] Generally, the hypervalent nature of iodine occurs when the iodine atom has more than 8 electrons in its valence shell. It is usually seen in two general structural types, iodine(III) compounds (λ^3-iodanes) and iodine(V) compounds (λ^5-iodanes). In iodine(III) compounds (Figure 1.5, **1.23** and **1.24**) the central iodine atom has a share in 10 electrons and the overall geometry of a distorted trigonal bipyramid with two heteroatom ligands X occupying the apical positions and with the least electronegative carbon ligand R and both electron pairs residing in equatorial positions.[39] Iodonium salts **1.24** have a similar pseudo trigonal bipyramidal geometry with the inclusion of a weakly bonded anionic part of the molecule. The λ^3-iodanes RIX_2 **1.23** have an approximately T-shaped structure, and the I−X bond lengths are longer than an average I−X covalent bond length. Bond angles R−I−R in iodonium salts, iodonium ylides, and iodonium imides are close to 90°.[40]

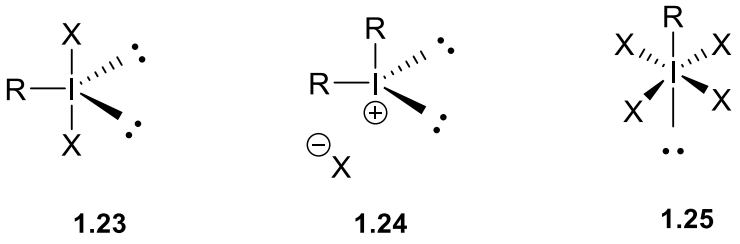


Figure 1.5: Types of hypervalent iodine structures.

On the other hand, iodine(V) compounds (**1.25**) have a distorted octahedral structure with the organic group R and the electron pair in the apical positions and four heteroatom ligands X in basal positions.[41]

Hypervalent iodine(III) reagents contain a 3-centre-4-electron (3c-4e) bond (X–I–X), which is formed by the overlap of a 5p orbital of the iodine atom with the orbitals of the two trans-ligands.[37] Hypervalent iodine(III) reagents are electrophilic in nature, resulting from the node in the hypervalent non-bonding orbital (Figure 1.6).

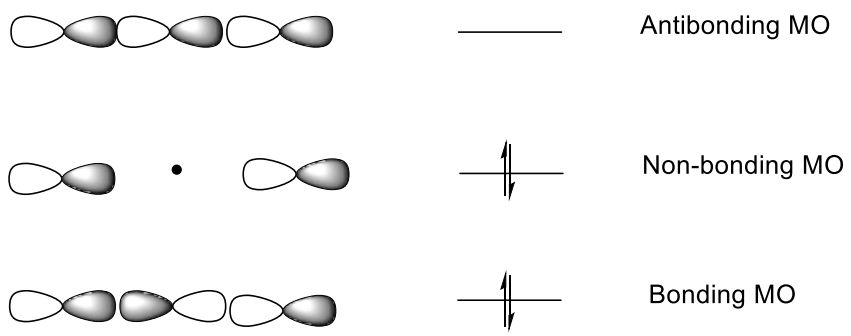


***Figure 1.6**: Molecular Orbital Diagram for the Hypervalent Iodine.*

What makes hypervalent iodine(III) reagents very important is that their reactivity and mode of reaction have been shown to be similar to those of transition metals such as Pt, and Pd, meaning that there is great potential for these to be safer and less expensive alternatives to these heavy metal-based synthetic routes.[42]

In 1886, Willgerodt prepared the first known hypervalent iodine compound (dichloroiodo)benzene **1.26** ($PhICl_2$) by passing chlorine gas over a cold iodobenzene solution.[43] With this discovery a new area of organic chemistry opened up, and this work soon led Willgerodt to the preparation of many hypervalent iodine molecules such as iodoxybenzene **1.27** which are still used to this day. However, research in this field stopped for many decades.

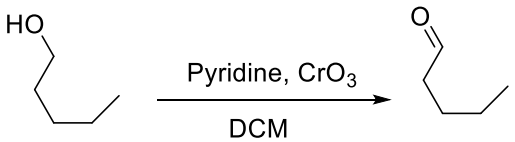
1.26 **1.27**

***Figure 1.7**: Hypervalent iodine reagents.*

The chemistry of hypervalent iodine(III) reagents is now a well established area in organic chemistry. They are efficient oxidants in many synthetic transformations, such as oxidation of alcohols and phenols, α-functionalization of carbonyl compounds,[44] as well as oxidation of alkenes.[45] Numerous reports have been published detailing the reactions of hypervalent iodine compounds. However, only a few of these will be considered in this part of this chapter.

Oxidation of alcohol and sulfides.

One particular reaction of hypervalent iodine(III) reagents is the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively. Generally, these types of reaction could be achieved by the use of CrO_3 based reagents, such as the Collins reagent which is a complex of CrO_3 with pyridine in DCM.[46] For instance, aldehyde **1.29** was produced upon treatment of alcohol **1.28** with Collins reagent (Scheme 1.10).

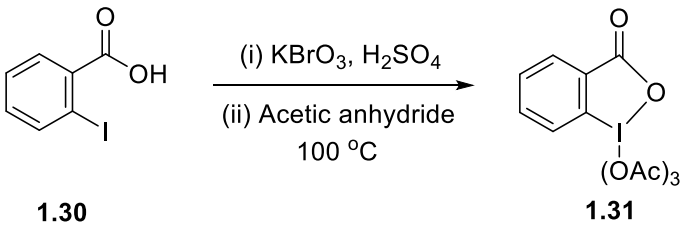


1.28 **1.29**

***Scheme 1.10**: Oxidation of alcohol using Collins reagent.*

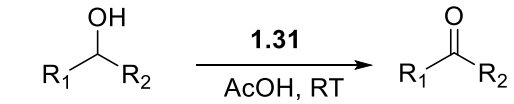
However, this reagent is both difficult and dangerous to synthesis, as it is very hygroscopic and can catch fire during the preparation.[47] This problem can be avoided by using hypervalent iodine(III) reagents. A popular modern route for the oxidation of alcohols under mild conditions is the use of Dess-Martin periodinane (DMP) **1.31** which

can be prepared by treatment of 2-iodobenzoic acid **1.30** with $KBrO_3$ in sulfuric acid, followed by heating to 100 °C with acetic anhydride (Scheme 1.11 and Scheme 1.12).[48,49]



1.30 **1.31**

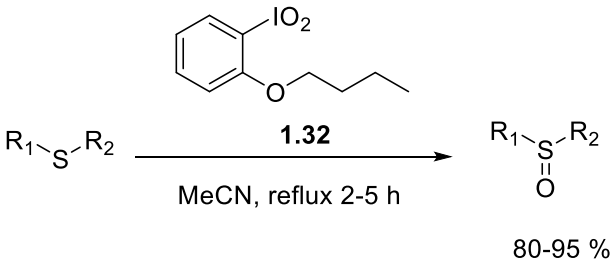
Scheme 1.11**: Preparation of **1.31



R_1: H, Alkyl, Aryl
R_2: Alkyl, Aryl

Scheme 1.12**: Oxidation of alcohols using **1.31

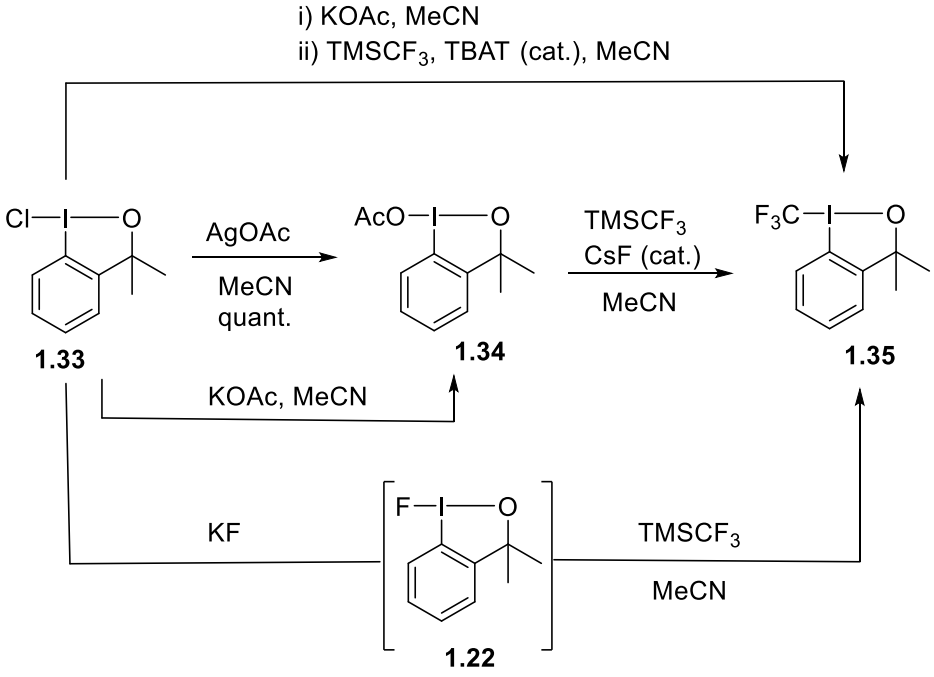
Zhdankin and co-workers have reported different hypervalent iodine(III) reagents, such as 1-butoxy-2-iodyl-benzene **1.32**, which were able to transform a selective oxidation of sulfides to sulfoxides. This reaction was achieved by heating to reflux sulfides with **1.32** in acetonitrile to generate the equivalent sulfoxides in high yields (Scheme 1.13). **1.32** was also found to be effective at oxidising alcohols to their equivalent carbonyl compounds.[50]



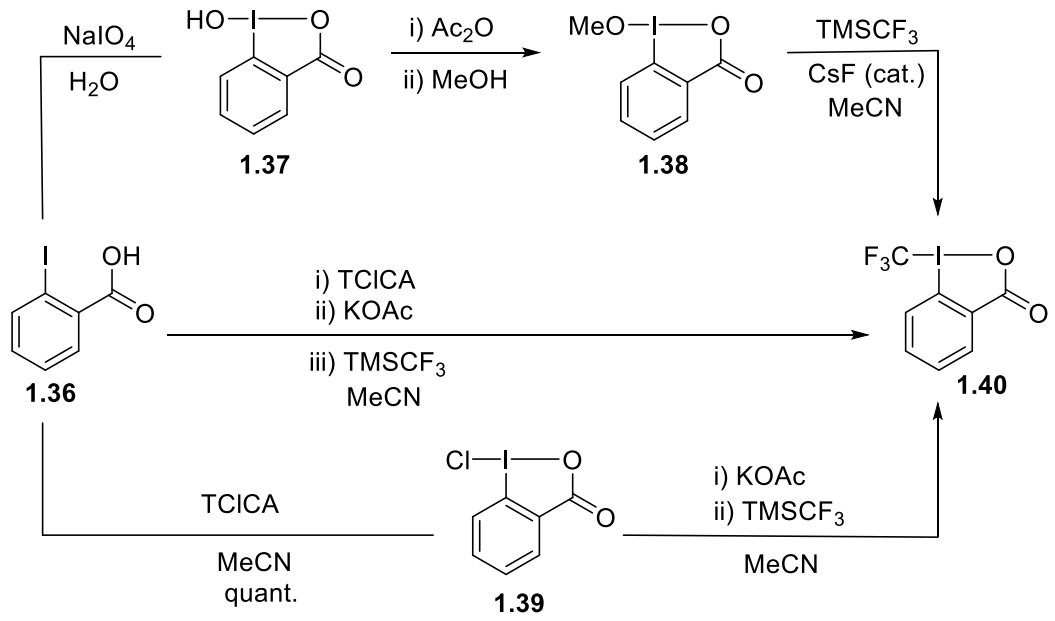
*Scheme 1.13: Oxidation of sulfides using **1.32***

1.3.1.1 Trifluoromethylation using Hypervalent Iodine Compounds

Due to the significant unique features that trifluoromethylated compounds have in pharmaceuticals and agrochemicals, several effective trifluoromethylating reagents have been reported such as the Umemoto reagent [51] and the Shibata reagent.[52] However, the use of Togni's reagents based on hypervalent iodine(III) (**1.35** and **1.40**) has increased exponentially in the last five years.[53] Different synthetic routes have been reported for the preparation of **1.35** and **1.40** as shown in Scheme 1.14 and Scheme 1.15, respectively.[54-57]

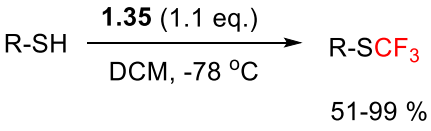


*Scheme 1.14: Synthetic routes for the preparation of **1.35***



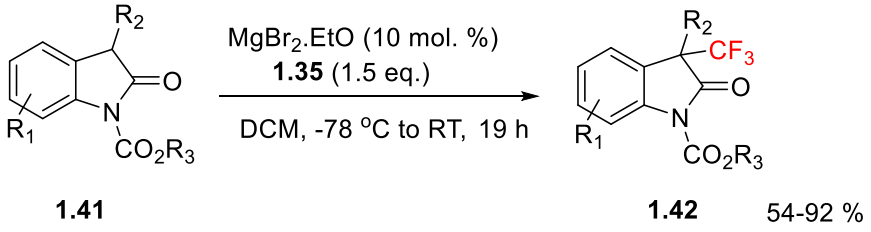
Scheme 1.15**: Synthetic routes for the preparation of **1.40

Thiols were the first nucleophiles that were trifluoromethylated by use of reagent **1.35**. They were found to react with both high yields and selectivity, and these reactions feature a wide substrate scope from a simple thiophenol to cysteine side chains in peptides. A range of functional groups, such as thioacetals, amines, alcohols, carboxylic acids and alkynes were tolerated (Scheme 1.16).[58]



***Scheme 1.16**: Trifluoromethylation of Thiols.*

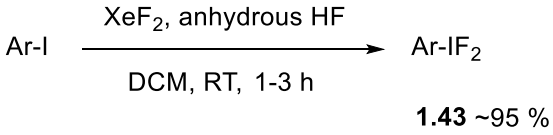
In a more recent development, Togni and co-workers have developed a magnesium-catalysed direct trifluoromethylation of oxindoles using **1.35** as source of the CF_3 group. The reaction was performed with high chemical efficiency under mild reaction conditions, leading to all-carbon quaternary oxindoles, and has a large functional group tolerance (Scheme 1.17).[59]



***Scheme 1.17**: Trifluoromethylation of 3-substituted oxindoles.*

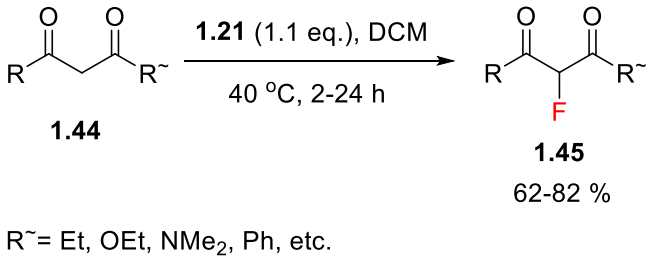
1.3.1.2 Fluorination reactions

Difluoroiodoarenes ($ArIF_2$) **1.43** are good examples of λ^3- hypervalent iodine(III) species which can be used for the fluorination of organic compounds. Two general routes have been reported for preparing these compounds: i) oxidative addition of fluorine to iodoarenes using strong fluorinating reagents, ii) ligand exchange in iodine(III) compounds using a fluoride anion source.[40] According to the first approach, a mild and selective method for the preparation of (difluoroiodo)arenes **1.43** could be achieved by treating aryl iodides with XeF_2 in anhydrous HF (Scheme 1.18).[60]



***Scheme 1.18**: Synthesis of (Difluoroiodo)arenes using XeF_2*

(Difluoroiodo)arenes **1.43** have been used as selective and powerful fluorinating regents. *β*-Dicarbonyl compounds are selectively fluorinated at the *α*-position by difluoroiodotoluene **1.21**. In a specific example, reactions of *β*-ketoamides, *β*-ketoesters and *β*-diketones **1.44** with **1.21** gave the respective monofluorinated **1.45** under mild conditions and in good yields (62-82 %) (Scheme 1.19).[61]

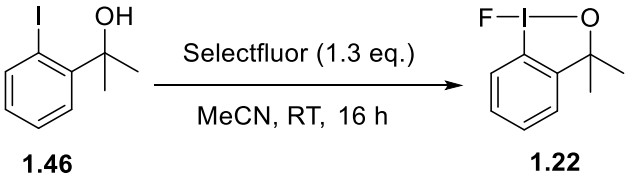


***Scheme 1.19**: Fluorination of β-Dicarbonyl Compounds.*

1.3.2 Synthesis of Fluoroiodane 1.22

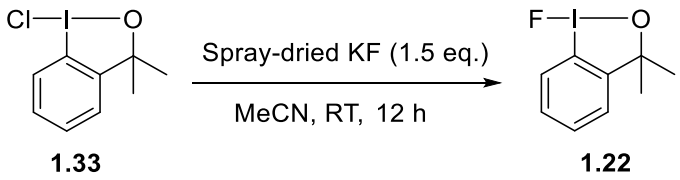
In 2011 Ritter and co-workers reported the synthesis of a fluoride-derived electrophilic fluorinating reagent that could be used in late stage ^{18}F labelling of aromatic compounds. This was the first example of a formal umpolung of fluoride which had used a palladium (IV)-based electrophilic fluorinating reagent.[62] Recently, an alternative, non-metal based strategy using the cyclic hypervalent iodine(III) compound, fluoroiodane **1.22**, was developed.

Fluoroiodane **1.22** hypervalent iodine(III) reagent which has an analogous structure to Togni's reagent (**1.35**). Fluoroiodane **1.22** was first synthesised by Legault [63] through the electrophilic fluorination of 2-(2-iodophenyl)propan-2-ol **1.46** with 1.3 equivalents of Selectfluor in acetonitrile (Scheme 1.20). This route is not viable for the large scale synthesis of the fluoroiodane **1.22** due to the high cost of Selectfluor.



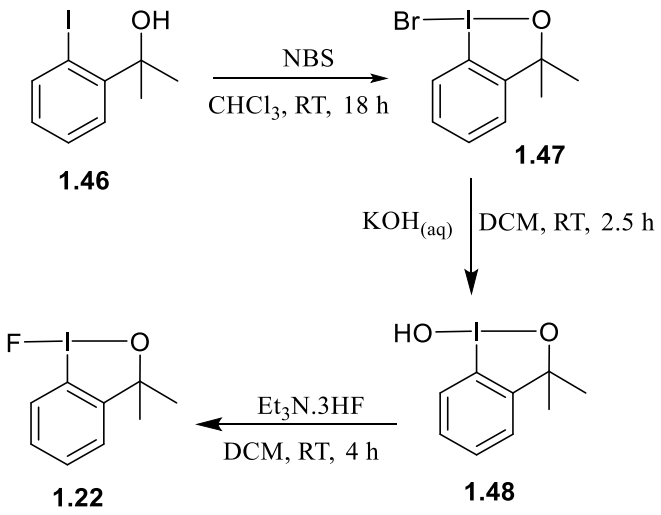
***Scheme 1.20**: Preparation of fluoroiodane using Selectfluor.*

Togni and co-workers reported an alternative nucleophilic pathway to **1.22** using halogen exchange of chloroiodane **1.33**. This reaction was carried out under argon using 1.5 equivalents of spray dried potassium fluoride in acetonitrile for 12 h at RT (Scheme 1.21).[55]



***Scheme 1.21**: Synthesis of fluoroiodane using KF.*

Stuart and co-workers[64] also discovered a way to synthesise fluoroiodane **1.22** by nucleophilic fluorination. This method consists of three steps starting with the synthesise of bromoiodane **1.47** using *N*-bromosuccinimide (NBS), followed by reaction with KOH to form hydroxyiodane **1.48**. Fluoroiodane **1.22** was then prepared via the nucleophilic fluorination of **1.48** with triethylamine trihydrofluoride (TREAT-HF) (Scheme 1.22).

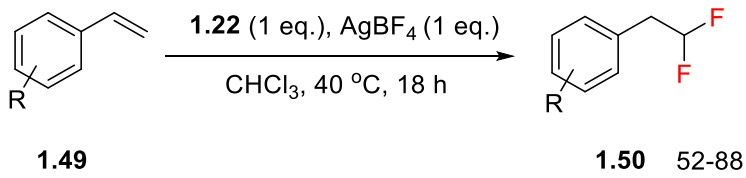


***Scheme 1.22**: Formation of fluoroiodane using TREAT-HF.*

1.3.3 Fluorination with fluoroiodane 1.22

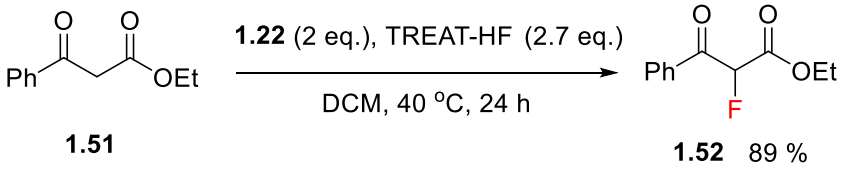
The applications of fluoroiodane **1.22** have been explored by many research groups and it has been found to have different uses as a fluorinating reagent due to it being stable, commercially available and an efficient fluorinating reagent often with different chemoselectivity to fluoraza reagents.

Szabo and co-workers reported a new route for the selective geminal difluorination of styrene derivatives using fluoroiodane **1.22** in the presence of $AgBF_4$ under mild reaction conditions (Scheme 1.23). Using equimolar amounts of **1.22** and styrene derivatives and obtaining more than 50 % yield indicated that one of the C-F bonds was formed by transfer of electrophilic fluorine from **1.22**, while the other one arises from $AgBF_4$.[65] Overall, this reaction is suitable for the mild synthesis of *β*-difluoro aromatic compounds, which are bioisosteres [66] of natural compounds with benzyl alcohol and thiol motifs. Recently, the same group developed geminal difluorination of α,α'-disubstituted styrenes using catalytic amounts of $[Pd(MeCN)_4](BF_4)_2$ and $[Cu(MeCN)_4]PF_6$ instead of $AgBF_4$.[67]



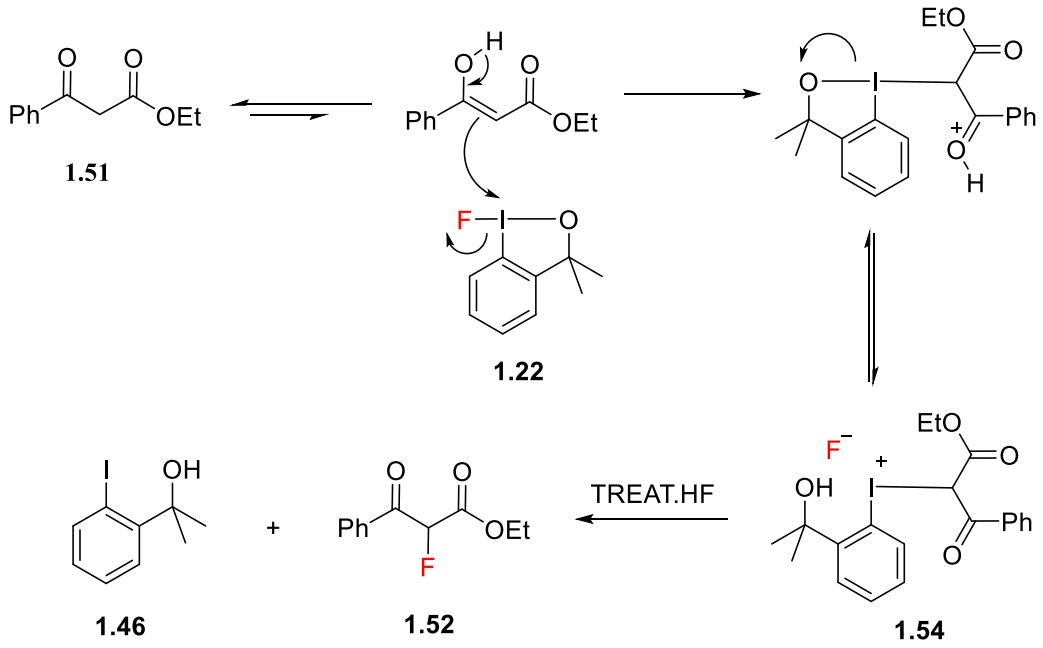
***Scheme 1.23**: Difluorination of styrene derivatives with fluoroiodane and $AgBF_4$.*

Stuart and co-workers reported that fluoroiodane **1.22** could be used to selectively introduce fluorine into a variety of 1,3-dicarbonyl substrates. Scheme 1.24 shows one such example of reacting fluoroiodane **1.22** with the 1,3-ketoester **1.51** in the presence of TREAT.HF generating the monofluorinated compound **1.52** in good yield.[64]



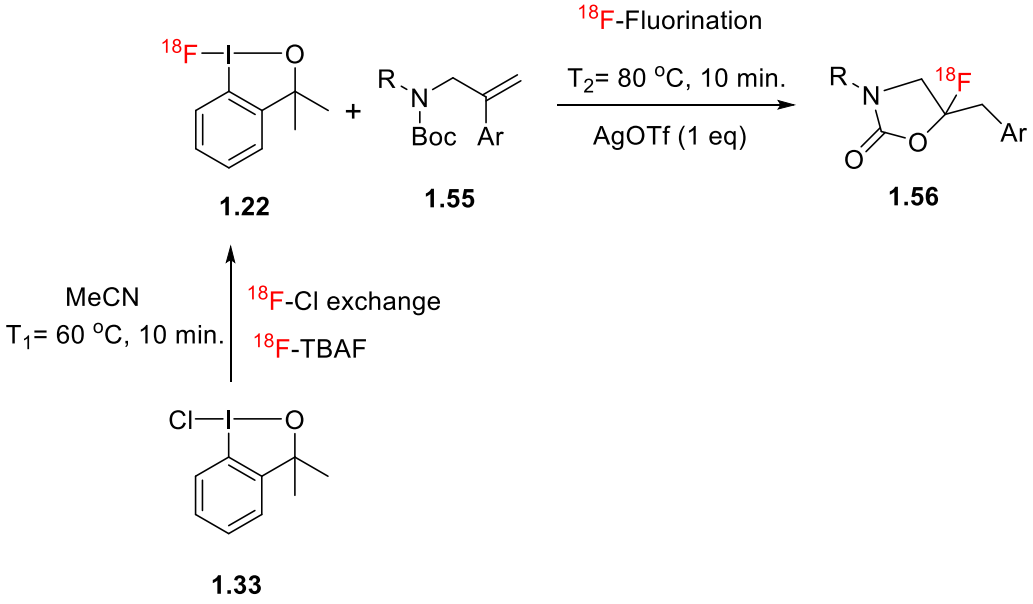
***Scheme 1.24**: Fluorination of 1,3-diketoester using fluoroiodane*

The reaction between **1.51** and **1.22** has been proposed to proceed via an iodonium intermediate and the suggested mechanism was found to be an addition/substitution mechanism involving formation of an iodonium salt **1.54**, which facilitated electrophilic fluorination (Scheme 1.25).[68]



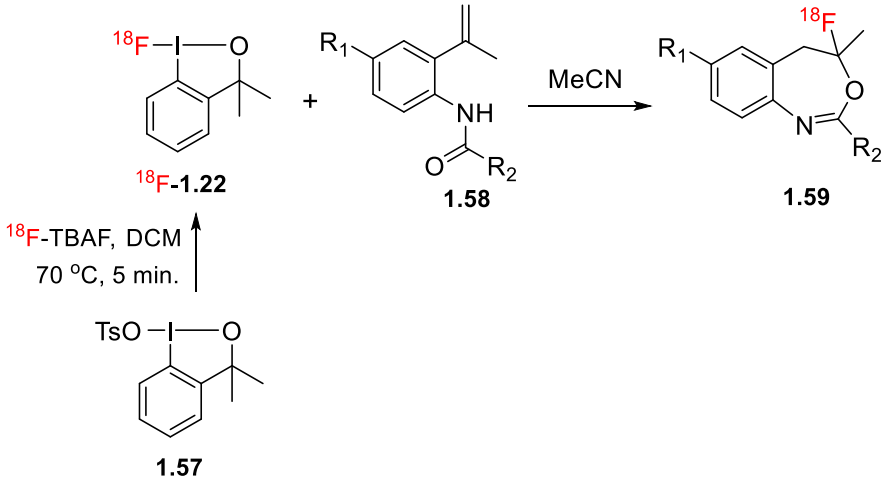
Scheme 1.25**: Proposed mechanism for the fluorination of **1.52

The intramolecular fluorocyclization of unsaturated carbamates was described by Lu [69] using ^{18}F-**1.22** in the presence of a silver catalyst. The transformation showed a broad substrate scope, such as acrylamides and (hetero)aryl-substituted olefins, with tolerance of diverse functional groups. Preliminary mechanistic studies suggested that the unique selectivity and reactivity profile of this synthetic reaction is caused by the involvement of an unusual radical mediated pathway. Furthermore, the modified one-pot, two-step process using no-carrier-added ^{18}F-nucleophilic reagents was used to form multiple bonds and produce ^{18}F-labeled heterocycles rapidly (Scheme 1.26).



***Scheme 1.26**: Radiosynthesis of acrylamides **1.56**.*

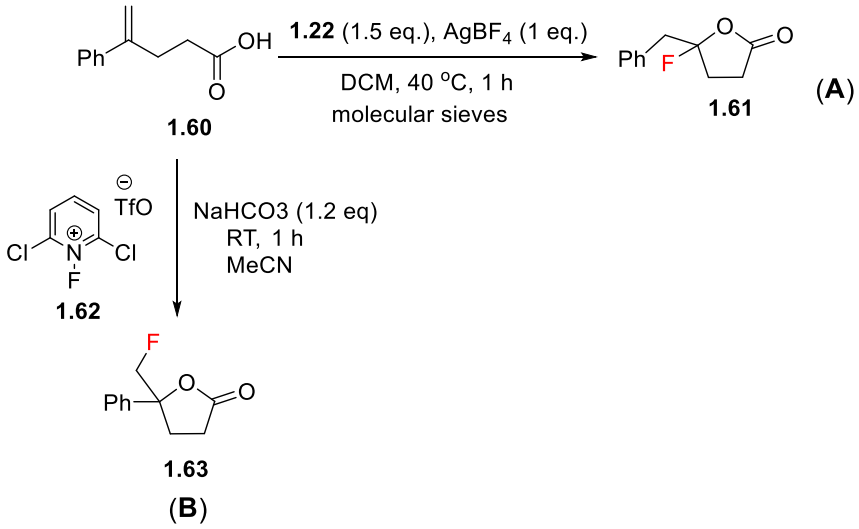
Synthesis of the fluorinating reagent ^{18}F-**1.22** was also achieved from a cyclotron produced [^{18}F]F$^-$ precursor, [^{18}F]TBAF, and tosyl-benziodoxole **1.57** and was used for the electrophilic fluorocyclization of *o*-styrylamides **1.58** (Scheme 1.27).[70] Metal-free fluorocyclisations of *o*-styrylamides with **1.22** had been reported previously by Gulder.[71]



***Scheme 1.27**: Electrophilic fluorocyclization of **1.58**.*

A new class of fluorinated lactones was prepared successfully by the intramolecular fluorocyclizations of unsaturated carboxylic acids using fluoroiodane **1.22** together with

equimolar amounts of $AgBF_4$ to deliver novel γ-lactones **1.61** containing a tertiary alkyl fluoride in good yields (43-98 %) (Scheme 1.28 A).[68] On the other hand, the fluorolactonizations of unsaturated carboxylic acids with the electrophilic fluorinating reagent **1.62** was reported to give γ-lactones containing a primary alkyl fluoride **1.63** (Scheme 1.28 B).[72] The reaction with fluoroiodane can also be achieved in the absence of metal catalyst to give moderate yields (55-61 %) within just 1 hour at 40 °C, thus indicating that it is also a suitable reagent for developing new ^{18}F-labelled radiotracers for PET imaging.

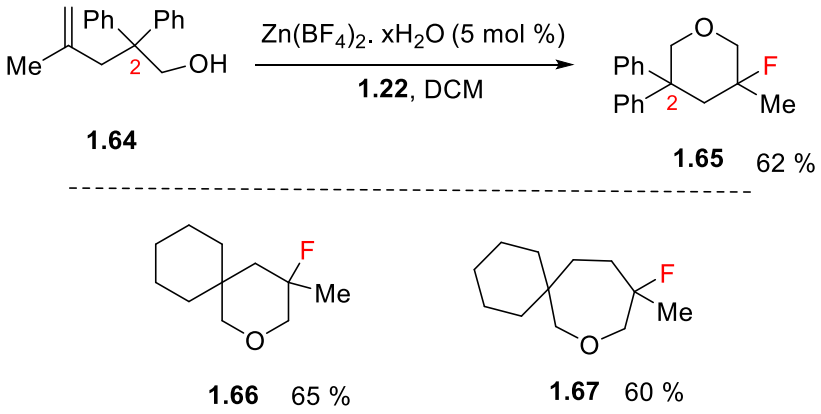


***Scheme 1.28**: Fluorolactonizations of unsaturated carboxylic acids.*

Recently, Stuart and co-workers reported the use of HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) as an excellent solvent for the fluorination with fluoroiodane **1.22** without using any transition metals or TREAT-HF activator. 1,3-Ketoamides and 1,3-ketoester gave monofluorinated products in excellent yields (71-93 %) in only 1-4 hours [73] compared to 24 hours in dichloromethane using fluoroiodane and TREAT-HF.[64] Fluorinated lactones were also obtained in good to high yields (36-86 %) in the reaction of unsaturated carboxylic acid with fluoroiodane **1.22** in HFIP.[73]

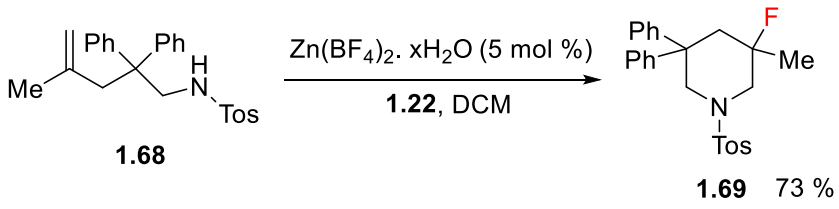
The cyclic ethers, **1.65** and **1.66**, as well as a seven membered cyclic ether **1.67** were obtained in moderate yields (up to 65%) by treatment of alcohols **1.64** with fluoroiodane

(Scheme 1.29).[74] Similar to previous reports,[65] activation of fluoroiodane by catalytic amounts of $AgBF_4$ was required for the reaction to proceed. The structural variety of starting materials **1.64** capable of generating the cyclic ethers under these conditions seemed rather limited to 1,1-disubstituted alkenes bearing a quaternary carbon atom at the C-2 position.



***Scheme 1.29**: Fluorocyclizations of hydroxyalkenes using fluoroiodane.*

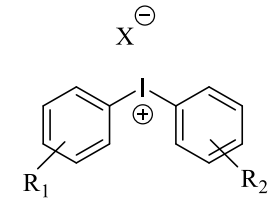
Besides forming of O-heterocycles (**1.65-1.67**), the corresponding fluoro-amino cyclised products **1.69** starting from amino alkenes **1.68** were also be prepared using fluoroiodane (Scheme 1.30). In general, this transformation delivered the cyclic amines **1.68** in higher yields (63–84%) in comparison with the corresponding O-heterocycle products. The substrate scope was also broader, tolerating alkyl, phenyl as well as sulfonamides as N-protecting groups.[74]



***Scheme 1.30**: Formation of N-heterocycles **1.69** in a fluoro-amino cyclization*

1.4 Diaryliodonium salts

Diaryliodonium salts are iodine(III) species possessing two aromatic ligands as well as an inorganic counteranion. The structure of diaryliodonium salts consists of two aryl groups bound to I(III) and a non-coordinating anion as seen in Figure 1.8. In this case, iodine has 8 electrons in its valance shell which gives a distorted bent geometry. In the solid-state, strong cation···anion intractions are often observed with the anion (X^-) occupying an apical position distorting the two lone pairs into equatorial positions in a distorted trigonal bipyramidal geometry. These salts are referred to as symmetric if $R_1=R_2$, and as unsymmetric if $R_1 \neq R_2$.[75] On average they have a C-I-C bond angle of 96° and C-I bond lengths of 2.0-2.1 Å.[76] Diaryliodonium salts with halide anions are generally sparingly soluble in organic solvents, whereas with TfO^- and BF_4^- anions they have higher solubilities.



X= Br, I, OTf, OTs, BF_4……

***Figure 1.8**: General structure of diaryliodonium salts.*

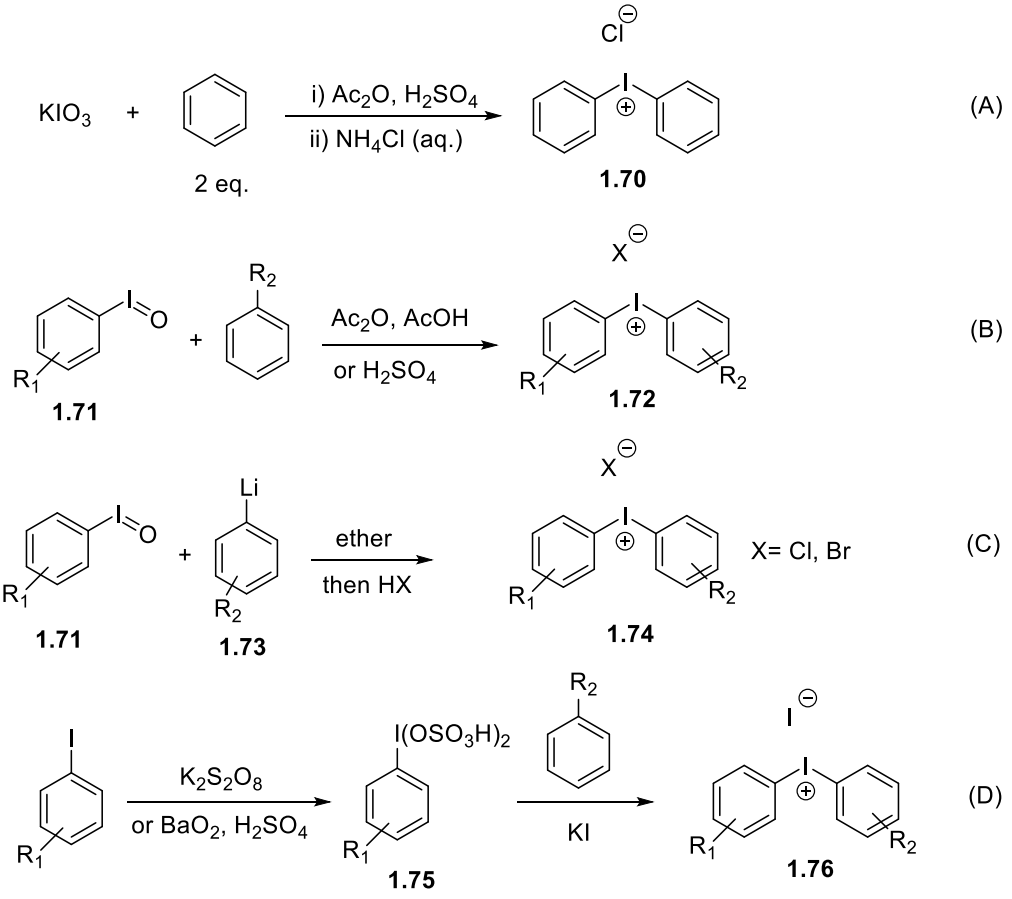
These compounds are very useful for many reasons, such as their ease of availability and applications in a host of metal and non-metal catalysed reactions. Furthermore, they are also favoured for their high selectivity, low toxicity and reactivity allowing many reactions to take place at ambient temperatures without using an excess of reagents. The similarity in reactivity to other aryl-substituted heavy metals, such as Hg and Pd, make them a much more environmentally-friendly alternative that solves a big problem for the pharmaceutical industry.[77]

In industry, diaryliodonium salts are used as oxidants via formation of phenyl radicals,[78] as photoinitiators in cationic polymerizations [79] as well as Lewis acids in acid catalysed reactions.[80] Since their discovery, these compounds have attracted significant attention

from synthetic organic chemists, and this has provided an incentive to find efficient routes to prepare them.

1.4.1 Synthesis of diaryliodonium salts

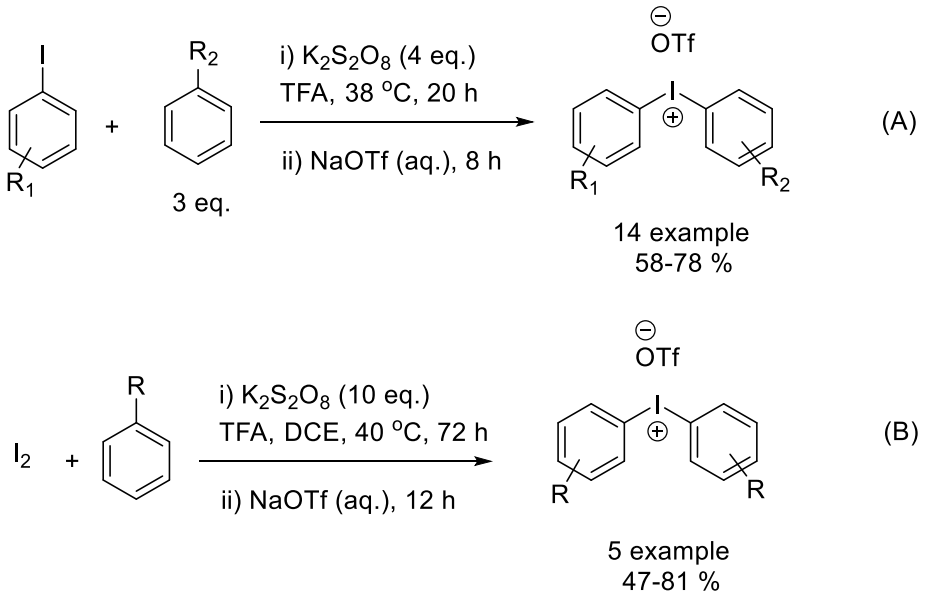
The first synthesis of diaryliodonium salts was reported over 100 years ago by Hartmann and Meyer by dissolution of iodosylbenzene in concentrated sulfuric acid.[81] The preparation of diaryliodonium salts can be achieved by the reaction between iodine(III) species with suitable arenes through electrophilic aromatic substitution (EAS). These routes were initially reported by Beringer in the 1950's in a series of papers detailing the use of inorganic hypervalent iodine(III) precursors (Scheme 1.31A),[82] the reaction of preformed organic hypervalent iodanes **1.71** with arenes (Scheme 1.31B)[82] or organometallic species **1.73** (Scheme 1.31C),[83] as well as the in *situ* oxidation of iodoarenes with $K_2S_2O_8$ or BaO_2 (Scheme 1.31D).[84]



***Scheme 1.31**: Preparation of diaryliodonium salts from the Beringer group.*

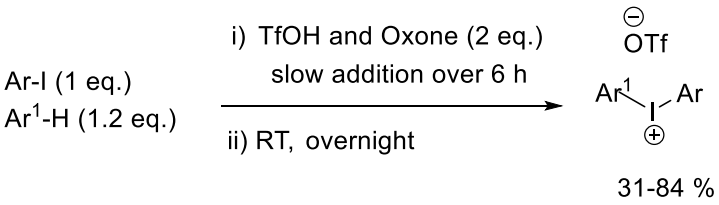
Generally it has been found that the preparation of diaryliodonium salts usually involves 2 to 3 steps including an initial oxidation of an Ar-I to an iodine(III) intermediate, followed by the addition of suitable arenes under acidic conditions, without isolation of the iodine(III) intermediates, followed by a ligand exchange mechanism with arenes to obtain the diaryliodonium salts (similar to Scheme 1.31D).

Building on this approach, Kitamura and co-workers employed $K_2S_2O_8$ in an improved modification of the Beringer routes (Scheme 1.32A).[85] In addition, symmetrical salts can be prepared by the oxidation of diiodine, followed by trifluoroacetic acid-catalysed condensation with arenes (Scheme 1.32B).[86] Unfortunately, both techniques suffer from long reaction times, limited scope and using a large excess of reagents.



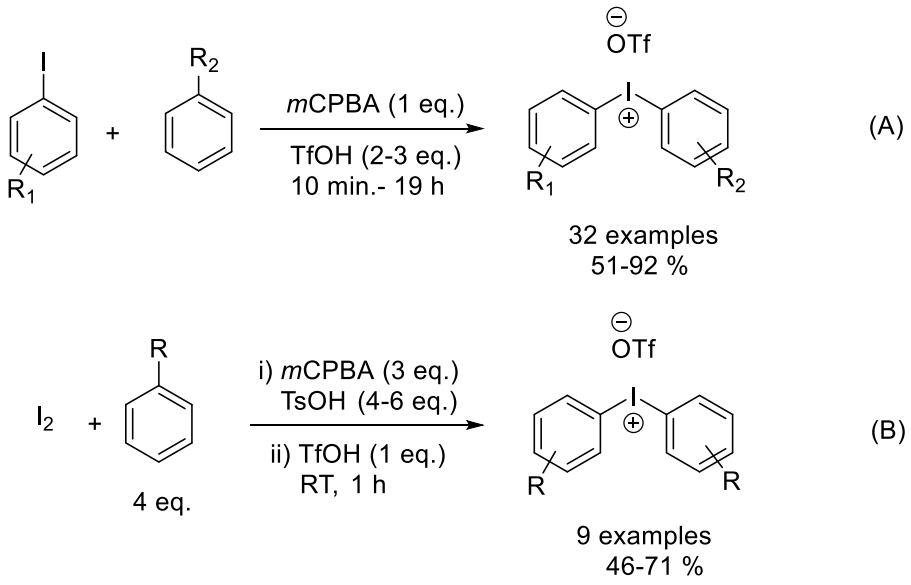
***Scheme 1.32**: Kitamura's routes for one-pot preparation of diaryliodonium triflates.*

Zhdankin and co-workers reported the use of oxone as a stoichiometric oxidant to prepare diaryliodonium triflates. This reaction can be achieved by the slow addition of a solution of oxone and triflic acid to mixture of Ar-I and arenes over 6 hours and then stirring overnight at RT (Scheme 1.33).[87] Moderate yields were obtained (31-84 %) and the only major drawbacks of the method were found to be the long reaction time and the limited substrate scope.



***Scheme 1.33**: Synthesis of diaryliodonium triflates using oxone.*

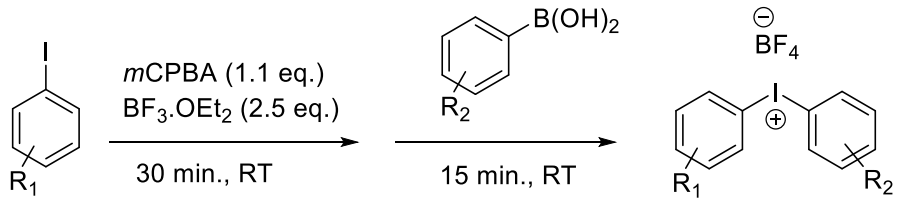
Olofsson and co-workers demonstrated a direct preparation of diaryliodonium triflates through oxidizing Ar-I using *meta*-chloroperoxybenzoic acid (*m*CPBA), followed by treatment of the iodoso derivative with triflic acid and an activated arene (Scheme 1.34A).[88] This method was unsatisfactory for the preparation of symmetrical triflate salts directly from I_2 and electron-rich arenes. However, this problem was resolved by operating in the presence of tosic acid, followed by anion exchange with triflate anion without isolation of the tosylate salt intermediate (Scheme 1.34B).[89]



***Scheme 1.34**: Olofsson's methods for one-pot synthesis of diaryliodonium triflates.*

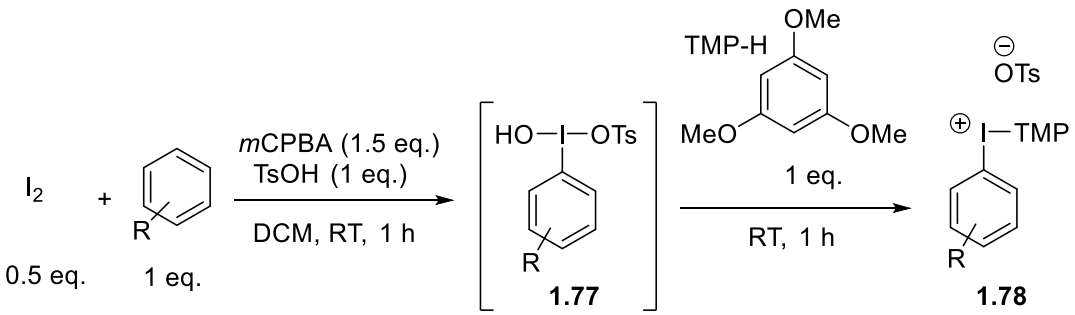
Olofsson also reported the synthesis of diaryliodonium tetrafluoroborates, which are normally used in metal-catalysed arylations. This route can be achieved by reacting Ar-I with an arylboronic acid in the presence of $BF_3.OEt_2$ and *m*CPBA producing

diaryliodonium tetrafluoroborates in good yields (56-88 %). Both electron-rich and electron-deficient products can be prepared in a regiospecific manner, and the substitution pattern can be easily varied (Scheme 1.35).[90]



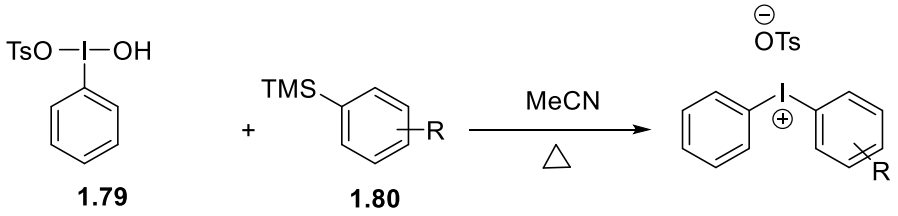
***Scheme 1.35**: Synthesis of diaryliodonium tetrafluoroborates.*

Synthesis of unsymmetric salts carrying the trimethoxyphenyl (TMP) dummy group has also been reported. The protocol employs iodine and arenes, instead of using Ar-I, under mild conditions. The scope includes a variety of arenes having at least one electron-donating group (EDG), to ensure efficient iodination and oxidation to iodine(III).[91] This reaction involves formation of [hydroxyl(tosyloxy)iodo]benzene (Koser's reagent) derivatives **1.77** first, which is considered to be the most difficult step due to limiting the substrate scope to arenes with EDG. In the second step, **1.77** reacts with trimethoxyphenyl to form unsymmetric diaryliodonium salts **1.78** in low to moderate yields (14-70 %) (Scheme 1.36).



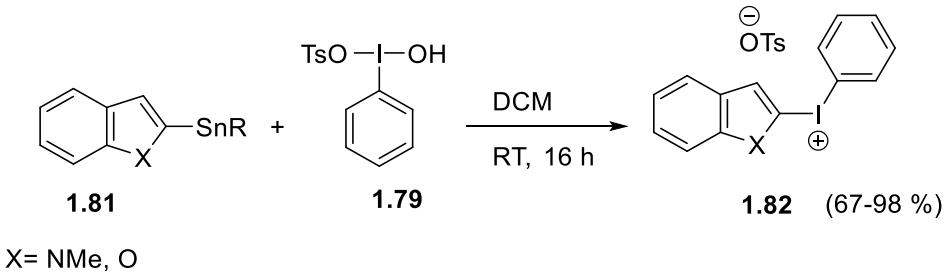
***Scheme 1.36**: Synthesis of unsymmetrical diaryliodonium salts with TMP.*

Recently, various iodine(III) reagents, such as Koser's reagent, which are suitable for the synthesis of diaryliodonium salts have become commercially available. In 1980, Koser and co-workers reported the first reigospecific synthesis of diaryliodonium tosylates. In this route, reaction of [PhI(OH)OTs] **1.79** with arylsilanes **1.80** occurred at the *ipso*-position, regardless of other substituents, under neutral conditions (Scheme 1.37).[92] Various Koser's reagent derivatives **1.79** have also been employed, producing diaryliodonium salts in moderate yields. Electron-rich arenes, like thiophene, can easily react with **1.77** without the need for the trimethylsilyl activating group.[93]



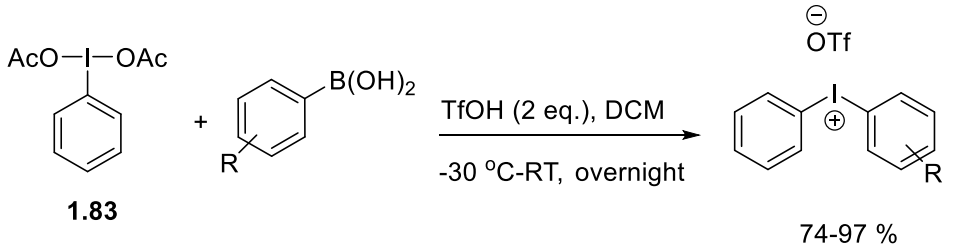
***Scheme 1.37**: Reaction of arylsilanes with Koser's reagent*

Arylstannanes **1.81** are more reactive than the corresponding arylsilanes **1.80** in the reaction with Koser's reagent **1.79** forming diaryliodonium tosylates under mild conditions in low to moderate yield (19-58 %).[94] Heteroaromatic iodonium salts were generated in excellent yields using this protocol (Scheme 1.38).[95]



***Scheme 1.38**: Synthesis of heteroaromatic iodonium salts.*

Widdowson and co-workers demonstrated a mild and regioselective preparation of diaryliodonium triflates in high yields (74-97 %) by treatment of arylboronic acids with (diacetoxy)iodobenzene using DCM as the solvent (Scheme 1.39). This protocol could also be employed to prepare heteroaryl(phenyl)iodonium salts.[96] In the same way, aryltrifluoroborates can react with (difluoroiodo)toluene **1.22** as a source of iodine(III).[97]



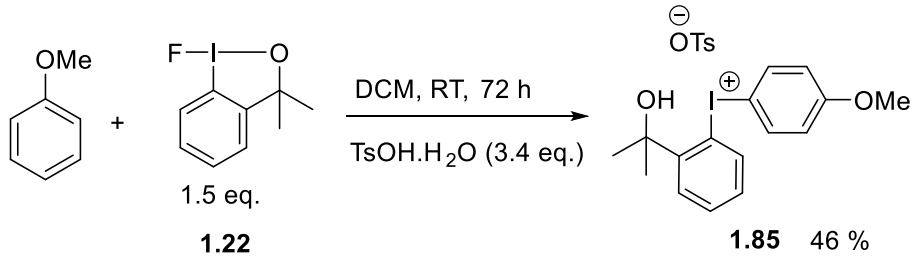
Scheme 1.39**: Formation of diaryliodonium triflates from arylboronic acid and **1.83

Sanford and co-workers have reported the reaction of commercially available 2-(diacetoxyiodo)mesitylene (MesI(OAc)$_2$) **1.84** with suitable arylboronic acids and $BF_3.OEt_2$ in DCM to generate a range of diaryliodonium tetrafluoroborates in good yields (56-77 %) (Scheme 1.40).[98]

***Scheme 1.40**: Synthesis of diaryliodonium tetrafluoroborates*

Unpublished work by the Stuart group showed that diaryliodonium tosylate **1.85** could be prepared successfully by reacting anisole with fluoroiodane **1.22**, as a hypervalent iodine(III) source using DCM as the solvent in the presence of *p*-toluenesulfonic acid (Scheme 1.41).[99] The major problem with this route is the length of the procedure and the low yield (46 %). Here, as a starting point for this research, optimisation of the reaction

conditions should be investigated in order to increase the yield and reduce the reaction time.

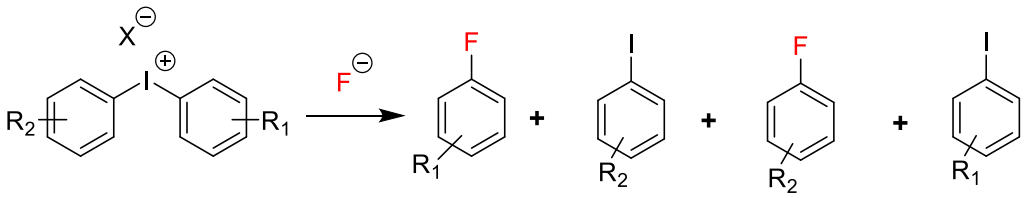


***Scheme 1.41**: Synthesis of **1.85** from fluoroiodane*

As a general point, the nature of the counteranion has a major influence on the reactivity of the diaryliodonium salt. In particular, diaryliodonium triflates and tetrafluoroborates display many desirable features, and their use is becoming very popular.[88] Fortunately, many protocols exist to induce anion exchange reactions of diaryliodonium salts; for example, to exchange halides, acetates, sulfates, tosylates, etc., into triflates. A simple method is the addition of triflic acid to a solution of a diaryliodonium salt to produce the corresponding diaryliodonium triflate.[90]

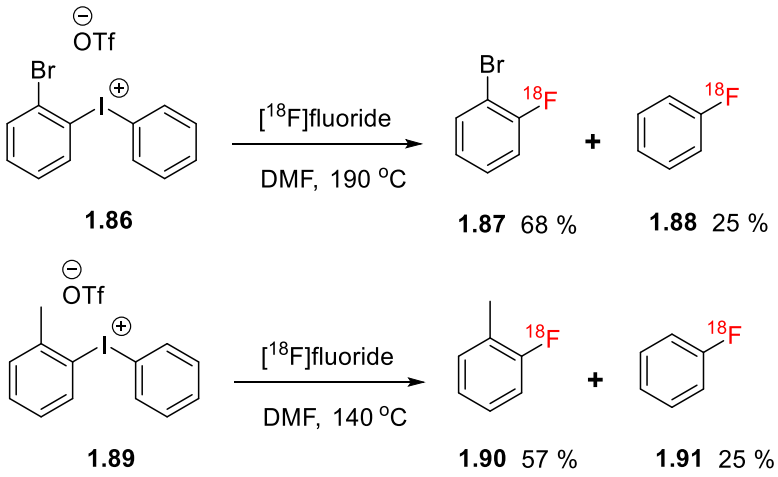
1.4.2 Fluorination of diaryliodonium salts

Diaryliodonium salts are used as electrophilic arylating reagents in both transition metal-catalysed [100] and metal free [101] processes. They react easily with both weak and strong nucleophiles due to their highly electron deficient nature and the presence of excellent leaving-groups.[102] The fluoride anion, F^-, is a very poor nucleophile, so fluorination of aromatic moieties can be very challenging. However, diaryliodonium salts can react with F^- due to these particular physical characteristics. A number of aromatic compounds can be generated when F^- reacts with diaryliodonium salts (Scheme 1.42).



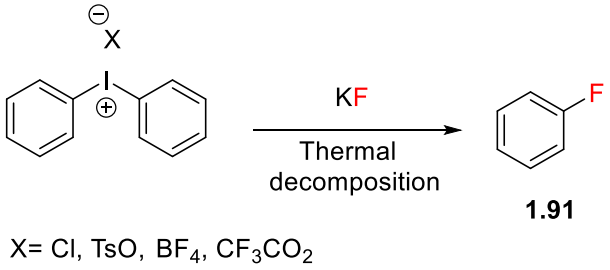
***Scheme 1.42**: Expected products from the fluorination of diaryliodonium salts.*[103]

The fluorination of unsymmetrical salts is more complicated than symmetrical diaryliodonium salts. For unsymmetrical salts the R groups will not be equal ($R_1 \neq R_2$), which means that two different fluoroaromatics can be produced. In uncatalysed reactions, electronic and steric effects[104] are the key factors for aryl transfer selectivity from unsymmetrical salts with the nucleophile. In terms of electronics, the nucleophile will attack the most electron deficient group due to it having a higher δ+ charge. The other factor is known as the "*ortho*" effect and is a steric control. If one of the aromatic rings is *ortho* substituted it will preferentially be attacked by the nucleophile. *Ortho* substitution makes the aryl group bulkier; therefore in the transition state it will favour the more easily attacked equatorial position in order to reduce steric strain.[105] in general, the abilities of *ortho* substitution patterns to import an *ortho* effect in the fluorination have been ranked as 2,6-di-Me > 2,4,6,-tri-Me > Br > Me > Et~*i*-Pr > H > OMe.As the "*ortho*" effect has a greater impact on the selectivity than the electronic effect, it can allow the fluorination of electron rich *ortho* substituted aromatics. Pike and co-workers [106] have observed a modest electronic and steric effect in the reaction of fluoride with diaryliodonium salts **1.86** and **1.89**, respectively, forming **1.87** and **1.91** as the major products (Scheme 1.43).



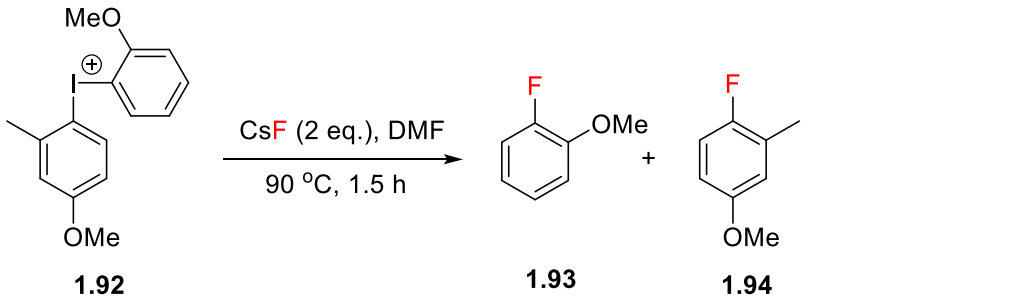
***Scheme 1.43**: Selectivity of aryl group transfer to fluoride.*

In 1982, Van der Puy reported the first example of the fluorination of diaryliodonium salts by the thermal decomposition of symmetrical tetrafluoroborate salts.[107] It was noted that reactions of diphenyliodonium salts containing different anions (X = Cl, TsO, BF_4, CF_3CO_2) upon heating with potassium fluoride in DMF produced fluorobenzene in 11-85% yield (Scheme 1.44). The lowest yield (11 %) of fluorobenzene was obtained in the reaction of diphenyliodonium chloride with KF in DMF at 115 °C, while the thermolysis of diphenyliodonium tetrafluoroborate with KF at 160-170 °C gave fluorobenzene **1.91** in 85% yield without using any solvent.



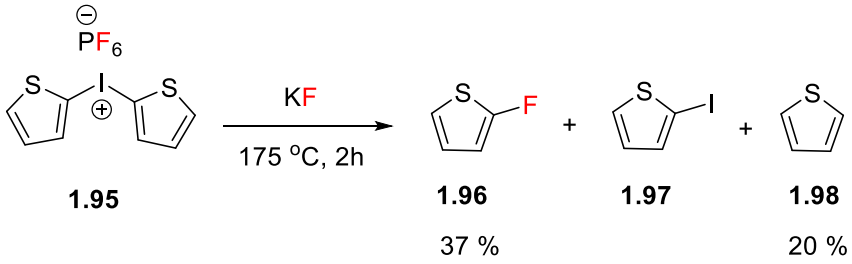
***Scheme 1.44**: Thermal decomposition of diaryliodonium salts.*

Carroll and co-workers have reported a series of papers on the fluorination of diaryliodonium salts, including those containing heteroaromatics, to prepare fluorinated products.[108,109] They found that the addition of radical scavengers such as (2,2,6,6-tetramethylpiperidine-1-oxyl) TEMPO to the fluorination reaction leads to a significant improvement in the yield of the desired fluoroarene products without any effect on the regioselectivity of the process. For instance, the reaction of iodonium salt **1.92** with CsF in different solvents (DMSO, DMF, *N*,*N*-dimethylacetamide and MeCN) in the absence of a radical trap produced a mixture of fluoroarenes **1.93** and **1.94** in 1:1 ratio with overall yields below 5 %. By using 20 mol % of TEMPO, the combined yield of **1.93** and **1.94** was increased up to 35 % with almost unchanged regioselectivity (Scheme 1.45).[110]



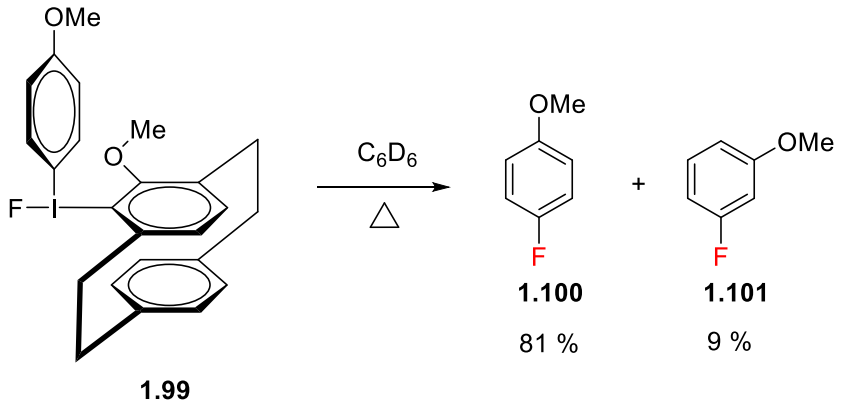
***Scheme 1.45**: Effect of TEMPO on the fluorination of diaryliodonium salts.*

Onys'ko, Gakh and co-workers have developed a selective synthesis of 2-fluorothiophene **1.96**. This can be achieved by the treatment of bis(2-thienyl)iodonium hexafluorophosphate **1.95** with KF (as a mechanical mixture) at 172-175 °C for 2 hours to produce **1.96**, 2-iodothiophene **1.97**, and thiophene (Scheme 1.46). Bis(2-thienyl)iodonium hexafluorophosphate **1.95** with more nucleophilic anions, such as trifluoroacetate, yielded only 2-3 % of **1.96**.[111]



***Scheme 1.46**: Synthesis of 2-fluorothiophene **1.96**.*

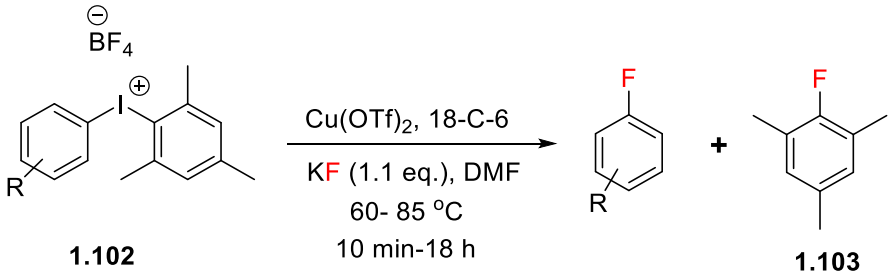
DiMagno and co-workers proposed that electron-rich arenes can be fluorinated with high regioselectivity through a reductive elimination from 5- methoxy[2.2]paracyclophan-4-yl iodonium salt **1.99** (Scheme 1.47). Application of the sterically hindered cyclophane directing group allowed a high degree of control in this process.[112,113] However, although it has excellent selectivity, the major problem of this approach is the use of inaccessible starting compounds and complex synthetic procedures.



***Scheme 1.47**: Regioselective fluorination of **1.99**.*

Recently, Sanford and co-workers [98] observed that the presence of a copper catalyst can change the aryl group preference. In the fluorination of $ArI^{+}(Mes)X^{-}$ **1.102**, chemoselectivity and yield for Ar-F versus mesityl fluoride **1.103** was observed to depend on the Cu pre-catalyst and the solvent. Under some conditions generation of aryl-fluoride is strongly favoured whilst under others mesityl fluoride is prefered. The use of commercially available $Cu(OTf)_2$ in DMF at 60-85 °C for 10 min-18 h give high

selectivity for Ar-F versus Mes-F for a wide range of aryl groups including electron rich ones (Scheme 1.48). Thus, the mesityl group works as an effective spectator group, giving very high chemoselectivity for Ar-F up to a ratio of 98:2.



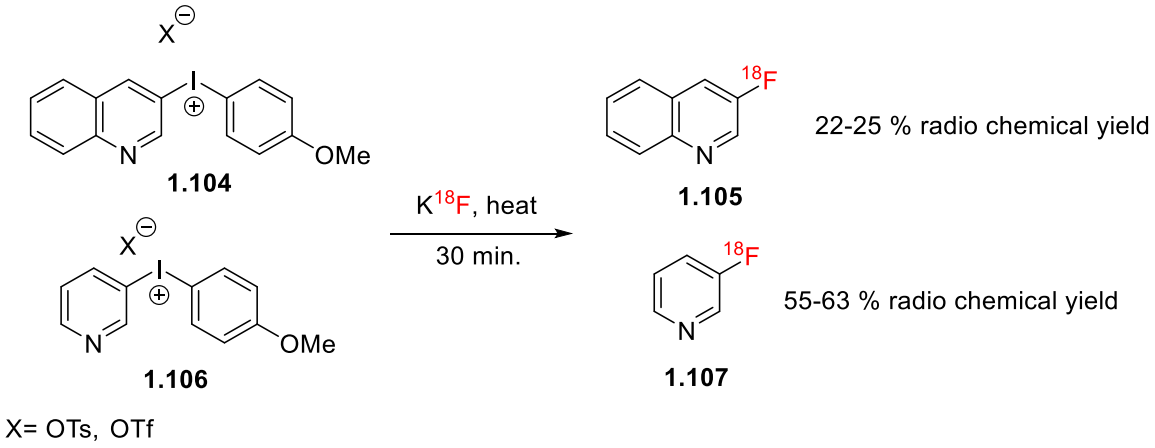
***Scheme 1.48**: Fluorination of aryl(mesityl)iodonium salts*

The fluorination of diaryliodonium salts have found wide applications in Positron Emission Tomography (PET) as a convenient and fast method for the introduction of [^{18}F]-fluoride into molecules. Fluorine-18 labelled fluoropyridines are used frequently in this medical imaging technique; however, they have been restricted to those with fluorine in the 2- or 6-position by synthetic limitations. In these positions, the fluorine has shown high lability *in vivo* which limits their potential for use in PET. The use of diaryliodonium salts has allowed the introduction of ^{18}F into the more stable 3- and 5-positions.[108] ^{18}F-DOPA (^{18}F-Fluorodopamine) can also be prepared in a convenient synthetic route via diaryliodonium salts. This radiotracer is particularly useful for diagnosing Parkinson's disease and neuroendocrine tumours. Generally, the use of the diaryliodonium salts has made for a simpler and more stable procedure that negates the need for anhydrous conditions.[114]

In 1995 Aigbirhio and Pike applied diaryliodonium salts for the preparation of ^{18}F-labeled Ar-F for the first time, using [^{18}F]KF in the presence of diazacrown ether Kryptofix (K_{222}) in MeCN at 85 °C or 110 °C. Under these conditions, the reaction of $Ph_2I^+Cl^-$ provided [^{18}F]Ph-F in 31-78 % radiochemical yield. The use of Kryptofix is required for the phase transfer of the [^{18}F]-fluoride ion.[115]

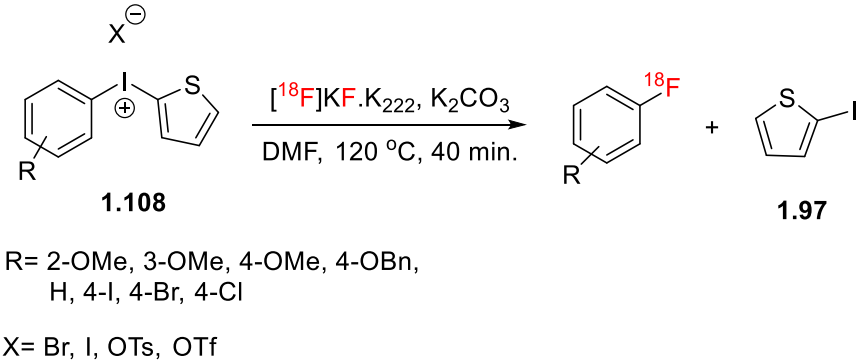
Carroll and co-workers have reported a selective and convenient route to fluorine-18 labelled 3-fluoroquinoline **1.105** and 3-fluoropyridine **1.107** by [^{18}F]-fluorination of

iodonium salts **1.104** and **1.06** (Scheme 1.49). The use of 4-methoxyphenyl as the aryl group in iodonium salts **1.104** and **1.106** provided the necessary degree of selectivity in the nucleophilic fluorination process.[108]



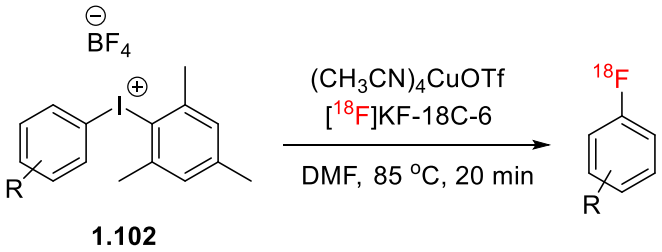
***Scheme 1.49**: Preparation of fluorine-18 labelled **1.105** and **1.107**.*

Coenen and co-workers have developed an efficient route for nucleophilic fluorination using aryl-(2-thienyl)iodonium salts **1.108** (Scheme 1.50). The 2-thienyl group is a highly electron-rich spectator group which allowed the introduction of ^{18}F into electron-rich arenes. They also found that the selectivity of the nucleophilic fluorination of **1.108** relies on the nature of the counteranion X^-, with the highest yields of $Ar^{18}F$ (more than 60 % radiochemical yield) obtained in the reactions of iodonium bromides.[116]



***Scheme 1.50**: Regioselective nucleophilic fluorination of aryl-(2-thienyl)iodonium salts.*

Building on their earlier initial work, Sanford's group [98] have developed a general, rapid and high yielding procedure for the radiofluorination of **1.102** in the presence of a copper catalyst.[98] The optimum conditions for this reaction used the commercially available $(CH_3CN)_4CuOTf$ and [^{18}F]KF-18-crown-6, and DMF as the solvent (Scheme 1.51). Copper(I) catalysts were found to give higher yields of Ar^{18}F in only 20 min. in comparison with those of copper(II). This protocol can be applied efficiently for the radiofluorination of electron-rich, -neutral and -deficient substrates, as well as to the synthesis of bioactive molecules, such as 6-[^{18}F]-fluoroDOPA and 4-[^{18}F]fluorophenylalanine.[117]



1.102

Scheme 1.51**: Copper-catalyzed [^{18}F] fluorination of **1.102

1.5 Project Aims

Hypervalent iodine(III) compounds have found many applications in organic synthesis, and various λ^3-iodane reagents have been reported as green oxidants or crucial reagents for selective group transfer reactions. Diaryliodonium salts are a type of hypervalent iodine(III) compound that are capable of arylating a variety of nucleophiles including fluoride. Unsymmetrical diaryliodonium salts provide varying degrees of selectivity during reactions with fluoride.

Building on this approach, this project was divided in to three parts:

1. The cyclic hypervalent iodine(III) reagents, fluoroiodane **1.22** and **3.5** (Figure 1.9), will be synthesised via a multi-stage reaction pathway following a synthetic route developed by Stuart's group. These reactions were carried out at room temperature without the need for inert conditions and the products were produced in high yields. In the last step, TREAT-HF was used as the nucleophilic source of fluoride since it is a very stable and cheap source.

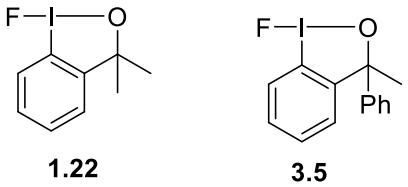
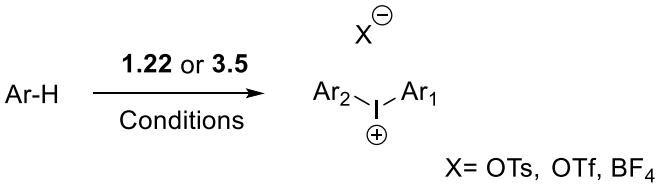


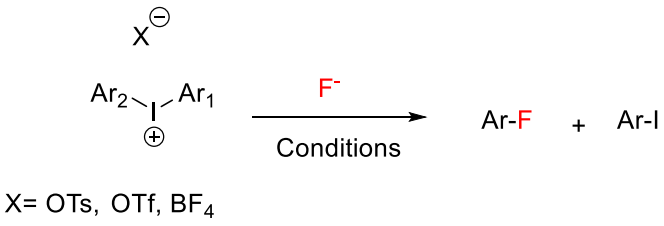
***Figure 1.9**: Hypervalent iodine(III) reagents.*

2. A series of novel diaryliodonium salts will be synthesised by reacting activated aromatics with hypervalent iodine(III) reagents, fluoroiodanes **1.22** and **3.5**, in the presence of tosyl acid, triflic acid, $BF_3.OEt_2$ and $Zn(BF_4)_2.xH_2O$ (Scheme 1.52). The reaction conditions, such as temperature, reaction time and solvents, were investigated in order to optimise the reaction.



***Scheme 1.52:** Synthesis of diaryliodonium salts from fluoroiodane*

3. The reactivity of the new unsymmetrical diaryliodonium salts will be investigated with fluoride in order to prepare a series of *p*-fluorinated arenes. The fluorination of the new salts will be first tested under the same reaction conditions that have been reported by Sanford's group.[98] The effect of using different temperatures, reaction times, solvents, copper catalysts and fluorinating reagents to be also investigated in order to optimise the reaction conditions (Scheme 1.53).



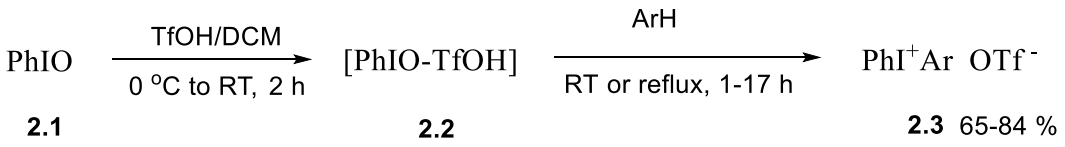
***Scheme 1.53**: Fluorination of diaryliodonium salts*

Chapter Two: Synthesis of unsymmetrical diaryliodonium salts

2.1 Introduction

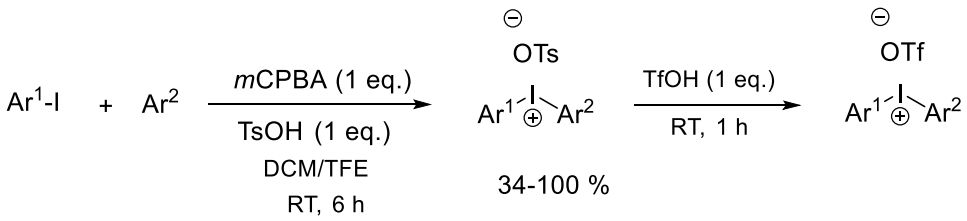
The aim of the research reported in chapter 2 was to investigate the synthesis of unsymmetrical diaryliodonium salts by reacting activated aromatics with fluoroiodane in the presence of either p-toluenesulphonic acid, triflic acid or boron trifluoride.

Several iodine(III) reagents have been employed with activated aromatics to produce diaryliodonium salts. Kitamura and co-workers reported the preparation of diaryliodonium triflate by reacting iodosylbenzene (PhIO) **2.1** with triflic acid (TfOH) to form a PhIO-TfOH reagent **2.2** which was reacted with activated aromatics such as anisole and diphenyl ether in DCM to produce diaryliodonium salts **2.3** in good yields (65-84 %).).[118] (Scheme 2.1).



Scheme 2.1: *Preparation of diaryliodonium triflates*

In 2008 Olofsson and co-workers reported a new route to prepare unsymmetrical diaryliodonium salts by reacting electron-rich arenes and aryl iodides using *m*-CPBA with *p*-toluenesulfonic acid. The tosylate counteranion in the unsymmetrical diaryliodonium salts can be exchanged easily with triflate using triflic acid (Scheme 2.2).[89]



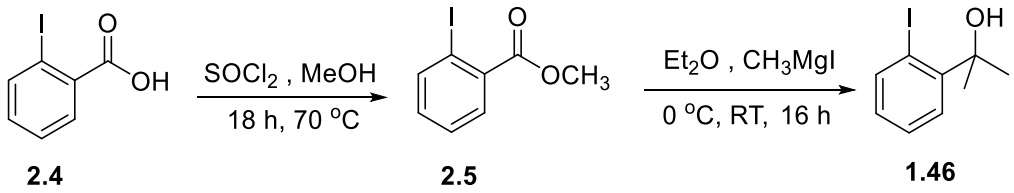
Scheme 2.2: *One-pot synthesis of diaryliodonium triflates*

Before this work could start, the fluoroiodane had to be prepared from 2-(2-iodophenyl)propan-2-ol.

2.2 Synthesis of Fluoroiodane

2.2.1 Preparation of 2-(2-iodophenyl)propan-2-ol

2-(2-Iodophenyl)propan-2-ol **1.46** was produced in two steps following Togni's procedure as shown in Scheme 2.3. The first step was the esterification of 2-iodobenzoic acid with methanol, followed by a Grignard reaction using methyl magnesium iodide.[119]



2.4 **2.5** **1.46**

Scheme 2.3**: Formation of 2-(2-iodophenyl)propan-2-ol **1.46

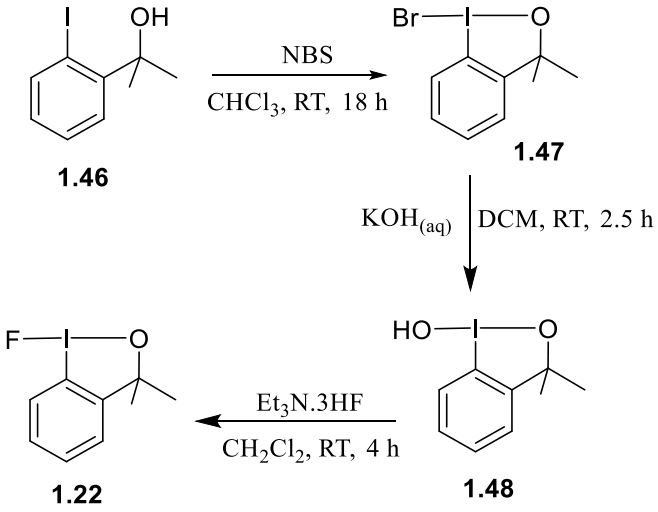
In the first reaction 2-iodobenzoic acid **2.4** was heated at 70 °C with thionyl chloride and methanol to produce methyl-2-iodobenzoate **2.5** in a very high yield (96 %). One advantage of this reaction is that no purification step was needed since the by-products of this reaction are HCl and SO_2. HCl can be removed by washing with a brine solution (NaCl saturated solution) and SO_2 is a gas, which is released during the reaction. In the ^{1}H NMR spectrum of **2.5**, a singlet peak at 3.93 ppm was observed for the methoxy group, which indicated that the ester had been formed. The ^{13}C NMR spectrum displayed a peak at 52.5 ppm which can be assigned to the carbon of the methoxy group and a signal in the ASAP-MS spectrum at *m/z* 262.9563 corresponded to MH^+.

Methyl-2-iodobenzoate **2.5** was reacted with a Grignard reagent to produce 2-(2-iodophenylpropan-2-ol **1.46**. The methyl magnesium iodide solution in dry diethyl ether was prepared under nitrogen by reacting methyl iodide with magnesium at a gentle reflux. The Grignard solution was then transferred to a new flask using a cannula and cooled to 0 °C before a solution of **2.5** in dry diethyl ether was added dropwise and left to react overnight at RT. The pure product was obtained finally as an orange oil in 73 % isolated yield.

The ^{1}H NMR spectrum of the product **1.46** had a singlet peak at 1.76 ppm corresponding to the two new methyl groups whilst the resonance assigned to the OH singlet was observed at 2.51 ppm. In addition, the resonance assigned to the OCH_3 group was no longer present in the ^{13}C NMR spectrum and a singlet peak, at 29.8 ppm, corresponding to the two methyl groups was observed, indicating that **1.46** had been formed. A peak in the ASAP-MS spectra corresponding to $[M\text{-}OH]^+$ at *m/z* 244.9814 was also observed.

2.2.2 Preparation of 1-fluoro-3,3-dimethyl-1,3-dihydro-λ3-benzo[d][1,2]iodoxole

1-Fluoro-3,3-dimethyl-1,3-dihydro-λ$_3$-benzo[d][1,2]iodoxole was produced in 3 steps. There are a few routes to prepare **1.22** reported in the literature,[63,120] but the route reported by Stuart was used in this work (Scheme 2.4).[64]



Scheme 2.4**: Formation of the fluoroiodane **1.22

The first step involved bromination of the tertiary alcohol **1.46**, which generated a λ3-iodane. The tertiary alcohol was dissolved in chloroform with *N*-bromosuccinimide (NBS), and the mixture was allowed to react at room temperature whilst being stirred overnight. A yellow crystalline solid was ultimately formed after recrystallization from warm ethyl acetate. Recrystallization is important to remove any impurities and the yield of bromoiodane **1.47** was 76 %, which was similar to that reported by Stuart (79 %).[64]

Compound **1.47** was analysed by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. In the ^{1}H NMR spectrum a characteristic downfield shift in one of the aromatic protons (7.50-7.55 ppm), as compared to that observed for the equivalent proton in the starting material (6.80 ppm), was observed. This shift occurs due to the change in oxidation state of iodine from (I) to (III). In addition, the absence of the OH peak at 2.51 ppm indicates that there was no starting material remaining.

Similarly, the ^{13}C NMR spectra for the starting material and product show that there is a significant shift downfield for the two quaternary carbon atoms bonded to the iodine and oxygen atoms. The carbon directly attached to iodine was shifted from 93.1 ppm in **1.46** to 112.0 ppm in **1.47** and the carbon directly attached to oxygen was shifted from 73.6 ppm in **1.46** to 84.2 ppm in **1.47**. These shifts indicated that the desired product had been formed. Furthermore, in the ASAP-MS spectrum, the isotopic pattern for bromine showed an approximately 50:50 ratio between ^{79}Br and ^{81}Br and thus there were peaks at *m/z* 340.9055 and *m/z* 342.9018 in the mass spectrometry data.

In the next step the bromoiodane **1.47** in dichloromethane was stirred with an aqueous solution of potassium hydroxide at room temperature for 2.5 hours. During the reaction, the colour of the reaction mixture changed from yellow to white. It is straightforward to produce pure product after extraction, since the hydroxyiodane is soluble in the organic phase and the by-product, potassium bromide, remains in the aqueous phase. ASAP-MS spectra showed a peak corresponding to MH^{+} at *m/z* 278.9880. In addition, formation of **1.48** was supported by the ^{1}H and ^{13}C NMR spectra, which were in agreement with those reported in the literature.[64]

In the key step hydroxyiodane **1.48** was reacted with a nucleophilic source of fluoride in DCM at room temperature for 4 hours with stirring. Triethylamine trihydrogen fluoride (TREAT-HF) was used as the source of fluoride since it is very stable and cheap in comparison with other reagents, even though it is somewhat toxic. During the work up, washing with water is important to remove the excess TREAT-HF. At this point, using $MgSO_4$ to dry the organic phase must be avoided because it can react with the fluoroiodane **1.22** product. Instead, co-evaporation with toluene was used to remove any residual water. Recrystallization from toluene was used to remove any impurities and the product was obtained as white crystals in a 98 % yield. To confirm that fluoride

substitution had occurred, the ^{19}F NMR spectrum was recorded, which showed a singlet peak at -143.1 ppm in agreement with that reported in the literature.[64] In addition, a peak in the ASAP-MS spectrum corresponding to MH^+ at *m/z* 280.99 was observed.

The fluoroiodane **1.22** was stored at -18 °C because it can become sticky when left for extended periods of time at room temperature. At -18 °C, the fluoroiodane **1.22** is stable for several months.

This three-step route, as reported by Stuart,[64] is a good way to produce the fluoroiodane reagent because of the mild reaction conditions and each step proceeds in high yield.

2.3 Synthesis of unsymmetrical diaryliodonium salts using *p*-toluenesulphonic acid

2.3.1 Optimisation of the synthetic approach

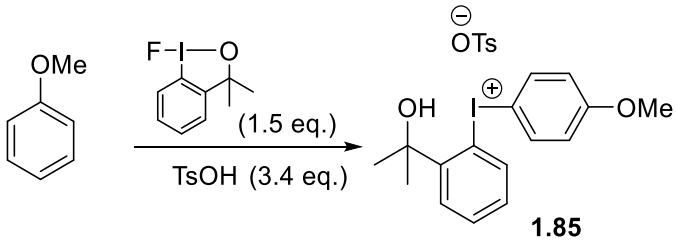
In order to produce unsymmetrical diaryliodonium salts, fluoroiodane **1.22** was used as the source of hypervalent iodine(III) reagent (1.5 equivalents) in a direct reaction with anisole (1.0 equivalent) in the presence of *p*-toluenesulphonic acid (3.4 equivalents) and the preliminary results are shown in Table 2.1.

Initially, DCM was used as the solvent but the room temperature reaction lead to low conversion and yield, even when the reaction was left for 72 h (entry 1). This was probably due to the low solubility of the *p*-toluenesulphonic acid. The conversion increased to 65 % when acetonitrile was used as a solvent in a room temperature reaction for 48 h. The reaction was improved by leaving the reaction mixture at 40 °C overnight forming the product in an excellent 87 % yield (entry 3). However, when the amounts of the *p*-toluenesulphonic acid and the fluoroiodane **1.22** were reduced to 2.6 and 1.1 equivalents respectively, both the conversion and yield decreased (entry 4). Similarly, these values decreased when the reaction time was reduced to 6 hours in entry 5.

Compound **1.85** was purified by a number of steps. The main step was washing with water to remove the excess of *p*-toluenesulphonic acid. The crude product was then washed with hot hexane and the final purification step was to reflux the product in diethyl

ether. The pure product **1.85** was obtained as a white solid in 87 % yield in entry 3 (Table 2.1).

Table 2.1**: Optimisation of the reaction between anisole and fluoroiodane **1.22** for the preparation of **1.85

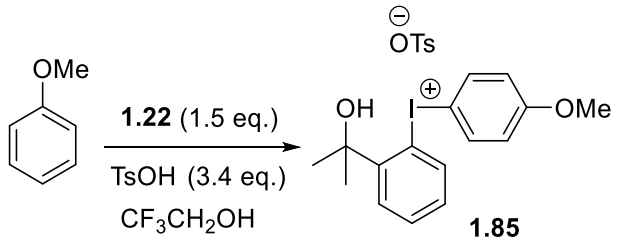


Entry	1.22 (equiv.)	TsOH (equiv.)	Solvent	Temp. (ºC)	Time (h)	Conversion[a] (%)	Yield[b] (%)
1	1.5	3.4	DCM	RT	72	45	19
2	1.5	3.4	MeCN	RT	48	65	61
3	1.5	3.4	MeCN	40	18	100	87
4	1.1	2.6	MeCN	40	18	83	68
5	1.5	3.4	MeCN	40	6	88	82

[a] Determined by ^{1}H NMR spectroscopy; [b] Isolated yield.

In entry 3, the ^{19}F NMR spectrum of the crude reaction mixture showed the absence of a peak at -143.1 ppm, indicating that there was no fluoroiodane **1.22** remaining. The ^{1}H NMR spectrum showed 100 % conversion of the anisole to only one product. Only the *p*-substituted diaryliodonium salt was isolated and there were two singlet peaks at 1.71 and 3.93 ppm corresponding to the protons of the two methyl groups and the methoxy group, respectively. In the ^{13}C NMR spectrum, the two peaks at 21.3 ppm and 55.7 ppm can be assigned to the two methyl groups and methoxy group, respectively. The ESI-MS spectrum gave a peak corresponding to M^{+} at *m/z* 369, representing the diaryliodonium salt cation and MS (ES^{-}) showed a peak at *m/z* 171 for the tosylate counteranion.

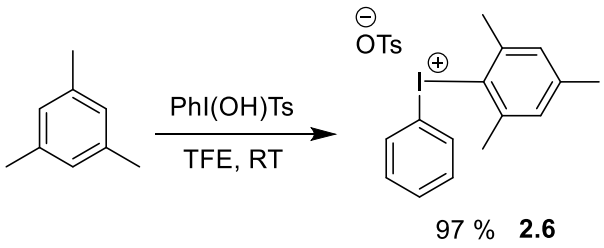
***Table 2.2**: Optimisation for the preparation of **1.85** using fluoroiodane **1.22** in TFE*



Entry	Temp. (ºC)	Time (h)	Conversion[a] (%)	Yield[b] (%)
1	40 ºC	6	100	94
2	40 ºC	2	100	94
3	RT	18	100	94
4	RT	2	100	90
5	RT	1	100	90

[a] Determined by ^{1}H NMR spectroscopy; [b] Isolated yield.

Table 2.2 shows the significant effect of using trifluoroethanol (TFE) as the solvent to form **1.85**. A 100 % conversion and 90 % yield was obtained even after just 1 hour at room temperature (entry 5). This effect is probably due to the useful properties of TFE, such as its high polarity, high ionization power and it is a good hydrogen bond donor.[121,122] The usefulness of TFE as a solvent has been demonstrated previously. No reaction was observed between Koser's reagent[123] and mesitylene in dichloromethane, acetonitrile and methanol during attempts to prepare an unsymmetrical diaryliodonium salt in one step. In contrast, a 97 % yield was obtained when TFE was used (Scheme 2.5).[121]



***Scheme 2.5**: The effect of TFE on the preparation an iodonium salt*

2.3.2 Scope of the reaction

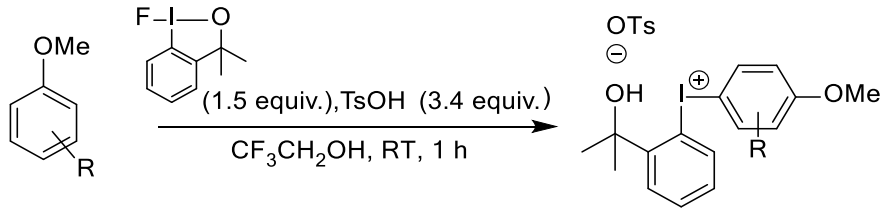
To investigate the scope of this reaction, the optimized protocol was applied to a series of activated aromatics. Fluoroiodane **1.22** was reacted with electron-rich aromatics that contained at least one methoxy group to form unsymmetrical diaryliodonium salts in 100 % conversions and high yields (86-97 %) (Table 2.3).

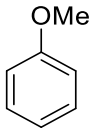
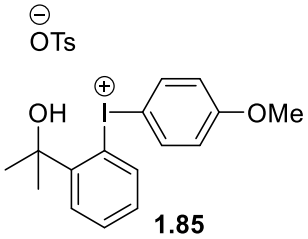
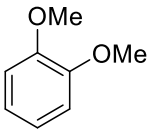
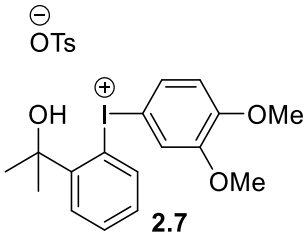
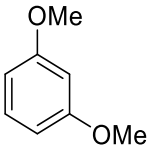
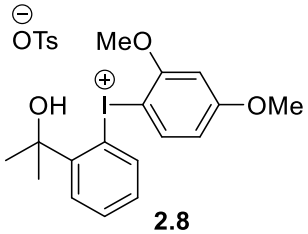
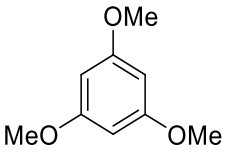
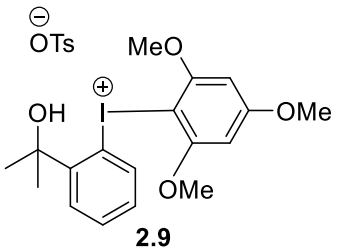
Fluoroiodane **1.22** was first reacted with 1,2-dimethoxybenzene to form (2-(2-hydroxypropan-2-yl)phenyl)(3,4-dimethoxyphenyl)iodonium-4-methylbenzene sulfonate **2.7** as a purple solid in 86 % yield (entry 2). The ^{1}H NMR spectrum of the pure product in $CDCl_3$ revealed two singlets at 3.90 ppm and 3.98 ppm corresponding to the two methoxy groups in different environments. Two singlets at 1.71 and 2.30 ppm corresponding to the two methyl groups on the sidearm and the methyl group of the tosylate anion were also observed. The ^{13}C NMR spectrum showed the two methoxy peaks at 56.2 and 56.5 ppm and the two C-I peaks at 99.9 and 108.9 ppm. In addition, analysis by ESI-MS showed a peak at *m/z* 399 corresponding to the [MH^+].

(2-(2-Hydroxypropan-2-yl)phenyl)(2,4-dimethoxyphenyl)iodonium-4-methylbenzene sulfonate **2.8** was obtained in a 97 % yield as a white solid by the reaction of **1.22** with 1,3-dimethoxybenzene (entry 3). The ^{1}H NMR spectrum showed two singlets at 3.83 and 3.92 ppm corresponding to the two methoxy groups. Two singlet peaks at 1.73 and 2.30 ppm corresponding to the two methyl groups on the sidearm at 1.73 ppm and the methyl group of the tosylate anion at 2.30 ppm were also observed. In the ^{13}C NMR spectrum, two singlets at 21.3 and 30.5 ppm corresponding to the three methyl groups (two have the same environment) and the two singlet methoxy peaks at 56.0 and 56.8 ppm were

observed. Furthermore, the two C-I peaks at 91.6 and 108.1 were also present. Analysis by ESI-MS showed a peak at *m/z* 399 corresponding to the [MH^+].

***Table 2.3**: Synthesis of substituted diaryliodonium salts with p-toluenesulphonic acid*

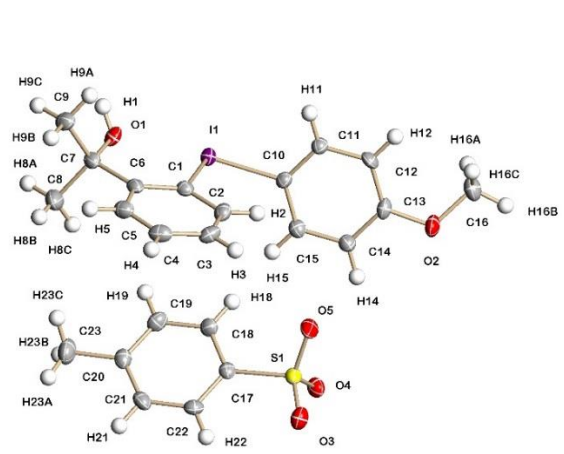


Entry	Substrate	Product	Yield[a] (%)
1		 **1.85**	90
2		 **2.7**	86
3		 **2.8**	97
4		 **2.9**	93

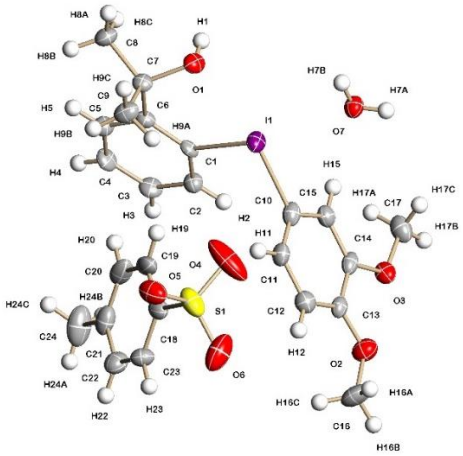
[a] Isolated yield

In entry 4, 1,3,5-trimethoxybenzene was reacted with **1.22** to give (2-(2-hydroxypropan-2-yl)phenyl)(2,4,6-trimethoxyphenyl) iodonium 4-methylbenzenesulfonate **2.9** in a 93 % yield as a white solid. The ^{1}H NMR spectrum of **2.9** showed two singlet peaks at 3.84 and 3.94 ppm corresponding to the three methoxy groups. Two of them have the same environment. The two singlets at 1.73 and 2.30 ppm corresponded to the two methyl groups on the sidearm and the methyl group of the tosylate anion. As expected, twenty signals were observed in the ^{13}C NMR spectrum, including two peaks at 56.1 and 56.9 ppm corresponding to the three methoxy groups and two singlet peaks at 83.0 and 107.8 ppm corresponding to the two C-I carbons. Analysis by ESI-MS showed a peak at *m/z* 429 corresponding to the [M^{+}].

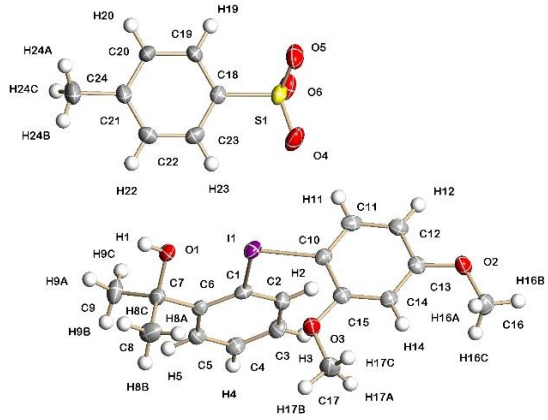
Crystals suitable for X-ray crystallography were obtained for **1.85**, **2.7**, **2.8** and **2.9** (Figure 2.1) and the key bond lengths and angles are presented in Table 2.4. As seen in Table 2.4, the C(1)-I(1) bond length of iodonium tosylates (2.129(3) – 2.142(4)Å) were slightly longer than C(10)-I(1) (2.085(3) – 2.129(5) Å) bond lengths and very similar to those reported for diaryliodonium salts (the iodine and carbon bond ranging generally from 2.00 to 2.10 Å).[124] What is atypical, however is the absence of any secondary bonding between the iodine and tosyl which is generally observed in compounds of this type.[124] The bond angles of the C(1)-I(1)-C(15) ranged from 95.50(14)^{o} to 97.74(17)^{o} which are smaller than that expected for the bent shape of iodonium compounds, which normally have bond angles between 97^{o} and 99^{o}.[125] In addition, the C(7)-O(1) bond lengths of these salts (1.430(4) – 1.441(5) Å) were similar to the C(7)-O(1) bond length of fluoroiodane **1.22** (1.450(6) Å).[63] Furthermore, there were strong intramolecular interactions (2.577(2) – 2.628(3) Å) between I(1) and O(1) in comparison with the I(1)-O(1) of fluoroiodane **1.22** (2.029(3) Å).[63] Finally, the O(1)···I(1)-C(10) bond angles (166.77(10) – 167.79(15)^{o}) were also very similar to the F(1)-I(1)-O(1) bond angle in fluoroiodane **1.22** (166.66 (14)).



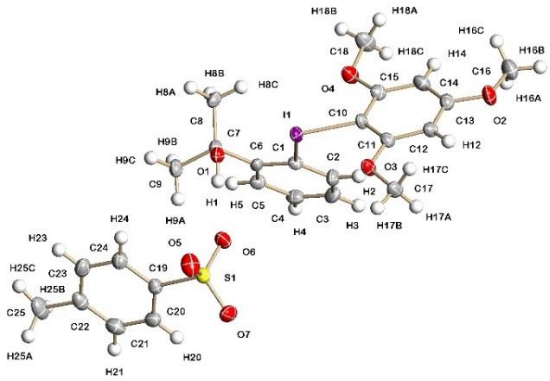
a) Solid-state structure of **1.85**



b) Solid-state structure of **2.7**



c) Solid-state structure of **2.8**



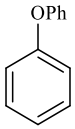
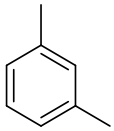
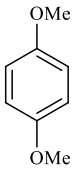
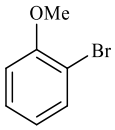
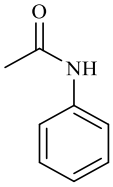
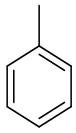
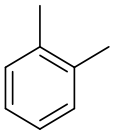
d) Solid-state structure of **2.9**

Figure 2.1*:Solid-state structures for diaryliodonium tosylates*

Table 2.4*: Key bond lengths (Å) and angles (°) for diaryliodonium tosylates*

	1.85	**2.7**	**2.8**	**2.9**
C(1)-I(1)	2.141(4)	2.142(4)	2.135(3)	2.129(3)
C(10)-I(1)	2.090(4)	2.129(5)	2.085(3)	2.087(3)
C(7)-O(1)	1.430(4)	1.441(5)	1.438(4)	1.438(5)
O(1)···I(1)	2.591(3)	2.624(3)	2.577(2)	2.628(3)
C(1)-I(1)-C(10)	95.50(14)	97.74(17)	96.90(12)	96.29(14)
O(1)···I(1)-C(10)	166.80(12)	167.79 (15)	166.77(10)	167.67(11)

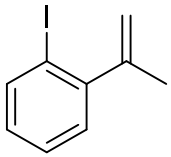
Table 2.5: *Arenes that did not react with* ***1.22***

Entry	Substrate	Entry	Substrate
1		5	
2		6	
3		7	
4			

Unfortunately, there have been many unsuccessful attempts to prepare other diaryliodonium salts by reacting **1.22** with different arenes in the presence of *p*-toluenesulphonic acid (Table 2.5). In the reaction with diphenyl ether, 1,4-dimethoxybenzene and acetanilide (entries 1-3), the ^{1}H NMR spectrum of the crude product showed that there was no reaction in TFE at room temperature for 1 hour or in MeCN at 40 ^{o}C for 18 hours. In addition, only starting material was observed in the crude ^{1}H NMR spectrum when **1.22** was reacted with *ortho*- and *meta*-xylene (entries 4 and 5) in TFE at room temperature for both 1 hour and overnight. Furthermore, 2-bromoanisole was the only aromatic that gave 3 % conversion to the diaryliodonium salt when it was reacted with **1.22** in TFE at room temperature for 1 hour or in MeCN at 40 ^{o}C for 18 hours (entry 6).

Although this route is a good method for the preparation of diaryliodonium salts due to the high yields and mild reaction conditions in comparison with those reported previously,[126] the limited substrate scope is the main drawback of this route.

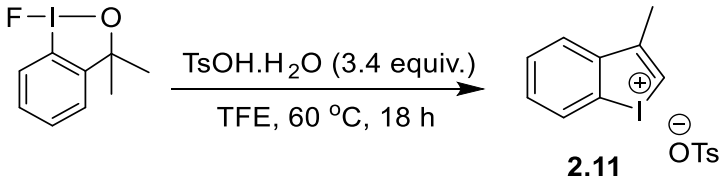
In the reaction with toluene (entry 7), the ^{1}H NMR spectrum of the crude product revealed that there had been no reaction in TFE at room temperature for 1 hour. However, increasing the temperature to 40 ^{o}C for 18 hours led to the formation of a number of products, including 1-iodo-2-(1-methylethenyl)benzene **2.10** (Figure 2.2) (for which there are two singlet peaks at 4.80 and 5.22 ppm corresponding to the two alkene protons and a singlet peak at 2.08 ppm corresponding to the methyl group, which in agreement with that in the literature)[127] and aldehydes (since there are two singlet peaks at 9.7 and 10.1 ppm). Interestingly, 7-iodonia-9-methylbicycle[4,3,O]nona-1,3,5,8-tetraene 4-methylbenzene sulfonate **2.11** was also formed and isolated.



2.10

Figure 2.2**: 1-iodo-2-(1-methylethenyl)benzene **2.10

It was also possible to form **2.11** without the addition of any aromatic substrate. Fluoroiodane **1.22** was reacted with *p*-toluenesulphonic acid in TFE at 60 ^{o}C overnight to give **2.11** as a light brown solid in a 37 % yield (Scheme 2.6).



2.11

***Scheme 2.6**: Preparation of a heterocyclic iodonium salt **2.11** with p-toluenesulphonic acid*

The ^{1}H NMR spectrum of product **2.11** included a 3H doublet peak at 2.34 ppm which, following a COSY experiment, was shown to couple with a downfield 1H signal at 8.37 ppm (Figure 2.3). As expected, fourteen signals were observed in the ^{13}C NMR spectrum, including five quaternary carbon atoms.

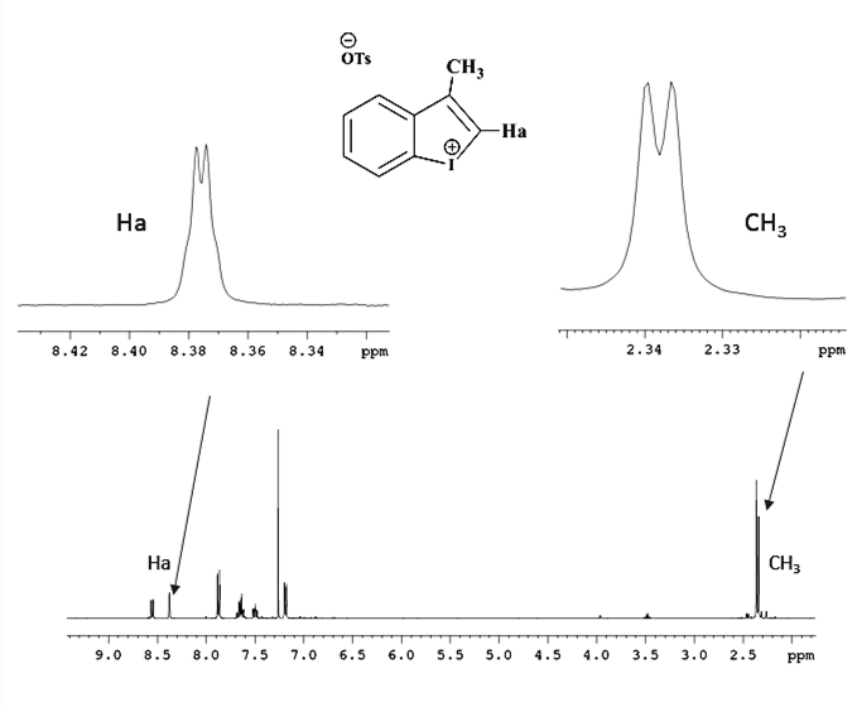


Figure 2.3**: ^{1}H NMR spectrum of **2.11

Single crystals of **2.11** suitable for X-ray crystallography were grown by slow evaporation of a chloroform:hexane (1:2) solution. The molecular structure of **2.11** is shown in Figure 2.4 and representative bond lengths and bond angles are reported in Table 2.6.

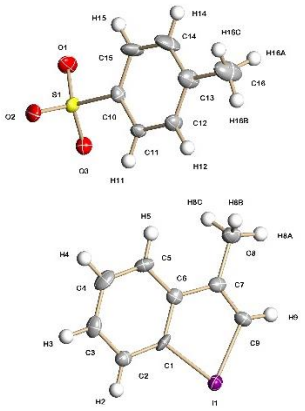


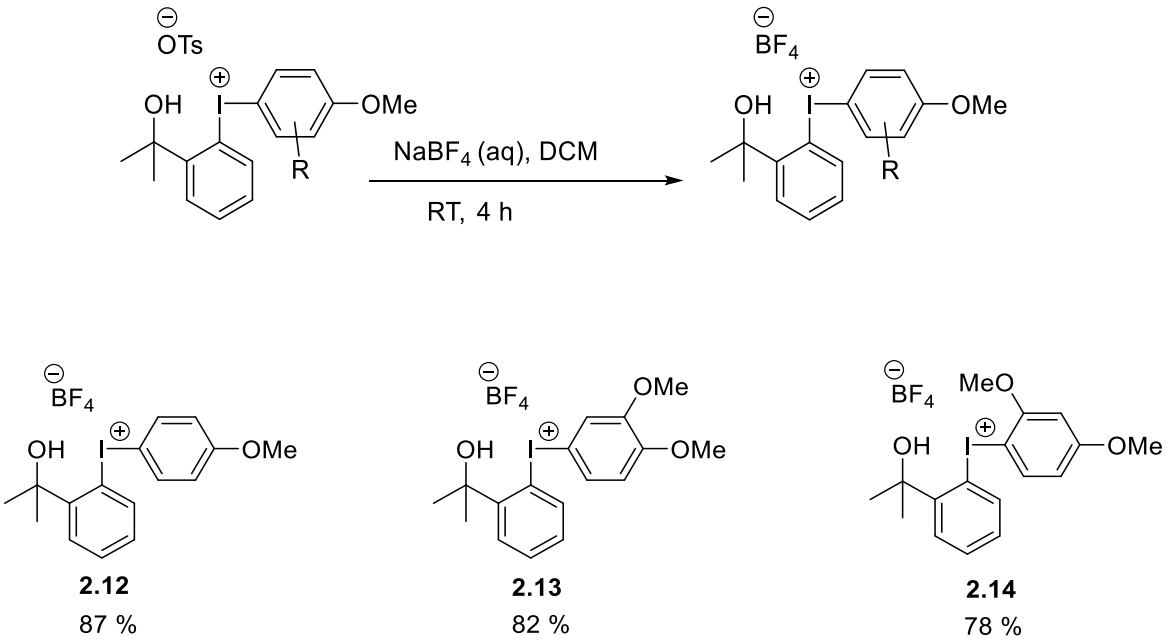
Figure 2.4**: Solid-state structure of **2.11

Table 2.6**: Selected bond lengths (Å) and angles (°) for **2.11

Bond lengths [Å]		Bond angles (°)	
I(1)-C(9)	2.081(5)	C(1)-I(1)-C(9)	81.6(2)
I(1)-C(1)	2.094(5)	C(2)-C(1)-I(1)	126.0(4)
C(7)-C(9)	1.333(7)	C(6)-C(7)-C(9)	117.3(5)
C(6)-C(7)	1.462(7)	-	-

2.3.3 Metathesis reactions with $NaBF_4$

The tosylate counteranion in the unsymmetrical diaryliodonium salts can be easily exchanged with tetrafluoroborate using $NaBF_4$ (aq). The metathesis reactions were carried out by stirring **1.85**, **2.7** and **2.8** in DCM with an aqueous solution of $NaBF_4$ for 4 hours at room temperature (Scheme 2.7) to form **2.12**, **2.13** and **2.14** in high yields (78 % - 87 %).

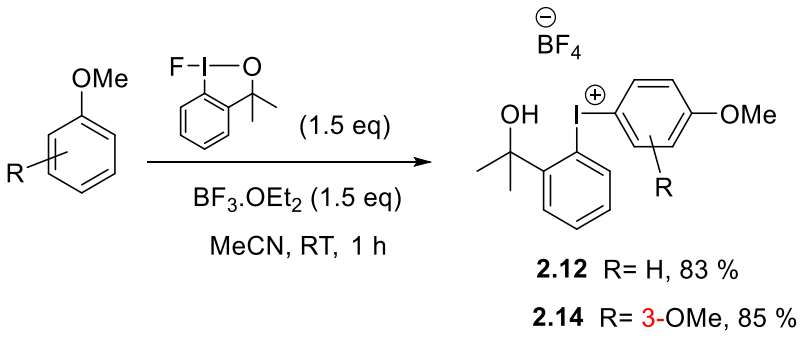


***Scheme 2.7**: Metathesis reactions of diaryliodonium tosylates with $NaBF_4$*

The ^{1}H NMR spectra of the pure products of **2.12**, **2.13**, and **2.14** showed that the singlet peak at 2.34 ppm, corresponding to the methyl group of the tosylate anion disappeared. In addition, the two doublets in the aromatic region also disappeared, indicating that there was no tosylate anion left. On the other hand, the ^{19}F NMR spectra of the pure products showed a singlet peak at -151.5 corresponding to the tetrafluoroborate anion. These salts were also characterised by MS (ES) and gave a peak at *m/z* 87 for the tetrafluoroborate anion.

2.4 Synthesis of unsymmetrical diaryliodonium salts using boron trifluoride

Instead of using *p*-toluenesulphonic acid to activate the fluoroiodane reagent **1.22**, the effect of using the Lewis acid, $BF_3.OEt_2$, was investigated by reacting anisole with **1.22** (1.5 equivalents) in the presence of $BF_3.OEt_2$ (1.5 equivalents). The reaction mixture containing anisole, **1.22** and acetonitrile was cooled to 0 ^{o}C before adding $BF_3.OEt_2$ and warming to room temperature to react for 1 h (Scheme 2.8). The reaction was carried out under nitrogen and using dry acetonitrile since $BF_3.OEt_2$ reacts with water to produce hydrofluoric acid. The pure solid product **2.12** was obtained after washing the crude product with hexane and diethyl ether to produce **2.12** in 83 % yield.



Scheme 2.8: Synthesis of diaryliodonium salts using $BF_3.OEt_2$

Although 1,3-dimethoxybenzene reacted with fluoroiodane **1.22** in the presence of $BF_3.OEt_2$ to form the iodonium salt **2.14** in 85 % yield, there was no reaction with 1,2-dimethoxybenzene under the same reaction conditions. Only 1,2-dimethoxybenzene and iodoalkene **2.10** were observed in the ^{1}H NMR spectrum of the crude product.

When 2-bromoanisole was reacted with **1.22** under the same conditions, only 5 % conversion was observed in the ^{1}H NMR spectrum of the crude product. The amounts of $BF_3.OEt_2$ was increased from 1.5 to 3 equivalents and the reaction time was increased to 2 hours, but this lead to only a 2 % conversion of 2-bromoanisole.

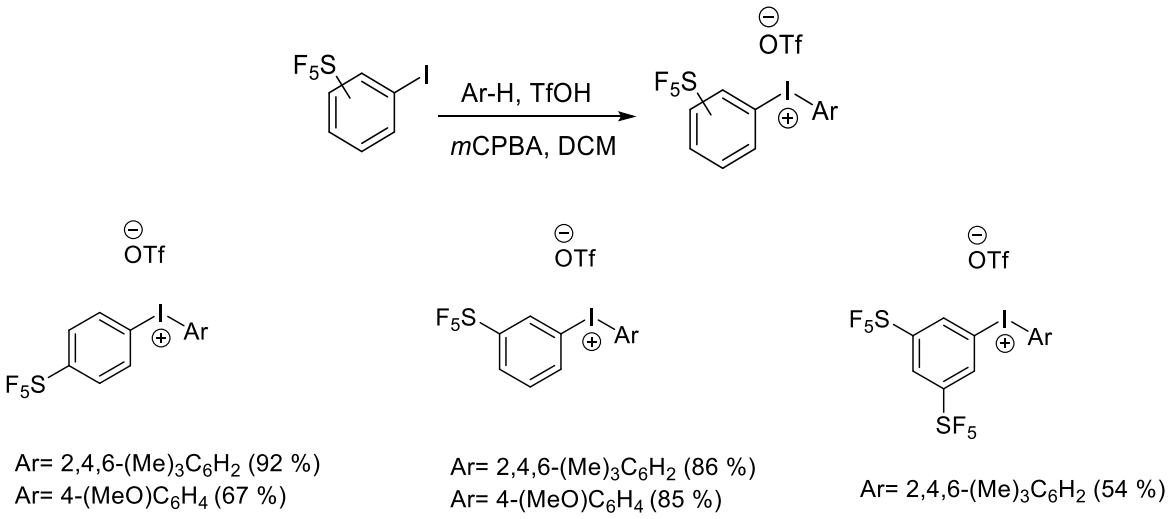
Although this reaction worked well with anisole and 1,3-dimethoxybenzene, there was a major problem with the narrow substrate scope of this reaction.

2.5 Synthesis of unsymmetrical diaryliodonium salts using triflic acid

2.5.1 Optimisation studies using 1.5 equivalents of triflic acid

In order to try to extend the scope of substrates for the preparation of diaryliodonium salts, the use of triflic acid instead of *p*-toluenesulphonic acid was investigated because of its higher acidity. Using triflic acid in organic solvents was an efficient alternative to the inorganic acids used previously to form diaryliodonium salts,[128,129] due to its higher reactivity and the triflate salts could be easily isolated without anion exchange.[88]

Recently, Matsuzaki reacted SF_5-aryliodides with arenes using DCM as the solvent in the presence of triflic acid giving unsymmetrical diaryliodonium salts in high yields (Scheme 2.9).[130]



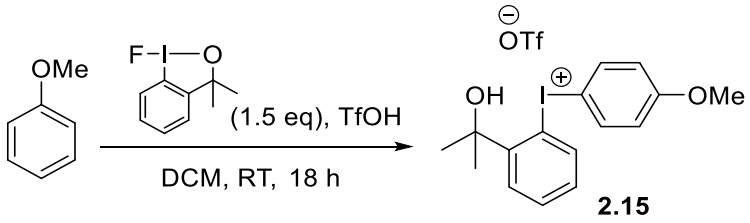
***Scheme 2.9**: Synthesis of SF_5-aryliodonium salts*

The initial attempt to react anisole with fluoroiodane **1.22** in the presence of triflic acid using TFE as the solvent failed, and the ^{1}H NMR spectrum of the crude product showed that the desired reaction had not occurred. Therefore, the reaction using triflic acid to activate fluoroiodane **1.22** was investigated using DCM as the solvent (Table 2.7). Three different methods of addition were investigated. In method A, fluoroiodane **1.22**, triflic acid and DCM, were stirred together for 1 h before adding anisole and the reaction mixture was stirred at RT for a further 18 h.[131] In entry 1 the reaction mixture turned black and there was no sign of any product formed. However, when the amount of triflic acid was reduced to 1.5 equivalents in entry 2, there was a 93 % conversion to the diaryliodonium salt which was isolated in 56 % yield.

In method B, fluoroiodane **1.22**, triflic acid and DCM were only stirred together for 5 min before adding anisole. Using 3.4 equivalents of triflic acid in entry 3, lead to the reaction mixture turning black indicating that decomposition was occurring and there was no sign of the desired product **2.15** in the ^{1}H NMR spectrum of the crude product.

In method C, fluoroiodane **1.22**, anisole and DCM was stirred together at RT for 5 minutes before adding the triflic acid. When this method was used with 1.5 equivalents of triflic acid in entry 4, the diaryliodonium salt was isolated in 78 % yield.

***Table 2.7**: Preparation of **2.15** in DCM*



Entry	Triflic acid (equiv.)	Solvent (mL)	Conversion[d] (%)	Yield[e] (%)
1[a]	3.4	3.5	0	-
2[a]	1.5	2	93	56
3[b]	3.4	2	0	-
4[c]	1.5	2	80	78

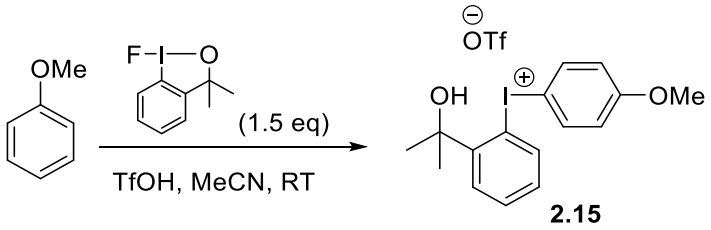
[a] Anisole was added last, after 1 hour; [b]Anisole was added last, after 3 – 5 min; [c] triflic acid was added last, after 3 – 5 min; [d] determined by ^{1}H NMR spectroscopy; [e] Isolated yield.

The crude product of **2.15** was purified by a number of steps. First, it was washed with water to remove the excess of triflic acid. Then, it was washed with hot hexane and the final purification step was to reflux the product in diethyl ether to form the pure product **2.15** as a white solid in 78 % yield in entry 4.

The ^{1}H NMR spectrum for the pure product **2.15** displayed two singlet peaks at 1.71 ppm and 3.93 ppm, corresponding to the two methyl and the methoxy groups, respectively. The ^{19}F NMR spectrum showed a singlet peak at -78.3 ppm corresponding to the CF_3 group of the triflate anion. Additionally, in the ^{13}C NMR spectrum a quartet (quaternary)

peak at 120.5 ppm was assigned to the CF_3 group of the triflate anion. ESI-MS spectrum showed a peak at *m/z* 369 which corresponded to M^+ and a peak at *m/z* 149 in the MS (ES^-) was observed for the triflate anion.

***Table 2.8**: Preparation of **2.15** in MeCN*



Entry	Triflic acid (equiv.)	Time (h)	Conversion[d] (%)	Yield[e] (%)
1[a]	3.4	18	0	-
2[b]	3.4	18	100	78
3[c]	3.4	18	83	75
4[b]	1.5	18	100	76
5[b]	1.5	2	100	86
6[b]	1.5	1	100	84

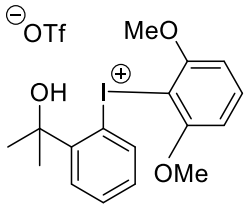
[a] Anisole was added last, after 1 hour; [b] Anisole was added last, after 3 – 5 min; [c]. Triflic acid was added last, after 3 – 5 min; [d] determined by ^{1}H NMR spectroscopy; [e] Isolated yield.

The effect of using MeCN as the solvent for the preparation of iodonium salt **2.15** is shown in Table 2.8. Initially, the three different methods of addition were compared directly in entries 1-3, each using 3.4 equivalents of triflic acid. Method B, in which the anisole is added after 5 minutes, gave the best result with a 100 % conversion and a 78 % yield. Decreasing the amount of triflic acid to 1.5 equivalents in entry 4 gave essentially the same result as using 3.4 equivalents in entry 2. However, the best yields were obtained when the reaction time was reduced to 1-2 hours (entries 5 and 6).

2.5.2 Scope of the reaction using 1.5 equivalents of triflic acid

The substrate scope of the reaction with fluoroiodane **1.22** and triflic acid (1.5 equivalents) was subsequently investigated. Unfortunately, this methodology only worked with a small number of activated aromatics, providing the diaryliodonium salts in 100 % conversions and high yields (Table 2.9). The pure products were easily isolated as white solids after washing with hexane and diethyl ether.

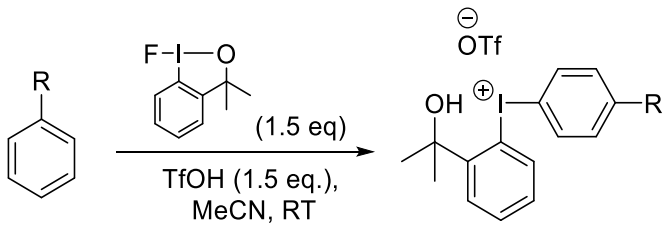
When 1,3-dimethoxybenzene was reacted under the optimised reaction conditions, there was a 100 % conversion of 1,3-dimethoxybenzene but two different diaryliodonium salts were formed in a 70:30 ratio. As well as forming the desired product **2.16** (entry 2) as the major product, the *ortho* isomer **2.18** (Figure 2.5) was also detected. Unfortunately, it was not possible to separate these two salts by recrystallization from different solvents such as ethyl acetate and dichloromethane in hexane. However, when the reaction was carried out at 0 °C for 1 h, the amount of *ortho*-isomer **2.18** decreased significantly to 5%.

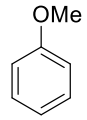
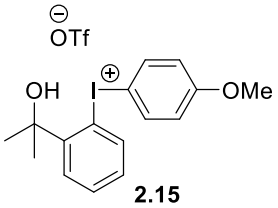
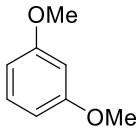
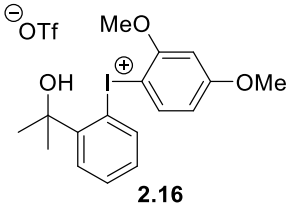
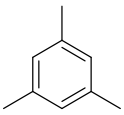
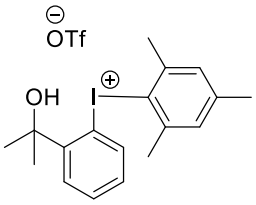
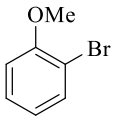
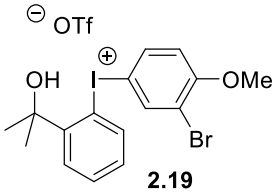
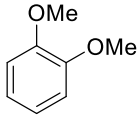
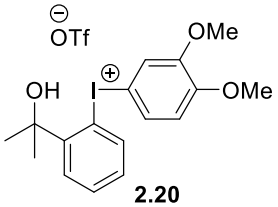


2.18

Figure 2.5**: The ortho isomer of the 1,3-dimethoxybenzene iodonium salt **2.18

***Table 2.9**: Synthesis of substituted diaryliodonium salts with triflate*



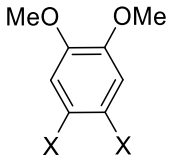
Entry	Substrate	Product	Conversion %	Yield[a] (%)
1		 **2.15**	100	84
2[b]		 **2.16**	100	90
3		 **2.17**	100	91
4		 **2.19**	63	58
5[c]		 **2.20**	57	0

[a] isolated yield; [b]About 5 % ortho isomer was detected by ^{1}H NMR spectroscopy, when the reaction mixture was stirred for 1 hour at 0 ^{o}C; [c] Could not be isolated in pure form.

In entry 3, mesitylene was reacted with **1.22** to give **2.17** in a 91 % yield. The ^{1}H NMR spectrum of the pure product showed two singlet peaks at 2.37 ppm and 2.48 ppm, corresponding to the two different environments for the three methyl groups. In addition, analysis by ESI-MS showed a peak at *m/z* 381 corresponding to [M^{+}].

In entry 4, only 63 % conversion with 58 % isolated yield was observed when 2-bromoanisole was reacted with the fluoroiodane **1.22** to form **2.19**. The ^{1}H NMR spectrum of the pure product in CD_3CN showed two singlet peaks at 1.67 and 3.99 ppm corresponding to the protons of the two methyl groups on the sidearm and the methoxy group, respectively. In the ^{13}C NMR spectrum, the two peaks at 29.1 ppm and 56.5 ppm can be assigned to the two methyl groups and methoxy group, respectively. Two peaks at 99.1 and 114.0 ppm corresponding to the two C-I bonds were also observed. The ESI-MS spectrum demonstrated a peak corresponding to M^{+} at *m/z* 446, representing the diaryliodonium cationic salt and MS (ES^{-}) showed a peak at *m/z* 149 corresponding to the triflate counteranion.

In the reaction with 1,2-dimethoxybenzene (entry 5), the ^{1}H NMR spectrum of the crude product showed a 57 % conversion to the desired product. Two singlet peaks at 3.91 ppm and 3.98 ppm corresponded to the two methoxy groups, indicating that the desired product **2.20** had been formed. However, two singlet peaks in the ^{1}H NMR spectrum at 4.12 and 7.80 ppm having an integration of 3:1, indicated that a side product had also been formed and could not be removed. Eight aromatic CH peaks were observed in the ^{13}C NMR spectrum, seven of which belong to **2.20** while the CH peak at 104.2 ppm most likely belonged to the side product. Two C-O peaks were also observed at 151.5 and 153.6 ppm. However, next to these is a third C-O peak. At this point, with the available data it was difficult to propose the exact structure of the side product, but the possible structure might be represented by **2.21** in Figure 2.6.



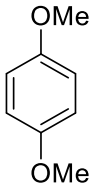
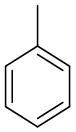
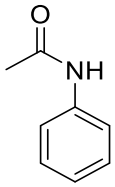
2.21

Figure 2.6**: The predicted structure of the side product **2.21

When 1,2-dimethoxybenzene was reacted at low temperature (-20, -40 or -78 °C) in acetonitrile, the ^{1}H NMR spectrum of the crude product indicated that there was 100 % conversion of 1,2-dimethoxybenzene. However, **2.21** was still formed and could not be removed by washing the salt.

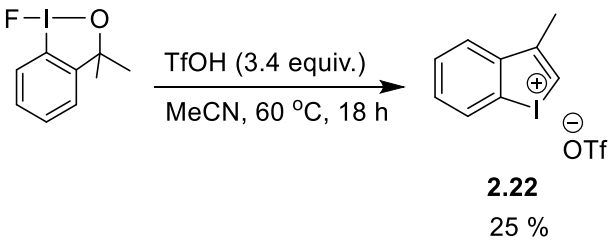
Unfortunately, attempts to extend the scope of the reaction between fluoroiodane **1.22** and other arenes in the presence of 1.5 equivalents of triflic acid were unsuccessful (Table 2.10). In the reaction with 1,4-dimethoxybenzene and acetanilide (entries 1 and 2), the ^{1}H NMR spectrum of the crude product showed that there was no reaction in acetonitrile for 1 hour at RT using 1.5 equivalents of triflic acid.

***Table 2.10**: Arenes that did not react with **1.22** in the presence of triflic acid (1.5 equivalents)*

Entry	Substrate	Entry	Substrate
1		**3**	
2			

In the reaction with toluene (entry 3), the ^{1}H NMR spectrum of the crude product revealed that there was no reaction in acetonitrile after 1 hour. Increasing the temperature to 40 °C for 18 hours in acetonitrile led to the formation of the same heterocycle with the triflate anion (7-iodonia-9-methylbicyclo[4,3,O]nona-1,3,5,8-tetraene **2.22**) as had been observed previously in the reaction with *p*-toluenesulphonic acid at 40 °C for 18 h forming **2.11**. Fluoroiodane **1.22** was also reacted with 3.4 equivalents of triflic acid in MeCN at 60 °C overnight to form **2.22** as a white solid in 25 % isolated yield without using any substrate (Scheme 2.10). Single crystals of **2.22** suitable for X-ray crystallography were grown by slow evaporation from a chloroform:hexane (1:1)

solution. The molecular structure of **2.22** is shown in Figure 2.7, and key bond lengths and angles are given in Table 2.11.



Scheme 2.10**: Formation of heterocyclic iodonium triflate **2.22

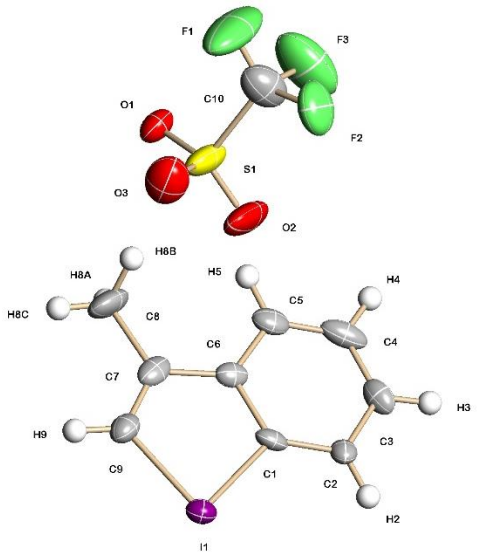


Figure 2.7**: Solid-state structure for **2.22

__Table 2.11__: Selected Bond lengths (Å) and angles (°) for __2.22__

Bond lengths (Å)		Bond angles (°)	
I(1)-C(9)	2.067(10)	C(1)-I(1)-C(9)	82.7(4)
I(1)-C(1)	2.100(9)	C(2)-C(1)-I(1)	127.1(7)
C(7)-C(9)	1.329(14)	C(6)-C(7)-C(9)	118.7(9)
C(6)-C(7)	1.462(14)	-	-

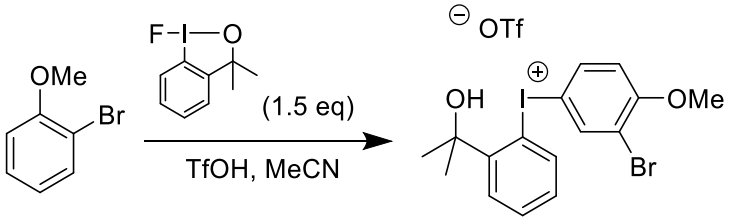
2.5.3 Optimisation studies using 3 equivalents of triflic acid

Since the methodology using 1.5 equivalents of triflic acid only worked with a limited range of activated aromatics, the reaction was investigated further with 2-bromoanisole as the model substrate in order to try to extend the scope of substrates for the preparation of diaryliodonium salts (Table 2.12).

When the amounts of triflic acid and fluoroiodane were increased from 1.5 to 2 equivalents at RT for 1 hour (entry 2), or at 0 °C for 2 hours (entry 3), the results were very similar to the initial conditions using 1.5 equivalents in entry 1. By increasing the amount of triflic acid to 3 equivalents, the conversion was increased to 84 % at RT for 1 hour with 75 % isolated yield (entry 4). These values were increased slightly to 89 % conversion and 86 % isolated yield when the reaction temperature was decreased to 0 °C (entry 5). Further increasing the amount of triflic acid from 3 to 4.5 equivalents gave essentially the same results at 0 °C for both a 1 hour (entry 6) and a 2 hour reaction (entry 7).

The crude product of **2.19** was purified by a number of washing steps. First, it was washed with water to remove the excess of triflic acid. Then, it was washed with hot hexane before stirring with diethyl ether at RT to give the pure product **2.19** as a white solid in 86 % isolated yield.

*Table 2.12: Preparation of **2.19** in acetonitrile*



2.19

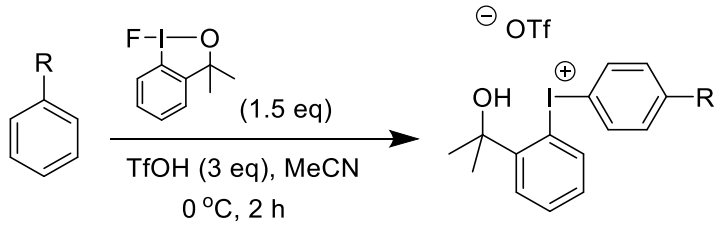
Entry	Triflic acid. (equiv.)	Temp (°C)	Time (h)	Conversion[a] (%)	Yield[b] (%)
1	1.5	RT	1	63	58
2[c]	2	RT	1	65	53
3[c]	2	0	2	66	58
4	3	RT	1	84	75
5	3	0	2	89	86
6	4.5	0	2	91	88
7	4.5	0	1	89	86

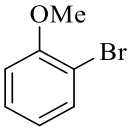
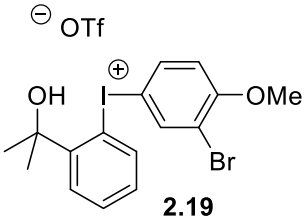
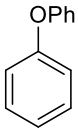
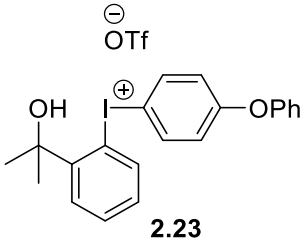
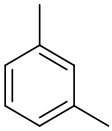
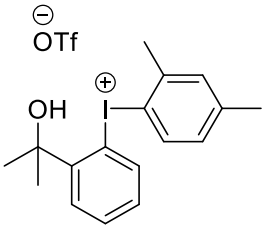
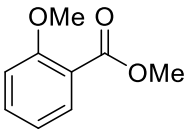
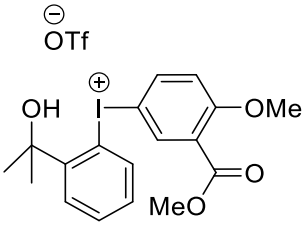
[a] determined by ^{1}H NMR spectroscopy; [b] Isolated yield; [c] 2 equivalents fluoroiodane **1.22**.

2.5.4 Scope of the reaction using 3 equivalents of triflic acid

The optimised protocol (entry 5, Table 2.12) was subsequently applied to a series of activated aromatics to prepare diaryliodonium triflates (Table 2.13). Diphenyl ether (entry 2) was reacted with fluoroiodane **1.22** to give **2.23** as a white solid in 75 % conversion and 70 % isolated yield. The ^{1}H NMR spectrum of the pure product in $CDCl_3$ showed thirteen protons corresponding to all of the aromatic protons and a peak at 1.71 ppm corresponding to the two methyl groups was also observed. As expected, seventeen signals were observed in the ^{13}C NMR spectrum, including seven quaternary carbon atoms.

Table 2.13: *Synthesis of substituted diaryliodonium salts with triflate acid*



Entry	Substrate	Product	Conversion[a] (%)	Yield[b] (%)
1		 **2.19**	89	86
2		 **2.23**	75	70
3		 **2.24**	57	51
4		 **2.25**	38	33

[a] Determined by ^{1}H NMR spectroscopy; [b] Isolated yield

The reaction with *m*-xylene delivered the unsymmetrical iodonium triflate **2.24** as a white solid with 57 % conversion and 51 % isolated yield (entry 3). The ^{1}H NMR spectrum of

2.24 showed three singlets corresponding to the four methyl groups at 1.73, 2.48 and 2.51 ppm. Additionally, analysis of the ^{13}C NMR spectrum showed three peaks at 21.6, 25.2 and 30.4 ppm for the four methyl groups. Analysis by ESI-MS showed a peak at *m/z* 367 corresponding to the $[M^+]$.

A somewhat low yield (33 %) was obtained from the reaction of methyl-2-methoxybenzoate with fluoroiodane **1.22** to form **2.25** (entry 4) and unreacted starting material was removed by washing with hot hexane. The ^1H NMR spectrum of **2.25** in $CDCl_3$ showed two singlets corresponding to the two methoxy groups at 3.90 and 4.04 ppm. In the ^{13}C NMR spectrum, eight quaternary carbon atoms were observed, including three singlets at 52.7, 56.7 and 164.1 ppm corresponding to the two methoxy and C=O groups, respectively. ESI-MS analysis supported this data with a $[M]^+$ peak at *m/z* 427.

Although only moderate to good yields (33-86 %) were obtained in Table 2.13, the scope of the reaction was much better than using *p*-toluenesulphonic acid because the aromatic substrates in entries 1-3 did not react with fluoroiodane **1.22** in the presence of TsOH.

On the other hand, attempts to extend the scope of the reaction between fluoroiodane **1.22** and other less activated aromatics (Figure 2.8) in the presence of 3 equivalents of triflic acid failed. The ^1H NMR spectrum of the crude product showed only the presence of unreacted starting materials and no reaction had occurred using the same reaction conditions.

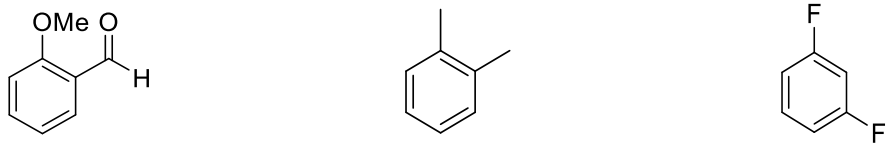
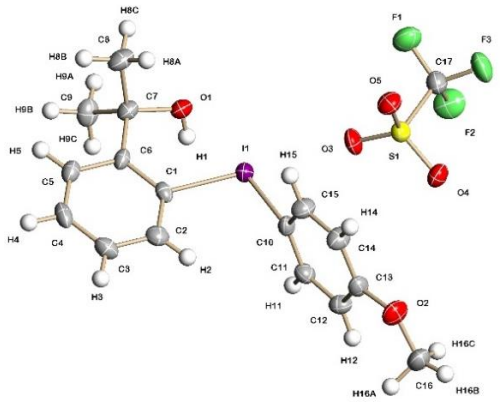


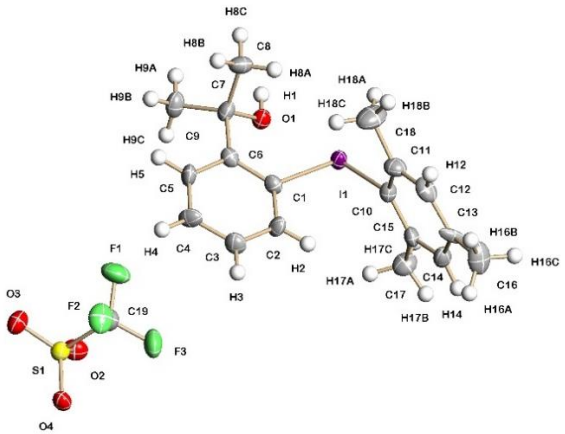
***Figure 2.8**: Arenes that did not react with **1.22** using 3 equivalents of triflic acid*

Crystals suitable for X-ray crystallography were obtained for some of these salts as shown in Figure 2.9 and the key bond lengths and angles are presented in Table 2.14. As seen previously in the diaryliodonium tosylates, the C(1)-I(1) bond lengths of diaryliodonium triflates (2.130(5)-2.140(4) Å) are slightly longer than C(10)-I(1) (2.093(2) - 2.117(6) Å) bond lengths and the bond angles of the C(1)-I(1)-C(10) are between 94.76(14) and 99.33(19)° and the absence of any secondary bonding between the iodine and triflate was

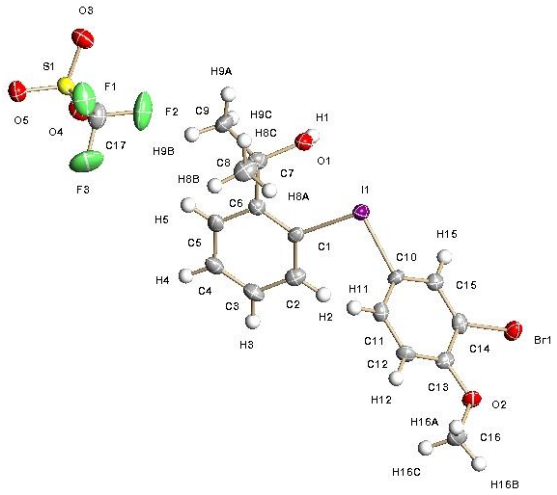
also observed. Furthermore, the C(7)-O(1) of these salts (1.429(3)-1.450(4) Å) are similar to the C(7)-O(1) of fluoroiodane **1.22** (1.450(6) Å).[63] In addition, there are strong intramolecular interactions (2.530(2)-2.607(5) Å) between I(1) and O(1) of the iodonium triflates in comparison with the I(1)-O(1) of the fluoroiodane **1.22** (2.029(3) Å).[63] The O(1)···I(1)-C(10) bond angles (171.73(16)-163.09(19)°) are also similar to the F(1)-I(1)-O(1) bond angle in fluoroiodane **1.22** (166.66 (14)°).



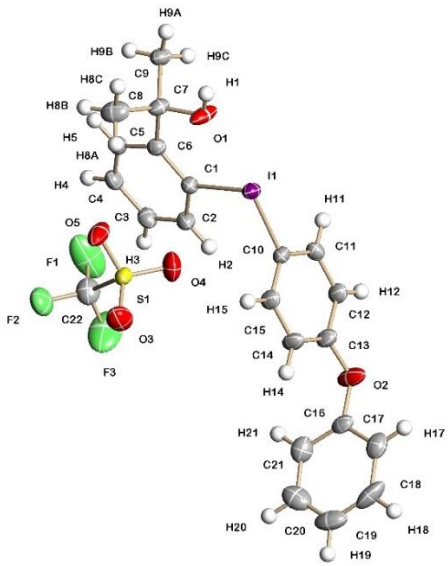
a) Solid-state structure of **2.15**



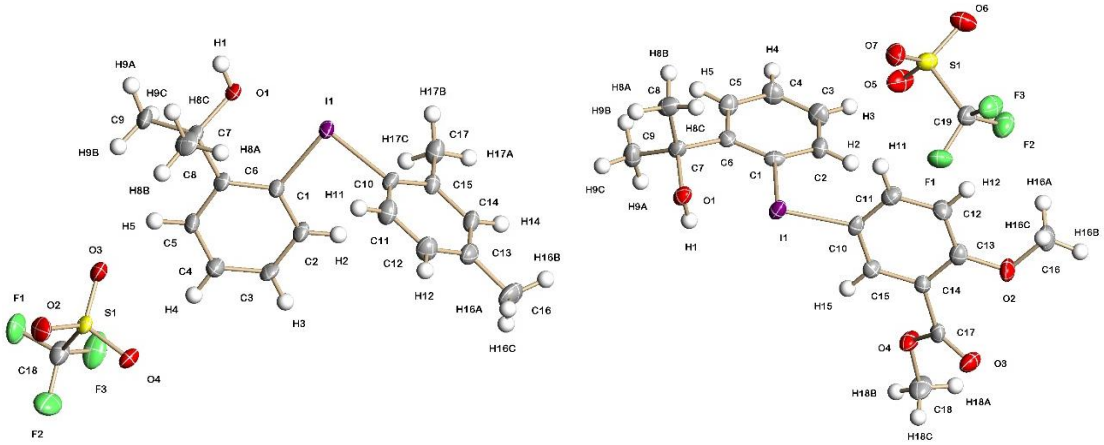
b) Solid-state structure of **2.17**



c) Solid-state structure of **2.19**



d) Solid-state structure of **2.23**



e) Solid-state structure of **2.24** f) Solid-state structure of **2.25**

***Figure 2.9**: Solid-state structures for diaryliodonium triflates*

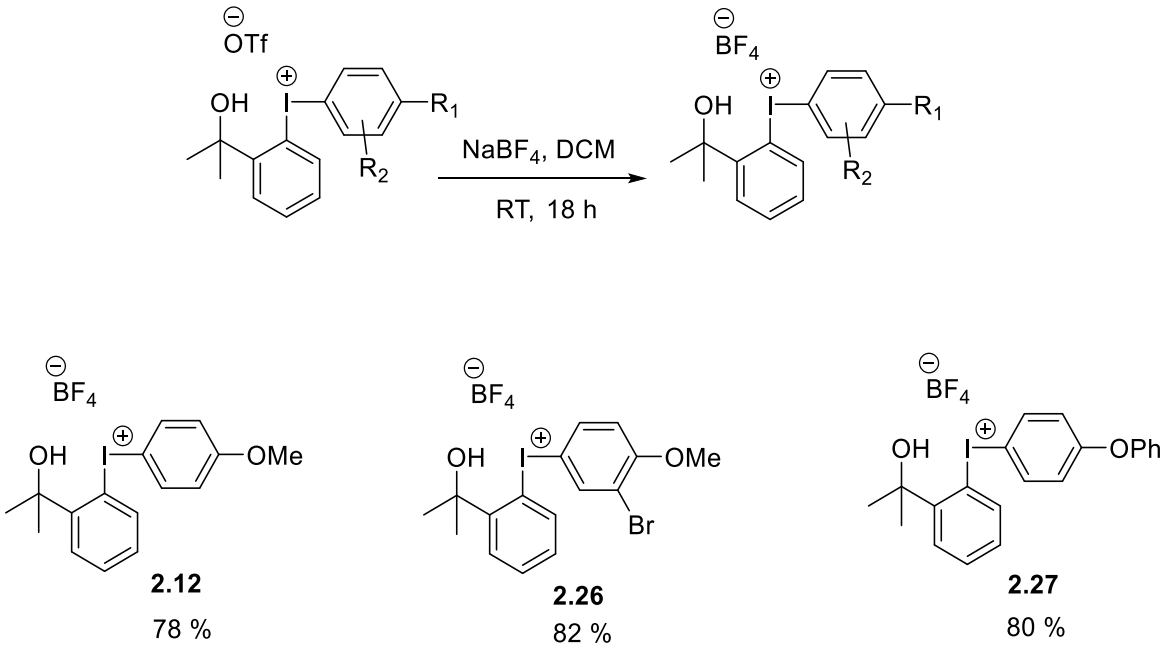
***Table 2.14**: Key bond lengths (Å) and angles (°) for diaryliodonium triflates*

	2.15	**2.17**	**2.19**	**2.23**	**2.24**	**2.25**
C(1)-I(1)	2.130(5)	2.135(6)	2.135(6)	2.138(2)	2.131(4)	2.140(4)
C(10)-I(1)	2.093(5)	2.117(6)	2.111(6)	2.093(2)	2.109(4)	2.100(4)
C(7)-O(1)	1.436(6)	1.435(8)	1.430(7)	1.429(3)	1.439(5)	1.450(4)
O(1)···I(1)	2.607(5)	2.607(5)	2.587(5)	2.530(2)	2.581(3)	2.577(3)
C(1)-I(1)-C(10)	99.33(19)	95.3(2)	97.8(2)	97.86(9)	94.76(14)	97.82(15)
O(1)···I(1)-C(10)	171.73(16)	163.09(19)	169.2(2)	169.30(8)	163.21(13)	166.01

2.5.5 Metathesis reactions with $NaBF_4$

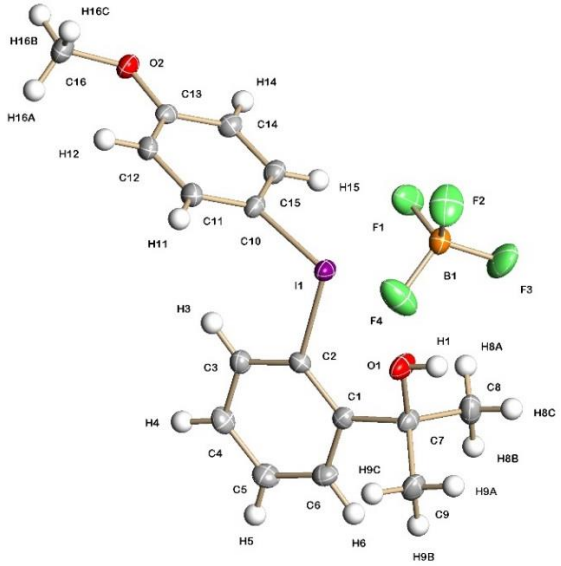
Similar to the iodonium tosylates, the triflate counteranion in the diaryliodonium salts can be exchanged with tetrafluoroborate. The metathesis was carried out by stirring the iodonium triflates (**2.15**, **2.19** and **2.23**) in DCM at RT with an aqueous solution of $NaBF_4$ overnight (Scheme 2.11), forming the tetrafluoroborate salts in high yields (78-82 %).

When the reaction mixture was stirred for 4 hours, the ^{19}F NMR spectra of the crude products of **2.12**, **2.26** and **2.27** showed two singlet peaks at -78.3 and -150.0 ppm corresponding to the CF_3 group of the triflate anion and BF_4^-. This indicated that some of the triflate anion still remained. However, the triflate peak disappeared when the reaction mixture was left to stir overnight at RT. The MS (ES) spectra of the pure products showed a peak at *m/z* 87 corresponding to the tetrafluoroborate anion.

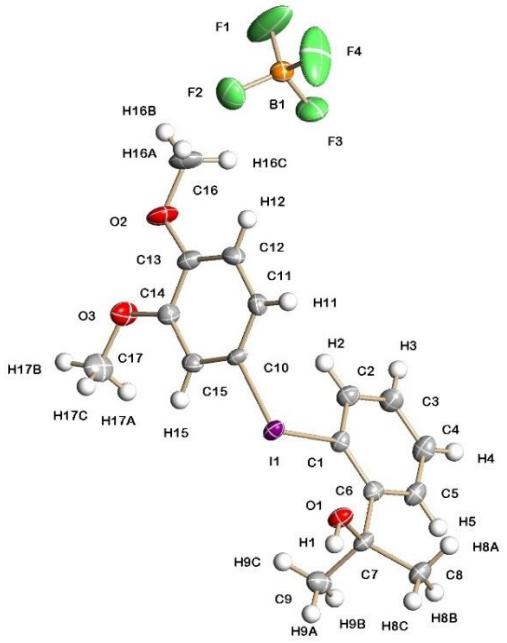


***Scheme 2.11**: Metathesis reactions of iodonium triflates with $NaBF_4$*

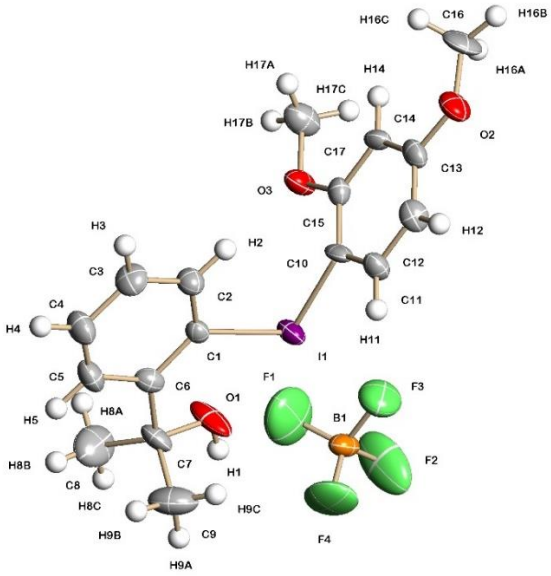
Crystals suitable for X-ray crystallography were obtained for some diaryliodonium tetrafluoroborates (**2.12**, **2.13**, **2.14**, **2.26** and **2.27**) as shown in Figure 2.10. The key bond lengths and angles are given in Table 2.15 along with the data for Sanford's salt [98] **2.28** (Figure 2.11) for comparison. The C(1)-I(1) (2.132(3)-2.144(3)) and C(10)-I(1) (2.081(7)- 2.096(3)) bond lengths for the diaryliodonium tetrafluoroborates are similar to the C(1)-I(1) (2.130(10)) and C(10)-I(1) (2.102(10)) bond lengths of **2.28**. In addition, the C(1)-I(1)-C(10) bond angles of these salts are between 96.67-98.40° which is very similar to the C(1)-I(1)-C(10) bond angle in **2.28** (96.7°). Furthermore, the intramolecular interactions of I(1) and O(1) (2.550-2.635 Å) and the O(1)···I(1)-C(10) bond angles (166.20(8)-169.24(8)) are very similar to the corresponding iodonium tosylates and triflates.



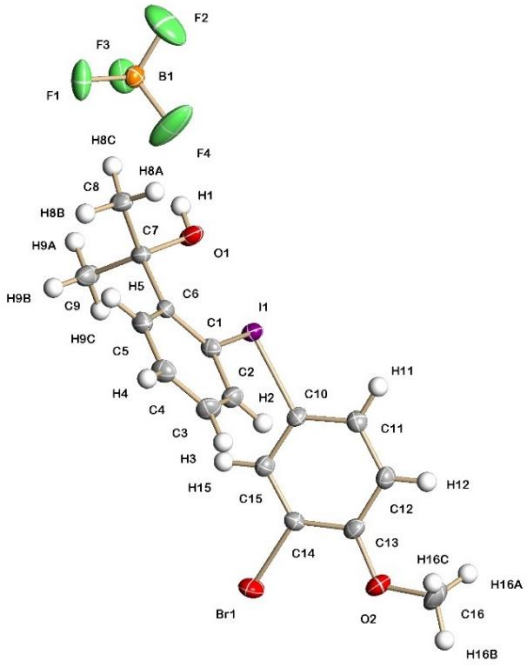
a) Solid-state structure of **2.12**



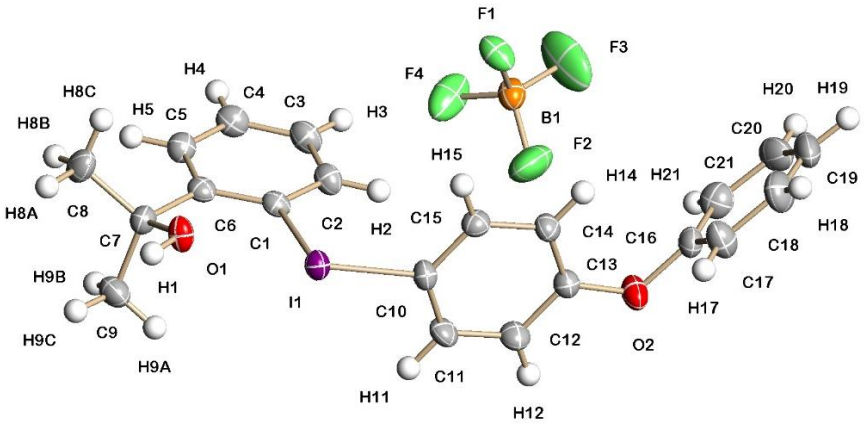
b) Solid-state structure of **2.13**



c) Solid-state structure of **2.14**



d) Solid-state structure of **2.26**



e) Solid-state structure of **2.27**

***Figure 2.10**: Solid-state structure of diaryliodonium tetrafluoroborate*

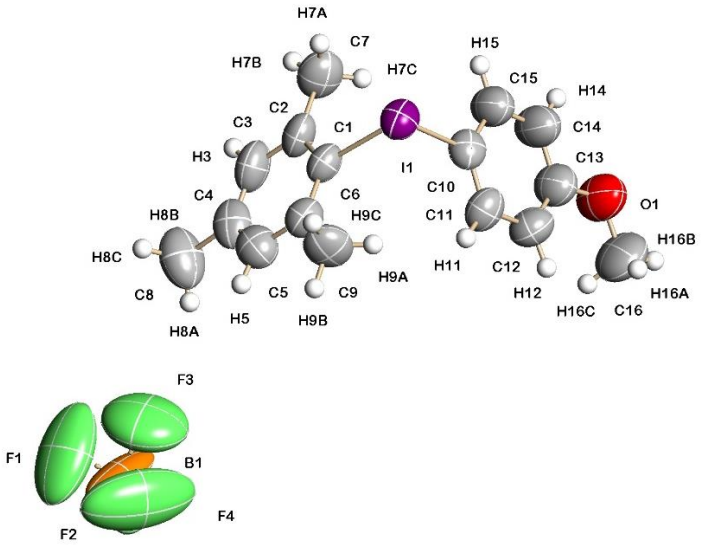


Figure 2.11**: Solid-state structure of **2.28

***Table 2.15**: Key bond lengths (Å) and angles (°) for the iodonium tetrafluoroborates and **2.28**.*

	2.12	**2.13**	**2.14**	**2.26**	**2.27**	**2.28**
C(1)-I(1)	2.132(3)	2.141(3)	2.142(7)	2.143(3)	2.144(3)	2.130(10)
C(10)-I(1)	2.087(3)	2.085(3)	2.081(7)	2.096(3)	2.090(3)	2.102(10)
C(7)-O(1)	1.441(3)	1.441(3)	1.419(8)	1.440(4)	1.445(4)	-
O(1)···I(1)	2.576(2)	2.635(2)	2.550(7)	2.613(2)	2.576(2)	-
C(1)-I(1)-C(10)	98.35(10)	96.81(10)	98.4(3)	96.80(12)	96.67(13)	96.7(4)
O(1)···I(1)-C(10)	169.24(8)	166.20(8)	168.3(2)	166.52(10)	166.91(10)	-

2.6 Synthesis of unsymmetrical diaryliodonium salts using transition metals

Acids with high *p*Ka values such as TfOH and TsOH as well as $BF_3.OEt_2$ are generally used in the synthetic routes used to prepare diaryliodonium salts.[132,133] They give rise to iodonium salts with anions (OTf, OTs, BF_4) without a subsequent anion exchange step.[88]

Biological compounds such as dopamine was affected by high acidic conditions, and a new strategy need to be investigated in order to prepare diaryliodonium salts including dopamine. The synthesis of unsymmetrical diaryliodonium salts using Lewis acidic transition metals such as Cu^{2+}, Ag^{+} and Zn^{2+} has never been reported before. Consequently, the reaction between anisole and fluoroiodane **1.22** in the presence of transition metals was also investigated.

2.6.1 Preliminary screening

The initial results of the reaction between anisole and fluoroiodane **1.22** using transition metal are shown in Table 2.16. Only unreacted starting material was observed in the ^1H NMR spectrum of the crude products when 1 equivalent of $AgBF_4$, or $[Cu(MeCN)_4]BF_4$ were used at 60 ºC for 18 hours in both DCM and MeCN as the solvent (entries 1-4).

Interestingly, all of the starting material was consumed using the same reaction conditions with $[Zn(BF_4)_2].xH_2O$ in DCM (entry 5), yielding 4-iodoanisole as the only product which was identified. It was thought that product **2.12** had been formed and then subsequently decomposed over the long reaction time at high temperature. This reaction was repeated using MeCN as the solvent, however, no reaction was observed (entry 6).

Table 2.16: Preliminary screening using transition metals

2.12

Entry	Catalyst	Solvent	Conversion[a] (%)	Yield (%)
1	$AgBF_4$	DCM	0	-
2	$AgBF_4$	MeCN	0	-
3	$[Cu(MeCN)_4]BF_4$	DCM	0	-
4	$[Cu(MeCN)_4]BF_4$	MeCN	0	-
5	$[Zn(BF_4)_2].xH_2O$	DCM	100	0
6	$[Zn(BF_4)_2].xH_2O$	MeCN	0	-

[a] determined by ^1H NMR spectroscopy.

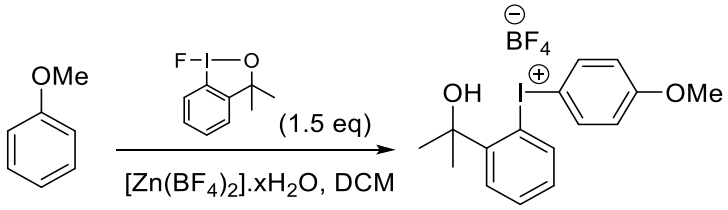
2.6.2 Optimization with $Zn(BF_4)_2.\ xH_2O$

Encouraged by the initial result, the reaction conditions with $[Zn(BF_4)_2].xH_2O$ were optimized using DCM as the solvent (Table 2.17). No reaction was observed in the ^1H NMR spectrum of the crude product when fluoroiodane **1.22** (1.5 equivalents) was reacted with anisole in the presence of 1.5 equivalents of $[Zn(BF_4)_2].xH_2O$ at RT or at 40 °C for 18 hours (entries 1 and 2). A 58 % conversion was observed when the reaction time was reduced to 4 hours at 60 °C and **2.12** was isolated in a 55 % yield (entry 3). These values were slightly decreased when 1 equivalent of $[Zn(BF_4)_2].xH_2O$ and fluoroiodane **1.22** were used (entry 4). A 63 % conversion to the desired product **2.12** was obtained with a 61 % isolated yield when 1 equivalent of $[Zn(BF_4)_2].xH_2O$ was reacted with 1.5 equivalents of **1.22** (entry 5). A decrease in $[Zn(BF_4)_2].xH_2O$ from 1 to 0.5 equivalent led to a dramatic decrease in the conversion to 25 % (entry 6). In order to achieve better conversion of the starting material, the reaction time was extended to 6 hours at 60 °C with 1 equivalent of $[Zn(BF_4)_2].xH_2O$. At this point, the conversion

increased to 81 % with a 72 % isolated yield (entry 7). Similar results were observed when the temperature was increased to 80 °C for 4 hours in 1,2-dichloroethane (1,2-DCE) as the solvent (entry 8).

Although promising results were achieved with this new synthetic route, it was not investigated further because it required using a stoichiometric amount of zinc.

***Table 2.17**: Optimisation for the preparation of **2.12** with $[Zn(BF_4)_2].xH_2O$*



2.12

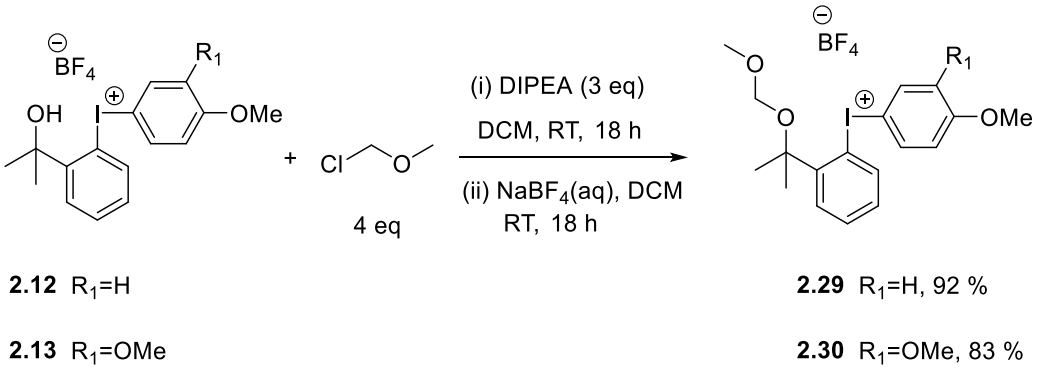
Entry	[Zn] (eq.)	Time (h)	Temp. (°C)	Conversion[a] (%)	Yield[b] (%)
1	1.5	18	40	0	-
2	1.5	18	RT	0	-
3	1.5	4	60	58	55
4[c]	1	4	60	52	46
5	1	4	60	63	61
6	0.5	4	60	25	20
7	1	6	60	81	72
8[d]	1	4	80	83	70

[a] determined by ^{1}H NMR spectroscopy; [b] Isolated yield; [c] Using 1 equivalent of **1.22**; [d] 1,2 Dichloroethane (1,2-DCE) was used as the solvent.

2.7 Protection of the free hydroxy group

Before attempting to fluorinate the unsymmetrical diaryliodonium salts, the free hydroxy group was protected with MOMCl. Protecting the hydroxyl group of **2.12** and **2.13** was achieved by reacting the salts with 3 equivalents of *N*,*N*-diisopropyl ethylamine (Hünig's base/DIPEA) and 4 equivalents of chloromethyl methyl ether (MOMCl) under inert conditions using DCM as the solvent following the literature procedure (Scheme 2.12).[134]

The ^{1}H NMR spectrum of the crude products showed a 100 % conversion to the desired products **2.29** and **2.30**. Only negligible amounts of BF_4^- were observed in the ^{19}F NMR spectrum, due to metathesis with chloride. The crude products were stirred with a saturated solution of $NaBF_4$ in order to successfully substitute any chloride followed by stirring with diethyl ether to produce the pure products as solids in high yields (83 and 92 % respectively). The **2.29** and **2.30** were fully characterised by NMR spectroscopy and mass spectrometry.



***Scheme 2.12**: Protection of the hydroxy group*

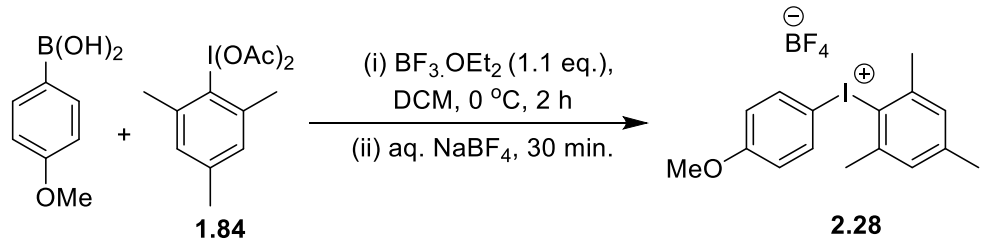
The most distinguishable feature observed in the ^{1}H NMR spectra of **2.29** and **2.30** were the absence of the OH peak and the appearance of two singlets which appeared around 3.50 and 5.0 ppm corresponding to the CH_3 and CH_2 of the protecting group. In addition, a singlet peak at -150.3 and -148.9 ppm can be assigned to the BF_4^- of **2.29** and **2.30** respectively. In the ^{13}C NMR spectrum of **2.29** and **2.30**, there were similarly extra signals around 56.9 and 91.5 ppm for the OCH_3 and CH_2 groups respectively. Mass spectrometry

confirmed the structure of the cation with a $[M]^+$ peak at *m/z* 413.0614 and *m/z* 443.719 for **2.29** and **2.30** respectively.

2.8 Preparation of 4-methoxyphenyl(mesityl)iodonium tetrafluoroborate 2.28

Sanford's diaryliodonium salt mesityl(4-methoxyphenyl)iodonium tetrafluoroborate **2.28**, was prepared in order to compare its reactivity with KF in DMF with the new unsymmetrical diaryliodonium salts prepared in this chapter. The synthesis of diaryliodonium salt **2.28** was achieved by reacting commercially available 4-methoxyphenylboronic acid with 1 equivalent of 2-(diacetoxyiodo)mesitylene **1.84** and 1.1 equivalents BF_3OEt_2 in dry DCM. The reagents were combined at 0 °C for 2 h, under inert conditions, before it was stirred with a saturated solution of $NaBF_4$ for 30 minutes at RT (Scheme 2.13). The pure product was obtained as an off-white solid in 93 % yield after stirring with diethyl ether.

The ^1H NMR spectrum of the pure product **2.28** showed three singlets at 2.33, 2.64 and 3.80 ppm corresponding to the three methyl (two of them have the same environment) and methoxy groups, respectively. In addition, there was a singlet peak at 7.08 ppm corresponding to the 2H of the mesitylene moiety. In the ^{19}F NMR spectrum, a peak at -147.8 ppm was assigned to the BF_4^- counteranion. As expected, eleven signals were observed in the ^{13}C NMR spectrum, including three peaks at 21.1, 27.1 and 55.8 ppm corresponding to the three methyl and methoxy groups, respectively. Two singlets at 98.8 and 119.8 ppm corresponding to the two C-I carbons were also observed. Analysis by ASAP -MS showed a peak at *m/z* 353 corresponding to $[M^+]$.



Scheme 2.13**: Synthesis of diaryliodonium salt **2.28

2.9 Conclusions

The cyclic hypervalent iodine(III) reagent, fluoroiodane **1.22**, was synthesised via a multi-stage reaction pathway following the synthetic route reported by Stuart.[64] These reactions were carried out at room temperature without the need for inert conditions and the products were produced in high yields. In the last step, TREAT-HF was used as the nucleophilic source of fluoride since it is a very stable and cheap source.

Initial testing of the reaction between fluoroiodane **1.22** and anisole in the presence of *p*-toluenesulphonic acid was promising in terms of the preparation of **1.85**. The screening of different reaction times, temperatures, and solvents (Table 2.1 and Table 2.2) was undertaken in order to find the optimum reaction conditions. Four unsymmetrical diaryliodonium salts (**1.85**, **2.7**, **2.8**, and **2.9**) were synthesised in high (86-93 %) yields in only 1 hour at RT using trifluoroethanol as the solvent.

Triflic acid was also used to prepare a small series of unsymmetrical diaryliodonium salts (**2.15**, **2.16**, **2.17** and **2.19**) in 1 h at RT using MeCN as the solvent. Initially, only 1.5 equivalents of triflic acid was used with highly activated aromatics (anisole, 1,3-dimethoxybenzene and mesitylene), but the scope of the reaction was expanded to less-activated aromatics (2-bromoanisole, diphenyl ether, *m*-xylene and methyl-2-methoxybenzoate) when the amount of triflic acid was increased to 3 equivalents and the reaction was conducted at 0 ^{o}C for 2 h.

Only two salts (**2.12** and **2.14**) were prepared when $BF_3.OEt_2$ was used to activate the fluoroiodane and form the iodonium tetrafluoroborates directly without anion exchange. However, triflates and tosylates were stirred with an aqueous solution of $NaBF_4$ to deliver the diaryliodonium tetrafluoroborates in high yields (78-87 %). The transition metal catalyst, $Zn(BF_4)_2.xH_2O$, was also used in a novel approach to prepare diaryliodonium tetrafluoroborate using DCM or 1,2-dichloroethane as the solvent at elevated temperatures.

It was also possible to protect the hydroxyl group in the diaryliodonium tetrafluoroborates **2.12** and **2.13** by reacting the salts with MOMCl in the presence of DIPEA to generate the product **2.29** and **2.30**, in good yields (83 and 92 %). Sanford's salt **2.28** was also prepared successfully by reacting 4-methoxyphenylboronic acid with 2-

(diacetoxyiodo)mesitylene and $BF_3.OEt_2$ under inert conditions to produce **2.28** in 93 % isolated yield.

All of the unsymmetrical diaryliodonium salts were characterised fully by NMR spectroscopy, mass spectrometry and in the majority of cases by X-ray crystallography.

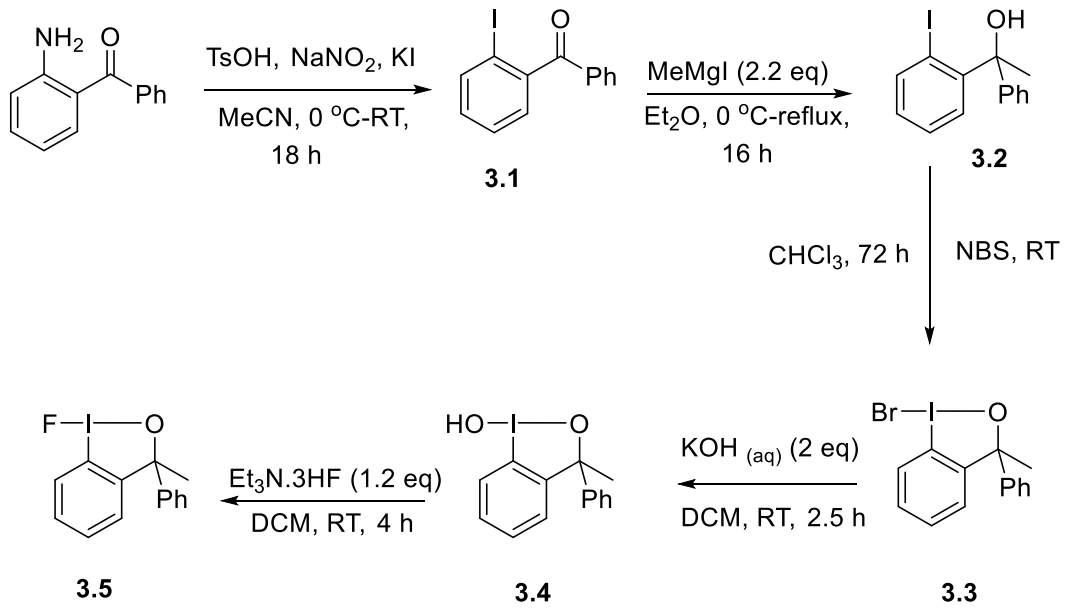
In general, there are no interactions between the I(III) and the counteranions in the X-ray crystallography. In addition, the key bond lengths and angles are very similar with a range of different counteranions.

Chapter Three: Synthesis of unsymmetrical diaryliodonium salts using new hypervalent iodine(III) reagent

3.1 Synthesis of new hypervalent iodine (III) reagent 3.5

The aim of chapter 3 was to prepare **3.5** a new analogue of fluoroiodane **1.22** where one of the methyl groups was replaced by a phenyl group, and use it to prepare a new class of diaryliodonium salts. The phenyl group was introduced in order to encourage the alcohol sidearm to undergo an elimination reaction to form an alkene in conjugation with two aromatic rings during the formation of the diaryliodonium salts. The reasons for this was the observation of short intramolecular I···O(1) distances in all the solid-state structures of diaryliodonium salts outlined in chapter 2. It was thought that this interaction might influence the subsequent reaction chemistry of these salts.

The five-step synthesis to the new hypervalent iodine(III) reagent **3.5** is outlined in Scheme 3.1.



Scheme 3.1**: Synthesis of fluoroiodane **3.5

In the first step 2-aminobenzophenone underwent a diazotisation to produce 2-iodobenzophenone **3.1** (Scheme 3.1). The reaction was carried out by adding an aqueous solution of potassium iodide and sodium nitrite dropwise to a solution of *p*-toluenesulphonic acid and 2-aminobenzophenone at 0 °C. The reaction mixture was left

overnight at RT. A 100 % conversion was observed when the solution of potassium iodide and sodium nitrite was added over 45 minutes and **3.1** was isolated in 88 % yield. The ^{1}H NMR spectrum of the crude product showed that there was no starting material remaining and the broad peak at 6.10 ppm corresponding to the NH_2 group had disappeared. A peak at 92.2 ppm in the ^{13}C NMR spectrum corresponded to C-I and a fragment peak in the ESI^{+}-MS spectrum at *m/z* 308.97 corresponded to M^{+} indicating that the desired product had been formed.

In the second step methylmagnesium iodide underwent a nucleophilic addition to the carbonyl group to form the tertiary alcohol **3.2**. This reaction was carried out under dry conditions in an inert atmosphere using iodomethane and magnesium in dry diethyl ether to form the Grignard reagent. 2-Iodoobenzophenone **3.1** was added dropwise at 0 ^{o}C and the reaction mixture was left to stir overnight at room temperature. A 100 % conversion to the product was observed when the reaction mixture was heated to reflux for 5 hours and the pure product **3.2** was obtained as a yellow oil in a 73 % isolated yield.

In the ^{1}H NMR spectrum of the pure product **3.2**, there was a singlet peak at 1.92 ppm corresponding to the new methyl group, and a singlet for the OH at 3.24 ppm. Further confirmation by ^{13}C NMR spectroscopy showed the absence of a CO peak at 197.2 ppm and a new singlet at 30.7 ppm for the methyl group. Furthermore, a fragment in the ASAP-MS spectrum at *m/z* 322.9940 was observed for MH^{+}.

The iodoalcohol **3.2** was converted to 1-bromo-3-methyl-3-phenyl-1,3-dihydro-1λ^{3}-benzo[d][1,2]iodaoxole **3.3** using *N*-bromosuccinimide with a 95 % yield. Unfortunately, only a 10 % conversion to **3.3** was observed when the reaction mixture was left to react overnight at room temperature; however, a 100 % conversion to the desired product was obtained when it was left to stir for 72 hours. The pure product was finally obtained as a yellow solid in a 95 % isolated yield with no additional purification processes required.

The bromoiodane **3.3** was identified in the ^{1}H NMR spectrum due to the large shift of the peaks in the aromatic region resulting from oxidation of **3.2** from iodine(I) to iodine(III). In addition, the loss of the signal at 3.24 ppm corresponding to the OH group of **3.2** and the significant shift of the C-I peak from 96.4 in **3.2** to 113.8 ppm in **3.3** indicated that iodine(III) had been formed. The formation of **3.3** was also demonstrated by ASAP-MS as the isotopic pattern for bromine showed an approximately 50:50 ratio between ^{79}Br

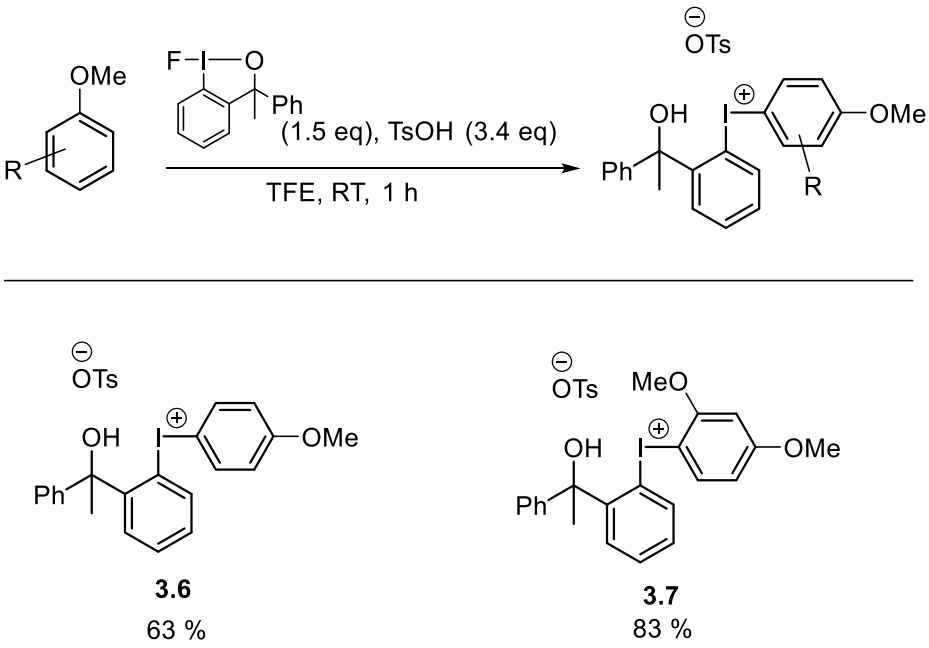
and ^{81}Br and thus there were peaks at 402.9 *m/z* and 404.9 *m/z* in the mass spectrometry data. Although this reaction took 72 h compared to 18 h for the dimethyl analogue **1.47** (Chapter 2), a higher yield was normally achieved.

The formation of 3-methyl-3-phenyl-1λ^3-benzo[d][1,2]iodaoxol-1(3*H*)-ol **3.4** constituted a straightforward step. This reaction was carried out by stirring a solution of the bromoiodane **3.3** in DCM with an aqueous solution of potassium hydroxide for 2 hours at room temperature. As the reaction progressed, there was a visible colour change from dark yellow to pale yellow. Any impurities could be removed by recrystallization from ethyl acetate, giving the pure product **3.4** as a white solid in 88 % yield. The OH group introduced in this step is yet to be observed in the ^{1}H NMR spectrum. However, the formation of **3.4** was identified by the significant shifts in the signals in the aromatic region due to the replacement of the bromide anion with the hydroxy anion.

The hydroxyiodane **3.4** was finally converted into the fluoroiodane **3.5** using TREAT.HF. A solution of **3.4** in dichloromethane was stirred with TREAT.HF for 4 hours at RT before it was washed with water to remove the excess of TREAT.HF. The pure product was obtained as a pale yellow solid in a 97 % isolated yield. Any residual water was removed by co-evaporation with toluene and the recrystallization from toluene was sufficient to remove any impurities. To confirm that the fluoroiodane **3.5** had formed, the ^{19}F NMR spectrum was recorded which showed a singlet peak at -143.2 ppm.

3.2 Synthesis of unsymmetrical diaryliodonium salts using *p*-toluenesulphonic acid.

The reactivity of fluoroiodane **3.5** with activated aromatics in the presence of *p*-toluenesulphonic acid was investigated in order to prepare unsymmetrical diaryliodonium salts following the protocol used previously (see Section 2.3). The activated aromatic (1 equivalent) was added to a solution of fluoroiodane **3.5** (1.5 equivalents) and *p*-toluenesulphonic (3.4 equivalents) in TFE and the reaction mixture was stirred at RT for 1 hour (Scheme 3.2). After washing the crude products with water to remove any *p*-toluenesulphonic acid, it was then washed with hexane and diethyl ether to produce the pure product as a white solid.



***Scheme 3.2**: Synthesis of diaryliodonium salts using p-toluenesulphonic acid*

When anisole was reacted with fluoroiodane **3.5**, the ^{1}H NMR spectrum of the crude product showed that there was a 66 % conversion to the desired product **3.6** and the ^{19}F NMR spectrum indicated that there was no fluoroiodane **3.5** remaining. The ^{1}H NMR spectrum of the pure product showed two singlet peaks at 2.07 and 3.85 ppm corresponding to the methyl group on the sidearm and the methoxy group on the aromatic ring respectively which indicated that the elimination is not occurred. In addition, the methyl group of the tosylate anion appeared as a singlet peak at 2.30 ppm. The ^{13}C NMR spectrum of **3.6** showed signals for all carbon atoms including eight quaternary carbons and three signals in the aliphatic region at 21.3, 30.1 and 55.7 ppm corresponding to the two methyl groups and methoxy group respectively. Further confirmation by ESI-MS showed a peak at *m/z* 431 corresponding to the parent cation, M^{+}.

In the reaction with 1,3-dimethoxybenzene, the ^{1}H NMR spectrum of the crude product showed that there was a 90 % conversion and **3.7** was isolated in 83 % yield. The ^{1}H NMR spectrum of **3.7** showed two singlet peaks at 3.68 and 3.89 ppm corresponding to the two methoxy groups in different environments whilst the singlet peak at 2.09 ppm can be assigned to the protons of the methyl group on the sidearm which indicated that

there is no elimination. In addition, a singlet peak at 2.30 ppm corresponding to the methyl group of the tosylate anion was also observed. The two methyl and two methoxy groups also appeared in the ^{13}C NMR spectrum as singlets at 21.3, 29.7, 56.1 and 56.7 ppm respectively. In addition, nine quaternary carbon atoms were observed including two C-I peaks at 91.5 and 126.1 ppm. The ESI-MS spectrum gave a peak corresponding to M^+ at *m/z* 461, representing the diaryliodonium cation. In addition, X-ray crystallography verified the structure of **3.7** (Figure 3.1). As seen in Table 3.1, the C(1)-I(1) bond length (2.132(3)Å) was slightly longer than the C(15)-I(1) (2.071(3) Å) bond length and the bond angle of the C(1)-I(1)-C(15) was 96.25(11)^o. In addition, the C(7)-O(1) bond length of **3.7** (1.442(3) Å) is similar to the C(7)-O(1) bond length of fluoroiodane **1.22** (1.450(6) Å).[63] Furthermore, there was a strong intramolecular interaction (2.645(2) Å) between I(1) and O(1) in comparison with the I(1)-O(1) bond length of fluoroiodane **1.22** (2.029(3) Å).[63] The O(1)···I(1)-C(15) bond angle (168.53(8)) was also very similar to the F(1)-I(1)-O(1) bond angle in fluoroiodane **1.22** (166.66 (14)).

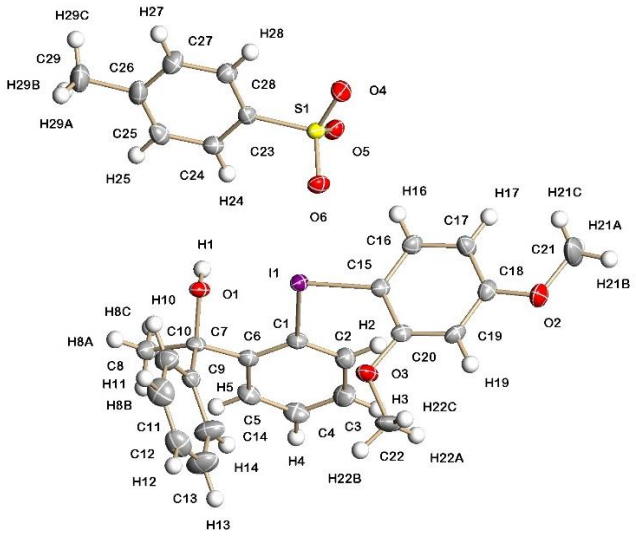
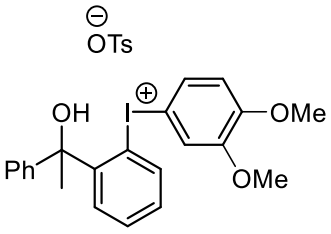


Figure 3.1**: Solid-state structure of **3.7

Table 3.1: Key bond lengths (Å) and angles (°) for 3.7

Bond lengths (Å)		Bond angles (°)	
I(1)-C(1)	2.132(3)	C(1)-I(1)-C(15)	96.25(11)
I(1)-C(15)	2.071(3)	O(1)···I(1)-C(15)	168.53(8)
C(7)-O(1)	1.442(3)	-	-
O(1)···I(1)	2.645(2)	-	-
O(3)···I(1)	3.087(4)		

On the other hand, there was only an 18 % conversion to **3.8** when 1,2-dimethoxybenzene was reacted with fluoroiodane **3.5** using the same reaction conditions (Figure 3.2). This value increased slightly to 27 % when the reaction was carried out for 4 hours or overnight at RT but the desired product **3.8** was not isolated. Furthermore, no reaction was observed when 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was used as the solvent at RT for 4 hours.



3.8

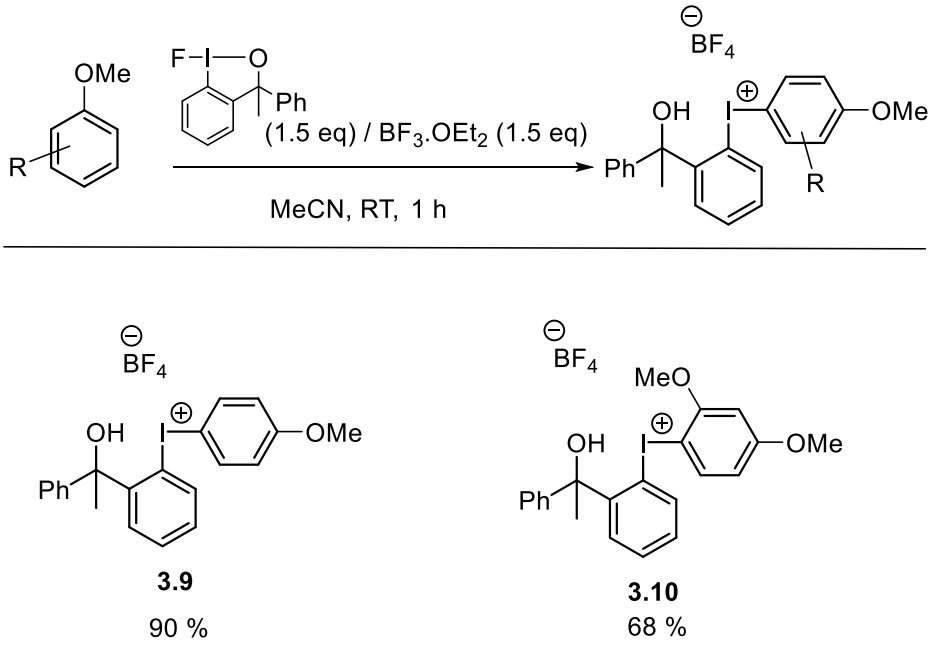
Figure 3.2: The structure of (3,4-dimethoxyphenyl)(2-(1-hydroxy-1-phenylethyl)phenyl)iodonium tosylate 3.8

3.3 Synthesis of unsymmetrical diaryliodonium salts using boron trifluoride

The use of the Lewis acid, $BF_3.OEt_2$, to activate fluoroiodane **3.5** was investigated in order to prepare unsymmetrical diaryliodonium tetrafluoroborates. This reaction was carried out by reacting anisole or 1,3-dimethoxybenzene with fluoroiodane **3.5** (1.5 equivalents) in acetonitrile (Scheme 3.3). The solution was cooled to 0 °C before adding

1.5 equivalents of $BF_3.OEt_2$ and the reaction mixture was then warmed to room temperature to react for 1 h.

Two new compounds, **3.9** and **3.10**, were prepared successfully (without elimination of the hydroxyl group) in high yields (90 and 68 %, respectively) and were characterised fully by multinuclear NMR spectroscopy and mass spectrometry. The ^{19}F NMR spectra of these salts revealed a signal at -150.4 ppm corresponding to the BF_4^- counteranion. Further confirmation was achieved by ESI-MS spectrum which gave peaks at *m/z* 431 and 461 corresponding to M^+ for **3.9** and **3.10**, respectively. In the ES-MS, a peak at *m/z* 87 corresponding to BF_4^- counteranion in **3.9** and **3.10** was also observed. In addition, crystals suitable for X-ray crystallography were obtained for **3.9** the solid-structure is shown in Figure 3.3 and the key bond lengths and angles are presented in Table 3.2.



***Scheme 3.3**: Synthesis of unsymmetrical diaryliodonium salts using boron trifluoride.*

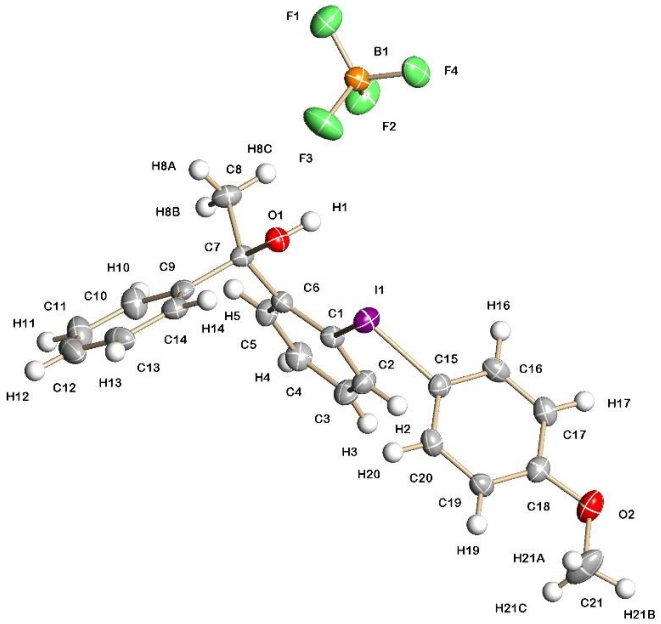


Figure 3.3**: Solid-state structure of **3.9

Table 3.2**: Key bond lengths (Å) and angles (°) for **3.9

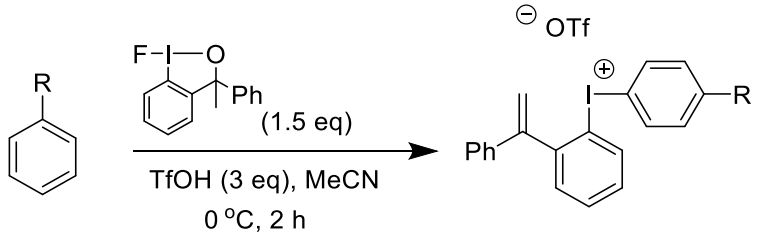
Bond lengths (Å)		Bond angles (°)	
I(1)-C(1)	2.134(3)	C(1)-I(1)-C(15)	97.12(11)
I(1)-C(15)	2.088(3)	O(1)···I(1)-C(15)	168.84(8)
C(7)-O(1)	1.439(3)	-	-
O(1)···I(1)	2.589(2)	-	-

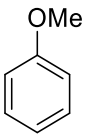
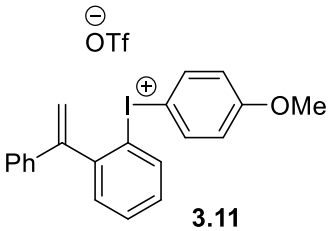
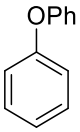
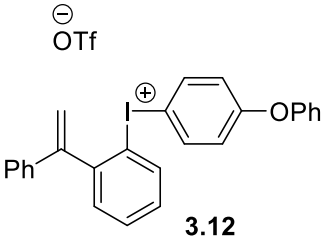
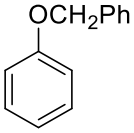
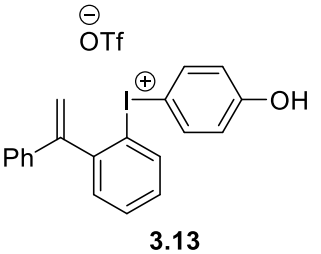
Despite anisole and 1,3-dimethoxybenzene reacting with **3.5** in the presence of $BF_3.OEt_2$, no reaction was observed with either 1,2-dimethoxybenzene or *N*-methylindole using the same reaction conditions.

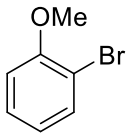
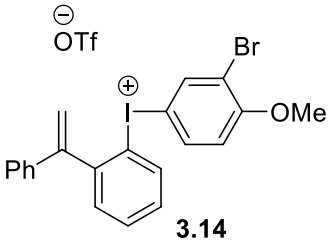
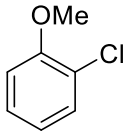
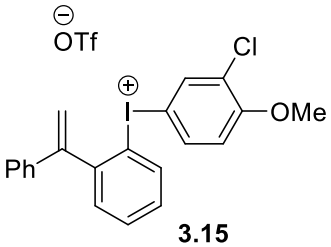
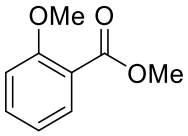
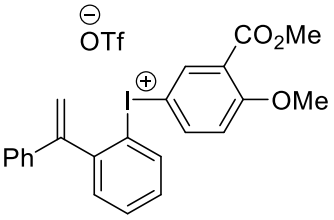
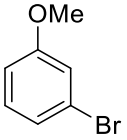
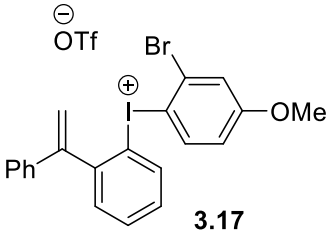
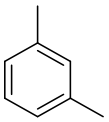
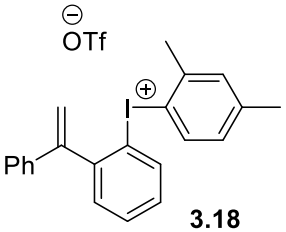
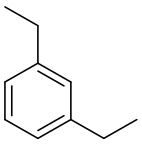
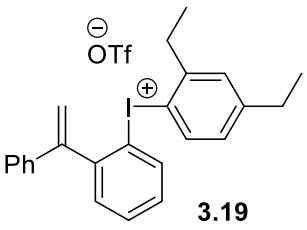
3.4 Synthesis of unsymmetrical diaryliodonium salts using triflic acid

Fluoroiodane **3.5** was also reacted with a series of monosubstituted and disubstituted aromatics in the presence of triflic acid instead of *p*-toluenesulphonic acid or $BF_3.OEt_2$. The reaction was carried out by adding the activated aromatics to the solution of fluoroiodane **3.5** (1.5 equivalents) and triflic acid (3 equivalents) in MeCN at 0 °C. The reaction mixture was left to react for 2 h before it was washed with water, hot hexane and diethyl ether to give the pure products in high yields (48-93 %) (Table 3.3).

Table 3.3: *Synthesis of diaryliodonium triflates with* ***3.5***



Entry	Ar-H	Product	Yield[a] (%)
1[b]		 **3.11**	79
2		 **3.12**	85
3		 **3.13**	63

4		 **3.14**	93
5		 **3.15**	80
6		 **3.16**	89
7[c]		 **3.17**	48
8		 **3.18**	89
9		 **3.19**	90

[a] Isolated yield; [b] triflic acid (1.5 eq) at RT for 1 h; [c] containing 10 % of isomer (*ortho* to methoxy group).

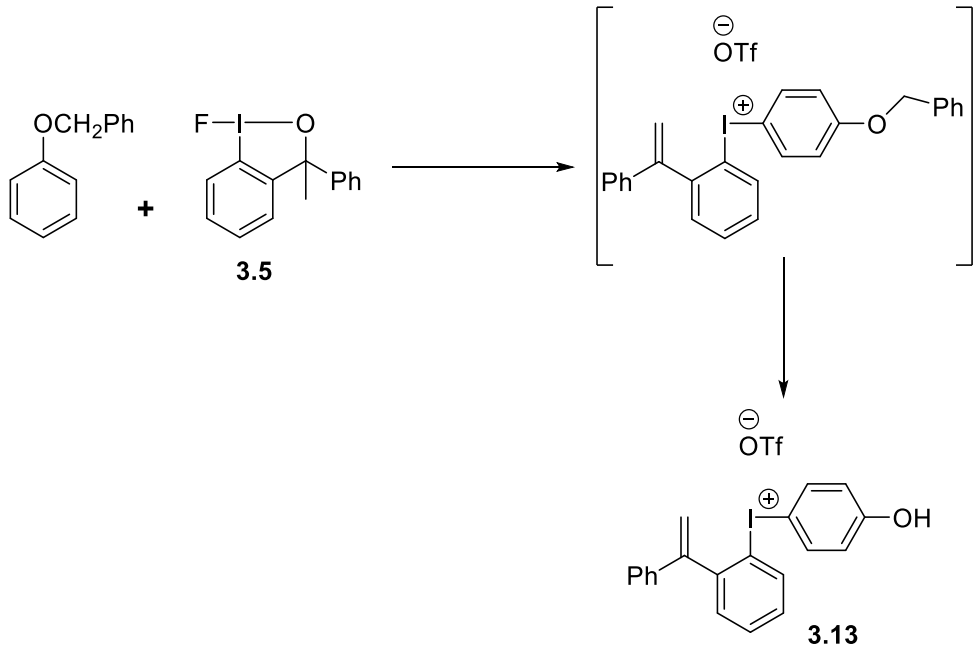
In all of these reactions the alcohol sidearm underwent an elimination to form an alkene sidearm under the strong acidic conditions. The driving force for these eliminations was the formation of the alkene in conjugation with two aromatic rings. As this effect is only observed in the triflic acid reaction, it can be inferred that *p*-toluenesulphonic acid is not a strong enough acid to dehydrate the molecule.

In entry 1 fluoroiodane **3.5** was reacted with anisole in the presence of triflic acid (1.5 equivalents) at RT for 1 h to form **3.11** as an off white solid in a 79 % isolated yield. The ^{1}H NMR spectrum of the pure product showed the absence of CH_3 and OH peaks. Instead, two clear singlets were observed at 5.43 and 6.06 ppm corresponding to the two protons of the alkene, indicating that elimination had occurred. In the ^{13}C NMR spectrum, the two peaks at 55.7 and 119.6 ppm were assigned to the methoxy and CH_2 groups, respectively. In the ^{19}F NMR spectrum, a singlet peak at -78.3 ppm was assigned to the CF_3 group of the triflate anion. The ESI-mass spectra of **3.11** showed a peak at *m/z* 413 corresponding to the parent cation, M^+, and a peak at *m/z* 149 for the triflate counteranion.

In the reaction with diphenyl ether, (4-phenoxyphenyl)(2-(1-phenylvinyl)phenyl) iodonium triflate **3.12** was formed and isolated in 85 % yield (entry 2). In the ^{1}H NMR spectrum, the two singlet peaks at 5.44 and 6.08 ppm were assigned to the alkene and all the protons of the aromatic rings were individually assigned in the aromatic region. In the ^{13}C NMR spectrum, seven quaternary carbon signals were observed, including two C-I signals at 103.4 and 117.5 ppm. Further confirmation was given by ^{19}F NMR spectroscopy, which showed a singlet peak at -78.3 ppm corresponding to the CF_3 group of the triflate anion. ESI-MS data of this compound revealed a peak at *m/z* 475 corresponding to the cation of **3.12**.

Interestingly, the ^{1}H NMR spectrum of the crude product from the reaction with benzyl phenyl ether (entry 3), did not contain a singlet for the benzylic CH_2 group. Instead, a broad peak at 7.69 ppm was assigned to the OH group which indicated that the benzyl protecting group was removed during the reaction and **3.13** was formed (Scheme 3.4). The pure product **3.13** was obtained as a white solid in 63 % isolated yield after recrystallization from hot DCM. All the carbon atoms were assigned in the ^{13}C NMR spectrum including seven quaternary carbons. The product was further confirmed by ESI-MS which gave a peak at *m/z* 399.0250 corresponding to M^+.

In the reaction of 2-bromoanisole with fluoroiodane **3.5** (entry 4), (3-bromo-4-methoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium triflate **3.14** was obtained in 93 % isolated yield as a white solid. The associated ^{1}H NMR spectrum showed a 1H doublet at 7.57 ppm with $^{4}J_{HH}$ = 2.3 Hz, corresponding to the *meta*-proton to the methoxy group on the 2-bromoanisole ring. In addition, the two singlet peaks at 5.45 and 6.07 ppm corresponding to the alkene were also observed. The ^{13}C NMR spectrum of this compound showed two peaks at 56.7 and 119.8 ppm which were assigned to the methoxy and CH_2 groups. ESI-MS data of **3.14** gave a peak at *m/z* 492.9 corresponding to M^+.



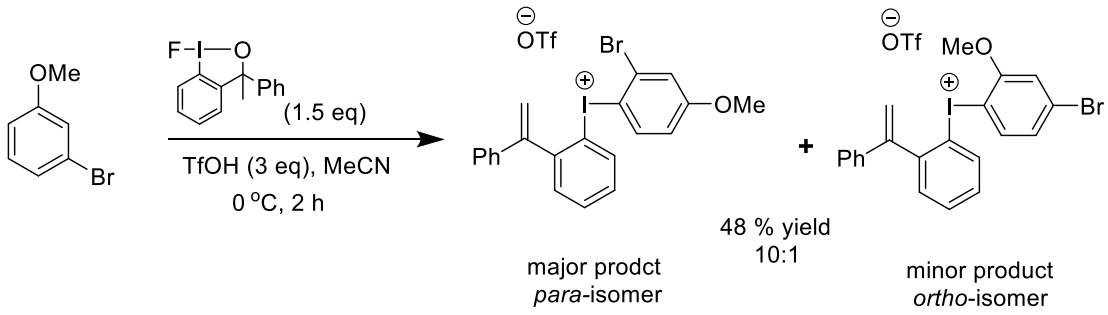
Scheme 3.4**: The reaction between diphenyl ether and **3.5

In entry 5 an 80 % isolated yield was obtained when 2-chloroanisole was reacted with fluoroiodane **3.5** to form **3.15**. In the ^{1}H NMR spectrum, the signal appearing as a 1H doublet at 7.40 ppm with $^{4}J_{HH}$ = 2.3 Hz was assigned to the *meta*-proton to the methoxy group on the 2-chloroanisole ring. Furthermore, protons for the methoxy and alkene appeared as singlets at 3.89, 5.45 and 6.08 ppm respectively. In the ^{13}C NMR spectrum, the two C-I bonds appeared at 100.7 and 118.0 ppm. ESI-MS revealed a peak at *m/z* 447 corresponding to the diaryliodonium cation.

Methyl-2-methoxybenzoate was also reacted with fluoroiodane **3.5** to produce **3.16** as a white solid in 89 % isolated yield (entry 6). In the ^{1}H NMR spectrum, two singlets at 3.85

and 3.89 ppm, corresponding to the two methoxy groups in different environments were observed. In addition, the signal due to the *meta*-proton to the methoxy group on the methyl-2-methoxybenzoate moiety appeared as a doublet at 8.00 ppm with $^{4}J_{HH} = 2.6$ Hz. In the ^{13}C NMR spectrum, three singlet peaks at 52.6, 56.7 and 119.7 ppm were assigned to the two methoxy groups and the alkene, respectively. Further confirmation was obtained by ESI-MS, which showed a peak at *m/z* 471 corresponding to M^{+}.

3-Bromoanisole was also reacted with **3.5** to give (2-bromo-4-methoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium triflate **3.17** as a white solid in 48 % isolated yield (entry 7). The ^{1}H NMR spectrum of the crude product showed 55 % conversion to the desired product (*para* isomer) and the *ortho* isomer in a 10:1 ratio for the *para*:*ortho*-isomer, but the *ortho* isomer could not be isolated after washing with hot hexane and diethyl ether (Scheme 3.5). This salt was fully characterised by ^{1}H and ^{13}C NMR spectroscopy and electrospray mass spectrometry.



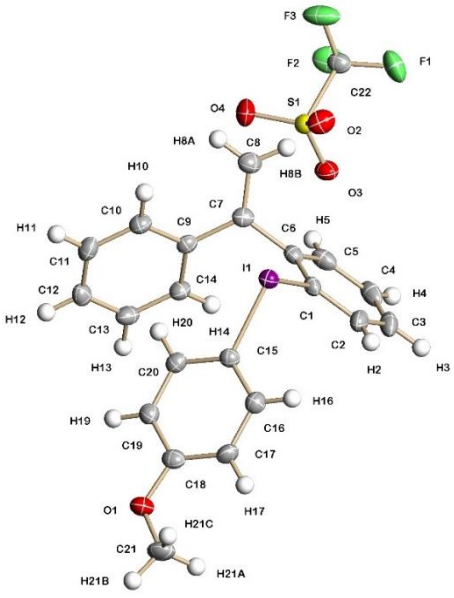
Scheme 3.5**: Reaction of 3-bromoanisole with **3.5

m-Xylene was also reacted with fluoroiodane **3.5** giving (2,4-dimethylphenyl)(2-(1-phenylvinyl)phenyl)iodonium triflate **3.18** in 89 % isolated yield (entry 8). The presence of the desired product **3.18** was confirmed in the ^{1}H NMR spectrum by the appearance of the two methyl peaks in the *m*-xylene moiety at 2.27 and 2.31 ppm. In the ^{13}C NMR spectrum, the two methyl groups appeared as two singlets at 21.3 and 25.3 ppm and the two C-I peaks were observed at 114.5 and 116.5 ppm. This compound was also

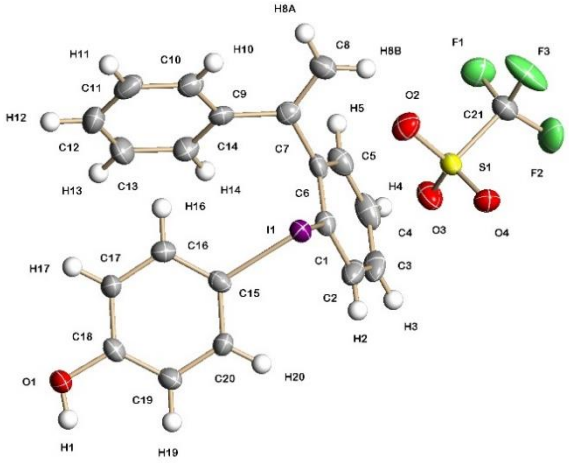
characterised by ESI-MS which showed an M^+ peak at *m/z* 411 corresponding to the cation.

In the reaction of 1,3-diethylbenzene with **3.5** (entry 9), (2,4-diethylphenyl)(2-(1-phenylvinyl)phenyl) iodonium triflate **3.19** was obtained as an orange/yellow oil in 94 % isolated yield. The ^{1}H NMR spectrum showed two triplets at 1.10 and 1.24 ppm corresponding to the two methyl groups in different environments. A multiplet peak between 2.61-2.68 ppm was assigned to the 4H of the two CH_2 groups. The ^{13}C NMR spectrum of **3.19** displayed 4 singlets at 14.7, 15.0, 28.6 and 32.2 ppm corresponding to the 2 CH_3 and 2 CH_2 groups respectively. ESI-MS data of this compound showed a peak at *m/z* 439.0934 corresponding to M^+.

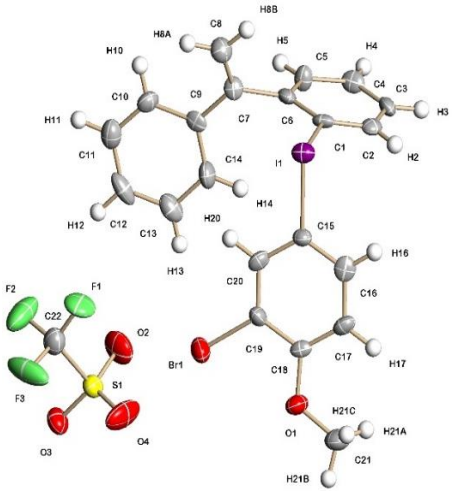
Crystals suitable for X-ray crystallography were obtained for some of these salts (Figure 3.4) and the key bond lengths and angles are presented in Table 3.4. As seen in Table 3.4, the C(1)-I(1) bond lengths of iodonium triflates (2.104(4) - 2.121(3) Å) were very similar to the bond lengths of the C(15)-I(1) (2.094(3) - 2.109(4) Å) and the distinct C(1)-I(1)-C(15) bond angles ranged from 96.20(3) to 100.99(17)°. In addition, the C(7)-C(8) bond lengths were 1.311(8) – 1.327(6) Å which is typical for an olefinic C=C bond length (1.322(4) Å) [135] and there were no intramolecular interactions between olefinic C=C bond and I.



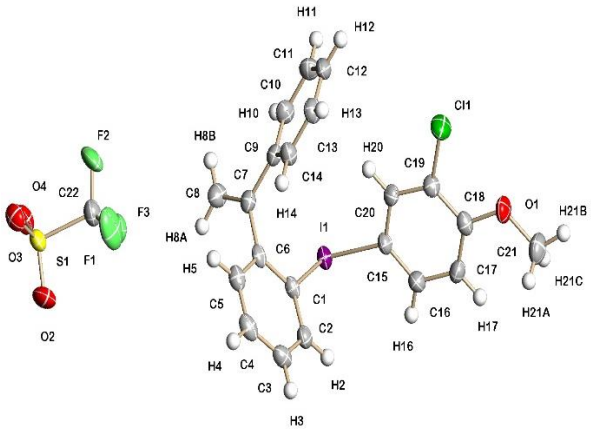
a) Solid-state structure of **3.11**



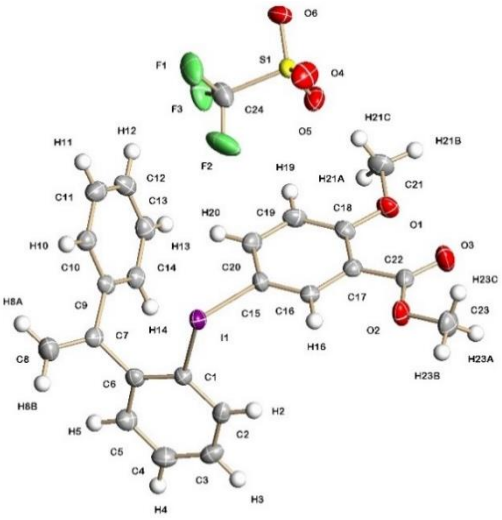
b) Solid-state structure of **3.13**



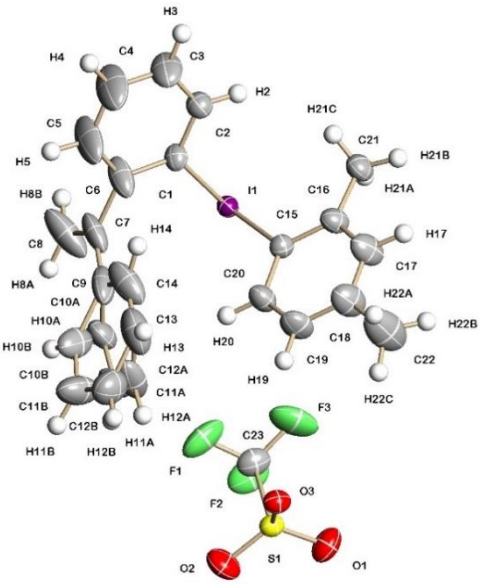
c) Solid-state structure of **3.14**



d) Solid-state structure of **3.15**



d) Solid-state structure of **3.16**



f) Solid-state structure of **3.18**

***Figure 3.4**: Solid-state structures for diaryliodonium triflates*

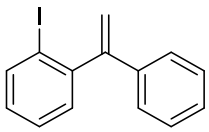
Table 3.4: Key bond lengths (Å) and angles (°) for diaryliodonium triflates

	3.11	3.13	3.14	3.15	3.16	3.18
C(1)-I(1)	2.108(3)	2.104(4)	2.116(7)	2.121(3)	2.115(3)	2.109(4)
C(15)-I(1)	2.094(3)	2.094(4)	2.101(7)	2.105(3)	2.102(3)	2.109(4)
C(7)-C(8)	1.327(4)	1.327(6)	1.318(10)	1.323(5)	1.325(5)	1.311(8)
C(1)-I(1)-C(15)	98.00(11)	100.99(17)	96.20(3)	97.40(13)	99.02(13)	97.10(15)
C(6)-C(7)-C(9)	117.3(2)	116.8(4)	117.9(7)	116.5(3)	116.9(3)	117.0(5)

The new hypervalent iodine reagent **3.5** was more reactive than the original fluoroiodane **1.22** which has two methyl groups in its sidearm, and reacted well with a range of monosubstituted and disubstituted aromatics to form the products in high yields. In addition, when **3.5** was used the diaryliodonium salt dehydrated easily in the presence of triflic acid to form an alkene sidearm. In general, the reaction with less activated aromatics such as diphenyl ether, methyl 2-methoxybenzoate and *m*-xylene gave better yields with the new hypervalent iodine **3.5** (85 %, 89 % and 89 % yield respectively) than with the original fluoroiodane **1.22** (70 %, 33 % and 51 % respectively).

Unfortunately, there have also been many unsuccessful attempts to extend the scope of the reaction between fluoroiodane **3.5** and other arenes in the presence of 3 equivalents of triflic acid, as seen in Table 3.5. Using the same reaction conditions with 1,2-dimethoxybenzene (entry 1), resulted in only starting material and 1-iodo-2-(1-phenylethenyl)benzene **3.20** (Figure 3.5) being observed in the ^{1}H NMR spectrum of the crude product. 1-Iodo-2-(1-phenylethenyl)benzene **3.20** was characterised by the two singlets at 5.16 and 5.77 ppm corresponding to the two alkene protons, and nine aromatics protons were also assigned in the aromatic region. In the ^{13}C NMR spectrum, four quaternary carbon signals were observed, including C-I signals at 99.0 ppm. The ^{19}F NMR spectrum indicated that there was no fluoroiodane **3.5** left. The same result was

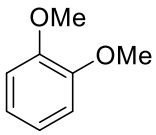
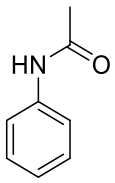
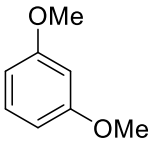
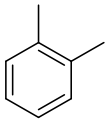
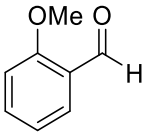
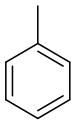
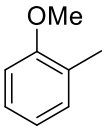
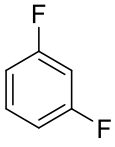
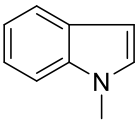
obtained when the amount of triflic acid was decreased from 3 to 1.5 equivalents for 6 hours (2 hours at 0 °C, then stirred for 4 hours at RT).



3.20

Figure 3.5**: Iodo-2-(1-phenylethenyl)benzene **3.20

***Table 3.5**: Arenes that did not react with **3.5** in the presence of triflic acid*

Entry	Substrate	Entry	Substrate
1		**6**	
2		**7**	
3		**8**	
4		**9**	
5			

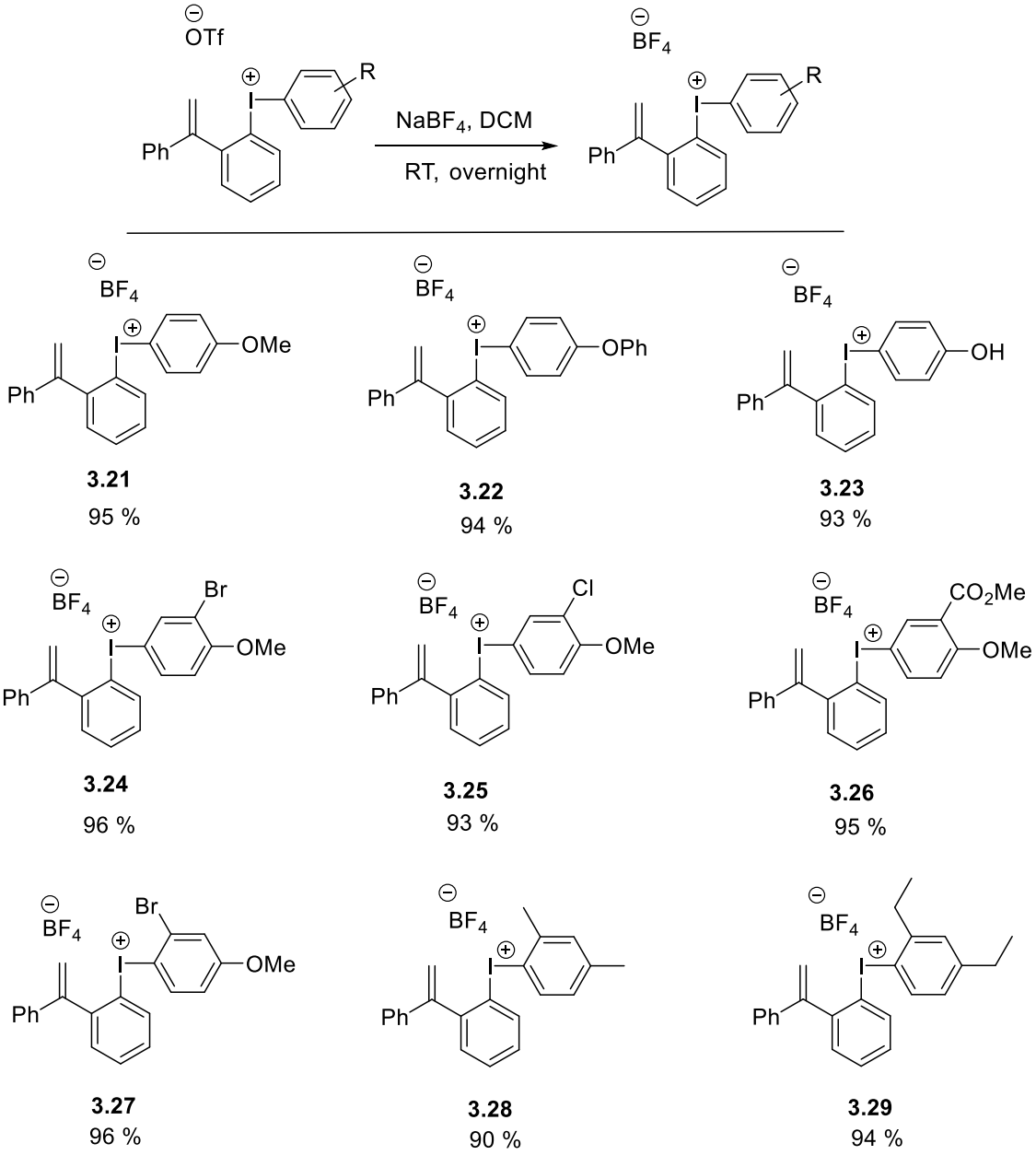
In the reaction with 1,3-dimethoxybenzene (entry 2), only starting material and **3.20** were observed in the ^{1}H NMR spectrum using 3 equivalents of triflic acid at 0 ^{o}C for 2 hours and the ^{19}F NMR spectrum showed that there was no fluoroiodane **3.5** left. No change was observed when the amount of triflic acid was reduced to 1.5 equivalents either at 0 ^{o}C for 1 hour or at -78 ^{o}C for 2 hours, and indeed **3.20** was formed in each reaction.

Only 20 % conversion was observed in the ^{1}H NMR spectrum of the crude product for entry 3 when fluoroiodane **3.5** was reacted with 2-methoxybenzaldehyde using the optimum reaction conditions. No change was observed when the reaction time was extended to 5 hours (1 hour at 0 ^{o}C then, then stirred at RT for a further 4 hours) or the temperature was lowered to -78 ^{o}C for 2 hours.

In the reactions with 1-methoxy-2-methylbenzene, N-methylindole, acetanilide, *o*-xylene, toluene and 1,3-difluorobenzene (entries 4-9), the ^{1}H NMR spectra of the crude products showed that there was no reaction in MeCN at 0 ^{o}C for 2 hours.

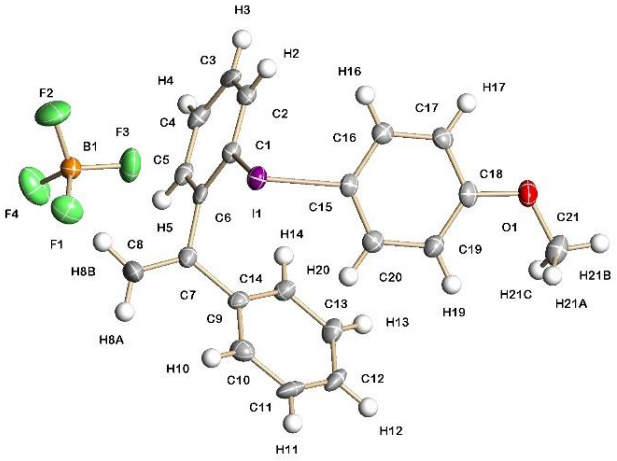
3.5 Metathesis reactions with $NaBF_4$

The triflate counteranion in the unsymmetrical diaryliodonium salts (Table 3.3) was easily exchanged with tetrafluoroborate (Scheme 3.6). The metathesis was achieved by stirring a solution of the diaryliodonium triflates **3.11-3.19** in DCM with an aqueous solution of $NaBF_4$ overnight at RT giving **3.21-3.29** in high yields (90-96 %). The key features of the NMR data for these compounds were the absence of a CF_3 peak at -78.3 ppm corresponding to the triflate anion and a strong singlet that appeared at -151.5 ppm corresponding to the BF_4^- group. In addition, a peak at *m/z* 87 in the ES-MS spectra was also observed for the tetrafluoroborate anion.

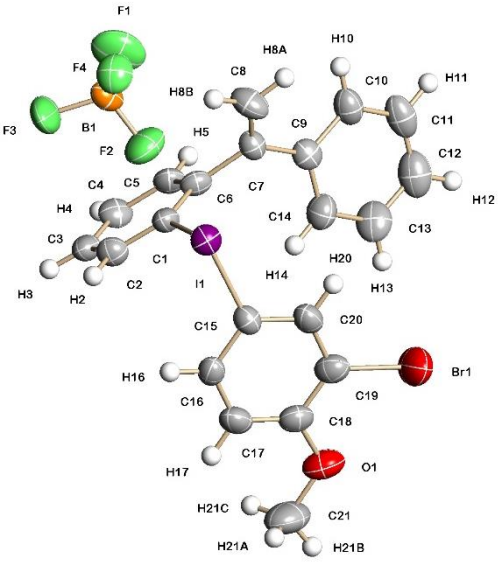


***Scheme 3.6**: Metathesis reactions with $NaBF_4$*

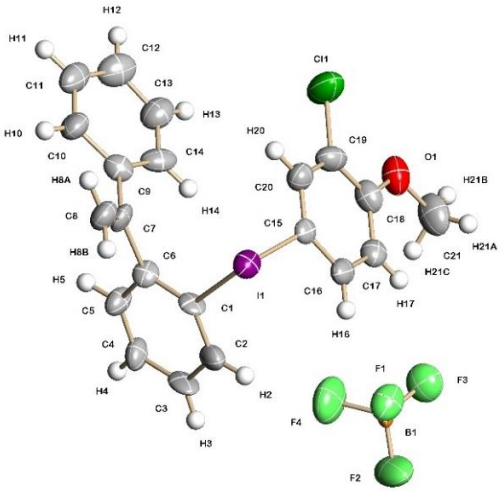
Crystals suitable for X-ray crystallography were obtained for **3.21**, **3.24**, **3.25** and **3.28** (Figure 3.6). The key bond lengths and angles are presented in Table 3.6 and they are very similar to the key bond lengths and bond angles for the diaryliodonium triflates.



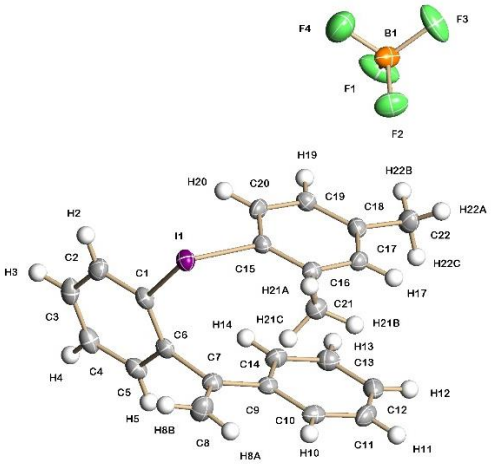
a) Solid-state structure of **3.21**



b) Solid-state structure of **3.24**



c) Solid-state structure of **3.25**



d) Solid-state structure of **3.28**

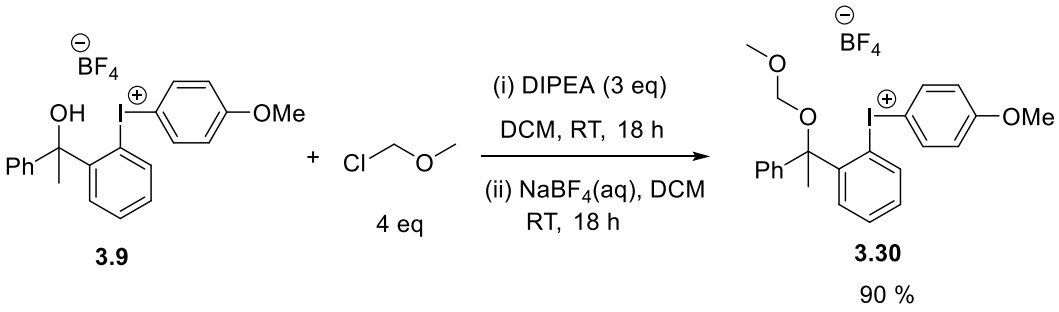
Figure 3.6**: Solid-state structures of a) **3.21**, b) **3.24**, c) **3.25** and d) **3.28

*Table 3.6: Key bond lengths (Å) and angles (°) for **3.21**, **3.24**, **3.25** and **3.28**.*

	3.21	3.24	3.25	3.28
C(1)-I(1)	2.118(4)	2.100(8)	2.140(10)	2.112(3)
C(15)-I(1)	2.099(4)	2.084(8)	2.120(12)	2.105(3)
C(7)-C(8)	1.327(6)	1.335(11)	1.341(15)	1.326(5)
C(1)-I(1)-C(15)	95.26(14)	92.6(3)	92.8(4)	95.04(13)
C(6)-C(7)-C(9)	116.1(3)	117.5(7)	118.7(11)	119.3(3)

3.6 Protection of free hydroxy group

Before investigating the fluorination of **3.9**, the alcohol in the sidearm was protected with chloromethyl methyl ether (MOMCl) (4 equivalents) in the presence of *N*,*N*-diisopropylethylamine (DIPEA) using dichloromethane as the solvent following the literature procedure (Scheme 3.7).[134]



Scheme 3.7: Protection of the hydroxy group

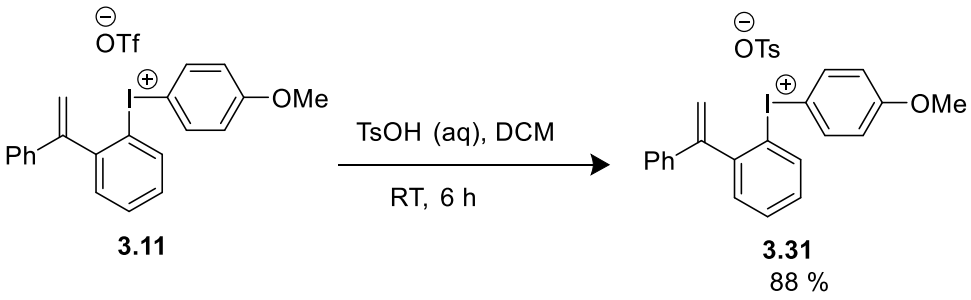
The crude product was then stirred with a saturated solution of $NaBF_4$ to remove any chloride counteranion which might be formed during the reaction. After stirring the product with diethyl ether **3.30** was obtained as a solid in 90 % yield. The ^1H NMR spectrum of the pure product showed a new singlet at 3.53 ppm corresponding to the CH_3 group of the protecting group. In addition, the CH_2 group appeared as AB multiplet

centered at 4.90 ppm corresponding to the two diastereotopic protons in the protecting group. In the ^{13}C NMR spectrum, the new CH_3 and CH_2 groups appeared as singlets at 55.5 and 92.4 ppm respectively. Furthermore, ESI-MS data of this compound showed a peak at *m/z* 475.0770 corresponding to M^+.

3.7 Synthesis of (4-methoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium tosylate 3.31

Before attempting to fluorinate diaryliodonium salts with different counteranions such as triflate and tetrafluoroborate which had been already prepared in this chapter (**3.11** and **3.21**), the diaryliodonium tosylate **3.31** need to be synthesised in order to investigate the fluorination of diaryliodonium tosylate.

The synthesis of (4-methoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium tosylate **3.31** was achieved by stirring a solution of **3.11** in DCM with an aqueous solution of $TsOH.H_2O$ for 6 h at RT (Scheme 3.8). The pure product was obtained as a light brown solid in 88 % isolated yield after trituration with diethyl ether. The ^1H NMR spectrum of the pure product showed a singlet peak at 2.31 ppm corresponding to the methyl group of the tosylate counteranion. In addition, 4 extra protons were also observed in the aromatic region corresponding to the 4 protons of the tosylate aromatic ring. In the ^{19}F NMR spectrum, the absence of the CF_3 peak at -78.3 ppm was observed indicating that there was no triflate anion remaining. This compound was further confirmed by ^{13}C NMR spectroscopy and mass spectrometry. Single crystals of **3.31**, suitable for X-ray crystallography, were grown by slow evaporation of a DCM and hexane solution (3:1). The molecular structure of **3.31** is shown in Figure 3.7 and representative bond lengths and bond angles are given in Table 3.7.



3.11 **3.31** 88 %

Scheme 3.8: *Synthesis of* ***3.31***

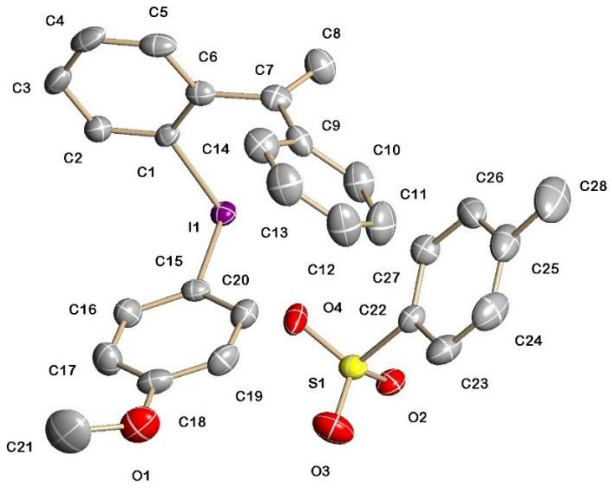


Figure 3.7: *Solid-state structure of* ***3.31****. The hydrogen atoms have been omitted*

Table 3.7: *Key bond lengths (Å) and angles (°) for* ***3.31***

Bond lengths (Å)		Bond angles (°)	
I(1)-C(1)	2.102(3)	C(1)-I(1)-C(15)	92.81(14)
I(1)-C(15)	2.100(4)	C(6)-C(7)-C(9)	118.30(3)
C(7)-C(8)	1.314(5)	O(4)···I(1)-C(1)	176.86(3)
I(1)···O(4)	2.721(3)	-	-

3.8 Conclusions

A new analogue of fluoroiodane **3.5** was prepared, where one of the methyl groups in the sidearm was replaced by a phenyl group, by a five-step synthesis. Each step gave high yields under mild reaction conditions.

Anisole and 1,3-dimethoxybenzene were reacted with the new fluoroiodane reagent **3.5** in the presence of *p*-toluenesulphonic acid and boron trifluoride forming the *para*-substituted diaryliodonium tosylates and diaryliodonium tetrafluoroborates respectively in good yields without any elimination of the hydroxy group.

However, when the new fluoroiodane reagent **3.5** was reacted with activated aromatics in the presence of triflic acid to form the diaryliodonium salts, the alcohol sidearm underwent elimination to form an alkene sidearm. Nine different salts were prepared successfully in good to excellent yields (48-93 %). The diaryliodonium triflates also underwent metathesis by stirring them in DCM with an aqueous solution of $NaBF_4$ overnight at RT to form the diaryliodonium tetrafluoroborates in high yields (90-96 %). The free hydroxy group in the diaryliodonium tetrafluoroborate **3.9** was protected by reacting with MOMCl in the presence of DIPEA to produce **3.30** in 90 % isolated yield.

All of the new diaryliodonium salts were characterised by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy, mass spectrometry and in many cases by X-ray crystallography.

Chapter Four: Fluorination of diaryliodonium salts

4.1 Introduction

Nowadays, diaryliodonium salts are used widely in the fluorination of aromatic compounds because they are excellent leaving groups with high electrophilic properties. More specifically, unsymmetrical diaryliodonium salts offer potential advantages over symmetrical ones in both their synthesis and applications.[104] However, the main challenge to overcome with the fluorination of unsymmetrical diaryliodonium salts is the chemoselectivityof the fluoride atom to the one aryl group over the other to give the desired fluorinated product.

4.1.1 Mechanisms of the fluorination of diaryliodonium salts "copper free"

The mechanism of the reactions of diaryliodonium salts with fluoride ion matches that of many other nucleophiles.[136] The reaction proceed through ligand exchange with the fluoride followed by "ligand coupling" and reductive elimination of iodoarene (**Figure 4.1**). For unsymmetrical iodonium salts, either iodoarene may be eliminated or fluoroarene may be produced. For diaryliodonium salts that do not carry *ortho* substituents, fluorination of the most electron-deficient aryl ring is favored.[137] For unsymmetrical salts that carry 1 or more *ortho* substituents, the *ortho* substituted ring may be fluorinated in preference to a more electron-deficient ring.[106]

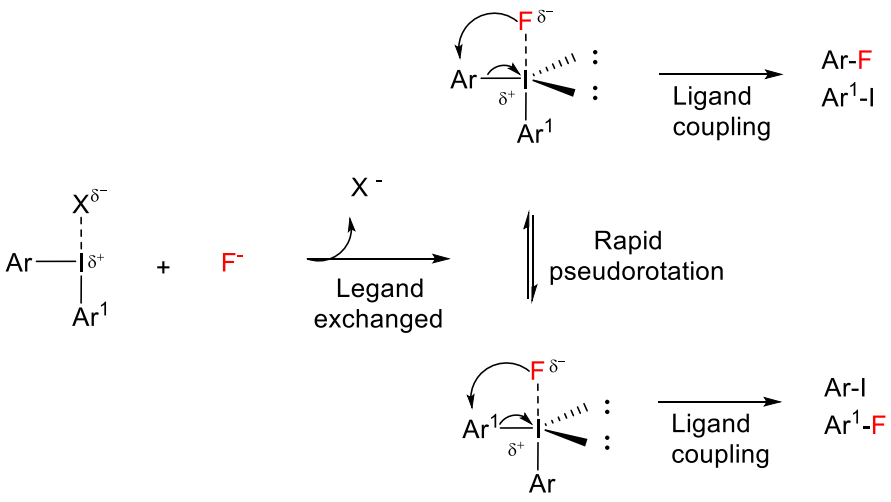


Figure 4.1: *Mechanism of the fluorination of unsymmetrical diaryliodonium salts*

4.1.2 Mechanisms of the fluorination of diaryliodonium salts "copper mediated"

The inclusion of a copper catalyst in the fluorination of diaryliodonium salts has a significant effect on the reaction mechanism and outcome. Sanford's group found that the *ortho* effect could be reversed, and the fluoride ion tended to go to the more electron-deficient ring by using copper catalyst.[98] In the fluorination of aryl(mesityl)iodonium salts ($ArI^+(Mes)X^-$), yield with the chemoselectivity for fluoroarene (Ar-F) production versus mesityl fluoride (Mes-F) have been found to depend strongly on the selected Cu catalyst and solvent, under some conditions strongly favoring production of the fluoroarene and under others mesityl fluoride. The use of $Cu(OTf)_2$ in DMF at 60 °C for 18 h gave high chemoselectivity for Ar-F versus Mes-F for a wide range of Ar groups. Detailed theoretical and experimental investigations suggest that the mechanism of this reaction involves a Cu(I/III) catalytic cycle (Figure 4.2). The Cu(II) catalyst ($Cu(OTf)_2$) was first reduced to a Cu(I) species by DMF, followed by the oxidation of Cu(I)species by the $MesI^+Ar$ which is considered to be the rate limiting step of the path to generate the desired fluorinated products.[98]

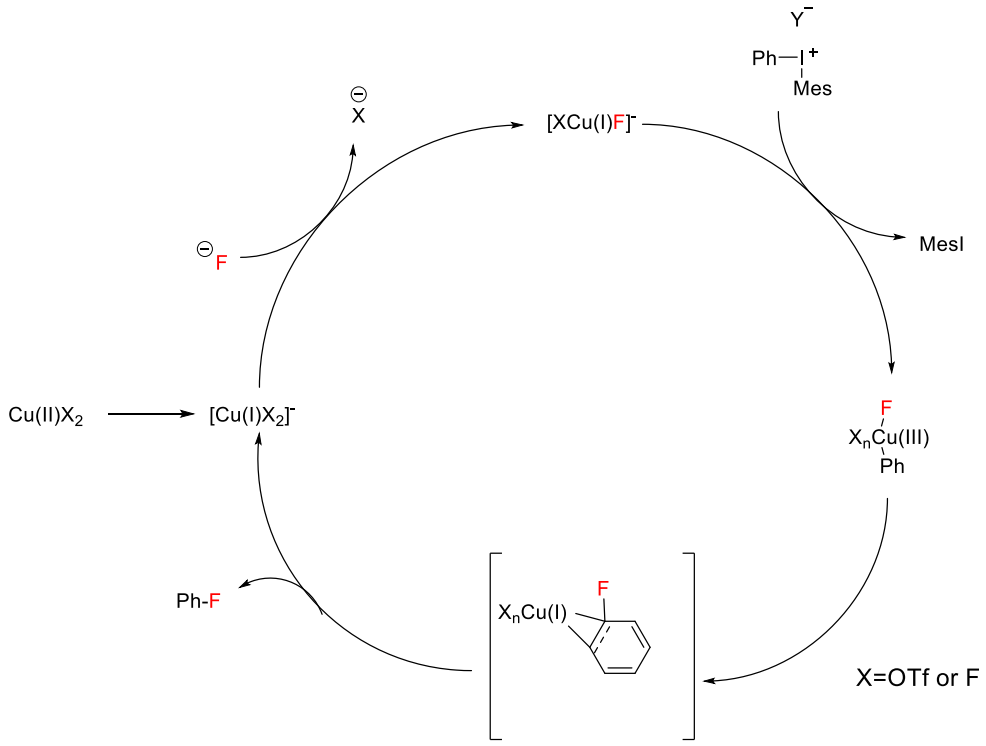
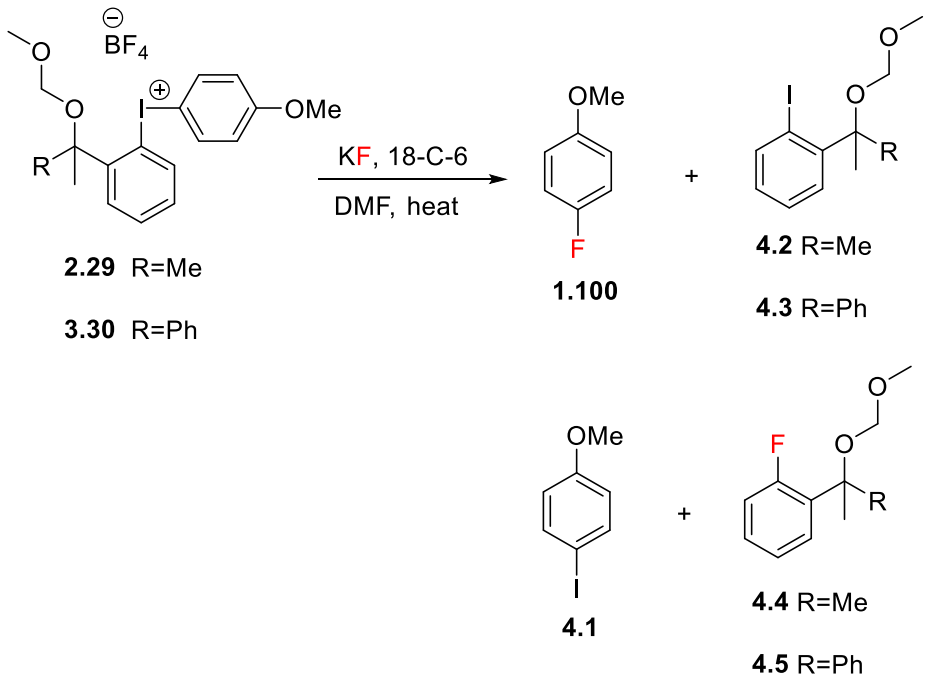


Figure 4.2: *Mechanism proposed for the fluorination of phenyl(mesityl)iodonium salt in the presence of $Cu(OTf)_2$*

4.2 Preparation of standards for the GC analysis

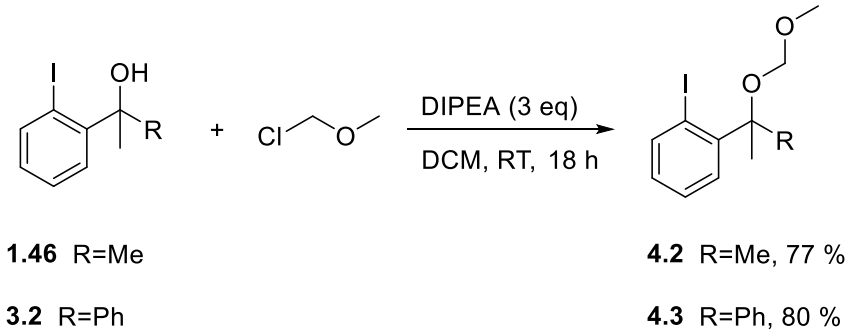
The aim of chapter 4 was to investigate the fluorination of unsymmetrical diaryliodonium salts which were prepared in chapters 2 and 3. Scheme 4.1 demonstrates that the fluorination of these diaryliodonium salts was complicated and four different aromatic products were produced. Gas chromatography (GC) was therefore used to determine the yield of each component in the crude reaction mixture using 3-nitro-1-fluorobenzene as the internal standard. In order to analyse the reaction mixture accurately, each product had to be synthesised and used to generate calibration plots on the GC. The calibration plots were constructed by making a series of dilutions for each product, analysing them on the GC and plotting them against 3-nitro-1-fluorobenzene.



***Scheme 4.1**: Fluorination of unsymmetrical diaryliodonium salts*

4-Fluoroanisole **1.100** and 4-iodoanisole **4.1** were commercially available, but compounds **4.2** to **4.5** had to be prepared. Since 2-(2-iodophenyl)propan-2-ol **1.46** and 2-(2-iodophenyl)-1-phenylethan-1-ol **3.2** had been made in order to prepare the two

different fluoroiodanes in chapters 2 and 3, it was straightforward to protect their hydroxy groups with chloromethyl methyl ether (MOMCl) in good yields (Scheme 4.2).



1.46 R=Me

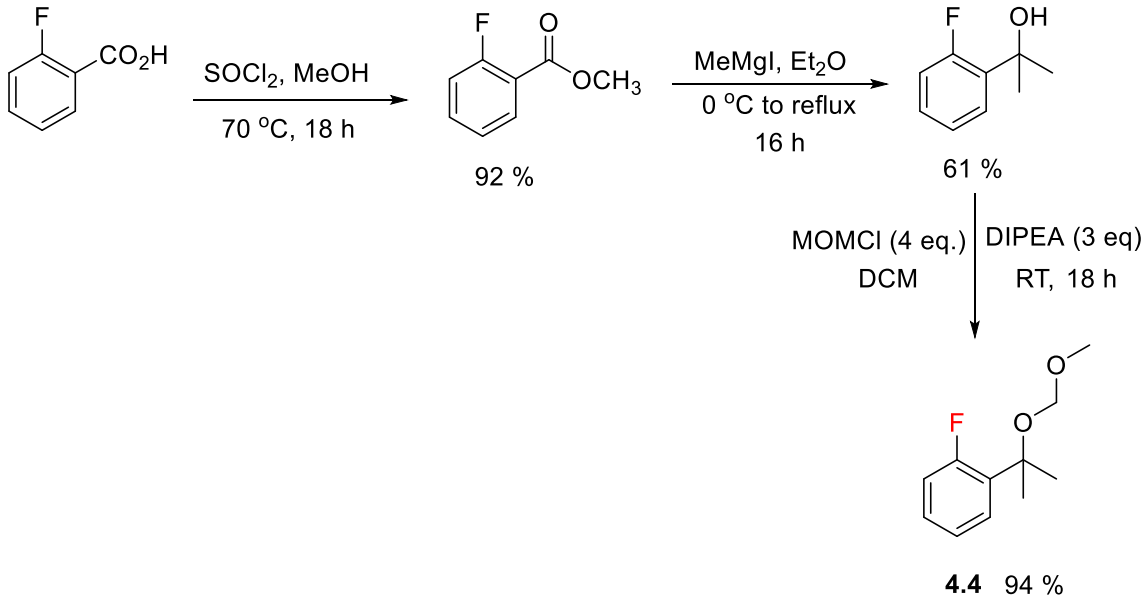
3.2 R=Ph

4.2 R=Me, 77 %

4.3 R=Ph, 80 %

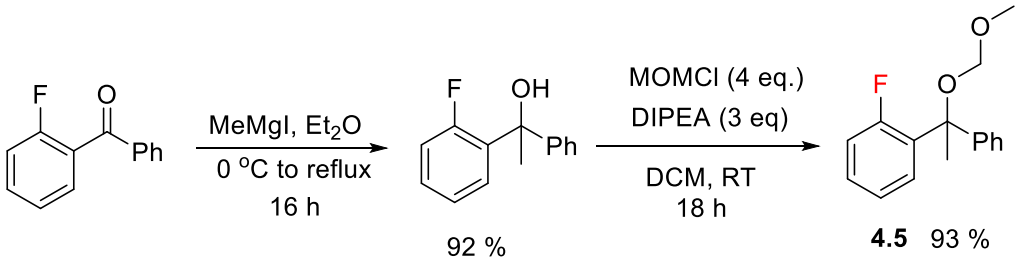
***Scheme 4.2**: Protection of iodoalcohols with MOMCl*

1-Fluoro-2-(2-(methoxymethoxy)propane-2-yl)benzene **4.4** was prepared from 2-fluorobenzoic acid by the three step synthesis shown in Scheme 4.3. After esterification of 2-fluorobenzoic acid to produce methyl 2-fluorobenzoate in 92 % yield, the ester was reacted with methylmagnesium iodide to form 2-(2-fluorophenyl)propan-2-ol. The protection of the hydroxy group with MOMCl in the final step gave the desired product **4.4** in an excellent 94 % yield.



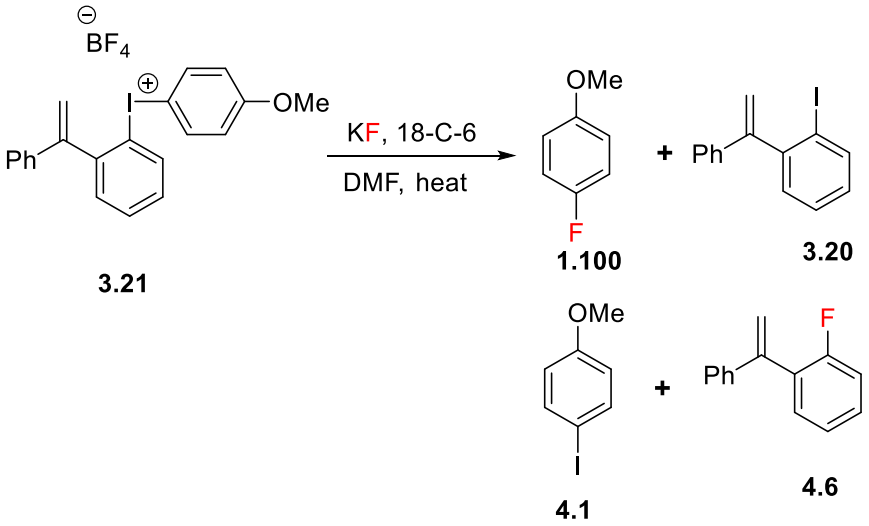
Scheme 4.3**: Preparation of 1-fluoro-2-(2-(methoxymethoxy)propan-2-yl)benzene **4.4

It was also necessary to prepare 1-fluoro-2-(1-(methoxymethoxy)-1-phenylethyl)benzene **4.5** from 2-fluorobenzophenone (Scheme 4.4). The Grignard reaction with 2-fluorobenzophenone gave 1-(2-fluorophenyl)-1-phenylethan-1-ol in an excellent 92 % yield and it was protected successfully with MOMCl.



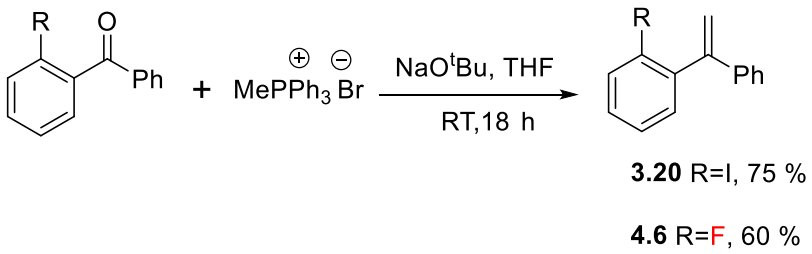
Scheme 4.4**: Preparation of 1-fluoro-2-(1-(methoxymethoxy)-1-phenylethyl)benzene **4.5

The fluorination of the diaryliodonium salts containing an alkene sidearm were also going to be investigated and would give four different aromatic products (Scheme 4.5). It was therefore necessary to prepare 1-iodo-2-(1-phenylvinyl)benzene **3.20** and 1-fluoro-2-(1-phenylvinyl) benzene **4.6** to generate their calibration plots on the GC.



Scheme 4.5: Fluorination of 3.21

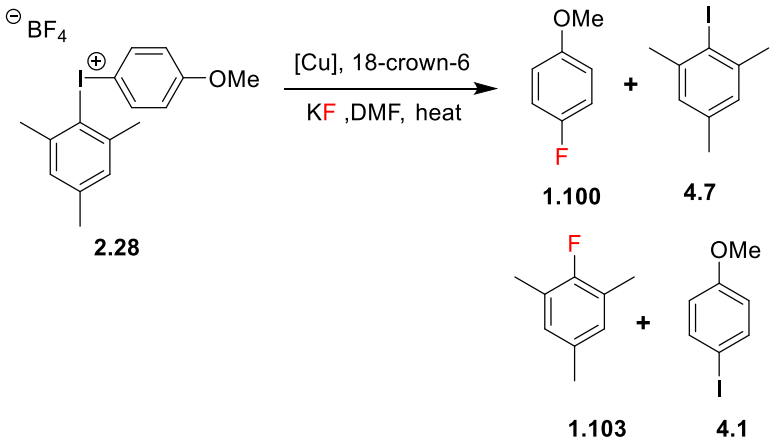
1-Iodo-2-(1-phenylvinyl)benzene **3.20** and 1-fluoro-2-(1-phenylvinyl)benzene **4.6** were prepared by a Wittig reaction. (2-Iodophenyl)(phenyl)methanone **3.1** and (2-fluorophenyl) (phenyl)methanone were each reacted with a suspension of methyltriphenylphosphonium bromide in dry THF using potassium *tert*-butoxide as the base. The reaction mixtures were left to react at RT for 18 h affording **3.20** and **4.6** in good yields (75 and 60 % respectively) (Scheme 4.6).



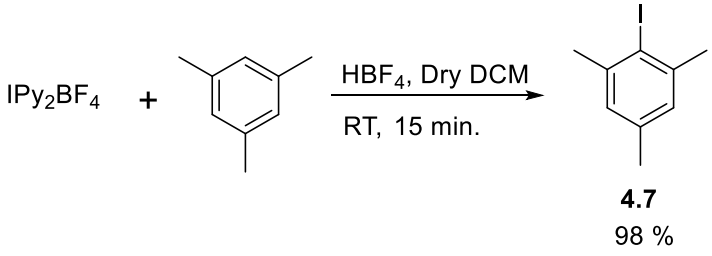
Scheme 4.6: Preparation of 3.20 and 4.6

4.3 Preliminary fluorination of unsymmetrical diaryliodonium salts

Before attempting to fluorinate the unsymmetrical diaryliodonium salts which have been prepared in this thesis, the fluorination of Sanford's salt **2.28** using mesitylene as the dummy aryl group was first investigated. Sanford [98] recently developed a new Cu-catalysed fluorination which reversed the *ortho*-effect and preferentially fluorinated the smaller aromatic ligand on iodine(III) to give 4-fluoroanisole in 84 % yield (Scheme 4.7).



Scheme 4.7**: Fluorination of **2.28



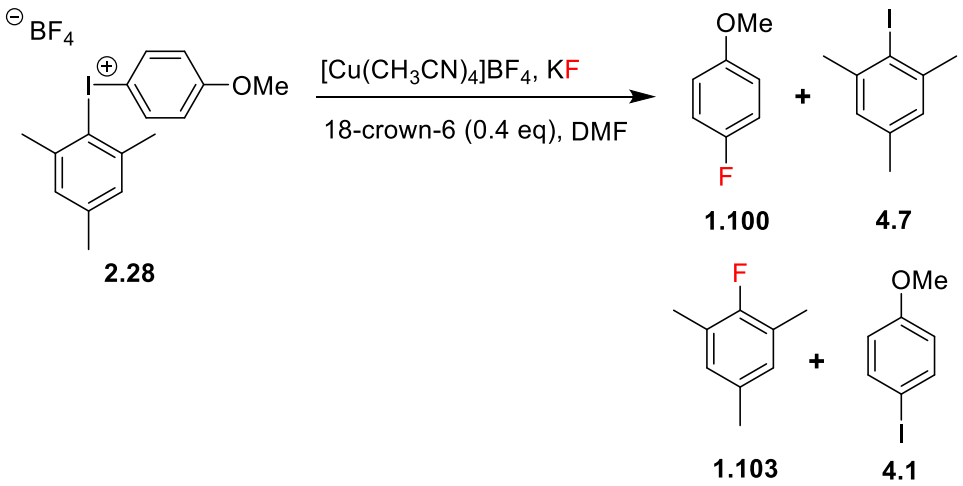
Scheme 4.8**: Preparation of 2-iodo-1,3,5-trimethylbenzene **4.7

2-Iodo-1,3,5-trimethylbenzene **4.7** was prepared by reacting mesitylene with Barluenga's reagent (IPy_2BF_4) in DCM and the reaction mixture was stirred for 15 minutes at RT. The pure product **4.7** was obtained as a pale yellow crystalline solid in a 98 % isolated yield (Scheme 4.8). It was then used to generate calibration plots on the GC, so that the amount

of each product formed in the fluorination could be determined accurately by both GC and ^{19}F MNR spectroscopy using internal standards (Scheme 4.7).

The fluorination conditions developed by Sanford, both with Cu (entry 2) and without Cu (entry 1), were applied to the unsymmetrical salt **2.28**. In entries 3 and 4 the reaction temperature was increased to 100 ^{o}C, the amount of KF was increased to 1.5 equivalents and the amount of copper catalyst was increased to 0.5 equivalents, but the reaction time was decreased from 18 h to 4 h and all of the results are summarised in Table 4.1.

Table 4.1**: Fluorination of **2.28



2.28 **1.100** **4.7** **1.103** **4.1**

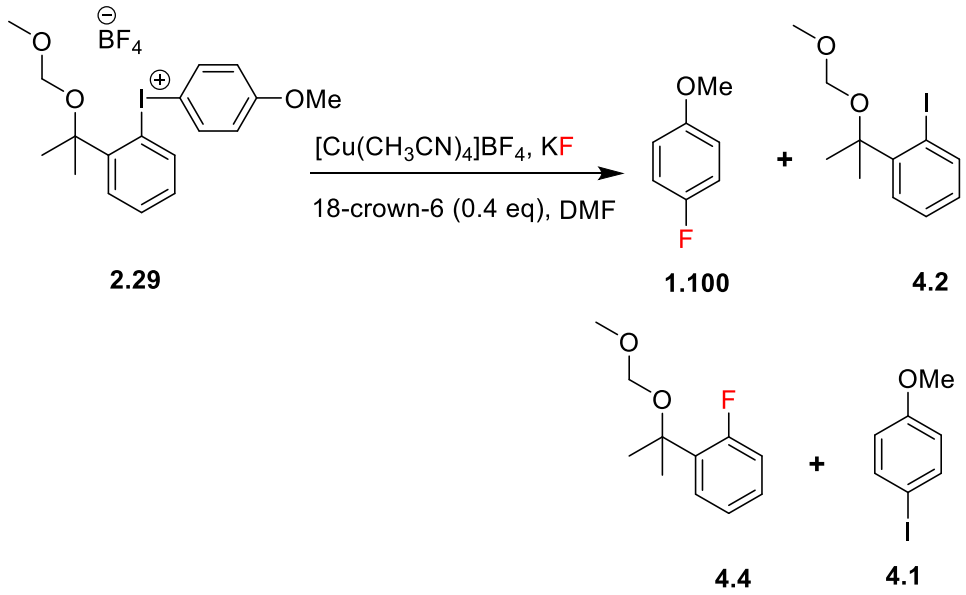
Entry	[Cu] (eq)	KF (eq)	Temp. (°C)	Time (h)	Yield (%)			
					1.100[a]	**4.7**[a]	**1.103**[b]	**4.1**[a]
1	0	1.1	60	18	1	19	88	80
2	0.2	1.1	60	18	68	92	1	0
3	0	1.5	100	4	1	6	90	85
4	0.5	1.5	100	4	38	87	1	0

[a] Determined by GC and ^{19}F NMR spectroscopy with internal standards; [b] Determined by ^{19}F NMR spectroscopy with internal standard.

As expected, the Cu-free reaction generated fluoromesitylene **1.103** as the major product in 88 % yield due to the *ortho*-effect. However, the opposite selectivity was obtained in the presence of 0.2 equivalents of $[Cu(CH_3CN)_4]BF_4$ giving the desired product, 4-fluoroanisole **1.100** in 68 % yield. Entry 3 gave essentially the same result as entry 1 resulting in fluoromesitylene **1.103** being produced in 90 % yield. Although the opposite selectivity was achieved in the copper-catalysed reaction in entry 4, 4-fluoroanisole **1.100** was only produced in a moderate 38 % yield.

Although entry 4 gave less of the desired product compared to entry 2, the fluorination of **2.29** was investigated using exactly the same set of 4 different reaction conditions and the results are reported in Table 4.2. 4-Iodoanisole **4.1** was obtained as the major product in 79 % yield in the absence of a copper catalyst, but surprisingly only 8 % of **4.4** was produced (entry 1). Although there was more fluorination in the copper-catalysed reaction (entry 2), the selectivity was not reversed and **4.4** was produced in 74 % due to the *ortho* effect. Entry 3 gave a similar result to entry 1 with 4-iodoanisole **4.1** being produced as the major product in 85 % yield, but this time there was slightly more fluorination with **4.4** formed in 20 % yield. Again, the *ortho* effect dominated in entry 4 and a moderate amount of **4.4** was produced (43 %) alongside 4-iodoanisole **4.1** (91 %).

Table 4.2**: Fluorination of **2.29

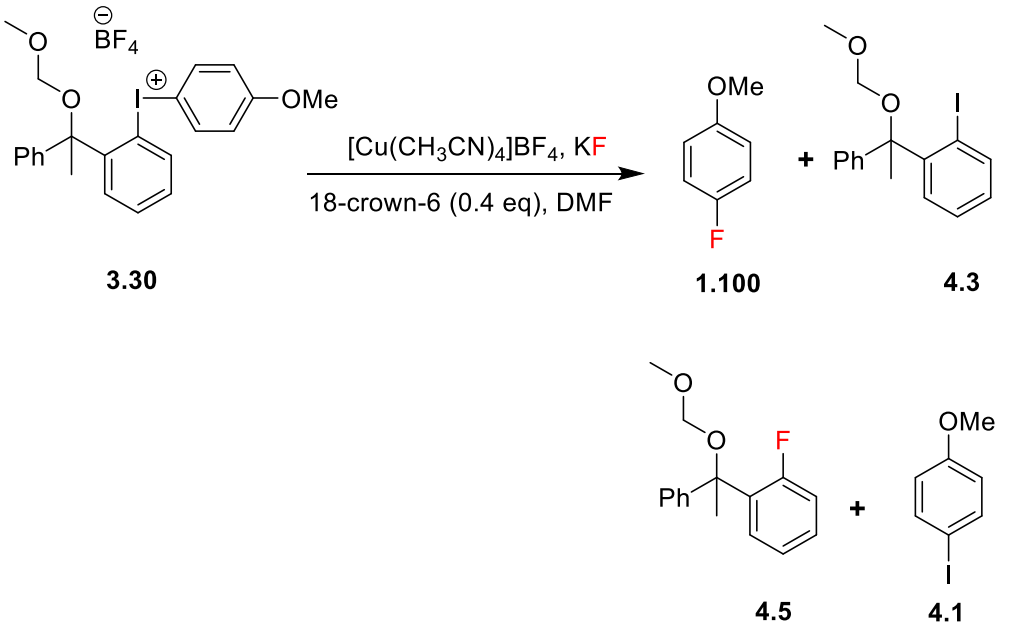


Entry	[Cu] (eq)	KF (eq)	Temp. (°C)	Time (h)	Yield[a] (%)			
					1.100	4.2	4.4	4.1
1	0	1.1	60	18	0	7	8	79
2	0.2	1.1	60	18	0	5	74	88
3	0	1.5	100	4	0	0	20	85
4	0.5	1.5	100	4	0	9	43	91

[a] Determined by GC and ^{19}F NMR spectroscopy with internal standards.

The unsymmetrical diaryliodonium salt **3.30** contained a phenyl group in the sidearm compared to a methyl group in the sidearm of **2.29**. Nevertheless, the fluorination of **3.30** gave very similar results to the fluorination of **2.29** under each of the different reaction conditions (entry 1-4, Table 4.3). The *ortho* effect dominated in each of the fluorinations giving 4-iodoanisole (73-88 %) as the major product and varying amounts of **4.5** (30-65 % yield in entries 2-4) both with and without the copper catalyst.

*Table 4.3: Fluorination of **3.30***



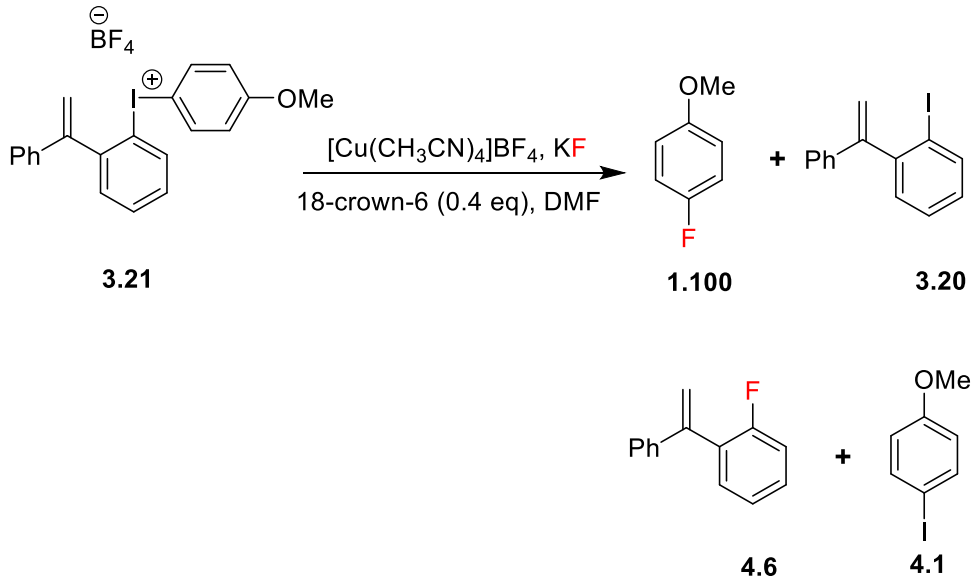
3.30 **1.100** **4.3** **4.5** **4.1**

Entry	[Cu] (eq)	KF (eq)	Temp. (°C)	Time (h)	Yield[a] (%)			
					1.100	4.3	4.5	4.1
1	0	1.1	60	18	0	13	6	85
2	0.2	1.1	60	18	0	6	65	88
3	0	1.5	100	4	7	21	30	73
4	0.5	1.5	100	4	0	6	30	87

[a] Determined by GC and ^{19}F NMR spectroscopy with internal standards.

In contrast to Sanford's salt **2.28**, the *ortho* effect still dominated in the copper-catalysed fluorinations of diaryliodonium salts **2.29** and **3.30** and this may be due to the strong interaction between the oxygen in the sidearm and the iodine which were observed in the solid-state structures. Therefore, the fluorination of **3.21**, which contained an alkene sidearm and no oxygen atom, was investigated using the same set of reaction conditions.

Table 4.4: Fluorination of 3.21



Entry	[Cu] (eq)	KF (eq)	Temp. (°C)	Time (h)	Yield[a] (%)			
					1.100	3.20	4.6	4.1
1	0	1.1	60	18	0	9	53	72
2	0.2	1.1	60	18	39	39	7	12
3	0	1.5	100	4	2	4	93	91
4	0.5	1.5	100	4	29	73	4	13

[a] Determined by GC and ^{19}F NMR spectroscopy with internal standards.

Table 4.4 showed that, as expected, there was an *ortho* effect in the copper-free reactions in entries 1 and 3 giving **4.6** and 4-iodoanisole **4.1** as the major products. In contrast to the earlier fluorinations of **2.29** and **3.30**, the opposite selectivity was achieved in the copper catalyzed fluorinations (entries 2 and 4) producing the desired product, 4-fluoroanisole **1.100**, in moderate amounts (39 % and 29 % respectively). In both of these reactions there were side products such as 4,4'-dimethoxybiphenyl (Figure 4.3) which was observed in the GC-mass spectrum. It was thought that the 4,4'-dimethoxybiphenyl was formed due to the coupling of two iodoanisole molecules (which was produced during the reaction) in the presence of a copper catalyst under high temperature (Ullmann

reaction[138]). Much more of 4,4'-dimethoxybiphenyl was formed in entry 4 compared to entry 2 due to higher temperature and higher catalyst loading.

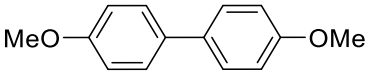


Figure 4.3: 4,4'-Dimethoxybiphenyl

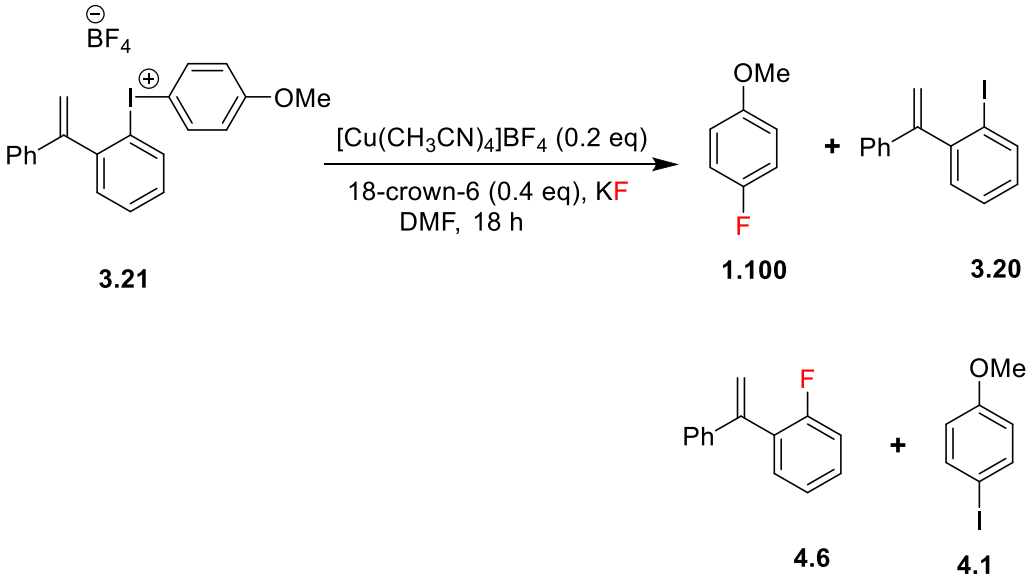
4.4 Optimising the fluorination conditions

4.4.1 Fluorinations with $[Cu(MeCN)_4]BF_4$

Encouraged by these results, the fluorination of **3.21** was further evaluated using a number of different reaction conditions including the temperature, reaction time, solvents, different copper catalysts and fluorinating reagents in order to increase the yield of the desired product **1.100**. The fluorination of **3.21** was first investigated with 0.2 equivalent of $[Cu(MeCN)_4]BF_4$ using different temperatures and the results are reported in Table 4.5.

Surprisingly, when the amount of 18-C-6 and KF was increased to 1 and 1.5 equivalents respectively (entry 2), the *ortho* selectivity dominated producing 4-iodoanisole and **4.6** as the major products. However, when the temperature was increased to 80 ^oC and 100 ^oC in entries 3 and 5, there was a small improvement in the amount of 4-fluoroanisole produced. 4,4'-Dimethoxybiphenyl was still observed as a strong peak at *m/z* 214 in the GC-Mass spectrum. The use of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), a free radical scavenger, has been found to be beneficial in some fluorinations of diaryliodonium salts.[110,139,140] This radical might be acting to inhibit photochemical or thermal decomposition of the iodonium salt precursor, depending on the iodonium salt structure. Unfortunately, no effect was observed and the same results were obtained when 1 equivalent of TEMPO was used in entry 4 using the same conditions as in entry 3 and 4,4'-dimethoxybiphenyl was still observed in the GC-mass spectrum.

***Table 4.5**: Optimising the fluorination of **3.21** with [Cu(CH$_3$CN)$_4$]BF$_4$*



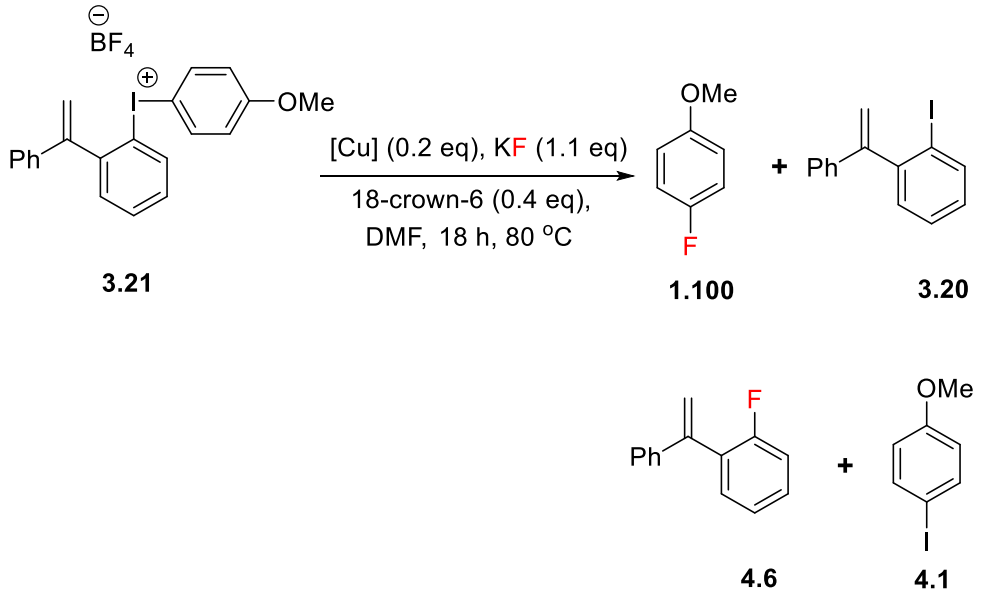
Entry	KF (eq)	Temp. (°C)	Yield[a] (%)				1.100:4.6
			1.100	3.20	4.6	4.1	
1	1.1	60	39	39	7	12	85:15
2[b]	1.5	60	3	19	32	64	9:91
3	1.1	80	45	67	5	16	90:10
4[c]	1.1	80	43	74	5	14	89:11
5	1.1	100	42	68	3	16	93:7

[a] Determined by GC and ^{19}F NMR spectroscopy with internal standards; [b] 1 equivalent of 18-C-6; [c] 1 equivalent of TEMPO in the dark.

4.4.2 Screening different Cu catalysts.

Since there was a small improvement in the yield of 4-fluoroanisole at 80 °C, a number of different catalysts, including [Cu(MeCN)$_4$]OTf, Cu(OTf)$_2$ and Cu(OAc)$_2$ were screened at 80 °C for 18 h (Table 4.6).

__Table 4.6__: Screening different copper catalysts



Entry	[Cu]	Yield[a] (%)				1.100:4.6
		1.100	3.20	4.6	4.1	
1	[Cu(MeCN)$_4$]BF$_4$	45	67	5	16	90:10
2	[Cu(MeCN)$_4$]OTf	50	76	7	15	88:12
3	Cu(OTf)$_2$	60	68	9	14	87:13
4	Cu(OAc)$_2$	13	85	5	17	72:28

[a] Determined by GC and ^{19}F NMR spectroscopy with an internal standard.

The yield of 4-fluoroanisole **1.100** increased slightly to 50 % with high selectivity over **4.6** (88:12) when [Cu(MeCN)$_4$]OTf was used (entry 2). The yield of 4-fluoroanisole **1.100** was increased further to 60 % when the reaction was carried out with Cu(OTf)$_2$

(entry 3) and no biphenyl product (4,4'-dimethoxybiphenyl) was observed in the GC-mass spectrum. When $Cu(OAc)_2$ was used in entry 4 there was only a low yield of fluorinated products and 4-iodoanisole **4.1** was obtained as the major product in 85 % yield.

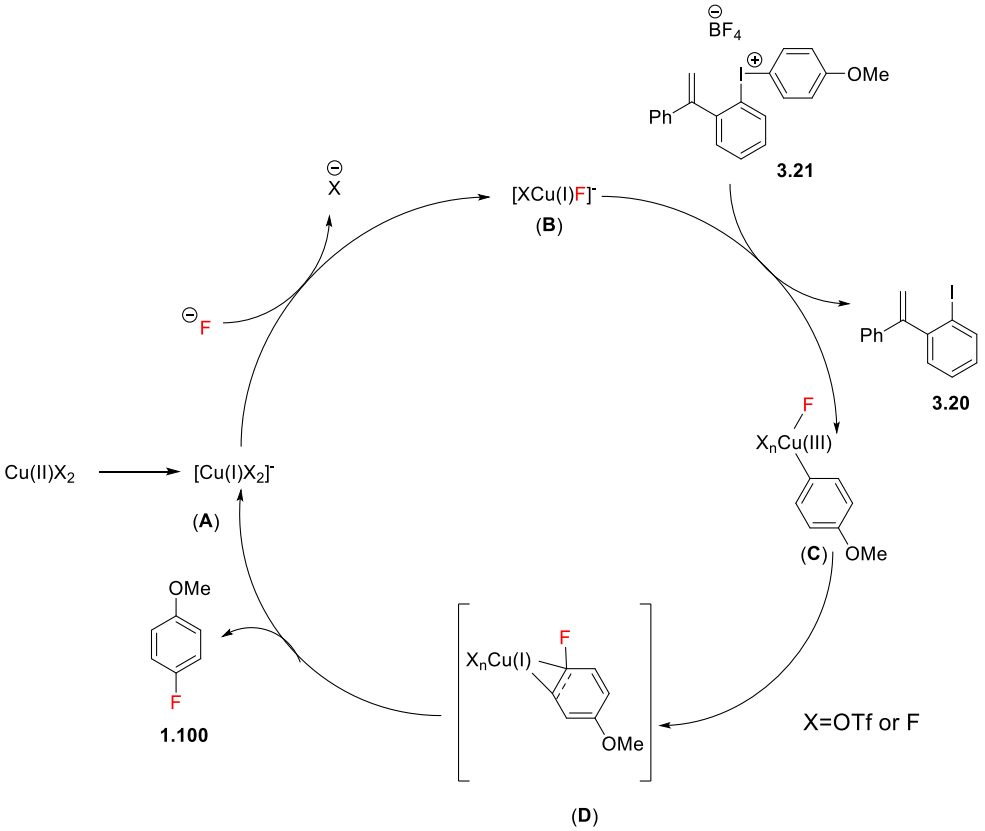


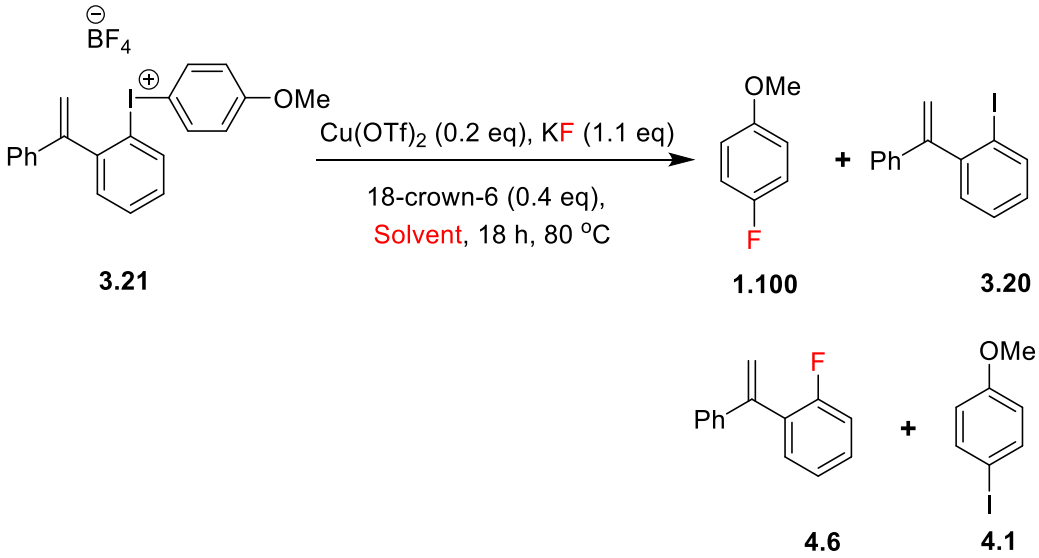
***Figure 4.4**: Proposed mechanism for the fluorination of **3.21** with $Cu(OTf)_2$*

Detailed experimental and theoretical investigations by Sanford lead to a proposed mechanism for fluorination reactions with a Cu(II) catalyst and involving a Cu(I/III) catalytic cycle.[98] In Figure 4.4 an analogous reaction mechanism using the diaryliodonium salt **3.21** is proposed for this work. In the suggested mechanism, the precatalyst Cu^{II} was reduced to Cu^{I} catalyst (**A**) by DMF or disproportionation.[141] Cu^{I}-F (**B**) was generated via ligand exchange and can subsequently be oxidized via **3.21** to give the Cu^{III}-aryl intermediate (**C**). This undergoes reductive elimination[142] liberating the proposed π-complex (**D**), which then releases 4-fluoroanisole **1.100**. Oxidation of Cu(I) by **3.21** is considered to be the rate limiting step (Hartwig's Ar-I reaction)[33] of this reaction.

4.4.3 Screening different solvents

A range of polar solvents, including DMA, MeCN and DMSO, were investigated for the fluorination of **3.21** using 0.2 equivalents of $Cu(OTf)_2$, 1.1 equivalents of KF and 0.4 equivalents of 18-C-6 at 80 °C for 18 h (Table 4.7). When DMA was used as the solvent 4-fluoroanisole **1.100** was only formed in a low yield (28 %), but with high selectivity (entry 2) and DMSO gave a very similar result (entry 3). The selectivity was completely reversed when acetonitrile was used as the solvent in entry 4 and 4-iodoanisole **4.1** was obtained as the major product (74 %).

Table 4.7: Screening different solvents



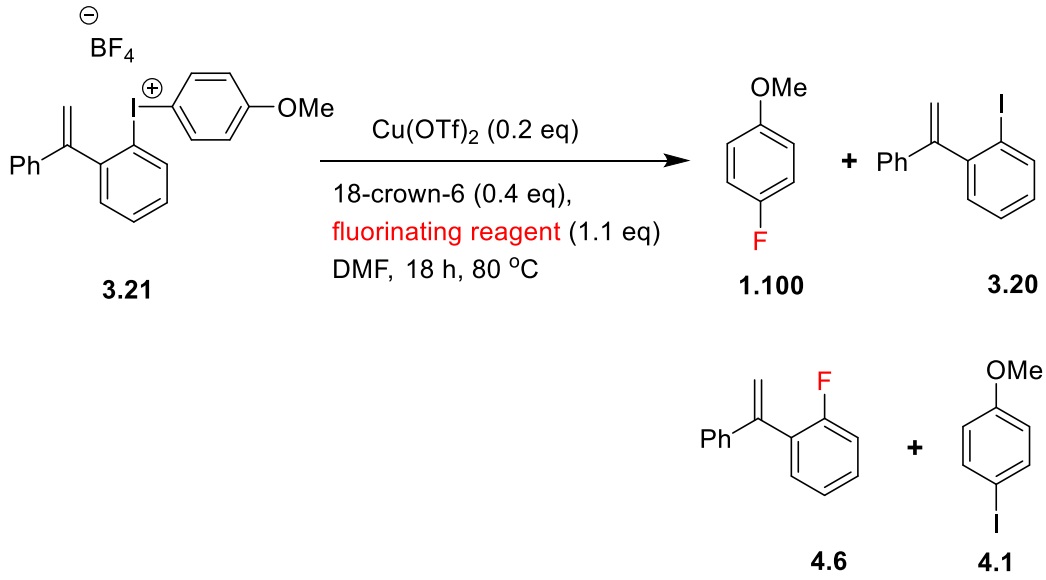
Entry	Solvent	Yield[a] (%)				1.100:4.6
		1.100	3.20	4.6	4.1	
1	DMF	60	68	9	14	87:13
2	DMA	28	87	0	11	100:0
3	DMSO	34	85	3	13	92:8
4	MeCN	0.5	35	14	74	3:97

[a] Determined by GC and ^{19}F NMR spectroscopy with internal standards.

4.4.4 Screening different fluorinating reagents

Having determined the optimum copper catalyst and solvent for the fluorination of **3.21**, the effect of using different fluorinating reagents such as cesium fluoride (CsF), silver fluoride (AgF), triethylamine trihydrogenfluoride ($Et_3N.3HF$) and tetrabutylammonium fluoride (TBAF), were examined in Table 4.8. When **3.21** was reacted with CsF, the overall yield of fluorinated products increased to 76 % but there was lower selectivity towards 4-fluoroanisole **1.100** (35:65) and more of **4.6** was formed (entry 2). The yield of fluorinated products dropped to 35 % when AgF was used as the fluorinating reagent (entry 3) and the reaction was more selective to the desired product **1.100** (86:14). In the reaction of $Et_3N.3HF$ with **3.21** (entry 4), only a 20 % yield of the fluorinated products was observed with low selectivity (40:60) towards 4-fluoroanisole and the main product was 1-iodo-2-(1-phenylvinyl)benzene **3.20** (58 % yield). Using TBAF led to the formation of only 24 % yield of 4-fluoroanisole **1.100** with ~ 1:1 selectivity for **1.100** to **4.6** (entry 5). At this point, it can be said that KF is the best fluorinating reagent which gave the best yield and selectivity under the same reaction conditions (entry 1) in comparison to the other fluorinating reagents.

Table 4.8: Screening different fluorinating reagents



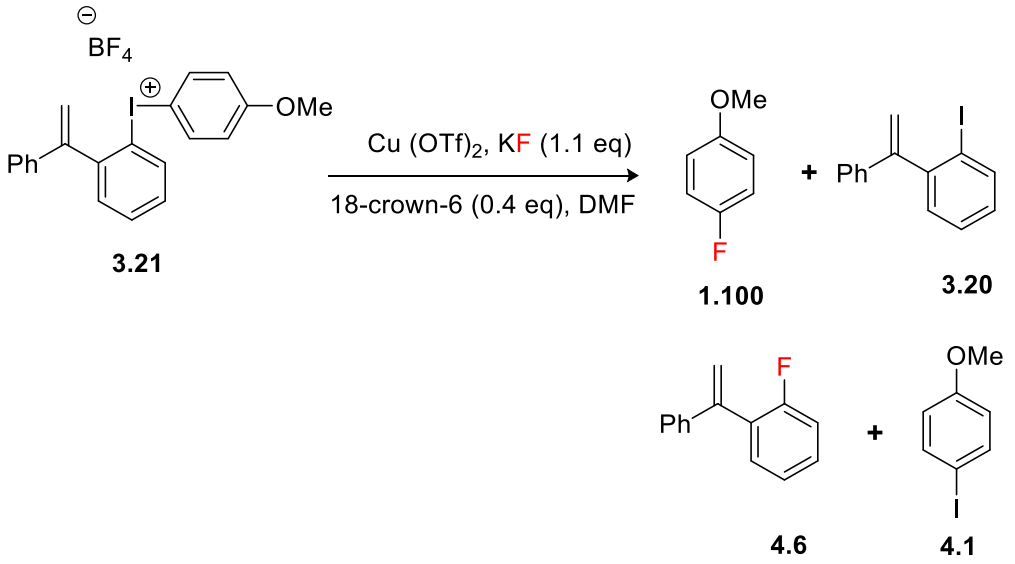
Entry	Fluorinating reagent	Yield[a] (%)				1.100:4.6
		1.100	3.20	4.6	4.1	
1	KF	60	68	9	14	89:11
2	CsF	27	35	49	50	35:65
3	AgF	30	61	5	30	86:14
4	$Et_3N.3HF$	8	58	12	26	40:60
5	TBAF	24	46	28	35	46:54

[a] Determined by GC and ^{19}F NMR spectroscopy with internal standards.

4.4.5 Final optimization with $Cu(OTf)_2$ and KF

In order to identify the optimum reaction conditions, the fluorination of **3.21** with $Cu(OTf)_2$ and KF in DMF was investigated further with respect to the amount of copper catalyst, reaction time, concentration and temperature (Table 4.9).

*Table 4.9: Final optimization of **3.21** with $Cu(OTf)_2$ and KF*



Entry	[Cu] (eq)	Time (h)	Temp. (°C)	Yield[a] %				1.100:4.6
				1.100	3.20	4.6	4.1	
1	0.2	18	80	60	68	9	14	87:13
2	0.2	4	80	65	75	6	15	92:8
3[b]	0.2	4	80	48	81	1	15	99:1
4	0.2	4	100	47	71	3	14	94:6
5	0.2	1	80	36	67	7	25	84:16
6	0.2	1	100	62	79	4	16	94:6
7[b]	0.2	1	100	41	77	1	14	98:2
8	0.2	0.5	100	34	68	1	15	97:3
9	0.2	1	120	20	71	1	15	95:5
10	0.5	1	80	43	73	3	17	93:7
11	0.5	1	100	45	74	2	15	96:4

[a] Determined by GC and ^{19}F NMR spectroscopy with internal standards; [b] 3 mL DMF.

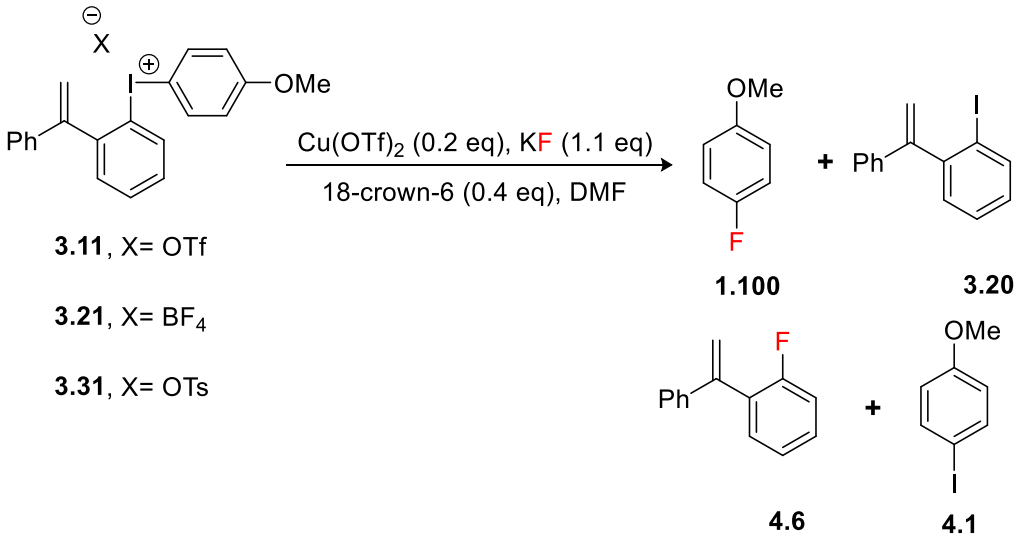
When the reaction time was decreased from 18 h to 4 h (entry 2), the yield of 4-fluoroanisole **1.100** increased to 65 % with 92:8 selectivity for **1.100** over **4.6**. The concentration of the reaction mixture proved to be an important factor and the yield of 4-fluoroanisole **1.100** decreased when the volume of DMF was decreased from 5 to 3 mL at both 80 °C for 4 h (48 %) and at 100 °C for 1 h (41 %) (entries 3 & 7, respectively). Compound **3.20** was generated as the major product in both reactions (81 and 77 %, respectively) and this was probably due to the low solubility of potassium fluoride at the higher concentration. A 47 % yield of 4-fluoroanisole **1.100** was observed at 100 °C for 4 h (entry 4) but this improved to 62 % when the reaction time was decreased to 1 h (entry 6) and gave essentially the same result as that in entry 2. Decreasing the reaction time from 4 to 1 h at 80 °C decreased the yield of 4-fluoroanisole **1.100** to 36 % with 84:16 selectivity (entry 5). When the reaction time was further reduced to 0.5 h at 100 °C, the overall yield of fluorinated products was reduced to 35 % (entry 8). Increasing the temperature to 120 °C for 1 h in entry 9, gave only a low 20 % yield of 4-fluoroanisole **1.100** with 95:5 selectivity for **1.100** over **4.6** (entry 9) and the biphenyl by-product 4,4'-dimethoxybiphenyl was present in the GC-mass spectum at *m/z* 214. Finally, the amount of [Cu] was increased to 0.5 equivalent for 1 h at both 80 °C and 100 °C but the same lower yield of 43-45 % for 4-fluoroanisole was observed for both entries 10 and 11.

4.4.6 Screening different counteranions

The best reaction conditions for the fluorination of **3.21** are with 0.2 equivalents of $Cu(OTf)_2$ at either 80 °C for 4 h or at 100 °C for 1 h (entries 1 and 5, Table 4.9). It was decided to test the effect of using different counteranions such as BF_4^-, OTs^- and OTf^- on the fluorination of the diaryliodonium salt under these reaction conditions.

In the fluorination of the diaryliodonium tosylate **3.31** (Table 4.10), the yield of 4-fluoroanisole **1.100** decreased significantly to 13 % at 80 °C for 4 h (entry 3) and to 28 % at 100 °C for 1 h (entry 4) and **3.20** was obtained as the major product. The yield of 4-fluoroanisole **1.100** increased slightly to 27-34 % in the fluorination of the diaryliodonium triflate **3.11** (entries 5 & 6). In conclusion, the highest yield was obtained with BF_4^- as the counteranion, which is in agreement with the literature.[117]

***Table 4.10**: The effect of counteranions on the fluorination of diaryliodonium salts*



Entry	X^-	Temp. (°C)	Time (h)	Yield[a] (%)				1.100:4.6
				1.100	3.20	4.6	4.1	
1	BF_4	80	4	65	79	6	15	92:8
2	BF_4	100	1	62	75	4	16	94:6
3	OTs	80	4	13	86	1	10	93:7
4	OTs	100	1	28	87	1	12	97:3
5	OTf	80	4	34	80	1	19	97:3
6	OTf	100	1	27	74	1	18	96:4

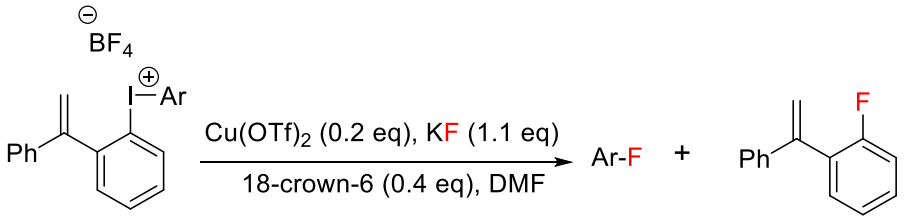
[a]Determined by GC and ^{19}F NMR spectroscopy with internal standards.

4.5 Substrate scope of the fluorination

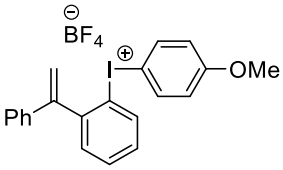
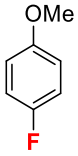
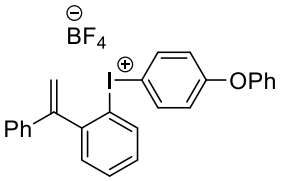
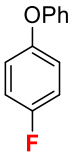
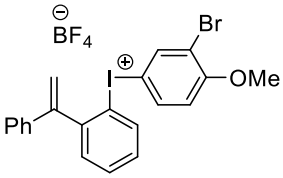
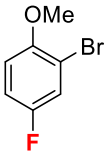
To investigate the scope of the fluorination reaction, the optimized protocol was applied to a series of diaryliodonium tetrafluoroborates which were prepared in chapter 3. The fluorinations of **3.21**, **3.22** and **3.24** were tested firstly with two different reaction conditions at 80 °C for 4 h and at 100 °C for 1 h (entries 1 and 2, Table 4.10) in the presence of $Cu(OTf)_2$. It was noted that the best yields for the desired fluorinated products were obtained at 80 °C for 4 h (Table 4.11). At this point, it was decided to use

these conditions in the absence and in the presence of [Cu] for the fluorination of the other diaryliodonium salts (Table 4.12).

Table 4.11**: Fluorination of **3.21**, **3.22** and **3.24

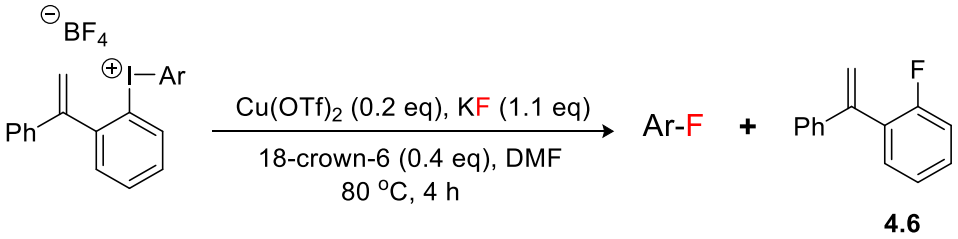


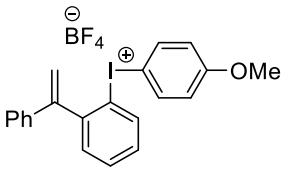
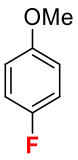
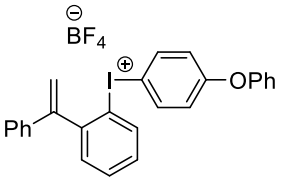
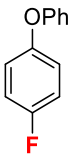
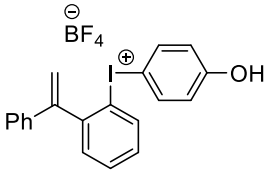
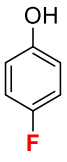
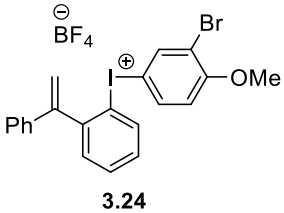
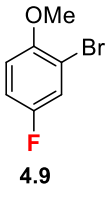
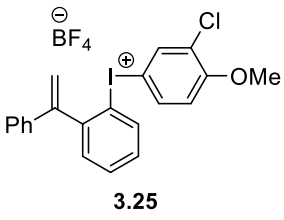
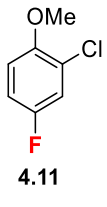
4.6

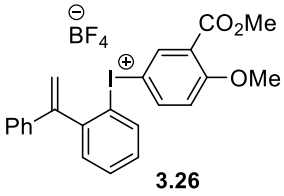
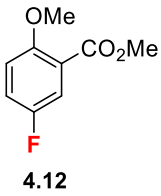
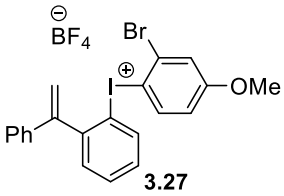
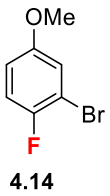
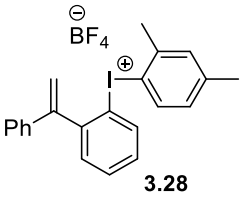
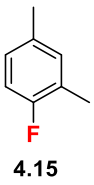
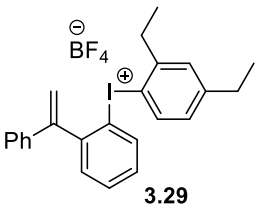
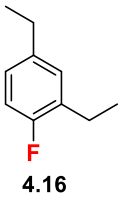
Entry	Iodonium salt	Ar-F	Time (h)	Temp. (°C)	Yield[a] of Ar-F (%)	Yield[a] of 4.6 (%)	Ar-F:4.6
1	 **3.21**	 **1.100**	1	100	62	4	94:6
2			4	80	65	6	92:8
3	 **3.22**	 **4.8**	1	100	50	3	94:6
4			4	80	61	6	91:9
5	 **3.24**	 **4.9**	1	100	50	4	93:7
6			4	80	87	6	94:6

[a] Determined by ^{19}F NMR spectroscopy with internal standards; [b] Determined by GC and ^{19}F NMR spectroscopy with internal standards.

Table 4.12: Substrate scope of the fluorination



Entry	Iodonium salt	Product	Yield[a] of Ar-F (%)	Yield[a] of 4.6 (%)	Ar-F:4.6
1	 3.21	 1.100	65	6	92:8
2[b]			1	80	1:99
3	 3.22	 4.8	61	6	91:9
4[b]			4	38	10:90
5	 3.23	 4.10	20	0	100:0
6[b]			0	0	0:0
7	 3.24	 4.9	87	6	94:6
8[b]			2	38	5:95
9	 3.25	 4.11	66	5	90:10
10[b]			1	21	5:95

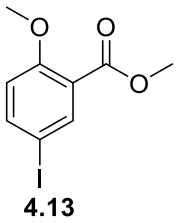
11	 **3.26**	 **4.12**	82	7	92:8
12[b]			4	52	7:93
13	 **3.27**	 **4.14**	17	21	44:56
14[b]			11	52	2:98
15	 **3.28**	 **4.15**	63	21	75:25
16[b]			23	71	24:76
17	 **3.29**	 **4.16**	23	26	47:53
18[b]			13	40	25:75

[a] Determined by ^{19}F NMR spectroscopy with internal standard; [b] without $Cu(OTf)_2$.

As summarised in Table 4.12, the fluorination of disubstituted aromatic salts **3.21** and **3.22** produced the desired fluorinated products **1.100** and **4.8** in good yields (61-65 %) in the presence of [Cu] (entries 1 and 3). However, **4.10** was obtained in a low 20 % yield in the fluorination of **3.23** (entry 5), probably, due to the free hydroxy group. On the other hand, when the fluorination was carried out in the absence of [Cu], the *ortho* effect dominated and **4.6** was the main product formed in entries 2 and 4.

In the fluorination of 1,2,4-trisubstituted aromatic salts **3.24**, **3.25** and **3.26**, the desired fluorinated products **4.9**, **4.11** and **4.12** were obtained in high yields (66-87 %) with high selectivity over **4.6** in the presence of $Cu(OTf)_2$ (entries 7, 9 and 11). As expected, the selectivity was reversed in the absence of $Cu(OTf)_2$ producing **4.6** as the major product (21-52 %) (enteries 8, 10, 12). In order to separate the individual components of the crude reaction mixture, the amount of **3.26** was increased from 0.3 to 1.1 mmol. Purification of

the crude products by column chromatography gave 1-iodo-2-(1-phenylvinyl)benzene **3.20** in 77 % isolated yield using 5 % ethyl acetate in petroleum ether as the solvent system. Unfortunately, **4.12** was obtained as a mixture with methyl 5-iodo-2-methoxybenzoate **4.13** (Figure 4.5) in a 2:1 ratio for **4.12** over **4.13** (in the ^{1}H NMR spectrum) because they have the same polarity and failed to separate.



4.13

Figure 4.5**: 5-Iodo-2-methoxybenzoate **4.13

In the fluorination of the 1,3,4-disubstituted aromatic salt **3.28**, 2,4-dimethylfluorobenzene **4.15** was obtained in a good yield (63 %) in the presence of [Cu], but lower selectivity than normal was observed due to the *ortho*-methyl group (entry 15). However, the selectivity of this reaction was changed significantly when the reaction was carried out without using [Cu] producing **4.6** as the major product (71 %). Due to the bulkier ethyl group and bromide atom in the *ortho* position of **3.27** and **3.29**, the selectivity of these reaction was reduced to ~ 45:55 and the desired fluorinated products **4.14** and **4.16** were only obtained in 17 and 23 % yield respectively in the presence of [Cu] (entries 13 and 17). As expected, the *ortho*-effect dominated in the reaction without Cu (entries 14 and 18) forming **4.6** in 52 and 40 % yield respectively.

4.6 Conclusions

This chapter investigated a Cu-catalysed fluorination of unsymmetrical diaryliodonium salts with KF to produce aromatic fluorides. In order to determine the yield of each component by GC, compounds **4.2** to **4.6** and **3.20** were synthesised and calibration plots were prepared by making a series of dilutions of the products and plotting them against 3-nitro-1-fluorobenzene.

The fluorination of protected diaryliodonium salts **2.29** and **3.30**, which have an oxygen atom in the side arm, were tested in the presence and in the absence of $[Cu(MeCN)_4]BF_4$. Unfortunately the desired fluorinated product **1.100** was not formed and the fluorination had a strong *ortho* effect even in the presence of a Cu catalyst. In contrast, 4-fluoroanisole **1.100** was obtained as the major product in the fluorination of Sanford's salt **2.28**. The yield of each product was determined by GC and ^{19}F NMR spectroscopy using 3-fluoronitrobenzene as the internal standard.

The preliminary fluorination of the 2nd generation salt, **3.21**, which has an alkene sidearm, gave 4-fluoroanisole in 39 % yield and the *ortho* effect was reversed succesfully in the presence of $[Cu(MeCN)_4]BF_4$. The fluorination of **3.21** was then further investigated in order to optimise the reaction conditions. There was a small improvement towards the desired fluorinated product 4-fluoroanisole **1.100** by increasing the reaction temperature to 80 and 100 ^oC. Different copper catalysts, fluorinating reagents, and solvents were also tested. The optimum reaction conditions were 4 h at 80 ^oC with 1.1 equivalents of KF as fluorinating reagent and 0.2 equivalent of $Cu(OTf)_2$ in DMF which gave 65 % yield of **1.100**. The effect of the counteranions on the fluorination of the diaryliodonium salts was then examined using diaryliodonium tosylate, triflate and tetrafluoroborate. It was found that the optimum reaction conditions were 4 h at 80 ^oC with 1.1 equivalents of KF and 0.2 equivalent of $Cu(OTf)_2$ in DMF with tetrafluoroborate salts.

The optimised protocol was subsequently applied to a series of diaryliodonium salts to yield the *para*-substituted arylfluoride. In general, the fluorination of 1,4-di and 1,2,4-trisubstituted aromatic salts produced the desired fluorinated products in good yields (61-87 %), but **4.9** was obtained in only a low yield (20 %) due to the hydroxy group. A good yield (63 %) of the desired fluorinated product **4.15** was obtained in the fluorination of the 1,3,4-trisubstituted aromatic salt **3.28**. However, in the fluorination of the 1,3,4-trisubstituted aromatic salts **3.27** and **3.29**, which contain bulkier ortho-substitutents (Br and Et respectively), the desired fluorinated products were obtained in much lower yields (17-23 %).

Chapter Five: Experimental

5.1 General remarks

5.1.1 Reagents

2-Iodobenzoic acid 98 %, thionyl chloride 99 %, methyl iodide 99 %, anisole 99 %, 1,2-dimethoxybenzene 99 %, 1,3,5-trimethoxybenzene 99 %, 2-bromoanisole 97 %, mesitylene 98 %, *p*-toluenesulfonic acid 98.5 %, chloromethyl methyl ether 99 %, 1-fluoro-3-nitrobenzene 97 % and 18-crown-6 98 % were all purchased from Aldrich. 2-Aminobenzophenone 99 %, *N*-bromosuccinimide 99 %, 1,3-dimethoxybenzene 98 %, 2-chloroanisole 98 % and diphenyl ether 99 % were all purchased from Alfa Aesar. 2-Fluorobenzoic acid 98 % and *o*-anisaldehyde 98 % were purchased from Acros. Triethylamine trihydrofluoride 98 % and triflic acid 97 % were purchased from Fluorochem. *m*-Xylene 99 % was purchased from Hopkin & Williams Ltd and *N*,*N*-diisopropylethylamine 98 % was purchased from Acros Organics. All of these chemicals were used as received without further purification.

5.1.2 Solvents

Acetonitrile, dichloromethane, and diethyl ether were obtained dry from a distillation machine model Puresolve^{TM} and were stored in sealed ampoules over 4Å molecular sieves under an atmosphere of dry nitrogen. Methanol, chloroform, dichloromethane (used for work up), hexane (fraction from petroleum ether), diethyl ether (used for work up), toluene, petroleum ether (40 - 60 ^{o}C), ethyl acetate and tetrahydrofuran (THF) were not subjected to any further purification and were used as received from Fisher Scientific Co. Trifluoroethanol (Fluorochem), anhydrous *N*,*N*-dimethylformide (DMF) (Alfa, 99.9 %) and 1,1,1,3,3,3-hexafluoroisopropanol **(**HFIP**)** (Fluorochem) were used as received.

5.1.3 Analytical Techniques

Nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz, ^{19}F, 375 MHz) and Bruker DPX 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz,) instruments at ambient temperature unless otherwise stated, using deuterated chloroform (Apollo Scientific Ltd, 99.8 %, 0.03 % TMS). The chemical shift (δ) was determined using the residual proton absorption of chloroform-d_1 at δ 7.26 (H) and 77.23 (C), and was recorded in parts per million (ppm). ^{19}F NMR spectra are referenced to an external standard of $CFCl_3$. Coupling constants are given in hertz (Hz). 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.

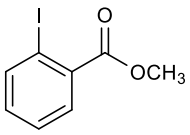
Atmospheric Solids Analysis probe (ASAP) mass spectra were recorded on a Xevo QT mass spectrometry (Waters). Electrospray (ESI) mass spectra were recorded using a micromass Quattra LC mass spectrometer with acetonitrile or methanol as the matrix. FAB mass spectra were recorded on a Kratos Concept spectrometer with NBA as matrix.

X-Ray crystallography data were collected on a Bruker Apex SMART 2000 diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073Å).

GC analysis was carried out on a PERKIN ELMER AUTOSYSTEM XL using a Restek XTI-5 (30 m, 0.25 mm ID, 0.25 μm df) column and helium as the carrier gas with a constant column flow of 1.56 pts/s. The hold oven temperature 45 ºC hold 5 min, ramp 15 ºC/min to 250 ºC, and hold for 5 min. heating programme was employed. The injector temperature was held constant at 250 ºC. Injection volume 1 μL, split ratio: 50:1. GC-MS analysis was performed on a Perkin Elmer Autosystem XL Gas Chromatography coupled to TurboMass Mass Spectrometer. The injector temperature was held constant at 300 ºC and the GC oven temperature program was as follows: 50 ºC hold 3 min, ramp 10 ºC/min to 300 ºC, and hold for 2 min.

5.2 Experimental for Chapter 2

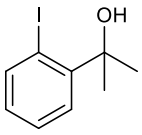
5.2.1 Preparation of Methyl-2-Iodobenzoate 2.5 [143]



2.5

The procedure was based on that described by Hosangadi.[143] In a 500 mL three-necked round bottomed flask equipped with a magnetic stirrer bar, 2-iodobenzoic acid **2.4** (25.05 g, 0.101 mol) was dissolved in methanol (151 mL) and cooled to 0 °C before thionyl chloride (11 mL, 0.146 mol) was added dropwise over 30 minutes. The solution was then heated at 70 °C for 18 hours. A yellow oil was obtained after the solution was concentrated *in vacuo*. After adding ethyl acetate (50 mL) to the crude product, the organic phase was washed with brine solution (3 × 50 mL), separated and dried using $MgSO_4$. Concentration *in vacuo* gave methyl-2-iodobenzoate **2.5** as a yellow oil (24.24 g, 96 %). The characterisation data was in agreement with the literature.[144] δ_H ($CDCl_3$, 400 MHz): 3.93 (3H, s, OCH_3), 7.15 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ =1.8, ArH), 7.39 (1H, td, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.2, ArH), 7.79 (1H, dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.7, ArH), 7.99 (1H, dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.2, ArH); δ_C ($CDCl_3$, 125 MHz): 52.5 (CH_3), 94.1 (C-I), 127.9 (CH), 130.9 (CH), 132.7 (CH), 135.2 (C), 141.3 (CH), 167.9 (CO); m/z (ASAP): 262.9563 (MH^+, $C_8H_8IO_2$ requires 262.9569, 100 %).

5.2.2 Preparation of 2-(2-iodophenyl)propan-2-ol 1.46 [119]

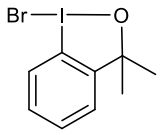


1.46

The procedure was based on that described by Eisenberger.[119] Magnesium (4.74 g, 0.198 mol) was placed into a 250 mL three necked flask (connected with a dropping funnel, condenser and nitrogen supply) which was evacuated and backfilled with nitrogen before dry diethyl ether (17.5 mL) was added. Methyl iodide (8.7 mL, 0.139 mol) in dry diethyl ether (12.5 mL) was added dropwise via the dropping funnel until reflux was observed. The solution was diluted with dry diethyl ether (10 mL) before the remaining methyl iodide was added dropwise over 20 min. The solution was cooled to room temperature before it was transferred to a new dry 500 mL three necked flask (which was evacuated and backfilled with nitrogen) using a cannula and unreacted magnesium was washed with dry diethyl ether (12.5 mL). The solution was cooled to 0 °C, then methyl-2-iodobenzoate **2.5** (16.46 g, 0.0628 mol) in dry

diethyl ether (10 mL) was added via a dropping funnel over 30 min. After that, dry diethyl ether (7 mL) was added via the same dropping funnel. The solution was warmed to room temperature overnight. The reaction mixture was then poured slowly into an ice cold, saturated ammonium chloride solution (75 mL) before water (100 mL) was added and the mixture was stirred for 15 minutes. The solution was filtered through Celite, the organic phase was separated and the aqueous layer was extracted with diethyl ether (3 × 75 mL). The combined organic layers were dried over K_2CO_3 and concentrated *in vacuo* to give 2-(2-iodophenyl)propan-2-ol **1.46** as an orange oil (12.09 g, 73 %). The characterisation data was in agreement with the literature.[145] δ_H ($CDCl_3$, 400 MHz): 1.76 (6H, s, CH_3), 2.51 (1H, br s, OH), 6.78 (1H, td, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.7, ArH), 7.34 (1H, td, $^3J_{HH}$ = 7.3, $^4J_{HH}$ = 1.3, ArH), 7.64 (1H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.7, ArH), 7.98 (1H, dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.3, ArH); δ_C ($CDCl_3$, 100 MHz): 29.8 (CH_3), 73.6 (C), 93.1 (C-I), 126.7 (CH), 128.1 (CH), 128.6 (CH), 142.7 (CH), 148.5 (C); m/z (ASAP): 244.9814 ([M-OH]$^+$, $C_9H_{10}I$ requires 244.9827, 100 %).

5.2.3 Preparation of 1-bromo-3,3-dimethyl-1,3-dihydro-λ3-benzo[d][1,2] iodoxole 1.47 [64]

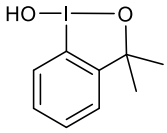


1.47

This procedure was based on that described by Stuart.[64] 2-(2-Iodophenyl)propan-2-ol **1.46** (4.79 g, 0.0183 mol) was dissolved in chloroform (50 mL) in a 250 mL round bottomed flask. *N*-Bromosuccinimide was added in two portions (2 × 2.5 g, 0.0281 mol) and the reaction mixture was stirred overnight at room temperature. The mixture was washed with water (2 x 100 mL) and with brine (2 × 50 mL). The organic phase was separated, dried over $MgSO_4$ and then concentrated *in vacuo* to produce a yellow solid. The product was recrystallized from ethyl acetate to produce 1-bromo-3,3-dimethyl-1,3-dihydro-λ3-benzo[d][1,2]iodoxole **1.47** as bright yellow crystals (4.76 g, 76 %). The characterisation data was in agreement with the literature.[146] mp 127–129 °C (lit.,[146] 126-128 °C). δ_H ($CDCl_3$, 400 MHz): 1.55 (6H, s, CH_3), 7.12-7.14 (1H, m, ArH), 7.5-7.55 (2H, m, ArH), 7.9-7.97 (1H, m, ArH); δ_C ($CDCl_3$, 100 MHz): 29.2 (CH_3), 84.2 (C), 112.0 (C-I), 125.9 (CH), 129.3 (CH), 130.4 (CH), 131.1 (CH), 149.8 (C); m/z (ASAP): 340.9047 (MH$^+$,

$C_9H_{11}{}^{79}BrIO$ requires 340.9038, 100 %), m/z (ASAP): 342.9037 (MH^+, $C_9H_{11}{}^{81}BrIO$ requires 342.9018, 100 %).

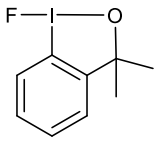
5.2.4 Preparation of 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ3-benzo[d][1,2] iodoxole 1.48 [64]



1.48

This procedure was based on that described by Stuart.[64] Potassium hydroxide (1.31 g, 0.024 mol) in water (50 mL) was added slowly to a solution of 1-bromo-3,3-dimethyl-1,3-dihydro-λ3-benzo[d][1,2]iodoxole **1.47** (4.02 g, 0.012 mol) in dichloromethane (50 mL) and the reaction mixture was stirred vigorously at room temperature for 2.5 h. After separating the organic phase, the aqueous layer was extracted with dichloromethane (3 x 50 mL). The organic layers were combined, dried with $MgSO_4$ and concentrated *in vacuo* to produce 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ3-benzo[d][1,2]iodoxole **1.48** as a pale yellow solid (2.73 g, 83 %). The characterisation data was in agreement with the literature.[147] mp 133-135 °C (lit.,[148] 126-128 °C). δ_H ($CDCl_3$, 500 MHz): 1.40 (6H, s, CH_3), 7.15 (1H, dd, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.4, ArH), 7.38 (1H, td, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.2, ArH), 7.44 (1H, td, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.3, ArH), 7.73 (1H, dd, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.1, ArH); δ_C ($CDCl_3$, 100 MHz): 30.1 (CH_3), 80.3 (C), 115.4 (C-I), 126.3 (CH), 126.8 (CH), 129.3 (CH), 130.0 (CH), 149.6 (C); m/z (ASAP): 278.9880 (MH^+, $C_9H_{12}IO_2$ requires 278.9882, 100 %).

5.2.5 Preparation of 1-fluoro-3,3-dimethyl-1,3-dihydro-λ3-benzo[d][1,2] iodoxole 1.22 [64]



1.22

This procedure was based on that described by Stuart.[64] Triethylamine trihydrogenfluoride (1.1 mL, 6.67 mmol) was added to a solution of 1-hydroxy-3,3-dimethyl-1,3-dihydro-λ3-benzo[d][1,2] iodoxole **1.48** (1.51 g, 5.45 mmol) in dichloromethane (80 mL) and the mixture was stirred at room temperature for 4 h. Water (50 mL) was then added to the reaction mixture and the organic phase was separated. The aqueous layer was extracted with dichloromethane (3 x 200 mL), the organic layers were combined and concentrated *in vacuo* to produce the crude product as a white solid. Toluene (3 × 50 mL) was added to

remove residual water by co-evaporation. Recrystallization from toluene gave pure 1-fluoro-3,3-dimethyl-1,3-dihydro-λ3-benzo[d][1,2]iodoxole **1.22** as a white crystalline solid (1.40 g, 91 %). The characterisation data was in agreement with the literature.[149] mp 81-83 °C (Lit.,[64] 82-84 °C). δ_H ($CDCl_3$, 400 MHz): 1.52 (6H, s, CH_3), 7.17 (1H, dd, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.4, ArH), 7.47 (1H, td, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.2, ArH), 7.55 (1H, td, $^3J_{HH}$ = 7.3, $^4J_{HH}$ = 1.4, ArH), 7.78 (1H, dd, $^3J_{HH}$ = 8.1, $^4J_{HH}$ = 0.9, ArH); δ_C ($CDCl_3$, 100 MHz): 29.0 (CH_3), 85.1 (C), 115.9 (C-I), 128.5 (CH), 128.6 (CH), 130.1 (CH), 130.5 (CH), 148.5 (C); δ_F ($CDCl_3$, 376 MHz): -143.1 (s); m/z (ASAP): 280.9900 (MH^+, $C_9H_{11}FIO$ requires 280.9839, 100 %).

5.2.6 General procedures for Tables 2.1 and 2.2

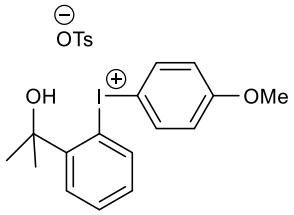
Anisole (77 µl, 0.72 mmol) was added to a solution of fluoroiodane **1.22** (0.30 g, 1.07 mmol) and *p*-toluenesulfonic acid (0.46 g, 2.43 mmol) in the required solvent (2 mL) in a Schlenk flask. The reaction mixture was left to stir at the required temperature for the required time. Dichloromethane (10 mL) was then added to this solution and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give the crude oil. This crude oil was washed with hot hexane (3 × 5 mL) and was heated at 47 °C in Et_2O (3 × 20 mL) three times for 30 minutes each, with decantation each time. The final product was analysed by ^1H and ^{19}F NMR spectroscopy.

5.3 General procedure for Table 2.3

The substrate (0.72 mmol) was added to a solution of fluoroiodane **1.22** (0.30 g, 1.07 mmol) and *p*-toluenesulfonic acid (0.46 g, 2.43 mmol) stirring at room temperature in trifluoroethanol (TFE) (2 mL) in a Schlenk flask. The reaction mixture was left to stir at room temperature for 1 hour. Dichloromethane (10 mL) was then added to this solution and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give the crude product. This material was washed with hot

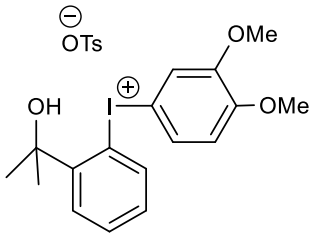
hexane (3 × 5 mL) and was heated at 47 °C in Et_2O (3 × 20 mL) three times for 30 minutes each, leaving the pure product which was dried *in vacuo*.

5.3.1 Characterisation data for the products in Table 2.3



1.85

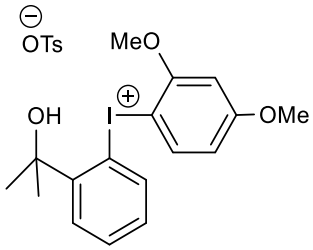
(2-(2-Hydroxypropan-2-yl)phenyl)(4-methoxyphenyl) iodonium-4-methylbenzenesulfonate **1.85** was obtained as a white solid (0.36 g, 93 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from a warm THF solution. mp 180-185 °C. δ_H ($CDCl_3$, 400 MHz): 1.68 (6H, s, $C(CH_3)_2$), 2.30 (3H, s, $ArCH_3$), 3.90 (3H, s, OCH_3), 6.77 (1H, d, $^3J_{HH}$ = 8.4, ArH), 7.0 (2H, dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.0, ArH), 6.96 (2H, d, $^3J_{HH}$ = 7.9, ArH), 7.09 (1H, td, $^3J_{HH}$ = 6.7, $^4J_{HH}$ = 2.2, ArH), 7.33-7.40 (2H, m, ArH), 7.69 (2H, dd, $^3J_{HH}$ = 6.5, $^4J_{HH}$ = 1.8, ArH), 7.80 (2H, dd, $^3J_{HH}$ = 6.8, $^4J_{HH}$ = 2.1, ArH), 8.64 (1H, br. s, OH); δ_C ($CDCl_3$, 125 MHz): 21.3 ($ArCH_3$), 30.5 (CH_3), 55.7 (CH_3), 74.1 (C), 100.4 (C-I), 109.0 (C-I), 118.0 (CH), 126.1 (CH), 128.1 (CH), 128.5 (CH), 128.6 (CH), 130.2 (CH), 130.7 (CH), 139.3 (C), 140.0 (CH), 143.0 (C), 147.0 (C), 163.4 (C); m/z (ASAP): 369.0339 ($[M\text{-}OTs]^+$, $C_{16}H_{18}IO_2$ requires 369.0352, 100 %); m/z (ES^-): 171 (TsO^-, 100 %).



2.7

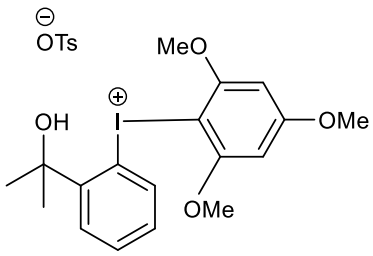
(2-(2-Hydroxypropan-2-yl)phenyl)(3,4-dimethoxyphenyl) iodonium-4-methylbenzene sulfonate **2.7** was obtained as a purple solid (0.34 g, 83 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from a dichloromethane and hexane (1:2) solution. mp 139–141 °C. δ_H ($CDCl_3$, 400 MHz): 1.71 (6H, s, $C(CH_3)_2$), 2.32 (3H, s, $ArCH_3$), 3.90 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.80 (1H, dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 0.8, ArH), 6.98 (1H, d, $^3J_{HH}$ = 8.5, ArH), 7.11 (2H, d, $^3J_{HH}$ = 7.9, ArH), 7.17 (1H, td, $^3J_{HH}$ = 6.6, $^4J_{HH}$ = 2.2, ArH), 7.40 – 7.48 (3H, m, ArH), 7.56 (1H, dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.0, ArH), 7.75 (2H, d, $^3J_{HH}$ = 8.3, ArH); δ_C ($CDCl_3$, 125 MHz): 21.3 (CH_3), 30.6 (CH_3), 56.2 (CH_3), 56.5 (CH_3), 74.2 (C), 99.9 (C-I), 108.9 (C-I), 113.9 (CH), 119.8 (CH), 126.0 (CH), 128.0 (CH), 128.6 (CH), 129.4 (CH), 130.2 (CH), 130.8 (CH), 132.2 (CH), 139.4 (C),

142.9 (C), 147.0 (C), 151.4 (C), 153.4 (C); m/z (ESI^+): 399.0457 ($[M\text{-}OTs]^+$, $C_{17}H_{20}IO_3$ requires 399.0457, 100 %); m/z (ES^-): 171 (TsO^-, 100 %).



2.8

(2-(2-Hydroxypropan-2-yl)phenyl)(2,4-dimethoxyphenyl) iodonium-4-methylbenzenesulfonate **2.8** was obtained as a white solid (0.40 g, 97 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from a dichloromethane and hexane solution (1:3). mp 155-158 ^oC. δ_H ($CDCl_3$, 400 MHz): 1.73 (6H, s, $C(CH_3)_2$), 2.30 (3H, s, $ArCH_3$), 3.83 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.60-6.30 (2H, m, ArH), 6.76 (1H, dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 0.9, ArH), 7.10 – 7.17 (3H, m, ArH), 7.39-7.47 (2H, m, ArH), 7.78–7.86 (3H, m, ArH), 8.82 (1H, br. s, OH); δ_C ($CDCl_3$, 125 MHz): 21.3 (CH_3), 30.5 (CH_3), 56.0 (CH_3), 56.8 (CH_3), 74.0 (C), 91.6 (C-I), 99.7 (CH), 108.1 (C-I), 108.8 (CH), 126.1 (CH), 127.5 (CH), 128.4 (CH), 128.6 (CH), 130.0 (CH), 130.7 (CH), 139.5 (C), 140.9 (CH), 142.9 (C), 147.0 (C), 160.6 (C), 166.3 (C); m/z (ESI^+): 399.0469 ($[M\text{-}OTs]^+$, $C_{17}H_{20}IO_3$ requires 399.0457, 100 %); m/z (ES^-): 171 (TsO^-, 100 %).



2.9

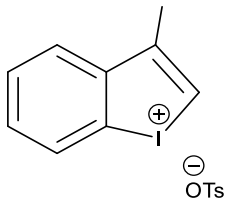
(2-(2-Hydroxypropan-2-yl)phenyl)(2,4,6-trimethoxy phenyl)iodonium4-methylbenzenesulfonate **2.9** was obtained as a white solid (0.40 g, 93 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from a dichloromethane and hexane (1:2) solution. mp 158-160 ^oC. δ_H ($CDCl_3$, 400 MHz): 1.73 (6H, s, $C(CH_3)_2$), 2.30 (3H, s, $ArCH_3$), 3.84 (6H, s, 2 OCH_3), 3.94 (3H, s, OCH_3), 6.25 (2H, s, ArH), 6.79 (1H, dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 2.2, ArH), 7.10-7.15 (3H, m, ArH), 7.37-7.44 (2H, m, ArH), 7.84 (2H, dd, $^3J_{HH}$ = 6.8, $^4J_{HH}$ = 1.9, ArH); δ_C ($CDCl_3$, 125 MHz): 21.3 (CH_3), 30.4 (CH_3), 56.1 (CH_3), 56.9 (CH_3), 73.8 (C), 83.0 (C-I), 91.4 (CH), 107.8 (C-I), 126.2 (CH), 127.0 (CH), 128.2 (CH), 128.6 (CH), 129.9 (CH), 130.5 (CH), 139.2 (C), 143.4

(C), 147.3 (C), 161.9 (C), 167.7 (C); m/z (ESI$^+$): 429.0566 ([M-OTs]$^+$, $C_{18}H_{22}IO_4$ requires 429.0563, 100 %); m/z (ES$^-$): 171 (TsO^-, 100 %).

5.3.2 General procedure for Table 2.5

The substrate (0.72 mmol) was added to a solution of fluoroiodane **1.22** (0.30 g, 1.07 mmol) and *p*-toluenesulfonic acid (0.46 g, 2.43 mmol) in trifluoroethanol (2 mL) in a Schlenk flask. The reaction mixture was left to stir at room temperature for 1 h time. Dichloromethane (10 mL) was then added to this solution and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give the crude product. This material was washed with hot hexane (3 × 5 mL) and was heated at 47 °C in Et_2O (3 × 20 mL) three times for 30 minutes each. The final product was analysed by ^1H and ^{19}F NMR spectroscopy.

5.3.3 7-Iodonia-9-methylbicycle[4,3,O]nona-1,3,5,8-tetraene-4-methylbenzene sulfonate 2.11



2.11

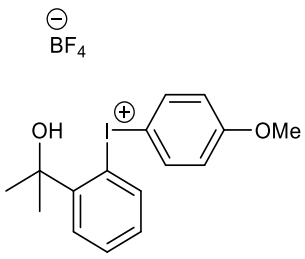
A solution of fluoroiodane **1.22** (0.20 g, 0.72 mmol) in TFE (2 mL) was added via syringe to the Schlenk flask containing $TsOH.H_2O$ (0.46 g, 2.43 mmol). The reaction mixture was heated at 60 °C for 18 h. After cooling the reaction mixture to room temperature, dichloromethane (10 mL) was added and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give a thick orange oil. This material was washed with hot hexane (3 × 5 mL). The crude product was stirred three times for 30 minutes each with Et_2O (3 × 20 mL) to give 7-iodonia-9-methylbicycle[4,3,O]nona-1,3,5,8-tetraene-4-methylbenzenesulfonate **2.11** as a light brown solid which was dried *in vacuo* (0.11 g, 37 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from a chloroform and hexane (1:2) solution. mp 145-147 °C. δ_H ($CDCl_3$, 400 MHz): 2.33 (3H, d, $^4J_{HH}$ = 1.3, CH_3), 2.36 (3H, s, $ArCH_3$), 7.20 (2H, d, $^3J_{HH}$ = 8.0, ArH), 7.49 (1H, td, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.9, ArH), 7.60-

7.70 (2H, m, ArH), 7.78 (2H, dd, $^{3}J_{HH}$ = 6.5, $^{4}J_{HH}$ = 1.8, ArH), 8.37 (1H, d, $^{4}J_{HH}$ = 1.4, CH), 8.55 (1H, dd, $^{3}J_{HH}$ = 8.3, $^{4}J_{HH}$ = 0.8, ArH); δ_C ($CDCl_3$, 100 MHz): 18.2 (CH_3), 21.3 (CH_3), 112.8 (CH), 124.1 (C-I), 126.0 (CH), 127.8 (CH), 129.0 (CH), 129.7 (CH), 129.8 (CH), 131.9 (CH), 140.3 (C), 142.2 (C), 146.3 (C), 147.1 (C); m/z (ASAP): 242.9671 ($[M\text{-}OTs]^+$, C_9H_8I requires 242.9671, 100 %); m/z (ES^-): 171 (TsO^-, 100 %).

5.3.4 General procedure for the metathesis reactions in Scheme 2.7

A one-necked 50 mL round bottomed flask was charged with the diaryliodonium tosylate (0.35-0.37 mmol), DCM (5 mL) and a saturated aqueous solution of $NaBF_4$ (5 mL). This mixture was stirred for 2 hours at room temperature. After separating the organic phase, it was washed with water (3 x 5 mL) and concentrated *in vacuo*. This crude product was dissolved in DCM (5 mL) and stirred again with a saturated aqueous solution of $NaBF_4$ (5 mL) for 2 hours. After separating the organic phase, it was washed with water (3 x 5 mL) and the aqueous phase was extracted with DCM (3 x 5 mL). The organic layers were combined and dried over $MgSO_4$, concentrated *in vacuo* to give a crude oil which was stirred with ether (25 mL) for 1 hour to give the pure product.

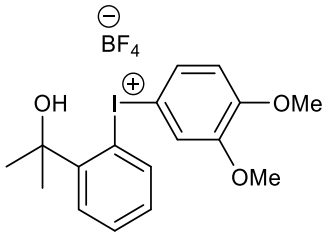
5.3.5 Characterisation data for the products in Scheme 2.7



2.12

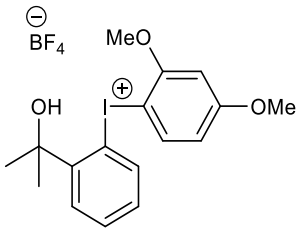
A solution of compound **1.85** (0.20 g, 0.37 mmol) in DCM (5 mL) was stirred with a saturated aqueous solution of $NaBF_4$ (5 mL) following the procedure above. The pure product **2.12** was obtained as a white solid (0.14 g, 84 %). mp 125-127 ^{o}C. Crystals suitable for X-ray crystallography were grown by slow evaporation from a DCM and hexane (1:3) solution. δ_H ($CDCl_3$, 400 MHz): 1.70 (6H, s, $C(CH_3)_2$), 3.93 (3H, s, OCH_3), 5.75 (1H, br. s, OH), 6.83 (1H, d, $^{3}J_{HH}$ = 8.5, ArH), 7.10 (2H, d, $^{3}J_{HH}$ = 8.8, ArH), 7.21 (1H, td, $^{3}J_{HH}$ = 6.7, $^{4}J_{HH}$ = 2.0, ArH), 7.43-7.49 (2H, m, ArH), 7.93 (2H, d, $^{3}J_{HH}$ = 7.1, ArH); δ_C ($CDCl_3$, 100 MHz): 29.5 (CH_3), 54.9 (CH_3), 73.7 (C), 97.4 (C-I), 107.1 (C-I), 117.5 (CH), 127.0 (CH), 127.9 (CH), 129.7 (CH), 130.2 (CH), 139.2 (CH), 145.0 (C), 162.9 (C); δ_F ($CDCl_3$, 376 MHz): -149.4

(s, BF_4); m/z (ESI^+): 369.0365 ($[M\text{-}BF_4]^+$, $C_{16}H_{18}IO_2$ requires 369.0352, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).



2.13

A solution of compound **2.7** (0.20 g, 0.35 mmol) in DCM (5 mL) was stirred with a saturated aqueous solution of $NaBF_4$ (5 mL) following the procedure above. The pure product **2.13** was obtained as a brown solid (0.14 g, 82 %). mp 183-185 ºC. Crystals suitable for X-ray crystallography were grown by slow evaporation from a DCM and hexane (1:3) solution. δ_H (CD_3CN, 400 MHz): 1.71 (6H, s, $C(CH_3)_2$), 3.88 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 7.0 (1H, dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.0, ArH), 7.18 (1H, d, $^3J_{HH}$ = 8.6, ArH), 7.30 (1H, td, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 2.0, ArH), 7.54-7.62 (3H, m, ArH), 7.71 (1H, dd, $^3J_{HH}$ = 8.7, $^4J_{HH}$ = 2.1, ArH); δ_C (CD_3CN, 125 MHz): 29.8 (CH_3), 55.5 (CH_3), 55.8 (CH_3), 74.6 (C), 99.4 (C-I), 108.7 (C-I), 114.2 (CH), 119.8 (CH), 128.5 (CH), 128.7 (CH), 130.6 (CH), 130.9 (CH), 132.1 (CH), 146.2 (C), 151.6 (C), 153.8 (C); δ_F ($CDCl_3$, 376 MHz): -151.4 (s, BF_4); m/z (ESI^+): 399.0472 ($[M\text{-}BF_4]^+$, $C_{17}H_{20}IO_3$ requires 399.0457, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).



2.14

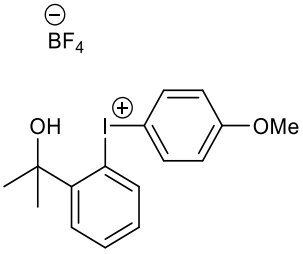
A solution of compound **2.8** (0.20 g, 0.35 mmol) in DCM (5 mL) was stirred with a saturated aqueous solution of $NaBF_4$ (5 mL) following the procedure above. The pure product **2.14** was obtained as a white solid (0.13 g, 78 %). mp 133-135 ºC. Crystals suitable for X-ray crystallography were grown by slow evaporation from a DCM and hexane (1:3) solution. δ_H (CD_3CN, 400 MHz): 1.71 (6H, s, $C(CH_3)_2$), 3.89 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 6.79 (1H, dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 2.7, ArH), 6.86 (1H, d, $^4J_{HH}$ = 2.5, ArH), 6.96 (1H, dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 1.0, ArH), 7.28 (1H, td, $^3J_{HH}$ = 6.8, $^4J_{HH}$ = 2.1, ArH), 7.54-7.61 (2H, m, ArH), 7.98 (1H, d, $^3J_{HH}$ = 8.8, ArH); δ_C (CD_3CN, 100 MHz): 29.2 (CH_3), 55.7 (CH_3), 56.7 (CH_3), 74.6 (C), 90.0 (C-I), 99.3 (CH), 107.8 (C-I), 109.4 (CH), 128.1 (CH), 128.4 (CH), 130.5 (CH), 130.8 (CH), 140.3 (CH), 145.8 (C), 160.3 (C), 166.5 (C); δ_F ($CDCl_3$, 376

MHz): -151.5 (s, BF_4); m/z (ESI^+): 399.0456 ($[M\text{-}BF_4]^+$, $C_{17}H_{20}IO_3$ requires 399.0457, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).

5.3.6 General procedure for the reaction in Scheme 2.8

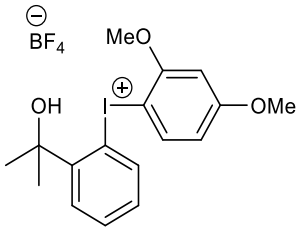
A solution of fluoroiodane **1.22** (0.30 g, 1.07 mmol) in dry MeCN (2 mL) was cooled to 0 °C before adding $BF_3.OEt_2$ (287 µl, 1.08 mmol). After 3 min. the substrate (0.72 mmol) was added to the solution at 0 °C. The reaction mixture was allowed to warm to room temperature and left to stir for 1 hour. After adding dichloromethane (10 mL), the organic phase was separated and washed with water (3 x 5 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude oil. This crude product was washed with hexane (3 × 5 mL), and then stirred with diethyl ether three times (3 × 20 mL) for 30 minutes each to give pure product.

5.3.7 Characterisation data for the products in Scheme 2.8



2.12

(2-(2-Hydroxypropan-2-yl)phenyl)(4-methoxyphenyl) iodonium tetrafluoroborate **2.12** was obtained as a white solid (0.29 g, 88 %).



2.14

(2-(2-Hydroxypropan-2-yl)phenyl)(2,4-dimethoxyphenyl) iodonium tetrafluoroborate **2.14** was obtained as a white solid (0.29 g, 83 %).

5.3.8 General procedures for Tables 2.7 and 2.8

Method A: A solution of fluoroiodane **1.22** (0.30 g, 1.07 mmol) in dry MeCN (2 mL) was charged in to a Schlenk flask. This solution was cooled to 0 °C before the required amount of triflic acid was added via syringe. After 1 h, anisole (77 µl, 0.72 mmol) was added to the solution stirring at 0 °C. The reaction mixture was warmed to room temperature and left to stir overnight. Dichloromethane (10 mL) was then added to this solution and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give the crude oil. This crude oil was washed with hot hexane (3 × 5 mL) and was heated at 47 °C in Et_2O (3 × 20 mL) three times for 30 minutes each. The final product was analysed by ^{1}H and ^{19}F NMR spectroscopy.

Method B: A solution of fluoroiodane **1.22** (0.30 g, 1.07 mmol) in dry MeCN (2 mL) was charged in to a Schlenk flask. This solution was cooled to 0 °C before the required amount of triflic acid was added via syringe. After 3-5 min, anisole (77 µl, 0.72 mmol) was added to this solution at 0 °C. The reaction mixture was warmed to room temperature and left to stir for the required amount of time. Dichloromethane (10 mL) was then added to this solution and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give the crude oil. This crude oil was washed with hot hexane (3 × 5 mL) and was heated at 47 °C in Et_2O (3 × 20 mL) three times for 30 minutes each. The final product was analysed by ^{1}H and ^{19}F NMR spectroscopy.

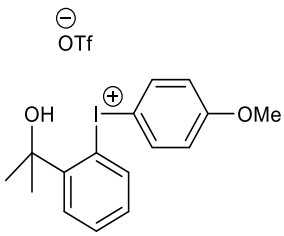
Method C: A solution of fluoroiodane **1.22** (0.30 g, 1.07 mmol) in dry MeCN (2 mL) was charged in to a Schlenk flask. This solution was cooled to 0 °C before anisole (77 µl, 0.72 mmol) was added. After 3-5 min, the required amount of triflic acid was added via syringe at 0 °C. The reaction mixture was warmed to room temperature and left to stir overnight. Dichloromethane (10 mL) was then added to this solution and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in*

vacuo to give the crude oil. This crude oil was washed with hot hexane (3 × 5 mL) and was heated at 47 °C in Et_2O (3 × 20 mL) three times for 30 minutes each. The final product was analysed by ^{1}H and ^{19}F NMR spectroscopy.

5.3.9 General procedure for Table 2.9

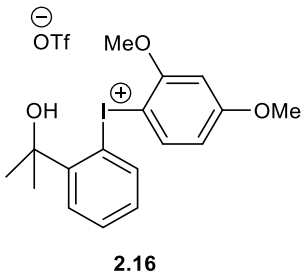
A solution of fluoroiodane **1.22** (0.30 g, 1.07 mmol) in dry MeCN (2 mL) was cooled to 0 °C before triflic acid (100 µl, 1.08 mmol) was added via syringe. After 3 min. the substrate (0.72 mmol) was added to the solution at 0 °C. The reaction mixture was warmed to room temperature and left to stir for 1 hour. Dichloromethane (10 mL) was added to the reaction mixture before washing it with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give a thick orange oil. This material was washed with hot hexane (3 × 5 mL) and then it was stirred three times for 30 minutes each with Et_2O (3 × 20 mL) to give pure product.

5.3.10 Characterisation data for the products in Table 2.9



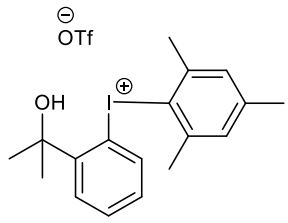
2.15

(2-(2-Hydroxypropan-2-yl)phenyl)(4-methoxyphenyl)iodonium triflate **2.15** was obtained as a white solid (0.32 g, 86 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from a chloroform and hexane (1:3) solution. mp 130-135 °C. δ_H ($CDCl_3$, 400 MHz): 1.70 (6H, s, $C(CH_3)_2$), 3.93 (3H, s, OCH_3), 6.81 (1H, dd, $^{3}J_{HH}$ = 8.4, $^{4}J_{HH}$ = 1.0, ArH), 7.10 (2H, dd, $^{3}J_{HH}$ = 7.0, $^{4}J_{HH}$ = 2.0, ArH), 7.21 (1H, td, $^{3}J_{HH}$ = 7.0, $^{4}J_{HH}$ = 2.1, ArH), 7.43-7.59 (2H, m, ArH), 7.92 (2H, dd, $^{3}J_{HH}$ = 7.0, $^{4}J_{HH}$ = 2.1, ArH); δ_C ($CDCl_3$, 125 MHz): 30.5 (CH_3), 55.9 (CH_3), 74.6 (C), 98.7 (C-I), 108.5 (C-I), 118.5 (CH), 120.4 (q, $^{1}J_{CF}$ = 314.0 Hz, CF_3) 127.8 (CH), 128.9 (CH), 130.7 (CH), 131.2 (CH), 140.1 (CH), 146.2 (C), 163.9 (C); δ_F ($CDCl_3$, 376 MHz): -78.3 (s, CF_3); m/z (ES^+): 369.0363 ($[M\text{-}OTf]^+$, $C_{16}H_{18}IO_2$ requires 369.0352, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).



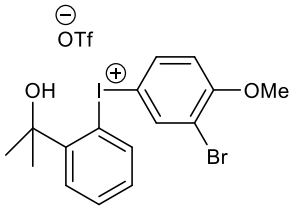
2.16

(2-(2-Hydroxypropan-2-yl)phenyl)(2,4-dimethoxyphenyl) iodonium triflate **2.16** was obtained as a white solid (0.36 g, 90 %). mp 128-130 ^{o}C. δ_H (CD_3CN, 400 MHz): 1.71 (6H, s, $C(CH_3)_2$), 3.90 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 5.60 (1H, br. s, OH), 6.79 (1H, dd, $^3J_{HH}$ = 8.8, $^4J_{HH}$ = 2.6, ArH), 6.86 (1H, d, $^4J_{HH}$ = 2.8, ArH), 6.96 (1H, dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 0.9, ArH), 7.28 (1H, td, $^3J_{HH}$ = 6.7, $^4J_{HH}$ = 2.1, ArH), 7.56-7.62 (2H, m, ArH), 7.98 (1H, d, $^3J_{HH}$ = 8.8, ArH); δ_C (CD_3CN, 100 MHz): 29.1 (CH_3), 55.7 (CH_3), 56.7 (CH_3), 74.5 (C), 90.0 (C-I), 99.6 (CH), 107.8 (C-I), 109.4 (CH), 120.6 (q, $^1J_{CF}$ = 312.0 Hz, CF_3), 128.1 (CH), 128.4 (CH), 130.5 (CH), 130.8 (CH), 140.3 (CH), 145.8 (C), 160.3 (C), 166.5 (C); δ_F (376 MHz, CD_3CN): -79.25 (s, CF_3); m/z (ESI^+): 399.0454 ($[M\text{-}OTf]^+$, $C_{17}H_{20}IO_3$ requires 399.0457, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).



2.17

(2-(2-Hydroxypropan-2-yl)phenyl)(2,4,6-trimethylbenzene) iodonium triflate **2.17** was obtained as a white solid which was dried *in vacuo* (0.35 g, 91 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from a DCM and hexane (1:2) solution. mp 171-173 ^{o}C. δ_H ($CDCl_3$, 400 MHz): 1.66 (6H, s, $C(CH_3)_2$), 2.37 (3H, s, $ArCH_3$), 2.48 (6H, s, 2 $ArCH_3$), 6.63 (1H, d, $^3J_{HH}$ = 8.2, ArH), 6.85 (1H, br. s, OH), 7.07-7.12 (3H, m, ArH), 7.40- 7.45 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz): 21.4 ($ArCH_3$), 26.7 ($ArCH_3$), 30.4 (CH_3), 74.2 (C), 106.4 (C-I), 116.4 (C-I), 120.4 (q, $^1J_{CF}$ = 324.0 Hz, CF_3), 126.9 (CH), 129.1 (CH), 130.3 (CH), 130.8 (CH), 131.3 (CH), 144.2 (C), 145.3 (C), 147.0 (C); δ_F (376 MHz, $CDCl_3$): -78.3 (s, CF_3); m/z (ESI^+): 381.0727 ($[M\text{-}OTf]^+$, $C_{18}H_{22}IO$ requires 381.0715, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).



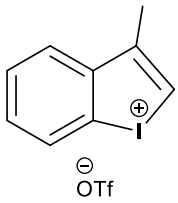
2.19

(2-(2-Hydroxypropan-2-yl)phenyl)(3-bromo-4-methoxy phenyl)iodonium triflate **2.19** was obtained as a white solid which was dried *in vacuo* (0.25 g, 58 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from a solution of methanol. mp 169-171 ^{o}C. δ_H (CD_3CN, 400 MHz): 1.67 (6H, s, $C(CH_3)_2$), 3.99 (3H, s, OCH_3), 5.83 (1H, br. s, OH), 7.01 (1H, dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.2, ArH), 7.29 (1H, td, $^3J_{HH}$ = 7.1, $^4J_{HH}$ = 1.6, ArH), 7.35 (1H, d, $^3J_{HH}$ = 8.8, ArH), 7.52 (1H, td, $^3J_{HH}$ = 7.1, $^4J_{HH}$ = 1.0, ArH), 7.63 (1H, dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.7, ArH), 8.24 (1H, dd, $^3J_{HH}$ = 8.8, $^4J_{HH}$ = 2.1, ArH), 8.45 (1H, d, $^4J_{HH}$ = 2.1, ArH); δ_C (CD_3CN, 100 MHz): 29.1 (CH_3), 56.5 (CH_3), 74.8 (C), 99.1 (C-I), 114.0 (C-I), 115.5 (C), 117.0 (CH), 120.5 (q, $^1J_{CF}$ = 320.0 Hz, CF_3), 128.5 (CH), 128.8 (CH), 130.7 (CH), 131.0 (CH), 139.1 (CH), 141.3 (CH), 145.6 (C), 160.1 (C); δ_F (376 MHz, CD_3CN): -79.3 (s, CF_3); m/z (ESI^+): 446.9459 ($[M\text{-}OTf]^+$, $C_{16}H_{17}{}^{79}BrIO_2$ requires 446.9457, 100 %), m/z (ESI^+): 448.9451, $C_{16}H_{17}{}^{81}BrIO_2$ requires 448.9436, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).

5.3.11 General procedure for Table 2.10

A solution of fluoroiodane **1.22** (0.30 g, 1.07 mmol) in dry MeCN (2 mL) was charged in to a Schlenk flask. This solution was cooled to 0 ^{o}C before the required amount of triflic acid was added. After 3 min, the substrate (0.72 mmol) was added to the solution at 0 ^{o}C. The reaction mixture was warmed to room temperature and left to stir for 1 h. Dichloromethane (10 mL) was then added to this solution and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give the crude product which was washed with hot hexane (3 × 5 mL). This crude product was stirred in Et_2O (3 × 20 mL) three times for 30 minutes each to give the final product which was analysed by ^{1}H and ^{19}F NMR spectroscopy.

5.3.12 Synthesis of 7-iodonia-9-methylbicycle[4,3,O]nona-1,3,5,8-tetraene triflate 2.22



2.22

A solution of fluoroiodane **1.22** (0.20 g, 0.72 mmol) in dry MeCN (2 mL) was charged in to a Schlenk flask. This solution was cooled to 0 °C before triflic acid (220 µl, 2.43 mmol) was added. The reaction mixture was heated to 60 °C and stirred for 18 h at that temperature. After the reaction mixture was cooled to room temperature, dichloromethane (10 mL) was added and the solution was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give a thick orange oil. This crude product was washed with hot hexane (3 × 5 mL) and was stirred three times for 30 minutes each with Et_2O (3 × 20 mL) to give 7-iodonia-9-methylbicycle[4,3,O]nona-1,3,5,8-tetraene triflate **2.22** as a white solid (0.07 g, 25 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from a chloroform and hexane (1:1) solution. mp 125–128 °C. δ_H ($CDCl_3$, 400 MHz): 2.44 (3H, d, $^4J_{HH}$ = 1.4, CH_3), 7.63 (1H, td, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.75, ArH), 7.71-7.78 (2H, m, ArH), 8.27 (1H, d, $^4J_{HH}$ = 1.4, CH), 8.55 (1H, dd, $^3J_{HH}$ = 8.34, $^4J_{HH}$ = 0.7, ArH); δ_C ($CDCl_3$, 125 MHz): 18.4 (CH_3), 110.4 (CH), 121.5 (q, $^1J_{CF}$ = 222.2 Hz, CF_3), 123.3 (C-I), 128.6 (CH), 130.3 (CH), 130.7 (CH), 131.4 (CH), 146.0 (C), 148.5 (C); δ_F ($CDCl_3$, 376 MHz): -78.2 (s, CF_3); m/z (ASAP): 242.9673 ($[M\text{-}OTf]^+$, C_9H_8I requires 242.9671, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).

5.3.13 General procedure for Table 2.12

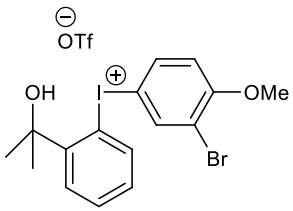
2-Bromoanisole (93 µl, 0.72 mmol) was added to a solution of fluoroiodane **1.22** (0.30 g, 1.07 mmol) in dry MeCN (2 mL) in a Schlenk flask. The reaction mixture was cooled to 0 °C before adding the required amount of triflic acid and the reaction mixture was stirred for the required amount of time at the required temperature. DCM (10 mL) was added to the reaction mixture and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give a thick orange oil. This crude oil was washed with hot hexane (3 × 5 mL) and then stirred three times for 20 minutes each

with Et_2O (3 × 20 mL) to give the pure product which was analysed by ^1H and ^{19}F NMR spectroscopy.

5.3.14 General procedure for Table 2.13

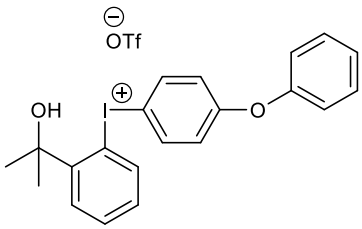
The substrate (0.72 mmol) was added to a solution of fluoroiodane **1.22** (0.30 g, 1.07 mmol) in dry MeCN (2 mL) in a Schlenk flask. The reaction mixture was cooled to 0 °C before adding triflic acid (200 µl, 2.16 mmol) and the reaction mixture was stirred for 2 h at 0 °C. DCM (10 mL) was added to the reaction mixture and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give the crude oil. This crude oil was washed with hot hexane (3 × 5 mL) and then stirred three times for 20 minutes each with Et_2O (3 × 20 mL) to give the pure product.

5.3.15 Characterisation data for the products in Table 2.13



2.19

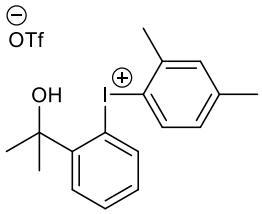
(2-(2-Hydroxypropan-2-yl)phenyl)(3-bromo-4-methoxy phenyl)iodonium triflate **2.19** was obtained as a white solid which was dried *in vacuo* (0.37 g, 86 %).



2.23

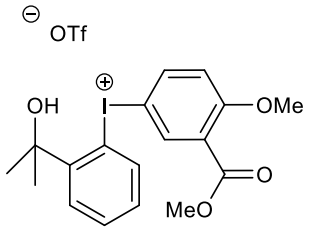
(2-(2-Hydroxypropan-2-yl)phenyl)(4-phenoxyphenyl) iodonium triflate **2.23** was obtained as a white solid (0.29 g, 70 %). mp 185-187 °C. Crystals suitable for X-ray crystallography were grown by slow evaporation from a DCM and hexane (1:3) solution. δ_H ($CDCl_3$, 400 MHz): 1.72 (6H, s, $C(CH_3)_2$), 6.88 (1H, dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.0, ArH), 6.99 (1H, br. s, OH), 7.10-7.17 (4H, m, ArH) 7.23-7.32 (2H, m, ArH), 7.45-7.52 (4H, m, ArH), 7.95 (2H, dd, $^3J_{HH}$ = 6.9, $^4J_{HH}$ = 2.1, ArH); δ_C ($CDCl_3$, 125 MHz): 30.4

(CH_3), 74.7 (C), 101.1 (C-I), 108.4 (C-I), 120.6 (CH), 120.8 (q, $^1J_{CF}$ = 320.5 Hz, CF_3), 121.0 (CH), 125.7 (CH), 128.0 (CH), 128.9 (CH), 130.4 (CH), 130.7 (CH), 131.2 (CH), 140.2 (CH), 146.4 (C), 154.3 (C), 162.8 (C); δ_F (376 MHz, $CDCl_3$): -78.3 (s, CF_3); m/z (ESI^+): 431.0505 ([M-OTf]$^+$, $C_{21}H_{20}IO_2$ requires 431.0508, 100 %), m/z (ES):149 (TfO^-, 100 %).



2.24

(2-(2-Hydroxypropan-2-yl)phenyl)(2,4-dimethylphenyl)iodonium triflate **2.24** was obtained as a white solid which was dried *in vacuo* (0.19 g, 51 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from a DCM and hexane (1:2) solution. mp 132-134 ^oC. δ_H ($CDCl_3$, 400 MHz): 1.73 (6H, s, $C(CH_3)_2$), 2.48 (3H, s, $ArCH_3$), 2.51 (3H, s, $ArCH_3$), 6.74 (1H, d, $^3J_{HH}$ = 8.5, ArH), 7.05 (1H, s, ArH) 7.14-7.21 (2H, m, ArH), 7.41 (1H, br. s, OH), 7.46-7.52 (2H, m, ArH), 7.93 (1H, d, $^3J_{HH}$ = 7.9, ArH); δ_C ($CDCl_3$, 125 MHz): 21.6 (CH_3), 25.2 (CH_3), 30.4 (CH_3), 74.4 (C), 107.0 (C-I), 111.2 (C-I), 120.3 (q, $^1J_{CF}$ = 321.0 Hz, CF_3), 127.6 (CH), 129.0 (CH), 130.7 (CH), 130.7 (CH), 131.2 (CH), 133.0 (CH), 139.6 (CH), 143.3 (C), 145.8 (C), 146.6 (C); δ_F (376 MHz, $CDCl_3$): -78.3 (s, CF_3); m/z (ASAP): 367.0545 ([M-OTf]$^+$, $C_{17}H_{20}IO$ requires 367.0559, 100 %); m/z (ES): 149 (TfO^-, 100 %).



2.25

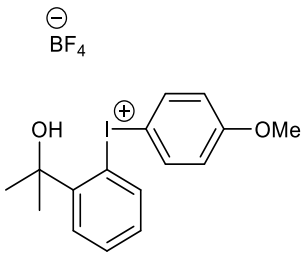
(2-(2-Hydroxypropan-2-yl)phenyl)(4-methoxy-3-(methoxy carbonyl)phenyl)iodonium triflate **2.25** was obtained as a white solid which was dried *in vacuo* (0.09 g, 33 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from a DCM and hexane (1:2) solution. mp 150-152 ^oC. δ_H ($CDCl_3$, 400 MHz): 1.72 (6H, s, $C(CH_3)_2$), 3.90 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 6.81 (1H, dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 1.0, ArH), 6.98 (1H, br., s, OH), 7.20-7.25 (2H, m, ArH), 7.44-7.52 (2H, m, ArH), 8.17 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.3, ArH), 8.37 (1H, d, $^4J_{HH}$ = 2.3, ArH); δ_C ($CDCl_3$, 125 MHz): 30.4 (CH_3), 52.7 (CH_3), 56.7 (CH_3), 74.8 (C), 98.8 (C-I), 108.4 (C-I), 116.3 (CH), 120.2 (q, $^1J_{CF}$ = 319.7 Hz, CF_3), 123.9 (C), 128.0 (CH), 128.9 (CH), 130.8 (CH), 131.2 (CH), 141.5 (CH), 143.6

(CH), 146.3 (C), 163.0 (C), 164.1 (C); δ_F ($CDCl_3$, 376 MHz): -78.3 (s, CF_3); m/z (ESI): 427.0409 ([M-OTf]$^+$, $C_{18}H_{20}IO_4$ requires 427.0406, 100 %); m/z (ES): 149 (TfO^-, 100 %).

5.3.16 General procedure for Scheme 2.11

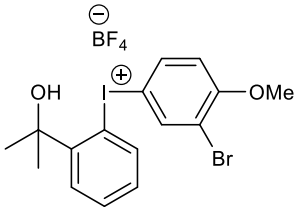
A one-necked 50 mL round bottomed flask was charged with the diaryliodonium triflate (0.34-0.38 mmol), DCM (5 mL) and a saturated aqueous solution of $NaBF_4$ (5 mL) and this mixture was stirred overnight at room temperature. After separating the organic phase, it was washed with water (3 x 5 mL) and the aqueous phase was extracted with DCM (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product which was stirred with diethyl ether (25 mL) for 1 hour leaving the pure product.

5.3.17 Characterisation data for the products in Scheme 2.11



2.12

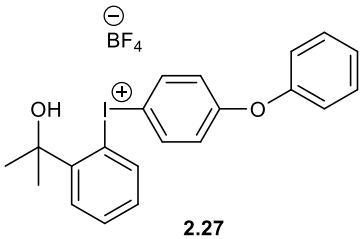
A solution of compound **2.15** (0.20 g, 0.38 mmol) in DCM (5 mL) was stirred overnight with a saturated aqueous solution of $NaBF_4$ (5 mL) following the procedure above. (2-(2-Hydroxypropan-2-yl)phenyl)(4-methoxyphenyl)iodonium tetrafluoroborate **2.12** was obtained as a white solid (0.15 g, 78 %).



2.26

A solution of compound **2.19** (0.20 g, 0.38 mmol) in DCM (5 mL) was stirred overnight with a saturated aqueous solution of $NaBF_4$ (5 mL) following the procedure for Scheme 2.9. (3-Bromo-4-methoxyphenyl)(2-(2-hydroxypropan-2-yl)phenyl) iodonium tetrafluoroborate **2.26** was obtained as a white solid (0.16 g, 82 %). mp 180–183 ^oC. δ_H (CD_3CN, 400 MHz): 1.71 (6H, s, $C(CH_3)_2$), 4.04 (3H,

s, OCH_3), 7.00 (1H, dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 1.0, ArH), 7.30 (2H, dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.7, ArH), 7.56-7.61 (2H, m, ArH), 8.10 (1H, dd, $^3J_{HH}$ = 8.8, $^4J_{HH}$ = 2.3, ArH), 8.30 (1H, d, $^4J_{HH}$ = 2.1, ArH); δ_C (CD_3CN, 100 MHz): 29.2 (CH_3), 56.5 (CH_3), 74.9 (C), 98.9 (C-I), 108.6 (C-I), 114.0 (C), 115.6 (CH), 128.6 (CH), 128.9 (CH), 130.7 (CH), 131.0 (CH), 139.2 (CH), 141.4 (CH), 145.5 (C), 160.1 (C); δ_F (376 MHz, CD_3CN): -151.3 (s, BF_4); m/z (ESI^+) 446.9450: ($[M\text{-}BF_4]^+$, $C_{16}H_{17}{}^{79}BrIO_2$ requires 446.9457, 100 %), m/z (ESI^+): 448.9451, ($[M\text{-}BF_4]^+$, $C_{16}H_{17}{}^{81}BrIO_2$ requires 448.9436, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).



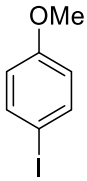
2.27

A solution of compound **2.23** (0.20 g, 0.38 mmol) in DCM (5 mL) was stirred overnight with a saturated aqueous solution of $NaBF_4$ (5 mL) following the procedure for Scheme 2.9. The pure product of **2.27** was obtained as a white solid (0.14 g, 80 %). mp 182-184 ^oC. Crystals suitable for X-ray crystallography were grown by slow evaporation from a DCM and hexane (1:3) solution. δ_H ($CDCl_3$, 400 MHz): 1.71 (6H, s, $C(CH_3)_2$), 6.88 (1H, dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 0.9, ArH), 7.08-7.15 (4H, m, ArH) 7.23-7.33 (2H, m, ArH), 7.43-7.51 (4H, m, ArH), 7.94 (2H, dd, $^3J_{HH}$ = 6.8, $^4J_{HH}$ = 2.0, ArH); δ_C ($CDCl_3$, 125 MHz): 30.5 (CH_3), 74.9 (C), 100.4 (C-I), 108.0 (C-I), 120.7 (CH), 121.0 (CH), 125.7 (CH), 128.0 (CH), 129.0 (CH), 130.5 (CH), 130.8 (CH), 131.2 (CH), 140.3 (CH), 146.1 (C), 154.2 (C), 162.9 (C); δ_F (376 MHz, $CDCl_3$): -149.1 (s, BF_4); m/z (ASAP): 431.0514 ($[M\text{-}BF_4]^+$, $C_{21}H_{20}IO_2$ requires 431.0508, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).

5.3.18 General procedure for Table 2.16

A solution of fluoroiodane **1.22** (0.20 g, 0.72 mmol) in the dry solvent (2 mL) was prepared under nitrogen. 1 Equivalent of catalyst ([Cu] and [Ag] was added in glovebox) was added to this solution. After 5 min, anisole (40 µl, 0.53 mmol, 1 eq.) was added and the reaction mixture was left to react overnight at 60 ^oC. After cooling the solution to room temperature, dichloromethane (10 mL) was added. The organic phase was separated and washed with water (3 x 5 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, dried over $MgSO_4$ and

concentrated *in vacuo* to give the crude product which was analysed by ^{1}H and ^{19}F NMR spectroscopy.



4-Iodoanisole was isolated as a white solid after washing the crude product from entry 5 in Table 2.13 with hot hexane. The characterisation data was in agreement with the literature.[150] δ_H ($CDCl_3$, 400 MHz): 3.77 (3H, s, OCH_3), 6.67 (2H, dd, $^{3}J_{HH}$ = 6.9, $^{4}J_{HH}$ = 2.3, ArH), 7.55 (2H, dd, $^{3}J_{HH}$ = 6.9, $^{4}J_{HH}$ = 2.2, ArH); δ_C ($CDCl_3$, 100 MHz): 55.3 (OCH_3), 82.7 (C-I), 116.4 (CH), 138.2 (CH), 159.5 (C).

5.3.19 General procedure for Table 2.17

The Schlenk flask was charged with fluoroiodane **1.22** (0.20 g, 0.72 mmol), dichloromethane (2 mL) and the required amount of $Zn(BF_4)_2.xH_2O$. After that, anisole (40 µl, 0.48 mmol) was added and the reaction mixture was left to react for the required amount of time at the required temperature. After cooling the solution to room temperature, dichloromethane (10 mL) was added. The organic phase was separated and washed with water (3 x 5 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give a thick yellow oil. This crude product was washed with hexane (3 × 5 mL), and then stirred with diethyl ether three times (3 × 20 mL) for 30 minutes each. The final product was analysed by ^{1}H and ^{19}F NMR spectroscopy.

5.3.20 Synthesis of 2.12 from Table 2.17 (entry 7).

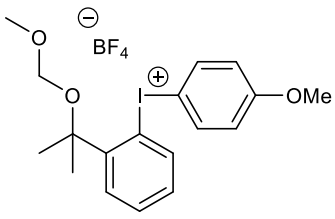
$Zn(BF_4)_2.xH_2O$ (0.126 g, 0.53 mmol) was added to a solution of fluoroiodane **1.22** (0.20 g, 0.72 mmol) in DCM (2 mL) (Table 2.17, entry 7). After 5 min, anisole (40 µl, 0.48 mmol) was added. The reaction mixture was heated to 60 ^{o}C for 6 h. After cooling the solution to room temperature, dichloromethane (10 mL) was added. The organic phase was separated and washed with water (3 x 5 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give a thick yellow oil. This crude product was washed with

hexane (3 × 5 mL), and then stirred with diethyl ether three times (3 × 20 mL) for 30 minutes each to give **2.12** as a white solid (0.173 g, 72 %).

5.3.21 General procedure for Scheme 2.12.

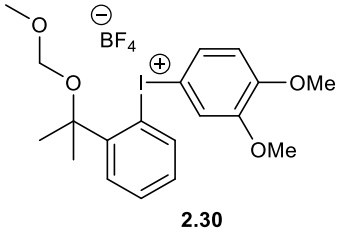
This procedure was based on that described by Desjardins.[134] A 100 mL oven-dried three-necked round bottomed flask equipped with a magnetic stir bar was evacuated and backfilled with nitrogen. This flask was charged with the substrate (2.2 mmol) and dry dichloromethane (20 mL). This solution was cooled to 0 °C before *N*,*N*-diisopropylethylamine (DIPEA) (1.2 mL, 6.6 mmol) followed by chloromethyl methyl ether (MOMCl) (0.7 mL, 8.8 mmol) was added. The mixture was warmed to room temperature and stirred for 18 h. After that, the reaction mixture was washed with water (3 × 20 mL). The aqueous phase was combined and extracted with DCM (3 × 20 mL). The organic layers were combined and stirred with a saturated solution of $NaBF_4$ (30 mL) overnight at room temperature. The aqueous phase was separated and extracted with DCM (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude oil product. This oil was stirred with diethyl ether (1 × 25 mL) for 1 hour to give the pure product as a solid.

5.3.22 Characterisation data for the products in Scheme 2.12.



2.29

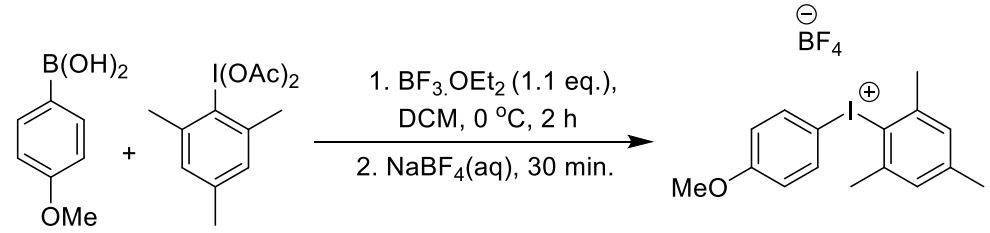
(2-(2-(Methoxymethoxy)propan-2-yl)phenyl)(4-methoxy phenyl)iodonium tetrafluoroborate **2.29** was obtained as a pale yellow solid (1.01 g, 92 %). mp 69-71 °C. δ_H ($CDCl_3$, 400 MHz): 1.75 (6H, s, $C(CH_3)_2$), 3.56 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.05 (2H, s, CH_2), 6.97 (1H, d, $^3J_{HH}$ = 8.1, ArH), 7.02 (2H, dd, $^3J_{HH}$ = 8.8, $^4J_{HH}$ = 2.2, ArH), 7.12-7.17 (1H, m, ArH), 7.41-7.45 (2H, m, ArH), 7.97 (2H, dd, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 2.1, ArH); δ_C ($CDCl_3$, 125 MHz): 27.7 (CH_3), 55.7 (CH_3), 56.9 (CH_3), 80.4 (C), 91.5 (CH_2), 103.6 (C-I), 115.2 (C-I), 118.0 (CH), 128.2 (CH), 130.3 (CH), 130.4 (CH), 130.8 (CH), 139.2 (CH), 146.2 (C), 162.9 (C); δ_F ($CDCl_3$, 376 MHz): -150.3 (s, BF_4); m/z (ES^+): 413.0627 ($[M\text{-}BF_4]^+$, $C_{18}H_{22}IO_3$ requires 413.0614, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).



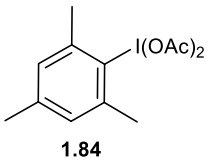
2.30

(3,4-Dimethoxyphenyl)(2-(2-(methoxymethoxy)propan-2-yl)phenyl)iodonium tetrafluoroborate **2.30** was obtained as a brown solid (1.07 g, 92 %). mp 98-100 °C. δ_H ($CDCl_3$, 500 MHz): 1.69 (6H, s, $C(CH_3)_2$), 3.46 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.02 (2H, s, OCH_2), 6.87 (1H, d, $^3J_{HH}$ = 8.3, ArH), 6.96 (1H, d, $^3J_{HH}$ = 8.6, ArH), 7.16 (1H, td, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.1, ArH), 7.40-7.45 (2H, m, ArH), 7.49 (1H, d, $^4J_{HH}$ = 1.3, ArH), 7.55 (1H, dd, $^3J_{HH}$ = 7.3, $^4J_{HH}$ = 1.4, ArH); δ_C ($CDCl_3$, 125 MHz): 27.6 (CH_3), 56.3 (CH_3), 56.7 (CH_3), 56.7 (CH_3), 79.9 (C), 91.3 (CH_2), 98.4 (C-I), 108.0 (C-I), 114.3 (CH), 120.0 (CH), 128.9 (CH), 129.1 (CH), 131.0 (CH), 131.3 (CH), 132.4 (CH), 145.8 (C), 151.6 (C), 153.8 (C); δ_F ($CDCl_3$, 376 MHz): -148.9 (s, BF_4^-); m/z (ESI^+): 443.0723 ($[M\text{-}BF_4]^+$, $C_{19}H_{24}IO_4$ requires 443.0719, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).

5.3.23 Preparation of 4-methoxyphenyl(mesityl)iodonium tetrafluoroborate 2.28.[98]



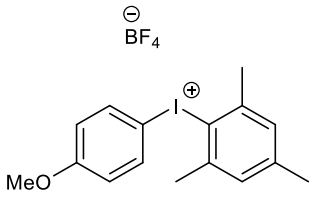
1.84 2.28



1.84

This procedure was based on that described by Wu.[151] To Selectfluor™ (15 mmol, 5.31 g) in CH_3CN (150 mL) was added a solution of mesitylene (6 mmol, 0.721 g), I_2 (0.761 g) and HOAc (7.5 mL) in a (250 mL) 3 neck flask. The reaction mixture was stirred at 40 °C for 1 h and then cooled to room temperature. This solution was concentrated *in vacuo* before water (50 mL) was added. The aqueous layer was extracted with dichloromethane (3 x 50 mL). Organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give pale yellow solid. This solid was washed with hexane (3 × 10 mL) and dried under vacuum leaving 1,3,5-methyl(2-diacetoxyiodo)benzene **1.84** as a white solid (2.14 g, 98 %). m.p 160-162 °C (lit.,[152] 158-159 °C). The characterisation data was agreement with that in the literature.[152,153] δ_H (400 MHz, $CDCl_3$) δ: 1.96 (6H, s, $COCH_3$), 2.35 (3H, s,

Me), 2.70 (6H, s, Me), 7.10 (s, 2H, ArH); δ_C (125 MHz, $CDCl_3$): 20.3 (CH_3), 21.2 (CH_3), 26.7 (CH_3), 129 (CH), 129.6 (C-I), 141.4 (C), 143.2 (C), 176.5 (CO). m/z (ASAP): 245.9905 ([M-$(OAc)_2$], $C_9H_{11}I$ requires 245.9906, 100 %).

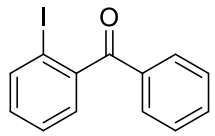


2.28

This procedure was based on that described by Sanford.[98] 4-Methoxyphenylboronic acid (0.792 g, 5.22 mmol) and dry dichloromethane (70 mL) were placed in an oven-dried 3 neck flask with a stir bar. This solution was cooled to 0 ºC before $BF_3.OEt_2$ (1.5 mL, 5.6 mmol) was added dropwise, and the reaction mixture was stirred for 10 min. After that, 1,3,5-methyl(2-diacetoxyiodo)benzene (2 g, 5.48 mmol) in dry dichloromethane (17 mL) was added via syringe. The reaction mixture was stirred for 2 h at 0 ºC. This mixture was warmed to room temperature before being stirred vigorously over 30 min with a saturated solution of $NaBF_4$ (100 mL). The aqueous layer was separated, extracted with dichloromethane (3 × 50 mL), dried over $MgSO_4$ and concentrated *in vacuo* giving a brown solid. This crude product was stirred with diethyl ether (3 × 20 mL) for 20 min. each leaving 4-methoxyphenyl(mesityl)iodonium tetrafluoroborate **2.28** as an off-white solid (2.14 g, 93 %). mp. 153-155 ºC (lit.,[154] 150-152 ºC). Crystals suitable for X-ray crystallography were grown by slow evaporation from DCM and hexane (1:2). The characterisation data was in agreement with the literature.[154] δ_H ($CDCl_3$, 400 MHz): 2.33 (3H, s, $ArCH_3$), 2.64 (6H, s, 2 $ArCH_3$), 3.80 (3H, s, OCH_3), 6.93 (2H, dd, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 2.1, ArH), 7.08 (2H, s, ArH), 7.70 (2H, dd, $^3J_{HH}$ = 7.1, $^4J_{HH}$ = 2.0, ArH); δ_C ($CDCl_3$, 125 MHz): 21.1 (CH_3), 27.1 (CH_3), 55.8 (CH_3), 98.8 (C-I), 118.3 (CH), 119.8 (C-I), 130.5 (CH), 135.7 (CH), 142.6 (C), 144.6 (C), 162.7 (C); δ_F ($CDCl_3$, 376 MHz): -147.8 (s, BF_4); m/z (ASAP): 353.0418 ([M-BF_4]$^+$, $C_{16}H_{18}IO$ requires 353.0402, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).

5.4 Experimental for Chapter 3

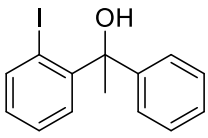
5.4.1 Synthesis of 2-Iodobenzophenone 3.1



3.1

To a three-neck flask equipped with an addition funnel and a magnetic stirrer bar, *p*-toluenesulfonic acid (21.74 g, 0.114 mol) was dissolved in acetonitrile (140 mL). 2-Aminobenzophenone (7.50 g, 0.038 mol) was added to the solution and the reaction mixture was then cooled to 0 ºC. As the solution cooled, the color changed from a clear yellow to white. Potassium iodide (16.48 g, 0.099 mol) and sodium nitrite (5.49 g, 0.080 mol) were dissolved in water (120 mL). This solution was added dropwise to the reaction mixture over 45 minutes via the dropping funnel. When the addition was complete, the reaction mixture was warmed to room temperature and stirred overnight. A saturated solution of sodium hydrogen carbonate (75 mL) was added to the reaction mixture until it tested basic with pH paper. A saturated solution of sodium thiosulfate (50 mL) was then added to the reaction mixture, and the reaction mixture separated into two phases. The reaction mixture was transferred to a separating funnel and the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 x 60 mL). The organic phases were combined, dried over magnesium sulphate and then filtered into a round bottom flask. The organic phase was concentrated *in vacuo* to afford the pure product **3.1** as a yellow oil (10.28 g, 88 %). The characterization data was in agreement with the literature.[155,156] δ_H ($CDCl_3$, 400 MHz): 7.18 (1H, td, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.6, ArH), 7.30 (1H, dd, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.5, ArH), 7.43-7.49 (3H, m, ArH), 7.60 (1H, t, $^3J_{HH}$ = 7.5, ArH), 7.81 (2H, d, $^3J_{HH}$ = 7.2, ArH), 7.93 (1H, d, $^3J_{HH}$ = 8.0, ArH); δ_C ($CDCl_3$, 125 MHz): 92.2 (C-I), 127.8 (CH), 128.5 (CH), 128.7 (CH), 130.5 (CH), 131.2 (CH), 133.7 (CH), 135.6 (C), 139.7 (CH), 144.4 (C), 197.3 (CO); m/z (ESI^+): 308.9777 (MH^+, $C_{13}H_{10}IO$ required 308.9776, 100 %).

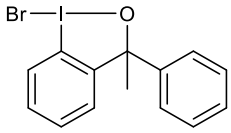
5.4.2 Synthesis of 1-(2-iodophenyl)-1-phenylethan-1-ol 3.2



3.2

All of the glassware and the magnesium turnings were dried overnight in an oven prior to the experiment. A three-neck flask was equipped with an addition funnel, condenser, N_2 supply, glass stopper, and a magnetic stirrer bar. Dried magnesium turnings (2.30 g, 0.096 mol) were added to the flask which was then evacuated and backfilled with N_2. Dry diethyl ether (15 mL) was added to the flask *via* syringe. Iodomethane (4.2 mL, 0.0675 mol) was first added to the addition funnel, after which dry diethyl ether (15 mL) was squirted into the additional funnel. The iodomethane solution was added dropwise to the magnesium over 20 minutes and with vigorous stirring. When the addition was complete, the addition funnel was rinsed with dry diethyl ether (10 mL) and the rinsing solution was added to the reaction mixture. The reaction solution was transferred from the excess Mg turnings to a new three-neck flask *via* cannula. The first reaction flask was rinsed with dry diethyl ether (10 mL) and the rinsing solution was also transferred to the new flask. The solution of Grignard reagent was cooled to 0 ºC with stirring before 2-iodobenzophenone **3.1** (8.10 g, 0.026 mol) in dry diethyl ether (20 mL) was added dropwise over 15 minutes. After leaving the reaction mixture to stir overnight at room temperature, it was then refluxed at 45 ºC for 5 hours. The reaction mixture was cooled to 0 ºC before a saturated solution of ammonium chloride (60 mL) was added to it slowly, followed by (50 mL) water. 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 **3.2** as a yellow oil (6.15 g, 73 %). The characterisation data was in agreement with the literature.[157] δ_H ($CDCl_3$, 400 MHz): 1.98 (3H, s, CH_3) 3.24 (1H, br. s, OH) 6.98 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.7, ArH), 7.22-7.32 (5H, m, ArH), 7.43 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.4, ArH), 7.82 (1H, d, $^3J_{HH}$ = 7.6, ArH), 7.89 (1H, d, $^3J_{HH}$ = 7.5, ArH); δ_C ($CDCl_3$, 125 MHz): 30.7 (CH_3), 78.2 (C), 96.4 (C-I), 126.4 (CH), 127.0 (CH), 128.0 (CH), 128.2 (CH), 128.2 (CH), 129.1 (CH), 142.3 (CH), 147.2 (C), 147.4 (C); m/z (ASAP): 322.9940 (M^+, $C_{14}H_{12}IO$ required 322.9933, 100 %).

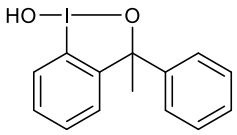
5.4.3 Synthesis of 1-bromo-3-methyl-3-phenyl-1,3-dihydro-λ^3-benzoiodoxole 3.3



3.3

2-Iodophenyl-1-phenylethanol **3.2** (6.02 g, 0.018 mol) and chloroform (80 mL) were added to a round-bottom flask. *N*-bromosuccinimide (5.03 g, 0.028 mol) was then added in three portions and stirred over 72 h at room temperature. The reaction mixture was transferred to a separating funnel and was washed with water (4 x 50 mL) and brine (3 x 30 mL). The organic phase was dried over magnesium sulphate and concentrated *in vacuo* to give the pure product as a yellow solid (6.9 g, 95 %). mp 115-117 ^{o}C. δ_H ($CDCl_3$, 500 MHz): 1.90 (3H, s, CH_3), 7.17-7.24 (1H, m, ArH), 7.27-7.36 (2H, m, ArH), 7.45-7.63 (5H, m, ArH), 7.99-8.08 (1H, m, ArH); δ_C ($CDCl_3$, 125 MHz): 29.3 (CH_3), 87.0 (C), 113.8 (C-I), 125.9 (CH), 126.4 (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^+, $C_{14}H_{13}I^{79}BrO$ required 402.9195, 100 %).

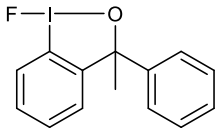
5.4.4 Synthesis of 1-hydroxy-3-methyl-3-phenyl-1,3-dihydro-λ^3-benzoiodoxole 3.4



3.4

1-Bromo-3-methyl-3-phenyl-1,3-dihydro-λ^3-benzoiodoxole **3.3** (6.35 g, 15.75 mmol) was dissolved in dichloromethane (80 mL) in a round-bottom flask. Potassium hydroxide (1.52 g, 27.0 mmol) was first dissolved in water (75 mL), and then added to the reaction mixture. This mixture was stirred vigorously at room temperature for 2 hours. After separating the organic layer, it was extracted with dichloromethane (4 x 50 mL). The organic extractions were combined, dried over magnesium sulphate, filtered and then concentrated *in vacuo* to afford the crude product as a pale yellow solid. The crude product was recrystallized from ethyl acetate affording the pure product **3.4** as a white solid (4.7 g, 88 %). mp 104-107 °C. δ_H (MeOD, 500 MHz): 1.83 (3H, s, CH_3), 7.22-7.37 (3H, m, ArH), 7.41 (3H, dd, $^3J_{HH}$ = 7.3, $^4J_{HH}$ = 1.3, ArH), 7.47-7.63 (2H, m, ArH), 7.65-7.75 (1H, m, ArH); δ_C (MeOD, 125 MHz): 30.3 (CH_3), 85.2 (C), 115.5 (C-I), 127.0 (CH), 128.1 (CH), 128.2 (CH), 129.2 (CH), 129.7 (CH), 130.8 (CH), 131.2 (CH), 147.9 (C), 149.4 (C). m/z (ESI^+): 341.0053 (MH^+, $C_{14}H_{14}IO_2$ required 341.0039, 100 %).

5.4.5 Synthesis of 1-fluoro-3-methyl-3-phenyl-1,3-dihydro-λ^3-benzo[d][1,2] iodoxole 3.5



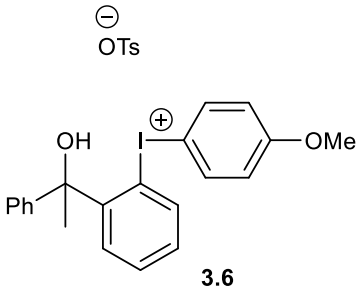
3.5

1-Hydroxy-3-methyl-3-phenyl-1,3-dihydro-λ^3-benzoiodoxole **3.4** (3.00 g, 8.82 mmol) was stirred in dichloromethane (150 mL) at room temperature until it all dissolved. Triethylamine trihydrofluoride (3.0 mL, 18.3 mmol) was then added slowly to the reaction mixture. This solution was stirred for 4 hours at room temperature. After washing the reaction mixture with water (3 x 60 mL), the aqueous phases were combined and extracted with dichloromethane (3 x 60 mL). The organic phases were combined and concentrated *in vacuo* to afford a yellow oil as the crude product. Toluene (3 × 40 mL) was added to remove residual water by co-evaporation. Recrystallization from toluene afforded the purified product as a pale yellow solid (2.92 g, 97 %). mp 86-88 ^{o}C. δ_H ($CDCl_3$, 500 MHz): 1.87 (3H, s, CH_3), 7.21-7.39 (6H, m, ArH), 7.42-7.53 (1H, m, ArH), 7.57 (1H, t, $^3J_{HH}$ = 7.8, ArH), 7.82 (1H, d, $^3J_{HH}$ = 8.2, ArH); δ_C ($CDCl_3$, 125 MHz): 28.0 (CH_3) 86.9 (C), 116.5 (C-I), 125.8 (CH), 126.7 (CH), 127.1 (CH), 127.3 (CH), 127.6 (CH), 129.2 (CH), 129.3 (CH), 143.5 (C), 145.7 (C); δ_F ($CDCl_3$, 376 MHz): -143.2 (s, F); m/z (ASAP): 322.9944 ($[M-F]^+$, $C_{14}H_{12}IO$ requires 322.9933, 100 %).

5.4.6 General procedure for Scheme 3.2.

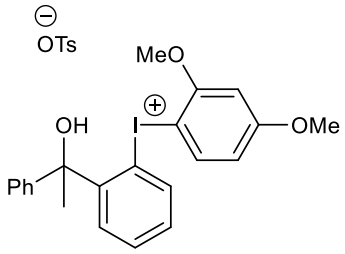
The substrate (0.72 mmol) was added to a solution of fluoroiodane **3.5** (0.36 g, 1.07 mmol) and *p*-toluenesulfonic acid (0.46 g, 2.43 mmol) stirring at room temperature in trifluoroethanol (TFE) (2 mL) in a Schlenk flask. The reaction mixture was left to stir at room temperature for 1 hour. Dichloromethane (10 mL) was then added to this solution and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give the crude product. This material was washed with hot hexane (3 × 5 mL) and then stirred with Et_2O (3 × 20 mL) three times for 30 minutes each, leaving the pure product which was dried *in vacuo*.

5.4.7 Characterisation data for the products in Scheme 3.2.



3.6

(2-(1-Hydroxy-1-phenylethyl)phenyl)(4-methoxyphenyl) iodonium-4-methylbenzene sulfonate **3.6** was obtained as a white solid which was dried *in vacuo* (0.27 g, 63 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from DCM and hexane (1:3). mp 153-155 ^{o}C. δ_H ($CDCl_3$, 400 MHz): 2.07 (3H, s, CH_3), 2.30 (3H, s, $ArCH_3$), 3.85 (3H, s, OCH_3), 6.82 (1H, d, $^3J_{HH}$ = 8.2, ArH), 6.91 (2H, d, $^3J_{HH}$ = 8.6, ArH), 6.96 (2H, d, $^3J_{HH}$ = 7.7, ArH), 7.10-7.15 (2H, m, ArH), 7.25-7.31 (3H, m, ArH), 7.39-7.44 (3H, m, ArH), 7.55 (2H, d, $^3J_{HH}$ = 8.1, ArH), 7.72 (2H, dd, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 2.0, ArH); δ_C ($CDCl_3$, 125 MHz): 21.3 (CH_3), 30.1 (CH_3), 55.7 (CH_3), 77.4 (C), 100.5 (C-I), 112.0 (C-I), 117.8 (CH), 126.1 (CH), 126.2 (CH), 127.6 (CH), 128.4 (CH), 128.5 (CH), 129.1 (CH), 130.0 (CH), 130.2 (CH), 130.3 (CH), 139.1 (C), 139.8 (CH), 143.0 (C), 144.9 (C), 146.3 (C), 163.2 (C); *m/z* (ESI): 431.0514 ([M-OTs]$^+$, $C_{21}H_{20}IO_2$ requires 431.0508, 100 %); m/z (ES$^-$): 171 (TsO^-, 100 %).



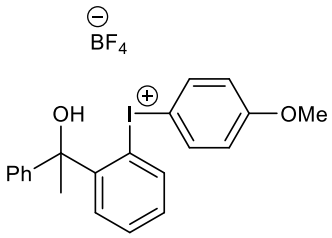
3.7

(2,4-Dimethoxyphenyl)(2-(1-hydroxy-1-phenylethyl) phenyl)iodonium-4-methylbenzene sulfonate **3.7** was obtained as a white solid which was dried *in vacuo* (0.38 g, 83 %). mp 183-185 ^{o}C. δ_H ($CDCl_3$, 400 MHz): 2.09 (3H, s, CH_3), 2.30 (3H, s, $ArCH_3$), 3.68 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.54-6.59 (2H, m, ArH), 6.81 (1H, dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 1.0, ArH), 7.06 (2H, d, $^3J_{HH}$ = 8.2, ArH), 7.14 (1H, t, $^3J_{HH}$ = 7.1, ArH), 7.27-7.36 (4H, m, ArH), 7.39 (1H, d, $^3J_{HH}$ = 7.5, ArH), 7.42-7.45 (2H, m, ArH), 7.66 (2H, d, $^3J_{HH}$ = 8.1, ArH), 7.82 (1H, d, $^3J_{HH}$ = 8.3, ArH); δ_C ($CDCl_3$, 125 MHz): 21.3 (CH_3), 29.7 (CH_3), 56.1 (CH_3), 56.7 (CH_3), 77.4 (C), 91.5 (C-I), 99.6 (CH), 108.8 (CH), 110.6 (C-I), 126.1 (CH), 126.4 (CH), 127.6 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 130.0 (CH), 130.2 (CH), 130.4 (CH), 139.2 (C), 140.8 (CH), 143.0 (C), 144.9 (C), 146.2 (C), 160.2 (C), 146.2 (C); m/z (ESI): 461.0613 ([M-OTs]$^+$, $C_{22}H_{22}IO_3$ requires 461.0614, 100 %); m/z (ES$^-$): 171 (TsO^-, 100 %).

5.4.8 General procedure for Scheme 3.3.

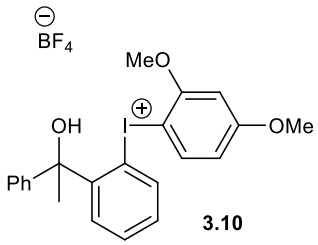
A solution of fluoroiodane **3.5** (0.36 g, 1.07 mmol) in dry MeCN (2 mL) was cooled to 0 ^{o}C before adding $BF_3.OEt_2$ (287 µl, 1.08 mmol). After 3 min., the substrate (0.72 mmol) was added to this solution at 0 ^{o}C. The reaction mixture was allowed to warm to room temperature and left to stir for 1 hour. After adding dichloromethane (10 mL), the organic phase was washed with water (3 x 5 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude oil. This crude product was washed with hexane (3 × 5 mL), and then stirred with diethyl ether three times (3 × 20 mL) for 30 minutes each to give pure product.

5.4.9 Characterisation data for the products in Scheme 3.3.



3.9

2-(1-Hydroxy-1-phenylethyl)phenyl)(4-methoxyphenyl) iodonium tetrafluoroborate **3.9** was obtained as an off white solid (0.33 g, 90 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from MeCN and hexane (1:3). mp 158-160 ^{o}C. δ_H (CD_3CN, 400 MHz): 2.08 (3H, s, CH_3), 3.93 (3H, s, OCH_3), 5.85 (1H, br, s, OH), 7.06 (1H, dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 0.9, ArH), 7.19 (2H, dd, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.9, ArH), 7.32 (1H, td, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.9, ArH), 7.40-7.45 (5H, m, ArH), 7.50-7.57 (2H, m, ArH), 7.88 (2H, dd, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 2.0, ArH); δ_C (CD_3CN, 125 MHz): 29.1 (CH_3), 55.5 (CH_3), 77.8 (C), 98.6 (C-I), 110.5 (C-I), 118.0 (CH), 125.9 (CH), 127.8 (CH), 128.3 (CH), 129.4 (CH), 130.2 (CH), 130.7 (CH), 130.8 (CH), 139.6 (CH), 144.1 (C), 145.0 (C), 163.6 (C); δ_F (CD_3CN, 376 MHz): -151.4 (s, BF_4); m/z (ESI^+): 431.0509 ($[M\text{-}BF_4]^+$, $C_{21}H_{20}IO_2$ requires 431.0508, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).



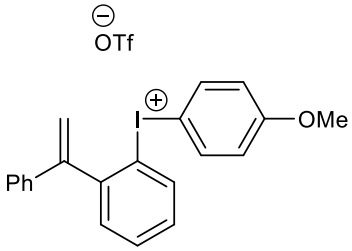
3.10

(2,4-Dimethoxyphenyl)(2-(1-hydroxy-1-phenylethyl) phenyl)iodonium tetrafluoroborate **3.10** was obtained as a brown solid (0.31 g, 68 %). mp 133-135 ^{o}C. δ_H ($CDCl_3$, 400 MHz): 2.08 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.14 (1H, br, s, OH), 6.62-6.66 (2H, m, ArH), 6.89 (1H, d, $^3J_{HH}$ = 8.1, ArH), 7.21 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.9, ArH), 7.27-7.36 (3H, m, ArH), 7.38-7.48 (4H, m, ArH), 7.79 (1H, dd, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.5, ArH); δ_C ($CDCl_3$, 125 MHz): 29.7 (CH_3), 56.2 (CH_3), 56.8 (CH_3), 77.8 (C), 89.5 (C-I), 99.9 (CH), 109.5 (CH), 110.3 (C-I), 126.3 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 130.4 (CH), 130.8 (CH), 130.9 (CH), 140.7 (CH), 143.9 (C), 145.4 (C), 160.4 (C), 166.8 (C); δ_F ($CDCl_3$, 376 MHz): -151.4 (s, BF_4); m/z (ES^+): 461.0614 ($[M\text{-}BF_4]^+$, $C_{22}H_{22}IO_3$ requires 461.0614, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).

5.4.10 General procedure for Table 3.3

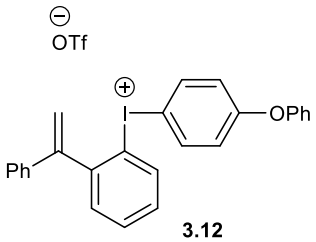
The substrate (0.72 mmol) was added to a solution of fluoroiodane **3.5** (0.36 g, 1.07 mmol) in dry MeCN (2 mL) in a Schlenk flask. The reaction mixture was cooled to 0 ^{o}C before adding triflic acid (200 µl, 2.16 mmol) and the reaction mixture was stirred for 2 h at 0 ^{o}C. DCM (10 mL) was added to the reaction mixture and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give the crude oil. This crude oil was washed with hot hexane (3 × 5 mL) and then stirred three times for 20 minutes each with Et_2O (3 × 20 mL) to give the pure product.

5.4.11 Characterisation data for the products in Table 3.3



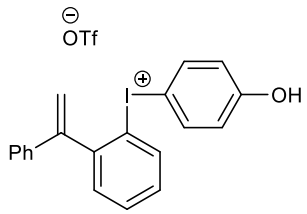
3.11

(4-Methoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium triflate **3.11** was obtained as an off white solid which was dried *in vacuo* (0.32 g, 79 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from chloroform and hexane (1:3). mp 126–128 ^{o}C. δ_H ($CDCl_3$, 400 MHz): 3.79 (3H, s, OCH_3), 5.43 (1H, s, C=CH), 6.06 (1H, s, C=CH), 6.81 (2H, dd, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 2.2, ArH), 7.17 (2H, td, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.7, ArH), 7.30-7.40 (4H, m, ArH), 7.48 (1H, dd, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.7, ArH), 7.57-7.64 (3H, m, ArH), 7.85 (1H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.1, ArH); δ_C ($CDCl_3$, 125 MHz): 55.7 (CH_3), 101.3 (C-I), 117.6 (C-I), 118.0 (CH), 119.6 ($=CH_2$), 120.4 (q, $^1J_{CF}$ = 322.0, CF_3), 127.2 (CH), 129.3 (CH), 129.4 (CH), 131.6 (CH), 132.1 (CH), 132.6 (CH), 135.1 (CH), 137.8 (CH), 144.8 (C), 148.4 (C), 148.4 (C), 163.1 (C); δ_F ($CDCl_3$, 376 MHz): -78.3 (s, CF_3); m/z (ESI^+): 413.0405 ($[M\text{-}TfO^-]^+$, $C_{21}H_{18}IO$ requires 413.0402, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).



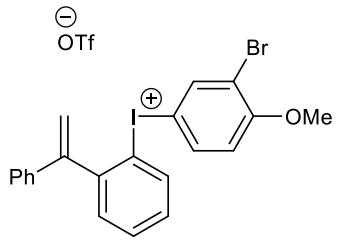
3.12

(4-Phenoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium triflate **3.12** was obtained as an off white solid (0.38 g, 85 %). mp 93-95 ^{o}C. δ_H ($CDCl_3$, 500 MHz): 5.44 (1H, s, C=CH), 6.06 (1H, s, C=CH), 6.83 (2H, d, $^3J_{HH}$ = 8.9, ArH), 7.02 (2H, dd, $^3J_{HH}$ = 8.7, $^4J_{HH}$ = 1.1, ArH), 7.16 (2H, dd, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.5, ArH), 7.23 (1H, t, $^3J_{HH}$ = 7.4, ArH), 7.32-7.36 (3H, m, ArH), 7.38-7.45 (3H, m, ArH), 7.51 (1H, dd, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.7, ArH), 7.57 (2H, d, $^3J_{HH}$ = 8.9, ArH), 7.63 (1H, t, $^3J_{HH}$ = 7.5, ArH), 7.99 (1H, d, $^3J_{HH}$ = 8.0, ArH); δ_C ($CDCl_3$, 125 MHz): 103.4 (C-I), 117.5 (C-I), 119.7 (CH_2), 120.2 (q, $^1J_{CF}$ = 320.5 Hz, CF_3), 120.5 (CH), 120.7 (CH), 125.5 (CH), 127.1 (CH), 129.3 (CH), 129.4 (CH), 130.3 (CH), 131.6 (CH), 132.1 (CH), 132.8 (CH), 135.5 (CH), 137.7 (CH), 137.8 (C), 145.0 (C), 148.4 (C), 154.4 (C), 161.9 (C); δ_F (376 MHz, $CDCl_3$): -78.3 (s, CF_3); m/z (ESI^+): 475.0557 ($[M\text{-}TfO^-]^+$, $C_{26}H_{20}IO$ requires 475.0559, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).



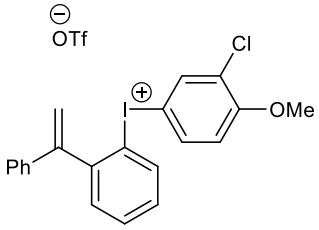
3.13

The final product was recrystallised from hot DCM to give (4-hydroxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium triflate **3.13** as a white solid (0.25 g, 63 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from CD_3CN and hexane (1:2). mp 150-152 ^oC. δ_H ($CDCl_3$, 400 MHz): 5.34 (1H, s, C=CH), 6.11 (1H, s, C=CH), 6.82 (2H, dd, $^3J_{HH}$ = 7.1, $^4J_{HH}$ = 2.2, ArH), 7.20-7.24 (2H, m, ArH), 7.34-7.42 (3H, m, ArH), 7.48-7.59 (4H, m, ArH), 7.75 (1H, td, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.2, ArH), 7.96 (1H, br, s, OH), 8.02 (1H, dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.1, ArH); δ_C ($CDCl_3$, 100 MHz): 100.2 (C-I), 117.7 (C-I), 119.9 (CH), 120.0 (CH_2), 120.2 (q, $^1J_{CF}$ = 316.5 Hz, CF_3), 127.7 (CH), 129.7 (CH), 129.7 (CH), 132.3 (CH), 132.9 (CH), 133.8 (CH), 136.4 (CH), 138.5 (CH), 138.6 (C), 145.4 (C), 149.0 (C), 161.9 (C); δ_F (376 MHz, $CDCl_3$): -78.3 (s, CF_3); m/z (ESI^+): 399.0250 ($[M\text{-}TfO^-]^+$, $C_{20}H_{16}IO$ requires 399.0246, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).



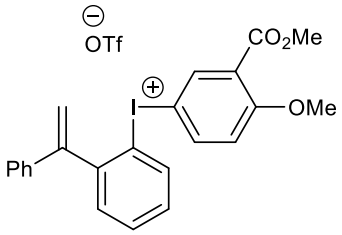
3.14

(3-Bromo-4-methoxyphenyl)(2-(1-phenylvinyl)phenyl) iodonium triflate **3.14** was obtained as a white solid (0.43 g, 93 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from DCM and hexane (1:2). mp 148-150 ^oC. δ_H ($CDCl_3$, 400 MHz): 3.87 (3H, s, OCH_3), 5.45 (1H, s, C=CH), 6.07 (1H, s, C=CH), 6.80 (1H, d, $^3J_{HH}$ = 8.8, ArH), 7.14 (2H, dd, $^3J_{HH}$ = 6.6, $^4J_{HH}$ = 1.4, ArH), 7.29-7.37 (3H, m, ArH), 7.43 (1H, td, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.9, ArH), 7.50 (1H, dd, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.8, ArH), 7.57 (1H, d, $^4J_{HH}$ = 2.3, ArH), 7.65 (1H, td, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.3, ArH), 7.74 (1H, dd, $^3J_{HH}$ = 8.8, $^4J_{HH}$ = 2.4, ArH), 7.98 (1H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.2, ArH); δ_C ($CDCl_3$, 100 MHz): 56.7 (CH_3), 101.2 (C-I), 114.4 (C-I), 114.6 (CH), 118.1 (C), 119.8 (CH_2) 120.5 (q, $^1J_{CF}$ = 320.0 Hz, CF_3), 127.0 (CH), 129.2 (CH), 129.4 (CH), 131.6 (CH), 132.1 (CH), 132.9 (CH), 136.0 (CH), 137.0 (CH), 137.8 (C), 139.2 (CH), 145.0 (C), 148.3 (C), 159.5 (C); δ_F (376 MHz, $CDCl_3$): -78.2 (s, CF_3); m/z (ESI^+): 490.9512 ($[M\text{-}OTf]^+$, $C_{21}H_{17}{}^{79}BrIO$ requires 490.9507, 100 %), m/z (ESI^+): 492.9494, $C_{21}H_{17}{}^{81}BrIO$ requires 492.9487, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).



3.15

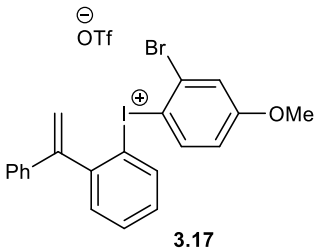
(3-Chloro-4-methoxyphenyl)(2-(1-phenylvinyl)phenyl) iodonium triflate **3.15** was obtained as a white solid (0.35 g, 80 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from $CDCl_3$ and hexane (1:2). mp 123-125 ^oC. δ_H ($CDCl_3$, 400 MHz): 3.89 (3H, s, OCH_3), 5.45 (1H, s, C=CH), 6.08 (1H, s, C=CH), 6.83 (1H, d, $^3J_{HH}$ = 8.9, ArH), 7.14 (2H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.4, ArH), 7.29-7.36 (3H, m, ArH), 7.40 (1H, d, $^4J_{HH}$ = 2.3, ArH), 7.43 (1H, td, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.7, ArH), 7.50 (1H, dd, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.8, ArH), 7.65 (1H, td, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.5, ArH), 7.69 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.2, ArH), 7.98 (1H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.2, ArH); δ_C ($CDCl_3$, 125 MHz): 56.6 (CH_3), 100.7 (C-I), 114.7 (CH), 118.0 (C-I), 119.8 (CH_2), 120.5 (q, $^1J_{CF}$ = 320.0 Hz, CF_3), 125.5 (C), 127.1 (CH), 129.2 (CH), 129.4 (CH), 131.6 (CH), 132.1 (CH), 132.9 (CH), 136.0 (CH), 136.4 (CH), 136.4 (CH), 137.8 (C), 145.0 (C), 148.2 (C), 158.6 (C); δ_F (376 MHz, $CDCl_3$): -78.3 (s, CF_3); m/z (ESI^+): 447.0011 ($[M\text{-}OTf]^+$, $C_{21}H_{17}{}^{35}ClIO$ requires 447.0013, 100 %); m/z (ESI^+): 448.9989 ($[M\text{-}OTf]^+$, $C_{21}H_{17}{}^{37}ClIO$ requires 448.9983); m/z (ES^-): 149 (TfO^-, 100 %).



3.16

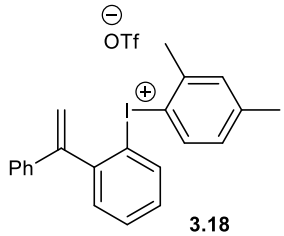
4-Methoxy-3-(methoxycarbonyl)phenyl)(2-(1-phenylvinyl) phenyl) iodonium triflate **3.16** was obtained as a white solid (0.40 g, 89 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from DCM and hexane (1:2). mp 140-142 ^oC. δ_H ($CDCl_3$, 500 MHz): 3.85 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.45 (1H, s, C=CH), 6.08 (1H, s, C=CH), 6.89 (1H, d, $^3J_{HH}$ = 8.7, ArH), 7.13 (2H, dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.4, ArH), 7.27-7.32 (3H, m, ArH), 7.43 (1H, td, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.6, ArH), 7.49 (1H, dd, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.8, ArH), 7.64 (1H, td, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.3, ArH), 7.85 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.7, ArH), 7.97 (1H, d, $^3J_{HH}$ = 8.3, ArH), 8.00 (1H, d, $^4J_{HH}$ = 2.6, ArH); δ_C ($CDCl_3$, 125 MHz): 52.6 (CH_3), 56.7 (CH_3), 100.1 (C-I), 115.6 (CH), 117.9 (C-I), 119.7 (CH_2), 120.5 (q, $^1J_{CF}$ = 321.0 Hz, CF_3), 123.2 (C), 127.0 (CH), 129.2 (CH), 129.3 (CH), 131.6 (CH), 132.2 (CH), 132.9 (CH), 135.8 (CH), 137.4 (C), 139.1 (CH), 141.4 (CH), 144.9 (C), 148.2 (C), 162.1 (C), 163.9 (C); δ_F (376 MHz, $CDCl_3$): -78.2 (s,

CF_3); m/z (ESI): 471.0457 ($[M\text{-}OTf]^+$, $C_{23}H_{20}IO_3$ requires 471.0457, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).



3.17

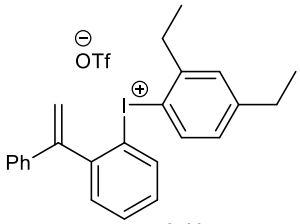
(2-Bromo-4-methoxyphenyl)(2-(1-phenylvinyl)phenyl) iodonium triflate **3.17** was obtained as a white solid (0.22 g, 48 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from DCM and hexane (1:3). mp 116-118 ^oC. δ_H ($CDCl_3$, 400 MHz): 3.81 (3H, s, OCH_3), 5.49 (1H, s, C=CH), 6.10 (1H, s, C=CH), 6.73 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.8, ArH), 7.15-7.21 (3H, m, ArH), 7.30-7.34 (3H, m, ArH), 7.42 (1H, td, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.9, ArH), 7.49 (1H, dd, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.9, ArH), 7.63 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2, ArH), 7.69 (1H, d, $^3J_{HH}$ = 8.9, ArH), 7.81 (1H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.1, ArH); δ_C ($CDCl_3$, 125 MHz): 56.2 (CH_3), 106.5 (C-I), 116.3 (CH), 118.4 (C-I), 119.5 (CH_2), 120.5 (q, $^1J_{CF}$ = 320.0 Hz, CF_3), 120.6 (CH), 127.1 (CH), 129.2 (CH), 129.3 (C), 129.4 (CH), 131.6 (CH), 132.2 (CH), 132.7 (CH), 134.9 (CH), 137.5 (C), 140.8 (CH), 144.7 (C), 148.5 (C), 163.91 (C); δ_F (376 MHz, $CDCl_3$): -78.2 (s, CF_3); m/z (ESI^+): 490.9512 ($[M\text{-}OTf]^+$, $C_{21}H_{17}{}^{79}BrIO$ requires 490.9507, 100 %), m/z (ESI^+): 492.9494, $C_{21}H_{17}{}^{81}BrIO$ requires 492.9487, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).



3.18

(2,4-Dimethylphenyl)(2-(1-phenylvinyl)phenyl)iodonium triflate **3.18** was obtained as a white solid (0.36 g, 89 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from $CDCl_3$ and hexane (1:2). mp 129-132 ^oC. δ_H ($CDCl_3$, 400 MHz): 2.27 (3H, s, $ArCH_3$), 2.31 (3H, s, $ArCH_3$), 5.37 (1H, s, C=CH), 6.00 (1H, s, C=CH), 6.89 (1H, d, $^3J_{HH}$ = 8.2, ArH), 7.08-7.15 (3H, m, ArH), 7.24-7.33 (4H, m, ArH), 7.43 (2H, t, $^3J_{HH}$ = 8.5, ArH), 7.53 (1H, t, $^3J_{HH}$ = 7.5, ArH), 7.64 (1H, d, $^3J_{HH}$ = 8.1, ArH); δ_C ($CDCl_3$, 125 MHz): 21.3 (CH_3), 25.3 (CH_3), 114.5 (C-I), 116.0 (C-I), 119.4 (CH_2), 120.3 (q, $^1J_{CF}$ = 321.0 Hz, CF_3), 127.1 (CH), 129.4 (CH), 129.6 (CH), 130.7 (CH), 131.7 (CH), 132.2 (CH), 132.3 (CH), 133.1 (CH), 133.2

(CH), 137.3 (C), 137.9 (CH), 141.5 (C), 144.5 (C) 145.0 (C), 148.7 (C); δ_F (376 MHz, $CDCl_3$): -78.2 (s, CF_3); m/z (ESI^+): 411.0612 ($[M\text{-}OTf]^+$, $C_{22}H_{20}I$ requires 411.0610, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).



3.19

(2,4-Diethylphenyl)(2-(1-phenylvinyl)phenyl)iodonium triflate **3.19** was obtained as an orange/yellow oil (0.38 g, 90 %). δ_H ($CDCl_3$, 400 MHz): 1.10 (3H, t, $^3J_{HH}$ = 7.7, CH_3), 1.24 (3H, t, $^3J_{HH}$ = 7.7, CH_3), 2.61-2.68 (4H, m, $2CH_2$), 5.47 (1H, s, C=CH), 6.10 (1H, s, C=CH), 7.03 (1H, dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.5, ArH), 7.19-7.23 (3H, m, ArH), 7.35-7.40 (4H, m, ArH), 7.46-7.52 (2H, m, ArH), 7.60 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2, ArH), 7.70 (1H, d, $^3J_{HH}$ = 8.5, ArH); δ_C ($CDCl_3$, 125 MHz): 14.7 (CH_3), 15.0 (CH_3), 28.6 (CH_2), 32.2 (CH_2), 114.3 (C-I), 116.3 (C-I), 119.5 (CH_2), 120.3 (q, $^1J_{CF}$ = 321.0 Hz, CF_3), 127.1 (CH), 127.1 (CH), 129.4 (CH), 129.7 (CH), 129.9 (CH), 130.4 (CH), 131.6 (CH), 132.2 (CH), 133.1 (CH), 136.3 (C), 138.4 (CH), 144.5 (C), 146.6 (C), 148.7 (C), 151.2 (C); δ_F (376 MHz, $CDCl_3$): -78.2 (s, CF_3); m/z (ESI^+): 439.0934 ($[M\text{-}OTf]^+$, $C_{24}H_{24}I$ requires 439.0923, 100 %); m/z (ES^-): 149 (TfO^-, 100 %).

5.4.12 General procedure for Table 3.5

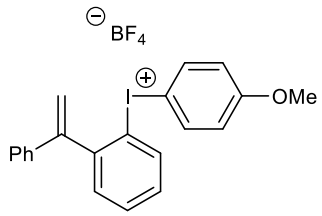
Entries 1-3: Substrate (0.72 mmol) was added to a solution of fluoroiodane **3.5** (0.36 g, 1.07 mmol) in dry MeCN (2 mL) in a Schlenk flask. The reaction mixture was cooled to 0 °C before the required amount of triflic acid was added and it was left to stir at the required time and temperature. DCM (10 mL) was added to the reaction mixture and it was washed with water (3 × 5 mL). The aqueous extracts were combined and extracted with dichloromethane (3 × 5 mL). The organic layers were combined and concentrated *in vacuo* to give the crude oil. This crude oil was washed with hot hexane (3 × 5 mL) and then stirred three times for 20 minutes each with Et_2O (3 × 20 mL) to give the final product which was analysed by ^1H and ^{19}F NMR spectroscopy.

Entries 4-9: The same general procedure for Table 3.3 were used (See section **5.3.10**).

5.4.13 General procedure for Scheme 3.6

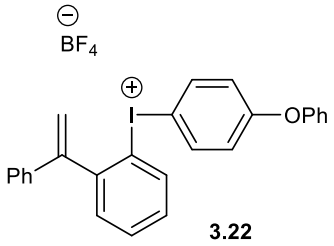
A one-necked 50 mL round bottomed flask was charged with the diaryliodonium triflate (1 mmol), DCM (10 mL) and a saturated aqueous solution of $NaBF_4$ (10 mL) and this mixture was stirred overnight at room temperature. After separating the organic phase, it was washed with water (3 x 5 mL) and the aqueous phase was extracted with DCM (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product which was stirred with diethyl ether (25 mL) for 1 hour leaving the pure product after decantation.

5.4.14 Characterisation data for the products in Scheme 3.6



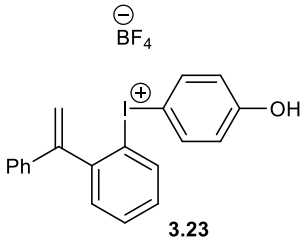
3.21

2-(1-Hydroxy-1-phenylethyl)phenyl)(4-methoxyphenyl) iodonium tetrafluoroborate **3.21** was obtained as an off white solid (0.47 g, 95 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from chloroform and hexane. mp 126-128 ^oC. δ_H ($CDCl_3$, 400 MHz): 3.78 (3H, s, OCH_3), 5.44 (1H, s, C=CH), 6.07 (1H, s, C=CH), 6.83 (2H, dd, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 2.2, ArH), 7.16-7.20 (2H, m, ArH), 7.31-7.36 (3H, m, ArH), 7.42 (1H, td, $^3J_{HH}$ = 7.4, $^4J_{HH}$= 1.9, ArH), 7.48 (1H, dd, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.8, ArH), 7.60-7.65 (3H, m, ArH), 7.85 (1H, dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 1.0, ArH); δ_C ($CDCl_3$, 125 MHz): 55.8 (CH_3), 99.8 (C-I), 116.9 (C-I), 118.2 (CH), 119.9 (CH_2), 127.2 (CH), 129.3 (CH), 129.4 (CH), 131.9 (CH), 132.1 (CH), 132.9 (CH), 135.1 (CH), 137.8 (C), 138.1 (CH), 144.7 (C), 148.5 (C), 163.3 (C); δ_F ($CDCl_3$, 376 MHz): -148.3 (s, BF_4); m/z (ESI^+): 413.0403 ($[M\text{-}BF_4^-]^+$, $C_{21}H_{18}IO$ requires 413.0402, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).



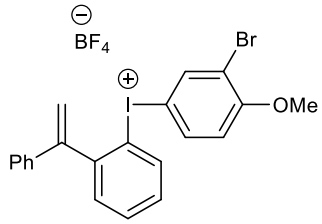
3.22

(4-Phenoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **3.22** was obtained as an off white solid (0.53 g, 94 %). mp 97-99 ^{o}C. δ_H ($CDCl_3$, 500 MHz): 5.44 (1H, s, C=CH), 6.07 (1H, s, C=CH), 6.83 (2H, dd, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 2.3, ArH), 7.01 (2H, dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 1.1, ArH), 7.16-7.20 (3H, m, ArH), 7.30-7.34 (3H, m, ArH), 7.37-7.43 (3H, m, ArH), 7.50 (1H, dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 2.0, ArH), 7.60 (2H, dd, $^3J_{HH}$ = 2.2, $^4J_{HH}$ = 7.1, ArH), 7.63 (1H, td, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.2, ArH), 7.99 (1H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.2, ArH); δ_C ($CDCl_3$, 125 MHz): 102.3 (C-I), 117.0 (C-I), 119.9 (CH_2), 120.5 (CH), 120.7 (CH), 125.5 (CH), 127.2 (CH), 129.3 (CH), 129.4 (CH), 130.3 (CH), 131.9 (CH), 132.1 (CH), 133.0 (CH), 135.7 (CH), 137.8 (C), 138.0 (CH), 145.0 (C), 148.4 (C), 154.3 (C), 162.0 (C); δ_F (376 MHz, $CDCl_3$): -148.5 (s, BF_4); m/z (ESI^+): 475.0559 ([M-BF_4^-]$^+$, $C_{26}H_{20}IO$ requires 475.0559, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).



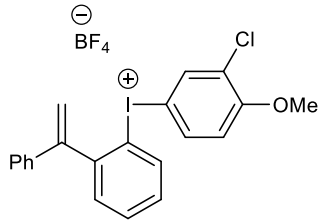
3.23

(4-Hydroxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **3.23** was obtained as a white solid (0.45 g, 93 %). mp 154-156 ^{o}C. δ_H ($CDCl_3$, 500 MHz): 5.34 (1H, s, C=CH), 6.11 (1H, s, C=CH), 6.82 (2H, d, $^3J_{HH}$ = 8.2, ArH), 7.22 (2H, d, $^3J_{HH}$ = 7.6, ArH), 7.32-7.43 (3H, m, ArH), 7.48-7.59 (4H, m, ArH), 7.74 (1H, td, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.2, ArH), 8.02 (1H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.1, ArH), 8.08 (1H, br, s, OH); δ_C ($CDCl_3$, 100 MHz): 100.2 (C-I), 117.7 (C-I), 120.0 (CH_2), 120.1 (CH), 127.7 (CH), 129.7 (CH), 129.7 (CH), 132.3 (CH), 133.0 (CH), 133.9 (CH), 136.3 (CH), 138.5 (CH), 138.6 (C), 145.4 (C), 149.0 (C), 161.8 (C); δ_F (376 MHz, $CDCl_3$): -151.2 (s, BF_4); m/z (ESI^+): 399.0255 ([M-BF_4^-]$^+$, $C_{20}H_{16}IO$ requires 399.0246, 100 %); m/z (ES^-): 87 (BF_4, 100 %).



3.24

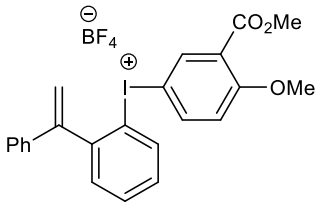
(3-Bromo-4-methoxyphenyl)(2-(1-phenylvinyl)phenyl) iodonium tetrafluoroburate **3.24** was obtained as a white solid (0.55 g, 96 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from $CDCl_3$ and hexane (1:2). mp 148-150 ^oC. δ_H ($CDCl_3$, 400 MHz): 3.87 (3H, s, OCH_3), 5.45 (1H, s, C=CH), 6.08 (1H, s, C=CH), 6.86 (1H, d, $^3J_{HH}$ = 8.8, ArH), 7.15 (2H, d, $^3J_{HH}$ = 6.9, ArH), 7.29-7.36 (3H, m, ArH), 7.43 (1H, td, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.5, ArH), 7.50 (1H, dd, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.4, ArH), 7.53 (1H, d, $^4J_{HH}$ = 2.2, ArH), 7.65 (1H, t, $^3J_{HH}$ = 7.4, ArH), 7.83 (1H, dd, $^3J_{HH}$ = 8.8, $^4J_{HH}$ = 2.0, ArH), 8.03 (1H, d, $^3J_{HH}$ = 8.2, ArH); δ_C ($CDCl_3$, 100 MHz): 56.8 (CH_3), 99.5 (C-I), 114.4 (C-I), 115.1 (CH), 117.2 (C), 119.9 (CH_2), 127.1 (CH), 129.3 (CH), 129.5 (CH), 132.0 (CH), 132.1 (CH), 133.2 (CH), 136.0 (CH), 137.5 (CH), 137.7 (C), 139.3 (CH), 145.0 (C), 148.3 (C), 159.8 (C); δ_F (376 MHz, $CDCl_3$): -147.3 (s, BF_4); m/z (ESI^+): 490.9514 ($[M\text{-}BF_4^-]^+$, $C_{21}H_{17}{}^{79}BrIO$ requires 490.9507, 100 %), m/z (ESI^+): ($[M\text{-}BF_4]^+$, 492.9497, $C_{21}H_{17}{}^{81}BrIO$ requires 492.9487, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).



3.25

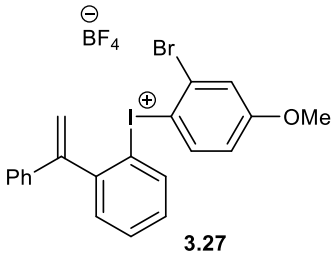
(3-Chloro-4-methoxyphenyl)(2-(1-phenylvinyl)phenyl) iodonium tetrafluoroburate **3.25** was obtained as a white solid (0.50 g, 93 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from $CDCl_3$ and hexane (1:2). mp 132-135 ^oC. δ_H ($CDCl_3$, 400 MHz): 3.87 (3H, s, OCH_3), 5.44 (1H, s, C=CH), 6.07 (1H, s, C=CH), 6.88 (1H, d, $^3J_{HH}$ = 9.0, ArH), 7.14 (2H, dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.6, ArH), 7.29-7.35 (3H, m, ArH), 7.36 (1H, d, $^4J_{HH}$ = 2.3, ArH), 7.43 (1H, td, $^3J_{HH}$ = 8.1, $^4J_{HH}$ = 2.2, ArH), 7.50 (1H, dd, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 2.0, ArH), 7.64 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.1, ArH), 7.77 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.5, ArH), 8.04 (1H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.2, ArH); δ_C ($CDCl_3$, 125 MHz): 56.6 (CH_3), 99.8 (C-I), 115.1 (CH), 117.7 (C-I), 119.9 (CH_2), 125.4 (C), 127.1 (CH), 129.2 (CH), 129.4 (CH), 131.9 (CH), 132.1 (CH), 133.1 (CH), 136.1 (CH), 136.4 (CH), 136.7 (CH), 137.8 (C), 145.0 (C), 148.3 (C), 158.8 (C); δ_F (376 MHz, $CDCl_3$): -147.5 (s, BF_4); m/z (ESI^+): 447.0013

([M-BF_4]$^+$, $C_{21}H_{17}{}^{35}ClIO$ requires 447.0013, 100 %); m/z (ESI^+): 448.9992 ([M-BF_4]$^+$, $C_{21}H_{17}{}^{37}ClIO$ requires 448.9983, 100 %); m/z (ES$^-$): 87 (BF_4^-, 100 %).



3.26

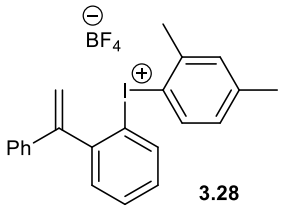
4-Methoxy-3-(methoxycarbonyl)phenyl)(2-(1-phenylvinyl) phenyl) iodonium tetrafluoroborate **3.26** was obtained as a white solid (0.53 g, 95 %). Crystals suitable for X-ray crystallography were grown by slow evaporation from $CDCl_3$ and hexane (1:2). mp 137-139 ^oC. δ_H (CD_3CN, 400 MHz): 3.82 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.34 (1H, s, C=CH), 6.12 (1H, s, C=CH), 7.02 (1H, d, $^3J_{HH}$ = 8.9, ArH), 7.13 (2H, dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.4, ArH), 7.28-7.35 (3H, m, ArH), 7.51-7.57 (2H, m, ArH), 7.74-7.79 (2H, m, ArH), 7.92 (1H, d, $^4J_{HH}$ = 2.5, ArH), 8.15 (1H, dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.0, ArH); δ_C (CD_3CN, 125 MHz): 57.4 (CH_3), 61.7 (CH_3), 105.6 (C-I), 121.6 (CH), 123.1 (C-I), 124.7 (CH_2), 128.9 (C), 132.3 (CH), 134.3 (CH), 134.4 (CH), 137.0 (CH), 137.8 (CH), 138.9 (CH), 141.9 (CH), 143.2 (C), 143.7 (CH), 145.9 (CH), 150.4 (C), 153.6 (C), 167.2 (C), 169.2 (C); δ_F (376 MHz, CD_3CN): -151.3 (s, BF_4); m/z (ESI^+): 471.0456 ([M-BF_4]$^+$, $C_{23}H_{20}IO_3$ requires 471.0457, 100 %); m/z (ES$^-$): 87 (BF_4^-, 100 %).



3.27

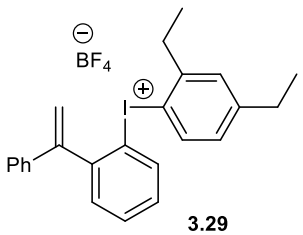
(2-Bromo-4-methoxyphenyl)(2-(1-phenylvinyl)phenyl) iodonium tetrafluoroburate **3.27** was obtained as a white solid (0.55 g, 96 %). mp 113-115 ^oC. δ_H ($CDCl_3$, 400 MHz): 3.73 (3H, s, OCH_3), 5.40 (1H, s, C=CH), 6.03 (1H, s, C=CH), 6.72 (1H, dd, $^3J_{HH}$ = 8.8, $^4J_{HH}$ = 2.6, ArH), 7.07-7.14 (3H, m, ArH), 7.21-7.26 (3H, m, ArH), 7.36-7.42 (2H, m, ArH), 7.57 (1H, t, $^3J_{HH}$ = 7.6, ArH), 7.70 (1H, d, $^3J_{HH}$ = 8.9, ArH), 7.74 (1H, d, $^3J_{HH}$ = 8.2, ArH); δ_C ($CDCl_3$, 125 MHz): 56.3 (CH_3), 105.4 (C-I), 116.5 (CH), 117.9 (C-I), 119.5 (CH_2), 120.5 (CH), 127.2 (CH), 129.2 (CH), 129.3 (C), 129.4 (CH), 131.9 (CH), 132.3 (CH), 132.8 (CH), 134.5 (CH), 137.4 (C), 141.2 (CH), 144.5 (C), 148.5 (C), 164.22 (C);

δ_F (376 MHz, $CDCl_3$): -151.5 (s, BF_4^-); m/z (ESI^+): 490.9514 ($[M\text{-}BF_4]^+$, $C_{21}H_{17}{}^{79}BrIO$ requires 490.9507, 100 %), m/z (ESI^+): 492.9497, $C_{21}H_{17}{}^{81}BrIO$ requires 492.9487, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).



3.28

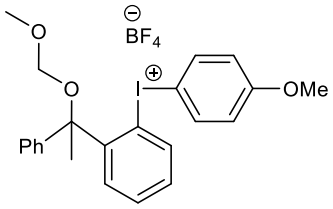
(2,4-Dimethylphenyl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **3.28** was obtained as a white solid (0.45 g, 90 %). mp 141-143 °C. δ_H ($CDCl_3$, 400 MHz): 2.35 (3H, s, $ArCH_3$), 2.38 (3H, s, $ArCH_3$), 5.46 (1H, s, C=CH), 6.10 (1H, s, C=CH), 6.98 (1H, d, $^3J_{HH}$ = 8.5, ArH), 7.16-7.22 (3H, m, ArH), 7.33-7.42 (4H, m, ArH), 7.54 (1H, d, $^3J_{HH}$ = 7.6, ArH), 7.57 (1H, d, $^3J_{HH}$ = 7.8, ArH), 7.62 (1H, t, $^3J_{HH}$ = 7.4, ArH), 7.75 (1H, d, $^3J_{HH}$ = 8.5, ArH); δ_C ($CDCl_3$, 125 MHz): 21.3 (CH_3), 25.3 (CH_3), 113.3 (C-I), 115.4 (C-I), 119.6 (CH_2), 127.1 (CH), 129.4 (CH), 129.6 (CH), 130.9 (CH), 131.9 (CH), 132.3 (CH), 132.5 (CH), 133.2 (CH), 133.4 (CH), 137.2 (C), 138.1 (CH), 141.7 (C), 144.7 (C) 145.3 (C), 148.7 (C); δ_F (376 MHz, $CDCl_3$): -148.8 (s, BF_4); m/z (ESI^+): 411.0610 ($[M\text{-}BF_4]^+$, $C_{22}H_{20}I$ requires 411.0610, 100 %); m/z (ES^-): 87 (BF_4, 100 %).



3.29

(2,4-Diethylphenyl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **3.29** was obtained as an orange/brown oil (0.49 g, 94 %). δ_H ($CDCl_3$, 400 MHz): 1.10 (3H, t, $^3J_{HH}$ = 7.7, CH_3), 1.24 (3H, t, $^3J_{HH}$ = 7.7, CH_3), 2.60-2.71 (4H, m, 2 CH_2), 5.49 (1H, s, C=CH), 6.11 (1H, s, C=CH), 7.05 (1H, dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.2, ArH), 7.19-7.23 (3H, m, ArH), 7.35-7.43 (4H, m, ArH), 7.50-7.56 (2H, m, ArH), 7.62 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.1, ArH), 7.80 (1H, d, $^3J_{HH}$ = 8.4, ArH); δ_C ($CDCl_3$, 100 MHz): 14.8 (CH_3), 14.9 (CH_3), 28.7 (CH_2), 32.2 (CH_2), 113.1 (C-I), 115.8 (C-I), 119.8 (CH_2), 127.1 (CH), 129.3 (CH), 129.7 (CH), 129.9 (CH), 130.6 (CH), 131.9 (CH), 132.3 (CH), 132.5 (CH), 133.4 (CH), 137.3 (C), 138.5 (CH), 144.6 (C), 146.9 (C), 148.7 (C), 151.4 (C); δ_F (376 MHz, $CDCl_3$): -150.5 (s, BF_4); m/z (ESI^+): 439.0926 ($[M\text{-}BF_4]^+$, $C_{24}H_{24}I$ requires 439.0923, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).

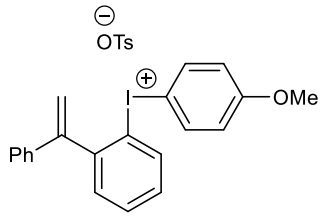
5.4.15 Preparation of (2-(1-(methoxymethoxy)-1-phenylethyl)phenyl)(4-methoxy phenyl)iodonium tetrafluoroborate 3.30



3.30

This procedure was based on that described by Desjardins.[134] A 100 mL oven-dried three-necked round bottomed flask equipped with a magnetic stir bar was evacuated and backfilled with nitrogen. This flask was charged with (2-(1-hydroxy-1-phenylethyl)phenyl)(4-methoxyphenyl) iodonium tetrafluoroborate **3.9** (1 g, 1.93 mmol) and dry MeCN (30 mL). This solution was cooled to 0 ^{o}C before *N*,*N*-diisopropylethylamine (DIPEA) (1.03 mL, 5.79 mmol) following by Chloromethyl methyl ether (MOMCl) (0.6 mL, 7.72 mmol) was added. The mixture was warmed to room temperature and it was stirred overnight. After that, the reaction mixture was washed with water (3 × 20 mL). The aqueous phase was combined and extracted with DCM (3 × 10 mL). The organic layers were combined and stirred with saturated aqueous solution of $NaBF_4$ (30 mL) overnight at room temperature. The aqueous phase was separated and extracted with DCM (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo* to give crude product as a brown oil. This oil was stirred with diethyl ether (1 × 25 mL) for 2 hours at 0 ^{o}C to give pure product as a brown solid (0.97 g, 90 %). mp 69-71 ^{o}C. δ_H ($CDCl_3$, 400 MHz): 2.01 (3H, s, CH_3), 3.53 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.90 (2H, m_{AB}, OCH_AH_B), 7.02 (3H, t, $^3J_{HH}$ = 8.7, ArH), 7.22 (2H, d, $^3J_{HH}$ = 7.5, ArH), 7.32-7.43 (6H, m, ArH), 7.85 (2H, d, $^3J_{HH}$ = 8.7, ArH); δ_C ($CDCl_3$, 125 MHz): 27.2 (CH_3), 55.9 (CH_3), 57.3 (CH_3), 83.6 (C), 92.4 (CH_2), 98.4 (C-I), 109.7 (C-I), 118.5 (CH), 127.3 (CH), 127.3 (CH), 129.7 (CH), 131.0 (CH), 131.3 (CH), 131.4 (CH), 140.0 (CH), 142.0 (C), 145.5 (C), 163.9 (C); δ_F ($CDCl_3$, 376 MHz): -150.3 (s, BF_4); m/z (ESI^+): 475.0782 ($[M\text{-}BF_4]^+$, $C_{23}H_{24}IO_3$ requires 475.0770, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).

5.4.16 (4-methoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium 4-methylbenzene sulfonate 3.31



3.31

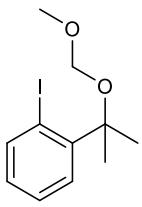
(4-methoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium triflate **3.11** (0.6 g, 1.07 mmol) was dissolved in DCM (15 mL) and it was stirred with an aqueous solution of $TsOH.H_2O$ (15 mL, 5.45 mmol) for 6 hours at room temperature. After that, the aqueous phase was separated and extracted with DCM (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product as a brown oil. This crude product was stirred with diethyl ether (25 mL) for 1 hour to give the pure product **3.31** as a light brown solid (0.55 g, 88 %). Crystals suitable for X-ray crystallography were grown by slow evaporation of a DCM : hexane (1:3) solution. mp 140-142 ^oC. δ_H ($CDCl_3$, 400 MHz): 2.31 (3H, s, $ArCH_3$), 3.78 (3H, s, OCH_3), 5.40 (1H, s, $C=CH_2$), 6.02 (1H, s, $C=CH_2$), 6.73 (2H, dd, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 2.1, ArH), 7.04 (2H, d, $^3J_{HH}$ = 7.0, ArH), 7.13 (2H, dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.3, ArH), 7.28-7.35 (4H, m, ArH), 7.43 (1H, dd, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.6, ArH), 7.40-7.66 (5H, m, ArH), 7.79 (1H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.1, ArH); δ_C ($CDCl_3$, 125 MHz): 21.3 (CH_3), 55.6 (CH_3), 103.7 (C-I), 117.4 (CH), 118.9 (C-I), 119.5 (CH_2), 126.0 (CH), 127.0 (CH), 128.4 (CH), 129.0 (CH), 129.1 (CH), 131.1 (CH), 131.7 (CH), 132.0 (CH), 135.4 (CH), 137.4 (CH), 138.0 (C), 139.2 (C), 142.9 (C), 144.9 (C), 148.3 (C), 162.4 (C); m/z (ESI^+): 413.0400 ($[M\text{-}OTs]^+$, $C_{21}H_{18}IO$ requires 413.0402, 100 %), m/z (ES^-): 149 (TsO^-, 100 %).

5.5 Experimental for Chapter 4

5.5.1 General procedure for Scheme 4.2

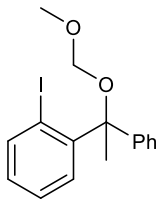
This procedure was based on that described by Desjardins.[134] A 100 mL oven-dried three-necked round bottomed flask equipped with a magnetic stirrer bar was evacuated and backfilled with nitrogen. The flask was charged with substrate (3.8 mmol) and dry dichloromethane (15 mL). The reaction mixture was cooled to 0 ^{o}C before adding Hunig's base (*N*,*N*-diisopropylethylamine, DIPEA) (2 mL, 11.4 mmol) and then chloromethyl methyl ether (MOMCl) (0.87 mL, 11.4 mmol). The mixture was warmed to room temperature and stirred overnight. After that, a saturated $NaHCO_3$ (20 mL) was added. The aqueous phase was separated and extracted with DCM (3 × 20 mL) and the combined organic layers were washed with brine (2 × 50 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give the pure product.

5.5.2 Characterisation data for the products in Scheme 4.2



4.2

The pure product 1-iodo-2-(2-(methoxymethoxy)propan-2-yl)benzene **4.2**, was obtained as a yellow oil (0.90 g, 77 %). δ_H ($CDCl_3$, 500 MHz): 1.75 (6H, s, $2CH_3$), 3.41 (3H, s, OCH_3), 4.58 (2H, s, OCH_2O), 6.90 (1H, td, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.3, ArH), 7.31 (1H, t, $^3J_{HH}$ = 7.3, ArH), 7.42 (1H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.1, ArH), 8.02 (1H, d, $^3J_{HH}$ = 7.9, ArH); δ_C ($CDCl_3$, 125 MHz): 28.3 (CH_3), 55.7 (CH_3) 78.9 (C), 92.7 (CH_2) 93.7 (C-I), 128.0 (CH), 128.1 (CH), 128.4 (CH), 143.4 (CH), 145.3 (C); m/z (FAB): 307 (MH^+, $C_{11}H_{16}IO_2$, 10 %).

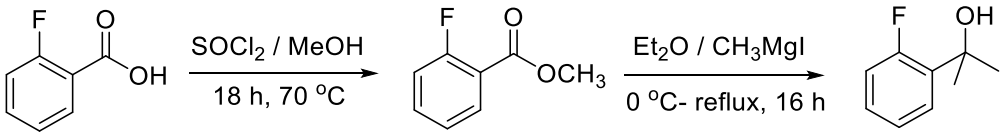


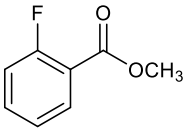
4.3

The pure product of 1-iodo-2-(1-(methoxymethoxy)-1-phenylethyl) benzene **4.3** was obtained as a colourless oil (1.12 g, 80 %). δ_H ($CDCl_3$, 400 MHz): 2.01 (3H, s, CH_3), 3.43 (3H, s, OCH_3), 4.55 (1H, d, $^2J_{HH}$ = 7.2, OCH_AH_BO), 4.63 (1H, d, $^2J_{HH}$ = 7.2, OCH_AH_BO), 6.90 (1H, td, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.8, ArH), 7.22-7.28 (5H, m, ArH), 7.40 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.5, ArH), 7.79 (1H, dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.7, ArH), 7.92 (1H, dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.5,

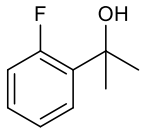
ArH); δ_C ($CDCl_3$, 125 MHz): 28.6 (CH_3), 55.9 (CH_3), 82.8 (C), 92.1 (CH_2), 96.9 (C-I), 126.8 (CH), 127.3 (CH), 127.6 (CH), 127.8 (CH), 129.1 (CH), 129.4 (CH), 143.0 (CH), 145.4 (C), 145.5 (C); m/z (GC-MS): 367.9505 (M^+, $C_{16}H_{17}IO_2$, 5 %), 352.9829 ([M-CH_3]$^+$, $C_{15}H_{14}IO_2$, 20 %).

5.5.3 Preparation of 2-(2-fluorophenyl) propan-2-ol.



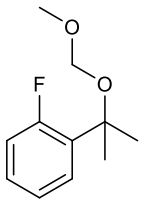


This procedure was based on that described by Hosangadi.[143] 2-Fluorobenzoic acid (6.0 g, 0.043 mol) was dissolved in methanol (50 mL) and cooled to 0 °C before thionyl chloride (4.7 mL, 0.064 mol) was added dropwise over 20 minutes. Then, the solution was heated to 70 °C for 18 hours. The solution was concentrated *in vacuo* to obtain a colourless oil and ethyl acetate (50 mL) was added. The organic phase was washed with brine solution (3 × 50 mL), separated and dried using $MgSO_4$. Concentration *in vacuo* gave the product methyl-2-fluorobenzoate as a colourless oil (6.09 g, 92 %). The characterisation data was agreement with that in the literature.[158] δ_H ($CDCl_3$, 400 MHz): 3.93 (3H, s, OCH_3), 7.10-7.22 (2H, m, ArH), 7.44-7.55 (1H, m, ArH), 7.93 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.9, ArH); $\delta_H\{^{19}F\}$ ($CDCl_3$, 400 MHz): 3.93 (3H, s, OCH_3), 7.13 (1H, d, $^3J_{HH}$ = 8.4, ArH), 7.20 (1H, td, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.1, ArH), 7.51 (1H, td, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.8, ArH), 7.93 (1H, dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.8, ArH); δ_F ($CDCl_3$, 376 MHz): -109.55 (s); δ_C ($CDCl_3$, 100 MHz): 52.7 (CH_3), 116.9 (d, $^2J_{CF}$ = 22.2, CH), 118.6 (d, $^2J_{CF}$ = 9.6, C), 123.9 (d, $^3J_{CF}$ = 3.3, CH), 132.1 (CH), 134.5 (d, $^3J_{CF}$ = 9.2, CH), 161.9 (d, $^1J_{CF}$ = 259.9, CF), 164.8 (d, $^3J_{CF}$ = 3.9, CO); m/z (ASAP): 155.0508 (MH^+, $C_8H_8FO_2$ requires 155.0508, 100 %).



This procedure was based on that described by Eisenberger.[119] Magnesium (1.41 g, 0.0582 mol) was placed into a 3 necked flask and dried under vacuum before dry diethyl ether (10 mL) was added. Methyl iodide (2.68 mL, 0.0426 mol) in dry diethyl ether (6 mL) was added drop-wise via the dropping funnel until reflux was observed. The solution was diluted with dry diethyl ether (5 mL) before the remaining methyl iodide was added dropwise over 15 min. The solution was cooled to room temperature before it was transferred to a new 3 necked flask using a transfer cannula needle and the unreacted magnesium was washed with dry diethyl ether (5 mL). The solution was cooled to 0 ^{o}C, then methyl-2-fluorobenzoate (3.00 g, 0.0194 mol) in dry diethyl ether (8 mL) was added via a dropping funnel over 20 min. After that, dry diethyl ether (5 mL) was added via the same dropping funnel. The solution was warmed to room temperature and stirred overnight. When the reaction was deemed to have finished, the reaction mixture was allowed to cool to room temperature. This solution was then poured slowly into an ice cold, saturated ammonium chloride solution (50 mL) before water (75 mL) was added and the reaction mixture stirred for 20 minutes. The solution was filtered through Celite, the organic phase was separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The organic layers were combined, dried over K_2CO_3 and concentrated *in vacuo* to give the crude product as pale yellow oil (2.19 g). The crude oil was purified using column chromatography (ethyl acetate**:**petroleum ether 40-60 ^{o}C = 1:9) to obtain 2-(2-fluorophenyl) propan-2-ol as a pale yellow oil (1.80 g, 61 %). δ_H ($CDCl_3$, 400 MHz): 1.63 (6H, s, CH_3), 2.30 (1H, br s, OH), 7.01 (1H, dd, $^3J_{HF}$ = 12.3, $^3J_{HH}$ = 8.1, ArH), 7.11 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.1, ArH), 7.19-7.25 (1H, m, ArH), 7.45 (1H, td, $^3J_{HH}$ = 8.1, $^4J_{HH}$ = 1.4, ArH); $\delta_H\{^{19}F\}$ ($CDCl_3$, 400 MHz): 1.63 (6H, s, CH_3), 2.30 (1H, br s, OH), 7.02 (1H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.1, ArH), 7.10 (1H, td, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.2, ArH), 7.22 (1H, td, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.8, ArH), 7.54 (1H, dd, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.8 ArH); δ_F ($CDCl_3$, 376 MHz): -113.43 (s); δ_C ($CDCl_3$, 100 MHz): 30.2 (CH_3), 71.6 (C), 116.0 (d, $^2J_{CF}$ = 22.3, CH), 124.0 (CH), 126.4 (d, $^3J_{CF}$ = 4.8, CH), 128.6 (d, $^3J_{CF}$ = 9.6, CH), 135.4 (d, $^2J_{CF}$ = 11.5, C), 160.0 (d, $^1J_{CF}$ = 244.6, CF); m/z (ASAP): 137.0762 ($[M\text{-}OH]^+$, $C_9H_{10}F$ requires 137.0767, 100 %).

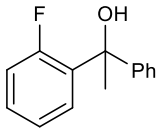
5.5.4 Preparation of 1-fluoro-2-(2-(methoxymethoxy)propan-2-yl)benzene 4.4



4.4

Following the general procedure for Scheme 4.2 (section 4.1), the pure product, 1-fluoro-2-(2-(methoxymethoxy)propan-2-yl)benzene **4.4** was obtained as a pale yellow oil (0.71 g, 94 %). δ_H ($CDCl_3$, 400 MHz): 1.67 (6H, s, CH_3), 3.40 (3H, s, OCH_3), 4.70 (2H, s, OCH_2O), 7.02 (1H, dd, $^3J_{HF}$ = 8.0, $^4J_{HH}$ = 1.3, ArH), 7.10 (1H, td, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.3, ArH), 7.24 (1H, td, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.7, ArH), 7.45 (1H, dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.8, ArH); $\delta_H\{^{19}F\}$ ($CDCl_3$, 400 MHz): 1.67 (6H, s, CH_3), 3.40 (3H, s, OCH_3), 4.70 (2H, s, OCH_3), 6.99-7.05 (1H, m, ArH), 7.10 (1H, td, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.3, ArH), 7.22-7.27 (1H, m, ArH), 7.45 (1H, td, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.6, ArH); δ_F ($CDCl_3$, 376 MHz): -111.3 (s); δ_C ($CDCl_3$, 125 MHz): 27.9 (d, $^4J_{CF}$ = 3.5, CH_3), 55.4 (CH_3), 61.3 (C), 92.1 (CH_2), 116.5 (d, $^2J_{CF}$ = 24.3, CH), 123.8 (d, $^4J_{CF}$ = 3.1, CH), 127.7 (d, $^3J_{CF}$ = 4.9, CH), 128.9 (d, $^3J_{CF}$ = 8.5, CH), 132.9 (d, $^2J_{CF}$ = 12.7, C), 160.0 (d, $^1J_{CF}$ = 250.0, CF); m/z (GC-MS): 183 ($[M\text{-}CH_3]^+$, $C_{10}H_{12}FO_2$, 100 %), 168 ([M-OCH_2], $C_{10}H_{13}FO$, 5 %).

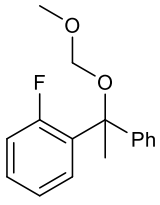
5.5.5 1-(2-Fluorophenyl)-1-phenylethan-1-ol



This procedure was based on that described by Eisenberger.[119] All glassware and the magnesium turnings were dried overnight in an oven prior to the experiment. A three-neck flask was equipped with an addition dropping funnel, condenser, N_2 supply, glass stopper, and a magnetic stirrer bar. After adding dried magnesium turnings (1.31 g, 0.054 mol) to the flask, the system was then evacuated and backfilled with N_2. After which, dry diethyl ether (10 mL) was added to the flask *via* syringe. Iodomethane (2.4 mL, 0.038 mol) was first added to the addition funnel, after which dry diethyl ether (10 mL) was squirted into the addition funnel, thoroughly mixing the solution. The iodomethane solution was added dropwise to the magnesium over 20 minutes and with vigorous stirring. When the addition was completed, the addition funnel was rinsed with dry diethyl ether (10 mL) and the rinsing solution added to the reaction mixture at once. The reaction mixture was transferred to the new three-neck flask *via* cannula, and the first reaction flask rinsed with dry diethyl ether (10 mL); the rinsing solution was also transferred to the new flask. The Grignard solution was cooled to 0 ºC with stirring before 2-fluorobenzophenone (3 g, 0.015 mol)

in dry diethyl ether (20 mL) was added dropwise via the dropping funnel over 15 minutes. After which, the reaction mixture was left stirring overnight at room temperature. The reaction mixture was then refluxed at 45 ºC for 5 hours, and then cooled to 0 ºC before a saturated solution of ammonium chloride (50 mL) was added to it 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 washed with diethyl ether (3 x 40 mL). The organic phases were combined, dried over magnesium sulphate and concentrated *in vacuo* to afford the pure product was obtained as a pale yellow oil (3.0 g, 92 %). The characterisation data was in agreement with the literature.[159] δ_H ($CDCl_3$, 400 MHz): 1.95 (3H, s, CH_3), 2.71 (1H, d, $^5J_{HF}$ = 5.8, OH), 6.94-7.00 (1H, m, ArH), 7.17 (1H, td, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.5, ArH), 7.21-7.32 (4H, m, ArH), 7.36 (2H, td, $^3J_{HH}$ =7.5, $^4J_{HH}$ =1.7 Hz, ArH) 7.61 (1H, td, $^3J_{HH}$ = 8.1, $^4J_{HH}$ = 1.8, ArH); $\delta_H\{^{19}F\}$ ($CDCl_3$, 400 MHz): 1.95 (3H, s, CH_3), 2.71 (1H, br s, OH), 6.97 (1H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.3 ArH), 7.17 (1H, td, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.3, ArH), 7.22-7.32 (4H, m, ArH), 7.36 (2H, td, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.7 Hz, ArH), 7.61 (1H, dd, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.8, ArH); δ_F ($CDCl_3$, 376 MHz): -112.1 (s); δ_C ($CDCl_3$, 125 MHz): 29.4 (CH_3), 75.1 (C), 116.2 (d, $^2J_{CF}$ = 21.4, CH), 123.9 (d, $^4J_{CF}$ = 3.5, CH), 125.2 (CH), 127.2 (CH), 127.4 (d, $^3J_{CF}$ = 3.8, CH), 128.2 (CH), 129.3 (d, $^3J_{CF}$ = 9.3, CH), 134.5 (d, $^2J_{CF}$ = 10.5, C), 147.4 (C), 160.2 (d, $^1J_{CF}$ = 246.5, CF); m/z (ASAP): 199.0928 ($[M\text{-}OH]^+$, $C_{14}H_{12}F$ requires 199.0923, 100 %).

5.5.6 Preparation of 1-fluoro-2-(1-(methoxymethoxy)-1-phenylethyl)benzene 4.5



4.5

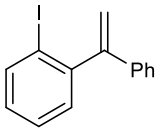
Following the general procedure for Scheme 4.2 (section 4.1), the pure product, 1-fluoro-2-(1-(methoxymethoxy)-1-phenylethyl)benzene **4.5** was obtained as an orange oil (0.92 g, 93 %). δ_H ($CDCl_3$, 400 MHz): 2.01 (3H, s, CH_3), 3.40 (3H, s, OCH_3), 4.60 (1H, d, $^2J_{HH}$ = 7.1, OCH_AH_BO), 4.64 (1H, d, $^2J_{HH}$ = 7.1, OCH_AH_BO), 6.88-6.95 (1H, m, ArH), 7.15 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3, ArH), 7.21-7.31 (4H, m, ArH), 7.35-7.39 (2H, m, ArH), 7.72 (1H, td, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.8, ArH); $\delta_H\{^{19}F\}$ ($CDCl_3$, 400 MHz): 2.01 (3H, s, CH_3), 3.40 (3H,

s, OCH_3), 4.60 (1H, d, $^2J_{HH}$ = 7.1, OCH_AH_BO), 4.64 (1H, d, $^2J_{HH}$ = 7.1, OCH_AH_BO), 6.91 (1H, dd, $^3J_{HH}$ = 6.8, $^4J_{HH}$ = 1.3, ArH), 7.15 (1H, td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3, ArH), 7.20-7.33 (4H, m, ArH), 7.35-7.39 (2H, m, ArH), 7.71 (1H, dd, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.8, ArH); δ_F ($CDCl_3$, 376 MHz): -110.3 (s); δ_C ($CDCl_3$, 125 MHz): 26.0 (d, $^4J_{CF}$ = 2.9, CH_3), 55.7 (CH_3), 79.6 (C), 91.9 (CH_2), 116.3 (d, $^2J_{CF}$ = 22.6, CH), 123.6 (d, $^4J_{CF}$ = 3.3, CH), 126.5 (CH), 127.1 (CH), 127.9 (CH), 128.2 (CH), 129.1 (d, $^3J_{CF}$ = 8.5, CH), 133.8 (d, $^2J_{CF}$ = 11.2, C), 145.2 (C), 159.9 (d, $^1J_{CF}$ = 250.0, CF); m/z (ASAP): 199.0928 ($[M-C_2H_5O_2]^+$, $C_{14}H_{12}F$ requires 199.0923, 100 %).

5.5.7 General procedure for Scheme 4.6

This procedure was based on that described by Takemiya.[160] Sodium *tert*-butoxide (1.62 g, 16.9 mmol) was added to a suspension of methyltriphenylphosphonium bromide (3.02 g, 8.45 mmol) stirring in dry THF (20 mL) at 0 °C under nitrogen. After stirring the mixture for 1 h at 0 °C, the substrate (6.50 mmol) was added at 0 °C. The mixture was allowed to warm to room temperature whilst stirring for 18 h. The reaction mixture was opened to the air and cooled to 0 °C before water (1 mL) was added very slowly. This solution was concentrated *in vacuo* before DCM (30 mL) was added. The reaction mixture was washed with water (30 mL) and the aqueous layer was extracted with DCM (2 × 20 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product as an orange oil. This crude oil was purified by column chromatography (petroleum ether 40-60 °C) to give the pure product.

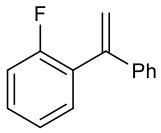
5.5.8 Characterisation data for the products in Scheme 4.6



3.20

The pure product 1-iodo-2-(1-phenylvinyl)benzene **3.20** was obtained as a yellow oil (1.50 g, 75 %). The characterisation data was in agreement with the literature.[161] δ_H ($CDCl_3$, 400 MHz): 5.16 (1H, s, $=CH_2$), 5.77 (1H, s, $=CH_2$), 7.18 (1H, td, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.5, ArH), 7.18-7.24 (6H, m, ArH), 7.32 (1H, t, $^3J_{HH}$ = 7.0, ArH), 7.81 (1H, d, $^3J_{HH}$ = 8.1, ArH); δ_C ($CDCl_3$, 125 MHz): 99.0 (C-I), 116.0 (CH_2), 126.9 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH), 129.0 (CH), 130.7

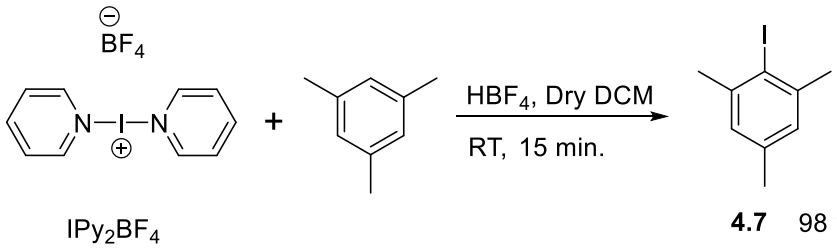
(CH), 139.2 (C), 139.5 (CH), 146.6 (C), 151.5 (C). m/z (ASAP): 307.0023 (MH^+, $C_{14}H_{12}I$ required 306.9984, 100 %).



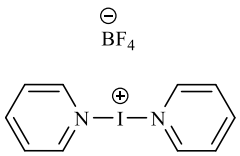
4.6

The pure product 1-fluoro-2-(1-phenylvinyl)benzene **4.6** was obtained as a colourless oil (0.81 g, 60 %). The characterisation data was in agreement with the literature.[162] δ_H ($CDCl_3$, 400 MHz): 5.42 (1H, s, $=CH_2$), 5.74 (1H, s, $=CH_2$), 7.06 (1H, td, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 1.1, ArH), 7.13 (1H, td, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.2, ArH), 7.25-7.33 (7H, m, ArH); $\delta_H\{^{19}F\}$ ($CDCl_3$, 400 MHz): 5.42 (1H, s, $=CH_2$), 5.74 (1H, s, $=CH_2$), 7.06 (1H, d, $^3J_{HH}$ = 8.3, ArH), 7.13 (1H, td, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.2 Hz, ArH), 7.25-7.33 (7H, m, ArH); δ_F ($CDCl_3$, 376 MHz): -113.2 (s); δ_C ($CDCl_3$, 125 MHz): 115.8 (d, $^2J_{CF}$ = 22.3, CH), 117.0 (CH_2), 123.9 (d, $^3J_{CF}$ = 4.0, CH), 126.8 (CH), 127.3 (CH), 128.3 (CH), 129.3 (d, $^2J_{CF}$ = 13.7, C), 129.4 (d, $^3J_{CF}$ = 8.4, CH), 131.5 (d, $^4J_{CF}$ = 3.3, CH), 140.6 (C), 144.2 (C), 160.1 (d, $^1J_{CF}$ = 250.0, C); m/z (ASAP): 199.0927 (MH^+, $C_{14}H_{12}F$ required 199.0923, 100 %).

5.5.9 Preparation of 2,4,6-trimethyliodobenzene.[163]

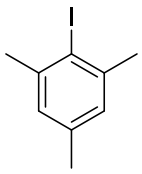


IPy_2BF_4 **4.7** 98 %



This procedure was based on that described by Chalker.[164] HBF_4 (6.5 mL, 50 mmol) was dissolved in deionized H_2O (50 mL) in a 500 mL round bottom flask. Ag_2CO_3 (6.89 g, 25.0 mmol) was added to the stirred solution in three portions as a solid. This mixture was stirred vigorously for 20 minutes. Silica gel (10.0 g) was added to the resulting solution. The slurry was stirred at room temperature for 10 minutes. After that, the stirrer bar was removed and the water was evaporated under reduced pressure (60 ºC, 10 mm Hg) to produce $AgBF_4$ on silica gel. The reaction mixture was cooled to room temperature before DCM (300 mL) was added and the mixture stirred for 10 minutes. After this time,

pyridine (9 mL, 111 mmol) and iodine (13.95 g, 55.0 mmol) were added sequentially to the reaction flask and AgI precipitated immediately. The reaction mixture was stirred vigorously at room temperature for 1 hour. After that, the solids (AgI and silica) were removed by filtration. The filter cake was washed thoroughly with DCM (100 mL) and the filtrate was concentrated under reduced pressure to give a red solid. This solid was dissolved in DCM and stirred at 0 ºC. Diethyl ether (200 mL) was poured into the stirred solution to precipitate the IPy_2BF_4. The crude product was isolated by filtration and dried under vacuum giving Barluenga's reagent as a yellow solid. The crude solid was recrystallized from DCM giving the pure product 2,2'-((tetrafluoro-λ^5-boraneyl)-λ^3-iodanediyl)dipyridine (IPy_2BF_4) as a pale yellow solid (9.0 g, 49 % yield). mp. 147-151 ºC (Lit:[164] 148-151 ºC). The characterisation data was in agreement with the literature.[164] δ_H (400 MHz, CD_3CN)= 7.65 (4H, t, $^3J_{HH}$ = 7.0, PyH), 8.28 (2H, tt, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.4, PyH), 8.81 (4H, d, $^3J_{HH}$ = 6.0, PyH); δ_C (125 MHz, CD_3CN): 127.5 (CH), 141.9 (CH), 149.3 (CH); δ_F (376 MHz, CD_3CN): -151.7 (s, BF_4^-); m/z (FAB): 285 (M^+, $C_{10}H_{10}IN_2$, 100 %); m/z (ES^-): 87 (BF_4^-, 100 %).



4.7

This procedure was based on that described by Barluenga.[163] IPy_2BF_4 (1.86 g, 5 mmol) was dissolved in dry DCM (50 mL) in a dry 3 neck flask under nitrogen. Mesitylene (0.64 mL, 4.5 mmol) was added to the reaction mixture by syringe. After that, a solution of HBF_4 (1.48 mL, 10 mmol) was added dropwise over 3 min. and the reaction mixture was left to react over 15 min at room temperature. This solution was then treated with aqueous sodium thiosulfate (50 mL, 10 % solution). The aqueous layer was separated and extracted with DCM (3 x 25 mL). The organic layers were combined, washed with brine (2 x 25 mL), dried over Na_2SO_4 and concentrated *in vacuo* at room temperature to give the product **4.7** as a pale yellow crystalline solid (1.09, 98 %). mp. 30-32 ºC (Lit:[165] 29-30 ºC). The characterisation data was in agreement with the literature.[166] δ_H ($CDCl_3$, 400 MHz): 2.15 (3H, s, $ArCH_3$), 2.35 (6H, s, $2ArCH_3$), 6.80 (2H, s, ArH); δ_C ($CDCl_3$, 125 MHz): 20.6 (CH_3), 29.5 (CH_3), 104.3 (C-I), 127.9 (CH), 137.3 (C), 141.7 (C); m/z (ASAP): 245.9911 (M^+, $C_9H_{11}I$ requires 245.9906, 100 %).

5.5.10 Plotting calibration curves for products by GC

To determine the yield of each component in the reaction mixture, it was important to confirm that the area of each of the corresponding peaks were changing linearly with the change of concentration of each compound. A series of samples were prepared from each component (**4.2** to **4.7** and **3.20**) (0.4 mmol) with 3-nitro-1-fluorobenzene (0.4 mmol) as the internal standard in a 10 mL volumetric flask and dissolved in DMF. Samples of that mixture (2 and 5 mL) were transferred to another flask and diluted to 10 mL in order to prepare samples 4 and 2. A further sample (5 mL) was taken from samples 2 and 4 and were diluted with DMF to 10 mL. A series of different concentrations (0.4 - 0.005 mmol) were prepared by repeating this procedure several times. Each sample was analysed three times by GC. The graphs for each component were plotted by drawing the number of equivalents (1 equivalent = 0.1 mmol) against the area for each concentration. R^2 values and the linear equations were displayed for each component against 3-nitro-1-fluorobenzene (see Appendix II).

5.5.11 General procedure for Tables 4.1 to 4.5

In a glove box, the diaryliodonium tetrafluoroborate salt (0.3 mmol) with the desired amount of potassium fluoride, 18-crown-6, and tetrakis(acetonitrile) copper(I) tetrafluoroborate ($[Cu(MeCN)_4]BF_4$) were weighed into the Schlenk flask. The flask was then charged with dry DMF (5 mL) via syringe, and heated to the required temperature for the required amount of time (see Tables 4.1 to 4.5 for reagent amounts, temperature and timings of each fluorination). After cooling to room temperature, 1-fluoro-3-nitrobenzene (16.5 µl, 0.15 mmol, 0.5 equiv) was added as an internal standard. DMF (5 mL) was added before filtering the mixture through silica and cotton wool and analysing via GC, ^{19}F NMR spectroscopy and GC-MS to give the yields of each product.

5.5.12 General procedure for Table 4.6

In a glove box, **3.21** (150 mg, 0.3 mmol), KF (19.0 mg, 0.33 mmol), 18-crown-6 (31.4 mg, 0.12 mmol), and the copper catalyst (0.06 mmol) were weighed into the Schlenk flask. The flask was then charged with dry DMF (5 mL) via syringe and the reaction

mixture was reacted at 80 °C for 18 h. After cooling to room temperature, 1-fluoro-3-nitrobenzene (16.5 µl, 0.15 mmol, 0.5 equiv) was added as the internal standard. DMF (5 mL) was added before filtering the mixture through silica and cotton wool and analysing via GC, ^{19}F NMR spectroscopy and GC-MS to give the yields of each product.

5.5.13 General procedure for Table 4.7

In a glove box, **3.21** (150 mg, 0.3 mmol), KF (19.0 mg, 0.33 mmol), 18-crown-6 (31.4 mg, 0.12 mmol), and $Cu(OTf)_2$ (21.7 mg, 0.06 mmol) were weighed into the Schlenk flask. The flask was then charged with the desired dry solvent (5 mL) via syringe and the reaction mixture was reacted at 80 °C for 18 h. After cooling to room temperature, 1-fluoro-3-nitrobenzene (16.5 µl, 0.15 mmol, 0.5 equiv) was added as the internal standard. Solvent (5 mL) was added before filtering the mixture through silica and cotton wool and analysing via GC, ^{19}F NMR spectroscopy and GC-MS to give the yields of each product.

5.5.14 General procedure for Table 4.8

In a glove box, **3.21** (150 mg, 0.3 mmol), the desired fluorinating reagent (0.33 mmol), 18-crown-6 (31.4 mg, 0.12 mmol) and $Cu(OTf)_2$ (21.7 mg, 0.06 mmol) were weighed into the Schlenk flask. The flask was then charged with dry DMF (5 mL) via syringe and the reaction mixture was reacted at 80 °C for 18 h. After cooling to room temperature, 1-fluoro-3-nitrobenzene (16.5 µl, 0.15 mmol, 0.5 equiv) was added as the internal standard. DMF (5 mL) was added before filtering the mixture through silica and cotton wool and analysing via GC, ^{19}F NMR spectroscopy and GC-MS to give the yields of each product.

5.5.15 General procedure for Table 4.9

In a glove box, **3.21** (0.3 mmol), KF (19.0 mg, 0.33 mmol), 18-crown-6 (31.4 mg, 0.12 mmol) with the desired amount of $Cu(OTf)_2$ were weighed into the Schlenk flask. The flask was then charged with dry DMF (5 mL) via syringe and heated at the required temperature for the required amount of time (see Table 4.9 for temperature and timings of each reaction). After cooling to room temperature, 1-fluoro-3-nitrobenzene (16.5 µl,

0.15 mmol, 0.5 equiv) was added as the internal standard. DMF (5 mL) was added before filtering the mixture through silica and cotton wool. The final product was analysed via GC, ^{19}F NMR spectroscopy and GC-MS to give the yields of each product.

5.5.16 General procedure for Table 4.10

In a glove box, the diaryliodonium salt (0.3 mmol), KF (19.0 mg, 0.33 mmol), 18-crown-6 (31.4 mg, 0.12 mmol) and $Cu(OTf)_2$ (21.7 mg, 0.06 mmol) were weighed into the Schlenk flask. The flask was then charged with dry DMF (5 mL) via syringe and heated at the required temperature for the required amount of time (see Table 4.10 for temperature and timings of each reaction). After cooling to room temperature, 1-fluoro-3-nitrobenzene (16.5 µl, 0.15 mmol, 0.5 equiv) was added as the internal standard. DMF (5 mL) was added before filtering the mixture through silica and cotton wool. The final product was analysed by GC, ^{19}F NMR spectroscopy and GC-MS to give the yields of each product.

5.5.17 General procedure for Table 4.11

In a glove box, the diaryliodonium salt (0.3 mmol), KF (19.0 mg, 0.33 mmol), 18-crown-6 (31.4 mg, 0.12 mmol) and $Cu(OTf)_2$ (21.7 mg, 0.06 mmol) were weighed into the Schlenk flask. The flask was then charged with dry DMF (5 mL) via syringe and heated at the required temperature for the required amount of time (see Table 4.11 for temperature and timings of each reaction). After cooling to room temperature, 1-fluoro-3-nitrobenzene (16.5 µl, 0.15 mmol, 0.5 equiv) was added as the internal standard. DMF (5 mL) was added before filtering the mixture through silica and cotton wool. The final product was analysed by ^{19}F NMR spectroscopy and GC-MS to give the yield of each product.

5.5.18 General procedure for Table 4.12

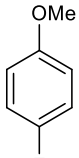
General procedure A: Cu-catalyzed reaction

In a glove box, the diaryliodonium salt (0.3 mmol), KF (19.0 mg, 0.33 mmol), 18-crown-6 (31.4 mg, 0.12 mmol) and $Cu(OTf)_2$ (21.7 mg, 0.06 mmol) were weighed into the Schlenk flask. The flask was then charged with dry DMF (5 mL) via syringe and heated at 80 °C for 4 h. After cooling to room temperature, 1-fluoro-3-nitrobenzene (16.5 µl, 0.15 mmol, 0.5 equiv) was added as the internal standard. DMF (5 mL) was added before filtering the mixture through silica and cotton wool. The final product was analysed by ^{19}F NMR spectroscopy and GC-MS.

General procedure B: non-catalysed (Cu-free) reaction.

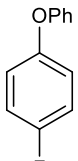
The reactions were conducted using an identical procedure to General Procedure A, but in the absence of $Cu(OTf)_2$.

5.5.19 Characterisation data for the products in Table 4.12



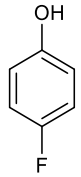
1.100

General procedure **A** was followed using (4-methoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **3.21** (150 mg, 0.3 mmol). 4-Fluoroanisole **1.100** was formed in 65 % yield as a 92:8 mixture of **1.100**:**4.6** as determined by ^{19}F NMR spectroscopy and GC analysis of the crude reaction mixture. The ^{19}F NMR data was in agreement with the literature (δ_F = -125.5 ppm).[167] GC-MS: m/z 126.1687 (M^+, C_7H_7FO, 90 %), m/z 111.1844 ($[M\text{-}CH_3]^+$, C_6H_4FO, 100 %); m/z (ASAP): 127.0557 (MH^+, C_7H_8FO requires 127.0559, 50 %).



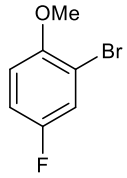
4.8

General procedure **A** was followed using (4-phenoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **3.22** (168 mg, 0.3 mmol). 1-Fluoro-4-phenoxybenzene **4.8** was formed in 61 % yield as a 91:9 mixture of **4.8**:**4.6** as determined by ^{19}F NMR spectroscopy of the crude reaction mixture. The ^{19}F NMR data was in agreement with the literature (δ_F = -120.5 ppm).[167] GC-MS: m/z 188 (M^+, $C_{12}H_9FO$, 100 %), m/z 170 ($[MH\text{-}F]^+$, $C_{12}H_{10}O$, 10 %).



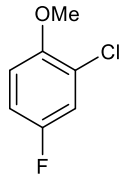
4.10

General procedure **A** was followed using (4-hydroxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **3.23** (146 mg, 0.3 mmol). 4-Fluorophenol **4.10** was formed in 20 % yield. The ^{19}F NMR spectrum was in agreement with the literature (δ_F = -127.2 ppm).[168,169] GC-MS: m/z 112.1605 (M^+, C_6H_5FO required 112.0324, 100 %).



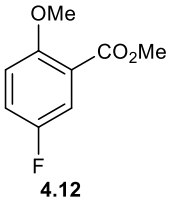
4.9

General procedure **A** was followed using (3-bromo-4-methoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **3.24** (173 mg, 0.3 mmol). 2-Bromo-4-fluoro-1-methoxybenzene **4.9** was formed in 87 % yield as a 94:6 mixture of **4.9**:**4.6** as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. The ^{19}F NMR spectrum was in agreement with the literature (δ_F = -123.0 ppm).[170] GC-MS: m/z 203.9567 (MH^+, $C_7H_6F^{79}BrO$ required 203.9586, 90 %); m/z 188.9389 ($[M\text{-}CH_3]^+$, $C_6H_3F^{79}BrO$, 80 %); GC-MS: m/z 205.9727 (MH^+, $C_7H_6F^{81}BrO$ required 205.9566, 90 %); m/z 190.9722 ($[M\text{-}CH_3]^+$, $C_6H_3F^{81}BrO$, 90 %); m/z (ASAP): 203.9582 (MH^+, $C_7H_7F^{79}BrO$ required 203.9586, 100 %); (ASAP): 205.9572 (MH^+, $C_7H_7F^{81}BrO$ required 205.9566, 100 %).



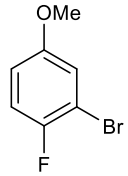
4.11

General procedure **A** was followed using (3-chloro-4-methoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **3.25** (160 mg, 0.3 mmol, 1.0 equiv). 2-Chloro-4-fluoro-1-methoxybenzene **4.11** was formed in 66 % yield as a 90:10 mixture of **4.11**:**4.6** as determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture. The ^{19}F NMR spectrum **4.11** matched that of an authentic sample (Apollo scientific, δ_F = -120.5 ppm). GC-MS: m/z 160 (M^+, $C_7H_6{}^{35}ClFO$, 90 %), m/z 145 ($[M\text{-}CH_3]^+$, $C_6H_3{}^{35}ClFO$, 90 %); GC-MS: m/z 162 (M^+, $C_7H_6{}^{37}ClFO$, 90 %), m/z 147 ($[M\text{-}CH_3]^+$, $C_6H_3{}^{37}ClFO$, 90 %); (ASAP): 160.0092 (M^+, $C_7H_6{}^{35}ClFO$ required 160.0091, 90 %); m/z (ASAP): 162.0067 (M^+, $C_7H_6{}^{37}ClFO$ required 162.0062, 40 %).



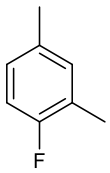
4.12

General procedure **A** was followed using (4-methoxy-3-(methoxycarbonyl)phenyl)(2-(1-phenylvinyl)phenyl) iodonium tetrafluoroborate **3.26** (167 mg, 0.3 mmol). Methyl 5-fluoro-2-methoxybenzoate **4.12** was formed in 82 % yield as a 92:8 mixture of **4.12**:**4.6** as determined by ^{19}F NMR spectroscopy of the crude reaction mixture. The ^{19}F NMR spectrum was in agreement with the literature (δ_F = -124.6 ppm).[171] δ_H ($CDCl_3$, 400 MHz): 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.92 (1H, dd, $^3J_{HF}$ = 8.4, $^4J_{HF}$ = 2.6, ArH), 7.15-7.20 (1H, m, ArH), 6.92 (1H, dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.6, ArH); GC-MS: m/z 184 (M^+, $C_9H_9FO_3$, 60 %), m/z 169 ($[M\text{-}CH_3]^+$, $C_8H_6FO_3$, 10 %); m/z (ASAP): 185.0621 (MH^+, $C_9H_{10}FO_3$ requires 185.0614, 10 %).



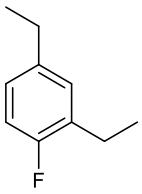
4.14

General procedure **A** was followed using (2-bromo-4-methoxyphenyl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **3.27** (173 mg, 0.3 mmol). 2-Bromo-1-fluoro-4-methoxybenzene **4.14** was formed in 17 % yield as a 44:56 mixture of **4.14**:**4.6** as determined by ^{19}F NMR spectroscopy of the crude reaction mixture. The ^{19}F NMR spectrum **4.14** matched that of an authentic sample (Fluorochem, δ_F = -120.3 ppm). GC-MS: m/z 203.8872 (M^+, $C_7H_6F^{79}BrO$ required 203.9586, 90 %); m/z 188.8694 ($[M\text{-}CH_3]^+$, $C_6H_3F^{79}BrO$, 80 %); GC-MS: m/z 205.8891 (M^+, $C_7H_6F^{81}BrO$ required 205.9566, 90 %); m/z 190.8726 ($[M\text{-}CH_3]^+$, $C_6H_3F^{81}BrO$, 50 %); m/z (ASAP): 203.9582 (M^+, $C_7H_6F^{79}BrO$ required 203.9586, 100 %); (ASAP): 205.9575 (MH^+, $C_7H_6F^{81}BrO$ required 205.9566, 100 %).



4.15

General procedure **A** was followed using (2,4-dimethylphenyl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **3.28** (149 mg, 0.3 mmol). 1-Fluoro-2,4-dimethylbenzene **4.15** was formed in 63 % yield as a 75:25 mixture of **4.15**:**4.6** as determined by ^{19}F NMR spectroscopy of the crude reaction mixture. The ^{19}F NMR spectrum was in agreement with the literature (δ_F = -123.7 ppm).[172] GC-MS: m/z 124 (M^+, C_8H_9F, 40 %), m/z 110 ($[M\text{-}CH_2]^+$, C_7H_7F, 100 %).



4.16

General procedure **A** was followed using (2,4-diethylphenyl)(2-(1-phenylvinyl)phenyl)iodonium tetrafluoroborate **3.29** (158 mg, 0.3 mmol, 1.0 equiv). 2,4-Diethyl-1-fluorobenzene **4.16** was formed in 23 % yield as a 47:53 mixture of **4.16**:**4.6** as determined by ^{19}F NMR spectroscopy of the crude reaction mixture. The ^{19}F NMR spectrum was δ_F = -125.2 ppm. GC-MS: m/z 152.2104 (M^+, $C_{10}H_{13}F$ required 152.1001, 40 %), m/z 137.1736 ($[M\text{-}CH_3]^+$, $C_9H_{10}F$, 100 %).

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Appendix I

Crystal Data and Structure Refinements

Table A1: Crystal Data and Structure Refinement for 1.85, 2.7 and 2.8

	1.85		**2.7**		**2.8**	
Identification code	16030		16077		16135	
Empirical formula	$C_{23}H_{25}IO_5S$		$C_{48}H_{57}I_2O_{13.50}S2$		$C_{24}H_{27}IO_6S$	
Formula weight	540.39		1167.86		570.42	
Temperature	150(2) K		150(2) K		150(2) K	
Wavelength	0.71073 Å		0.71073 Å		0.71073 Å	
Crystal system	Triclinic		Triclinic		Monoclinic	
Space group	P-1		P-1		P2(1)/c	
Unit cell dimensions	a = 10.782(3) Å	α= 73.338(5)°.	a = 8.3441(18) Å	α= 80.932(4)°.	a = 14.754(3) Å	α= 90°.
	b = 13.629(4) Å	β= 87.133(5)°.	b = 9.936(2) Å	β= 84.657(4)°.	b = 7.9554(14) Å	β= 108.842(3)°.
	c = 16.183(5) Å	γ = 78.761(5)°.	c = 15.220(3) Å	γ= 89.566(4)°.	c = 21.528(4) Å	γ = 90°.
Volume	2234.4(12) $Å^3$		1240.6(4) $Å^3$		2391.3(7) $Å^3$	
Z	4		1		4	
Density (calculated)	1.606 Mg/m^3		1.563 Mg/m^3		1.584 Mg/m^3	
Absorption coefficient	1.558 mm^{-1}		1.415 mm^{-1}		1.464 mm^{-1}	
F(000)	1088		591		1152	
Crystal size	0.37 x 0.30 x 0.14 mm^3		0.32 x 0.11 x 0.06 mm^3		0.26 x 0.15 x 0.10 mm^3	
Theta range for data collection	1.31 to 26.00°.		1.36 to 26.00°.		1.46 to 27.00°.	
Index ranges	-13<=h<=13, -16<=k<=16, -19<=l<=19		-10<=h<=10, -12<=k<=12, -18<=l<=18		-18<=h<=18, -10<=k<=10, -27<=l<=27	
Reflections collected	17039		9687		19198	
Independent reflections	8514 [R(int) = 0.0467]		4785 [R(int) = 0.0547]		5208 [R(int) = 0.0437]	
Completeness to theta = 26.00°	96.8 %		98.1 %		99.9 %	
Absorption correction	Empirical		Empirical		Empirical	
Max. and min. transmission	0.894 and 0.572		0.928 and 0.704		0.894 and 0.690	
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	
Data / restraints / parameters	8514 / 0 / 551		4785 / 3 / 304		5208 / 0 / 294	
Goodness-of-fit on F^2	0.936		1.029		1.017	
Final R indices [I>2sigma(I)]	R1 = 0.0359, wR2 = 0.0695		R1 = 0.0473, wR2 = 0.1040		R1 = 0.0348, wR2 = 0.0861	
R indices (all data)	R1 = 0.0472, wR2 = 0.0723		R1 = 0.0623, wR2 = 0.1109		R1 = 0.0425, wR2 = 0.0884	
Largest diff. peak and hole	0.717 and -0.722 e.$Å^{-3}$		1.356 and -0.689 e.$Å^{-3}$		1.918 and -0.635 e.$Å^{-3}$	

Table A2: Crystal Data and Structure Refinement for 2.9, 2.11 and 2.15

	2.9		**2.11**		**2.15**	
Identification code	17124		16065		16032	
Empirical formula	$C_{25}H_{29}IO_7S$		$C_{16}H_{15}IO_3S$		$C_{17}H_{18}F_3IO_5S$	
Formula weight	600.44		414.24		518.27	
Temperature	150(2) K		150(2) K		150(2) K	
Wavelength	0.71073 Å		0.71073 Å		0.71073 Å	
Crystal system	Triclinic		Monoclinic		Monoclinic	
Space group	P-1		P2(1)/n		P2(1)/n	
Unit cell dimensions	a = 8.0439(16) Å	α= 91.045(3)°.	a = 8.167(3) Å	α= 90°.	a = 12.109(3) Å	α= 90°.
	b = 12.578(3) Å	β= 91.611(3)°.	b = 8.283(3) Å	β= 94.906(6)°.	b = 10.597(2) Å	β= 99.901(4)°.
	c = 12.949(3) Å	γ = 106.734(3)°.	c = 23.791(8) Å	γ = 90°.	c = 15.583(3) Å	γ = 90°.
Volume	1253.7(4) $Å^3$		1603.4(10) $Å^3$		1969.9(7) $Å^3$	
Z	2		4		4	
Density (calculated)	1.591 Mg/m^3		1.716 Mg/m^3		1.748 Mg/m^3	
Absorption coefficient	1.403 mm^{-1}		2.134 mm^{-1}		1.784 mm^{-1}	
F(000)	608		816		1024	
Crystal size	0.26 x 0.18 x 0.16 mm^3		0.37 x 0.13 x 0.03 mm^3		0.29 x 0.17 x 0.04 mm^3	
Theta range for data collection	1.57 to 26.00°.		1.72 to 26.00°.		1.97 to 26.00°.	
Index ranges	-9<=h<=9, -15<=k<=15, -15<=l<=15		-9<=h<=10, -10<=k<=10, -29<=l<=29		-14<=h<=14, -13<=k<=13, -19<=l<=19	
Reflections collected	8301		12077		15098	
Independent reflections	4739 [R(int) = 0.0330]		3143 [R(int) = 0.0864]		3862 [R(int) = 0.1013]	
Completeness to theta = 26.00°	96.4 %		99.8 %		99.9 %	
Absorption correction	Empirical		Empirical		Empirical	
Max. and min. transmission	0.894 and 0.616		0.894 and 0.653		0.928 and 0.693	
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	
Data / restraints / parameters	4739 / 0 / 313		3143 / 0 / 192		3862 / 0 / 247	
Goodness-of-fit on F^2	1.029		0.927		0.844	
Final R indices [I>2sigma(I)]	R1 = 0.0391, wR2 = 0.0960		R1 = 0.0434, wR2 = 0.0824		R1 = 0.0437, wR2 = 0.0687	
R indices (all data)	R1 = 0.0433, wR2 = 0.0992		R1 = 0.0728, wR2 = 0.0891		R1 = 0.0693, wR2 = 0.0748	
Largest diff. peak and hole	1.291 and -0.813 $e.Å^{-3}$		1.369 and -0.926 $e.Å^{-3}$		0.720 and -0.889 $e.Å^{-3}$	

Table A3: Crystal Data and Structure Refinement for 2.17, 2.19 and 2.23

	2.17		**2.19**		**2.23**	
Identification code	16152		16108		16141	
Empirical formula	$C_{19}H_{22}F_3IO_4S$		$C_{17}H_{17}BrF_3IO_5S$		$C_{22}H_{20}F_3IO_5S$	
Formula weight	530.33		597.18		580.34	
Temperature	150(2) K		150(2) K		150(2) K	
Wavelength	0.71073 Å		0.71073 Å		0.71073 Å	
Crystal system	Monoclinic		Triclinic		Monoclinic	
Space group	P2(1)/c		P-1		P2(1)/c	
Unit cell dimensions	a = 11.455(3) Å	α= 90°.	a = 9.284(2) Å	α= 96.182(4)°.	a = 8.552(2) Å	α= 90°.
	b = 12.487(3) Å	β= 106.999(4)°.	b = 10.899(3) Å	β= 110.212(4)°.	b = 20.734(5) Å	β= 105.886(4)°.
	c = 15.451(3) Å	γ = 90°.	c = 12.373(3) Å	γ = 112.896(4)°.	c = 13.453(3) Å	γ = 90°.
Volume	2113.5(8) $Å^3$		1039.0(4) $Å^3$		2294.3(10) $Å^3$	
Z	4		2		4	
Density (calculated)	1.667 Mg/m^3		1.909 Mg/m^3		1.680 Mg/m^3	
Absorption coefficient	1.661 mm^{-1}		3.616 mm^{-1}		1.542 mm^{-1}	
F(000)	1056		580		1152	
Crystal size	0.21 x 0.07 x 0.05 mm^3		0.28 x 0.15 x 0.12 mm^3		0.28 x 0.26 x 0.18 mm^3	
Theta range for data collection	1.86 to 26.00°.		1.83 to 26.00°.		1.86 to 27.00°.	
Index ranges	-14<=h<=14, -15<=k<=15, -19<=l<=19		-11<=h<=11, -13<=k<=13, -15<=l<=15		-10<=h<=10, -26<=k<=26, -17<=l<=16	
Reflections collected	16205		8139		18840	
Independent reflections	4140 [R(int) = 0.0890]		4040 [R(int) = 0.0643]		4996 [R(int) = 0.0358]	
Completeness to theta = 26.00°	99.8 %		98.6 %		99.8 %	
Absorption correction	Empirical		Empirical		Empirical	
Max. and min. transmission	0.894 and 0.744		0.843 and 0.480		0.894 and 0.567	
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	
Data / restraints / parameters	4140 / 0 / 258		4040 / 0 / 256		4996 / 0 / 291	
Goodness-of-fit on F^2	0.979		0.899		1.016	
Final R indices [I>2sigma(I)]	R1 = 0.0551, wR2 = 0.1278		R1 = 0.0491, wR2 = 0.1014		R1 = 0.0291, wR2 = 0.0690	
R indices (all data)	R1 = 0.0763, wR2 = 0.1350		R1 = 0.0679, wR2 = 0.1059		R1 = 0.0343, wR2 = 0.0709	
Largest diff. peak and hole	2113.5(8) $Å^3$		1.998 and -1.032 e.$Å^{-3}$		0.639 and -0.486 e.$Å^{-3}$	

Table A4: Crystal Data and Structure Refinement for 2.24, 2.25 and 2.22

	2.24		**2.25**		**2.22**	
Identification code	17001		17122		16053	
Empirical formula	$C_{18}H_{20}F_3IO_4S$		$C_{19}H_{20}F_3IO_7S$		$C_{10}H_8F_3IO_3S$	
Formula weight	516.30		576.31		392.12	
Temperature	150(2) K		150(2) K		150(2) K	
Wavelength	0.71073 Å		0.71073 Å		0.71073 Å	
Crystal system	Monoclinic		Monoclinic		Monoclinic	
Space group	P2(1)/c		P2(1)/c		P2(1)/c	
Unit cell dimensions	a = 11.202(4) Å	α= 90°.	a = 10.425(2) Å	α= 90°.	a = 7.4197(19) Å	α= 90°.
	b = 12.491(4) Å	β= 103.549(5)°.	b = 7.9231(17) Å	β= 96.426(4)°.	b = 15.279(4) Å	β= 93.490(5)°.
	c = 15.040(5) Å	γ = 90°.	c = 26.655(6) Å	γ = 90°.	c = 11.425(3) Å	γ = 90°.
Volume	2045.9(12) $Å^3$		2187.8(8) $Å^3$		1292.8(6) $Å^3$	
Z	4		4		4	
Density (calculated)	1.676 Mg/m^3		1.750 Mg/m^3		2.015 Mg/m^3	
Absorption coefficient	1.714 mm^{-1}		1.623 mm^{-1}		2.671 mm^{-1}	
F(000)	1024		1144		752	
Crystal size	0.30 x 0.20 x 0.17 mm^3		0.23 x 0.12 x 0.07 mm^3		0.30 x 0.11 x 0.04 mm^3	
Theta range for data collection	1.87 to 26.00°.		1.54 to 26.00°.		2.23 to 26.00°.	
Index ranges	-13<=h<=13, -15<=k<=15, -18<=l<=18		-12<=h<=12, -9<=k<=9, -32<=l<=32		-9<=h<=9, -18<=k<=18, -14<=l<=14	
Reflections collected	15409		16548		9967	
Independent reflections	4023 [R(int) = 0.0729]		4291 [R(int) = 0.0804]		2539 [R(int) = 0.0838]	
Completeness to theta = 26.00°	99.8 %		100.0 %		100.0 %	
Absorption correction	Empirical		Empirical		Empirical	
Max. and min. transmission	0.894 and 0.537		0.894 and 0.703		0.894 and 0.637	
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	
Data / restraints / parameters	4023 / 0 / 248		4291 / 0 / 284		2539 / 25 / 164	
Goodness-of-fit on F^2	1.037		0.932		1.085	
Final R indices [I>2sigma(I)]	R1 = 0.0468, wR2 = 0.1144		R1 = 0.0414, wR2 = 0.0704		R1 = 0.0628, wR2 = 0.1598	
R indices (all data)	R1 = 0.0527, wR2 = 0.1180		R1 = 0.0565, wR2 = 0.0745		R1 = 0.0867, wR2 = 0.1698	
Largest diff. peak and hole	3.118 and -1.323 e.$Å^{-3}$		0.784 and -0.672 e.$Å^{-3}$		3.114 and -2.039 e.$Å^{-3}$	

Table A5: Crystal Data and Structure Refinement for 2.12, 2.13 and 2.14

	2.12		**2.13**		**2.14**	
Identification code	16120		16127		17026	
Empirical formula	$C_{16}H_{18}B\ F_4IO_2$		$C_{17}H_{20}BF_4IO_3$		$C_{17}H_{20}BF_4IO_3$	
Formula weight	456.01		486.04		486.04	
Temperature	150(2) K		150(2) K		150(2) K	
Wavelength	0.71073 Å		0.71073 Å		0.71073 Å	
Crystal system	Triclinic		Monoclinic		Monoclinic	
Space group	P-1		P2(1)/n		P2(1)/c	
Unit cell dimensions	a = 7.4922(19) Å	α= 87.810(4)°.	a = 7.7893(16) Å	α= 90°.	a = 10.692(19) Å	α= 90°.
	b = 10.184(3) Å	β= 75.567(4)°.	b = 14.097(3) Å	β= 98.685(4)°.	b = 7.683(15) Å	β= 94.07(3)°.
	c = 11.624(3) Å	γ = 79.756(4)°.	c = 17.063(4) Å	γ = 90°.	c = 23.02(4) Å	γ = 90°.
Volume	845.2(4) $Å^3$		1852.1(7) $Å^3$		1886(6) $Å^3$	
Z	2		4		4	
Density (calculated)	1.792 Mg/m^3		1.743 Mg/m^3		1.712 Mg/m^3	
Absorption coefficient	1.941 mm^{-1}		1.781 mm^{-1}		1.749 mm^{-1}	
F(000)	448		960		960	
Crystal size	0.44 x 0.28 x 0.05 mm^3		0.25 x 0.15 x 0.09 mm^3		0.36 x 0.13 x 0.07 mm^3	
Theta range for data collection	1.81 to 25.99°.		1.88 to 27.00°.		1.77 to 26.00°.	
Index ranges	-9<=h<=9, -12<=k<=12, -14<=l<=14		-9<=h<=9, -18<=k<=17, -21<=l<=21		-13<=h<=11, -8<=k<=9, -28<=l<=28	
Reflections collected	6586		15217		9833	
Independent reflections	3290 [R(int) = 0.0366]		4029 [R(int) = 0.0421]		3649 [R(int) = 0.1307]	
Completeness to theta = 26.00°	98.8 %		99.9 %		98.5 %	
Absorption correction	Empirical		Empirical		Empirical	
Max. and min. transmission	0.862 and 0.534		0.862 and 0.668		0.894 and 0.376	
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	
Data / restraints / parameters	3290 / 0 / 220		4029 / 0 / 239		3649 / 0 / 239	
Goodness-of-fit on F^2	1.028		0.978		0.960	
Final R indices [I>2sigma(I)]	R1 = 0.0283, wR2 = 0.0703		R1 = 0.0303, wR2 = 0.0707		R1 = 0.0704, wR2 = 0.1467	
R indices (all data)	R1 = 0.0300, wR2 = 0.0710		R1 = 0.0366, wR2 = 0.0726		R1 = 0.1001, wR2 = 0.1592	
Largest diff. peak and hole	0.676 and -0.592 e.$Å^{-3}$		0.958 and -0.857 e.$Å^{-3}$		2.100 and -1.571 e.$Å^{-3}$	

Table A6: Crystal Data and Structure Refinement for 2.26, 2.27 and 2.28

	2.26		**2.27**		**2.28**	
Identification code	17007		17047		17067n	
Empirical formula	$C_{16}H_{17}BBrF_4IO_2$		$C_{21}H_{20}BF_4IO_2$		$C_{16}H_{18}BF_4IO$	
Formula weight	534.92		518.08		440.01	
Temperature	150(2) K		150(2) K		150(2) K	
Wavelength	0.71073 Å		0.71073 Å		0.71073 Å	
Crystal system	Monoclinic		Monoclinic		Monoclinic	
Space group	P2(1)/n		P2(1)/c		P2(1)/c	
Unit cell dimensions	a = 7.7858(18) Å	α= 90°.	a = 9.624(3) Å	α= 90°.	a = 8.310(2) Å	α= 90°.
	b = 14.281(3) Å	β= 98.719(4)°.	b = 14.403(4) Å	β= 107.240(4)°.	b = 21.508(6) Å	β= 97.818(6)°.
	c = 16.557(4) Å	γ = 90°.	c = 15.635(4) Å	γ = 90°.	c = 20.153(6) Å	γ = 90°.
Volume	1819.7(7) $Å^3$		2070.0(10) $Å^3$		3568.5(17) $Å^3$	
Z	4		4		8	
Density (calculated)	1.953 Mg/m^3		1.662 Mg/m^3		1.638 Mg/m^3	
Absorption coefficient	4.001 mm^{-1}		1.596 mm^{-1}		1.832 mm^{-1}	
F(000)	1032		1024		1728	
Crystal size	0.41 x 0.21 x 0.16 mm^3		0.48 x 0.27 x 0.06 mm^3		0.46 x 0.15 x 0.08 mm^3	
Theta range for data collection	1.89 to 27.00°.		1.96 to 26.00°.		1.39 to 24.72°.	
Index ranges	-9<=h<=9, -18<=k<=18, -20<=l<=21		-11<=h<=11, -17<=k<=17, -19<=l<=19		-9<=h<=9, 0<=k<=25, 0<=l<=23	
Reflections collected	14818		15764		6090	
Independent reflections	3948 [R(int) = 0.0457]		4066 [R(int) = 0.0482]		6090 [R(int) = 0.0000]	
Completeness to theta = 26.00°	99.8 %		100.0 %		100.0 %	
Absorption correction	Empirical		Empirical		Empirical	
Max. and min. transmission	0.862 and 0.518		0.894 and 0.560		0.962 and 0.639	
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	
Data / restraints / parameters	3948 / 0 / 229		4066 / 0 / 264		6090 / 418 / 442	
Goodness-of-fit on F^2	1.009		1.066		0.923	
Final R indices [I>2sigma(I)]	R1 = 0.0314, wR2 = 0.0697		R1 = 0.0352, wR2 = 0.0832		R1 = 0.0715, wR2 = 0.1565	
R indices (all data)	R1 = 0.0389, wR2 = 0.0722		R1 = 0.0403, wR2 = 0.0858		R1 = 0.1547, wR2 = 0.1865	
Largest diff. peak and hole	0.827 and -0.675 $e.Å^{-3}$		1.179 and -0.511 $e.Å^{-3}$		0.801 and -0.503 $e.Å^{-3}$	

Table A7: Crystal Data and Structure Refinement for 3.7, 3.11 and 3.13

	3.7		3.11		3.13	
Identification code	18082		17070		18073	
Empirical formula	$C_{29}H_{29}IO_6S$		$C_{22}H_{18}F_3IO_4S$		$C_{21}H_{16}F_3IO_4S$	
Formula weight	632.48		562.32		548.30	
Temperature	150(2) K		150(2) K		150(2) K	
Wavelength	0.71073 Å		0.71073 Å		0.71073 Å	
Crystal system	Triclinic		Triclinic		Triclinic	
Space group	P-1		P-1		P-1	
Unit cell dimensions	a = 10.091(2) Å	α= 91.013(4)°.	a = 8.4537(14) Å	α= 66.609(2)°.	a = 8.5129(17) Å	α= 66.665(3)°.
	b = 11.801(3) Å	β= 101.750(4)°.	b = 11.6591(19) Å	β= 87.336(3)°.	b = 11.311(2) Å	β= 80.638(4)°.
	c = 12.148(3) Å	γ = 107.098(4)°.	c = 12.124(2) Å	γ = 76.601(2)°.	c = 12.442(3) Å	γ = 74.710(4)°.
Volume	1349.0(5) $Å^3$		1065.5(3) $Å^3$		1058.8(4) $Å^3$	
Z	2		2		2	
Density (calculated)	1.557 Mg/m^3		1.753 Mg/m^3		1.720 Mg/m^3	
Absorption coefficient	1.306 mm^{-1}		1.654 mm^{-1}		1.662 mm^{-1}	
F(000)	640		556		540	
Crystal size	0.41 x 0.28 x 0.10 mm^3		0.40 x 0.27 x 0.19 mm^3		1.79 to 26.00°.	
Theta range for data collection	1.72 to 26.00°.		1.83 to 25.99°.		0.13 x 0.11 x 0.09 mm^3	
Index ranges	-12<=h<=12, -14<=k<=14, -14<=l<=14		-10<=h<=10, -14<=k<=14, -14<=l<=14		-10<=h<=10, -13<=k<=13, -15<=l<=15	
Reflections collected	10472		8303		8299	
Independent reflections	5232 [R(int) = 0.0310]		4139 [R(int) = 0.0300]		4093 [R(int) = 0.0579]	
Completeness to theta = 26.00°	98.7 %		98.7 %		98.6 %	
Absorption correction	Empirical		Empirical		Empirical	
Max. and min. transmission	0.888 and 0.657		0.914 and 0.578		0.894 and 0.602	
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	
Data / restraints / parameters	5232 / 0 / 338		4139 / 0 / 281		4093 / 0 / 271	
Goodness-of-fit on F^2	1.022		1.041		0.926	
Final R indices [I>2sigma(I)]	R1 = 0.0310, wR2 = 0.0700		R1 = 0.0299, wR2 = 0.0735		R1 = 0.0448, wR2 = 0.0796	
R indices (all data)	R1 = 0.0349, wR2 = 0.0714		R1 = 0.0323, wR2 = 0.0747		R1 = 0.0565, wR2 = 0.0825	
Largest diff. peak and hole	0.858 and -0.442 $e.Å^{-3}$		1.070 and -0.762 $e.Å^{-3}$		0.889 and -0.880 $e.Å^{-3}$	

Table A8: Crystal Data and Structure Refinement for 3.14, 3.15 and 3.16

	3.14		3.15		3.16	
Identification code	18015		18067		18061	
Empirical formula	$C_{22}H_{17}BrF_3IO_4S$		$C_{22}H_{17}ClF_3IO_4S$		$C_{24}H_{20}F_3IO_6S$	
Formula weight	641.23		596.77		620.36	
Temperature	150(2) K		150(2) K		150(2) K	
Wavelength	0.71073 Å		0.71073 Å		0.71073 Å	
Crystal system	Monoclinic		Triclinic		Triclinic	
Space group	P2(1)/n		P-1		P-1	
Unit cell dimensions	a = 11.949(2) Å	α= 90°.	a = 8.030(3) Å	α= 71.367(6)°.	a = 7.892(2) Å	α= 113.866(4)°.
	b = 7.7173(14) Å	β= 100.152(4)°.	b = 12.151(5) Å	β= 74.096(6)°.	b = 12.750(3) Å	β= 97.406(4)°.
	c = 24.678(5) Å	γ = 90°.	c = 12.837(5) Å	γ = 82.476(6)°.	c = 13.435(3) Å	γ = 94.830(4)°.
Volume	2240.1(7) $Å^3$		1140.2(8) $Å^3$		1212.0(5) $Å^3$	
Z	4		2		2	
Density (calculated)	1.901 Mg/m^3		1.738 Mg/m^3		1.700 Mg/m^3	
Absorption coefficient	3.359 mm^{-1}		1.664 mm^{-1}		1.469 mm^{-1}	
F(000)	1248		588		616	
Crystal size	0.43 x 0.04 x 0.02 mm^3		0.32 x 0.15 x 0.06 mm^3		0.43 x 0.21 x 0.05 mm^3	
Theta range for data collection	1.68 to 26.00°.		1.73 to 26.00°.		1.68 to 26.00°.	
Index ranges	-14<=h<=14, -9<=k<=9, -30<=l<=30		-9<=h<=9, -14<=k<=14, -15<=l<=15		-9<=h<=9, -15<=k<=15, -16<=l<=16	
Reflections collected	17016		8901		9451	
Independent reflections	4398 [R(int) = 0.1604]		4414 [R(int) = 0.0431]		4695 [R(int) = 0.0424]	
Completeness to theta = 26.00°	99.9 %		98.7 %		98.6 %	
Absorption correction	Empirical		Empirical		Empirical	
Max. and min. transmission	0.894 and 0.633		0.825 and 0.494		0.894 and 0.601	
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	
Data / restraints / parameters	4398 / 0 / 290		4414 / 0 / 290		4695 / 0 / 318	
Goodness-of-fit on F^2	0.747		0.973		0.973	
Final R indices [I>2sigma(I)]	R1 = 0.0595, wR2 = 0.0841		R1 = 0.0364, wR2 = 0.0732		R1 = 0.0367, wR2 = 0.0766	
R indices (all data)	R1 = 0.1243, wR2 = 0.0974		R1 = 0.0435, wR2 = 0.0756		R1 = 0.0433, wR2 = 0.0788	
Largest diff. peak and hole	0.840 and -0.843 e.$Å^{-3}$		1.122 and -0.511 e.$Å^{-3}$		1.084 and -0.435 e.$Å^{-3}$	

Table A9: Crystal Data and Structure Refinement for 3.18, 3.10, 3.21

	3.18		**3.10**		**3.21**	
Identification code	18053		17098		17107	
Empirical formula	$C_{23}H_{20}F_3IO_3S$		$C_{21}H_{20}BF_4IO_2$		$C_{21}H_{18}BF_4IO$	
Formula weight	560.35		518.08		500.06	
Temperature	150(2) K		150(2) K		150(2) K	
Wavelength	0.71073 Å		0.71073 Å		0.71073 Å	
Crystal system	Triclinic		Monoclinic		Orthorhombic	
Space group	P-1		P2(1)/n		Pbca	
Unit cell dimensions	a = 8.4676(16) Å	α= 88.995(3)°.	a = 12.965(2) Å	α= 90°.	a = 11.995(5) Å	α= 90°.
	b = 10.0588(19) Å	β= 88.796(3)°.	b = 11.911(2) Å	β= 102.163(3)°.	b = 14.196(6) Å	β= 90°.
	c = 13.290(3) Å	γ = 85.825(3)°.	c = 13.389(2) Å	γ = 90°.	c = 22.602(10) Å	γ = 90°.
Volume	1128.6(4) $Å^3$		2021.2(6) $Å^3$		3849(3) $Å^3$	
Z	2		4		8	
Density (calculated)	1.649 Mg/m^3		1.703 Mg/m^3		1.726 Mg/m^3	
Absorption coefficient	1.558 mm^{-1}		1.635 mm^{-1}		1.710 mm^{-1}	
F(000)	556		1024		1968	
Crystal size	0.36 x 0.22 x 0.17 mm^3		0.34 x 0.22 x 0.12 mm^3		0.40 x 0.32 x 0.03 mm^3	
Theta range for data collection	1.53 to 25.99°.		1.99 to 26.00°.		1.80 to 26.00°.	
Index ranges	-10<=h<=10, -12<=k<=12, -16<=l<=16		-15<=h<=15, -14<=k<=14, -16<=l<=16		-14<=h<=14, -17<=k<=17, -27<=l<=27	
Reflections collected	8830		15347		27920	
Independent reflections	4398 [R(int) = 0.0333]		3974 [R(int) = 0.0421]		3778 [R(int) = 0.0881]	
Completeness to theta = 26.00°	98.7 %		100.0 %		100.0 %	
Absorption correction	Empirical		Empirical		Empirical	
Max. and min. transmission	0.894 and 0.704		0.894 and 0.662		0.894 and 0.263	
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	
Data / restraints / parameters	4398 / 24 / 309		3974 / 0 / 264		3778 / 0 / 254	
Goodness-of-fit on F^2	1.028		1.032		1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0877		R1 = 0.0308, wR2 = 0.0735		R1 = 0.0388, wR2 = 0.0814	
R indices (all data)	R1 = 0.0415, wR2 = 0.0898		R1 = 0.0358, wR2 = 0.0758		R1 = 0.0528, wR2 = 0.0862	
Largest diff. peak and hole	1.215 and -0.536 $e.Å^{-3}$		0.910 and -0.514 $e.Å^{-3}$		0.698 and -0.896 $e.Å^{-3}$	

Table A10: Crystal Data and Structure Refinement for 3.24, 3.25 and 3.28

	3.24		3.25		3.28	
Identification code	18008		18074		18098	
Empirical formula	$C_{22}H_{18}BBrCl_3F_4IO$		$C_{22}H_{18}BCl_4F_4IO$		$C_{22}H_{20}BF_4I$	
Formula weight	698.33		653.87		498.09	
Temperature	150(2) K		150(2) K		150(2) K	
Wavelength	0.71073 Å		0.71073 Å		0.71073 Å	
Crystal system	Monoclinic		Monoclinic		Orthorhombic	
Space group	P2(1)/c		P2(1)/c		Pbca	
Unit cell dimensions	a = 16.679(16) Å	α= 90°.	a = 16.512(6) Å	α= 90°.	a = 10.365(2) Å	α= 90°.
	b = 9.368(9) Å	β= 94.534(14)°.	b = 9.354(4) Å	β= 94.607(6)°.	b = 15.001(3) Å	β= 90°.
	c = 16.580(16) Å	γ = 90°.	c = 16.566(6) Å	γ = 90°.	c = 25.100(5) Å	γ = 90°.
Volume	2582(4) $Å^3$		2550.5(16) $Å^3$		3902.7(14) $Å^3$	
Z	4		4		8	
Density (calculated)	1.796 Mg/m^3		1.703 Mg/m^3		1.695 Mg/m^3	
Absorption coefficient	3.140 mm^{-1}		1.718 mm^{-1}		1.683 mm^{-1}	
F(000)	1352		1280		1968	
Crystal size	0.38 x 0.13 x 0.04 mm^3		0.43 x 0.11 x 0.03 mm^3		0.41 x 0.27 x 0.17 mm^3	
Theta range for data collection	2.45 to 26.00°.		2.47 to 26.00°.		1.62 to 27.00°.	
Index ranges	-20<=h<=19, -11<=k<=11, -20<=l<=20		-20<=h<=20, -11<=k<=11, -20<=l<=20		-13<=h<=13, -19<=k<=19, -31<=l<=30	
Reflections collected	19591		19343		30285	
Independent reflections	5082 [R(int) = 0.1803]		5022 [R(int) = 0.2372]		4254 [R(int) = 0.0521]	
Completeness to theta = 26.00°	99.9 %		99.9 %		99.9 %	
Absorption correction	Empirical		Empirical		Empirical	
Max. and min. transmission	0.894 and 0.374		0.894 and 0.356		0.928 and 0.506	
Refinement method	Full-matrix least-squares on F^2		Full-matrix least-squares on F^2		Full-matrix least-squares on F^2	
Data / restraints / parameters	5082 / 0 / 299		5022 / 0 / 299		4254 / 0 / 255	
Goodness-of-fit on F^2	0.863		0.901		1.139	
Final R indices [I>2sigma(I)]	R1 = 0.0644, wR2 = 0.1237		R1 = 0.0839, wR2 = 0.1518		R1 = 0.0386, wR2 = 0.0845	
R indices (all data)	R1 = 0.1394, wR2 = 0.1482		R1 = 0.2115, wR2 = 0.1914		R1 = 0.0484, wR2 = 0.0881	
Largest diff. peak and hole	0.812 and -1.293 $e.Å^{-3}$		1.452 and -1.098 $e.Å^{-3}$		0.947 and -0.552 $e.Å^{-3}$	

Table A11: Crystal Data and Structure Refinement for 3.31

	3.31					
Identification code	18089					
Empirical formula	$C_{28}H_{25}IO_4S$					
Formula weight	584.44					
Temperature	150(2) K					
Wavelength	0.71073 Å					
Crystal system	Triclinic					
Space group	P-1					
Unit cell dimensions	a = 13.148(3) Å	α= 83.966(3)°.				
	b = 13.175(2) Å	β= 86.472(3)°.				
	c = 16.115(3) Å	γ = 60.099(3)°.				
Volume	2406.2(8) $Å^3$					
Z	4					
Density (calculated)	1.613 Mg/m^3					
Absorption coefficient	1.451 mm^{-1}					
F(000)	1176					
Crystal size	0.39 x 0.21 x 0.09 mm^3					
Theta range for data collection	1.79 to 26.00°.					
Index ranges	-16<=h<=16, -16<=k<=16, -19<=l<=19					
Reflections collected	18860					
Independent reflections	9333 [R(int) = 0.0401]					
Completeness to theta = 26.00°	98.7 %					
Absorption correction	Empirical					
Max. and min. transmission	0.894 and 0.711					
Refinement method	Full-matrix least-squares on F^2					
Data / restraints / parameters	9333 / 0 / 617					
Goodness-of-fit on F^2	0.947					
Final R indices [I>2sigma(I)]	R1 = 0.0377, wR2 = 0.0713					
R indices (all data)	R1 = 0.0503, wR2 = 0.0750					
Largest diff. peak and hole	1.179 and -0.817 $e.Å^{-3}$					

Appendix II

Calibration Plots

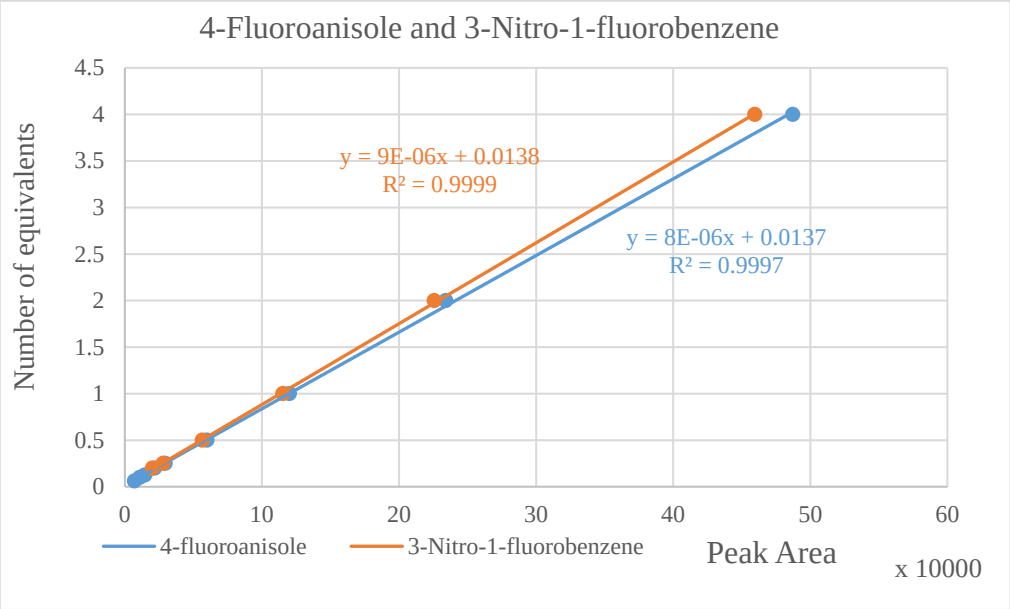

Figure A1: *Calibration plots of 4-fluoroanisole* ***1.100***

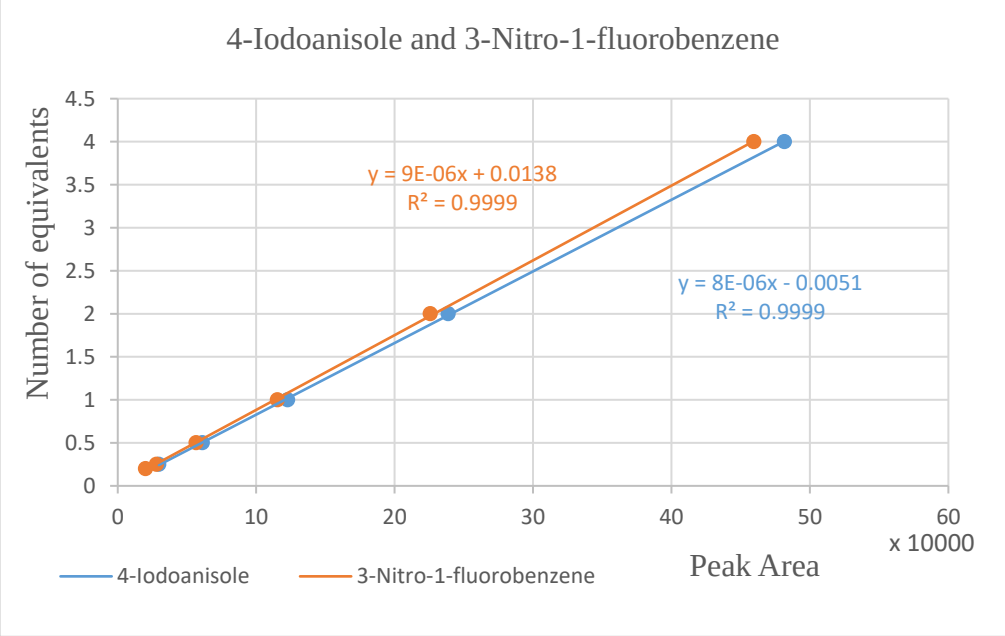

Figure A2: *Calibration plots of 4-iodoanisole* ***4.1***

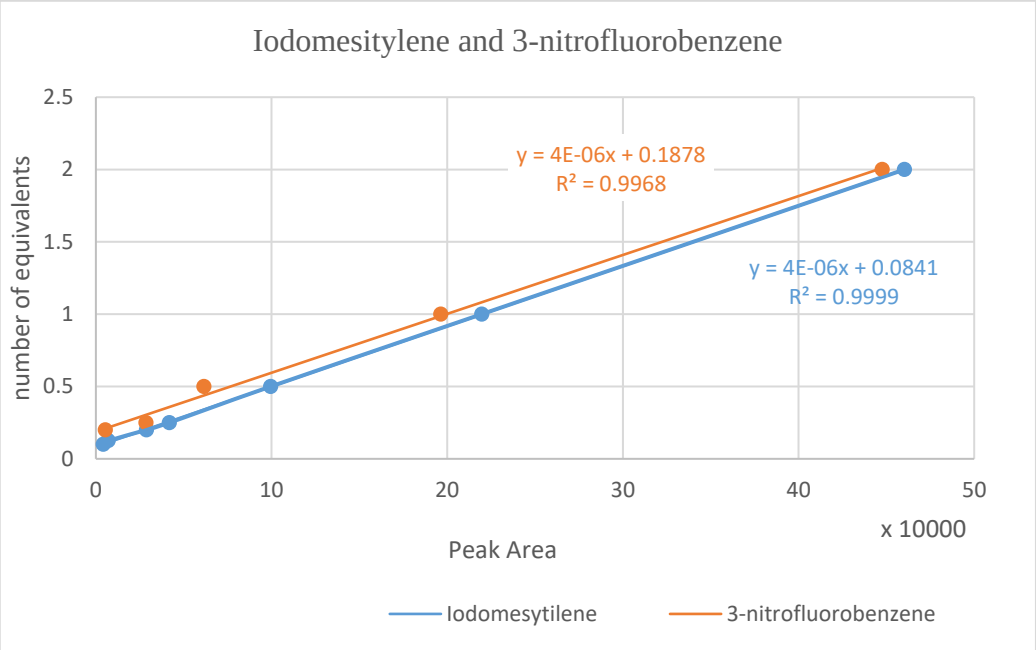

Figure A3: *Calibration plots of iodomesitylene* ***4.7***

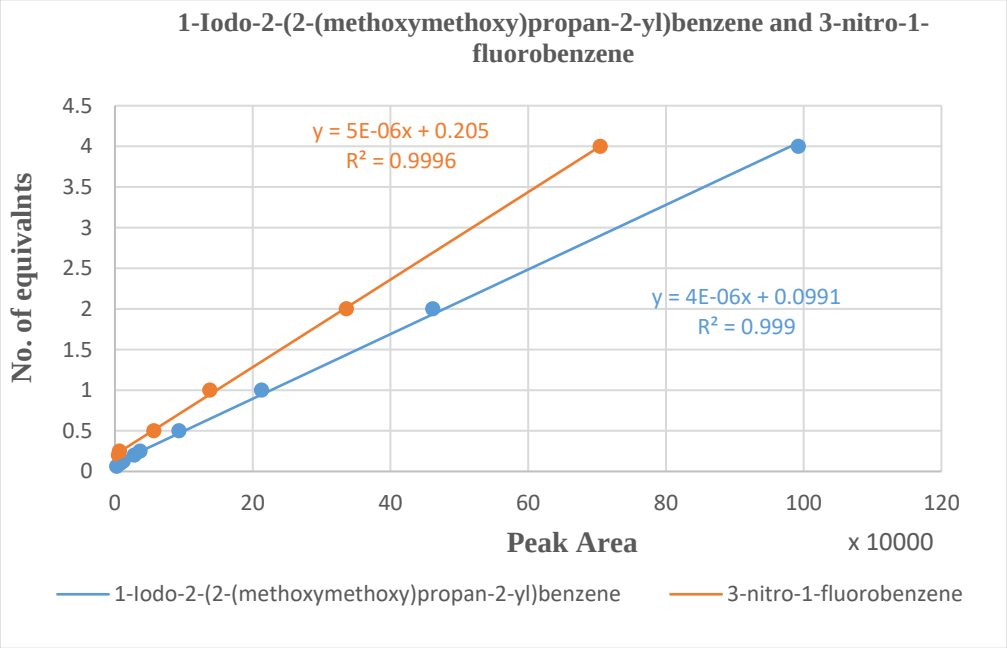

Figure A4: *Calibration plots of 1-iodo-2-(2-(methoxymethoxy)propan-2-yl)benzene* ***4.2***

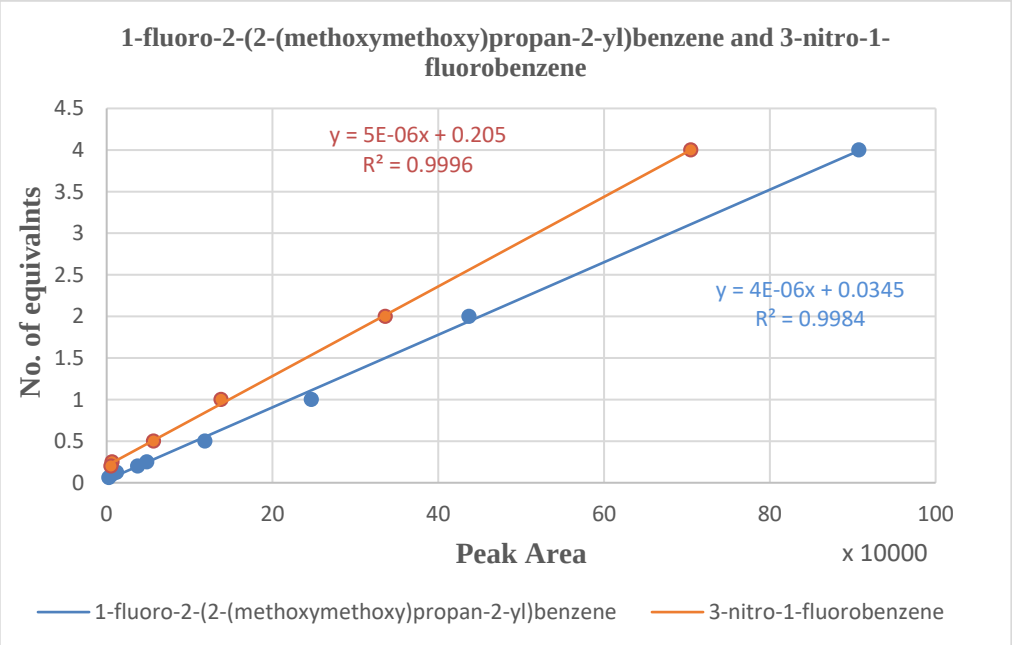

Figure A5: *Calibration plots of 1-fluoro-2-(2-(methoxymethoxy)propan-2-yl)benzene*

4.4

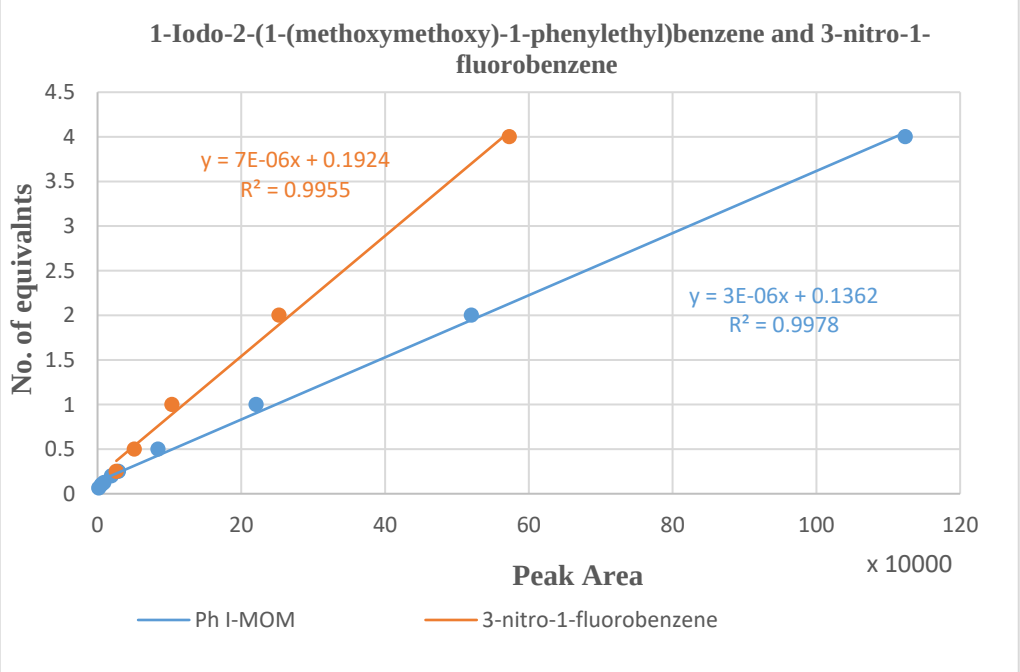

Figure A6: *Calibration plots of 1-iodo-2-(1-(methoxymethoxy)-1-phenylethyl)benzene*

4.3

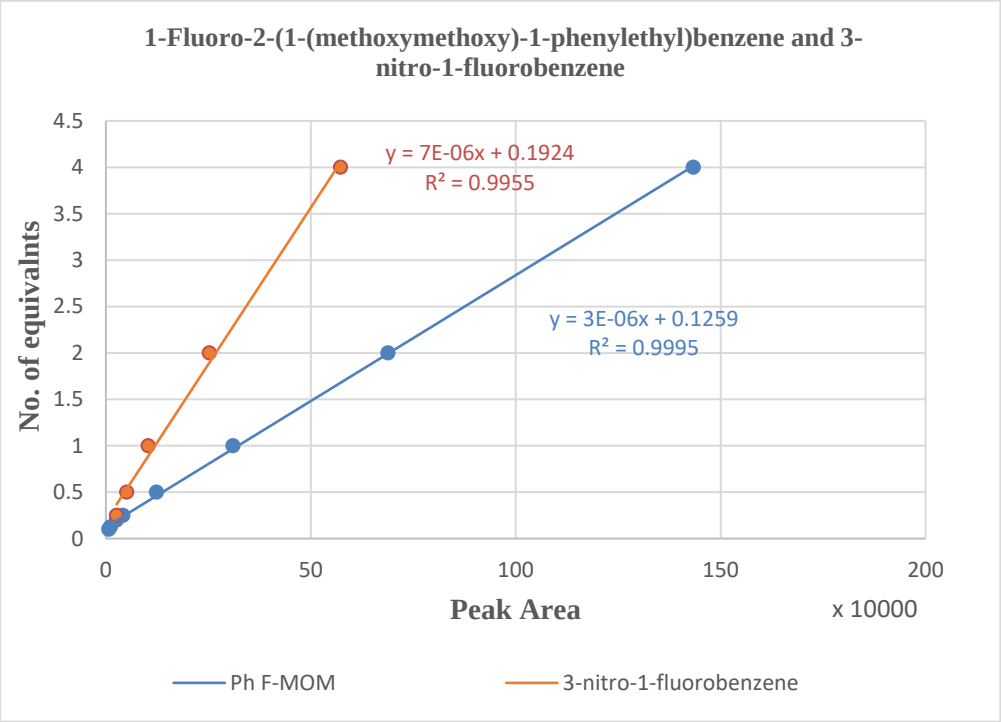

Figure A7: *Calibration plots of 1-fluoro-2-(1-(methoxymethoxy)-1-phenylethyl)benzene* ***4.5***

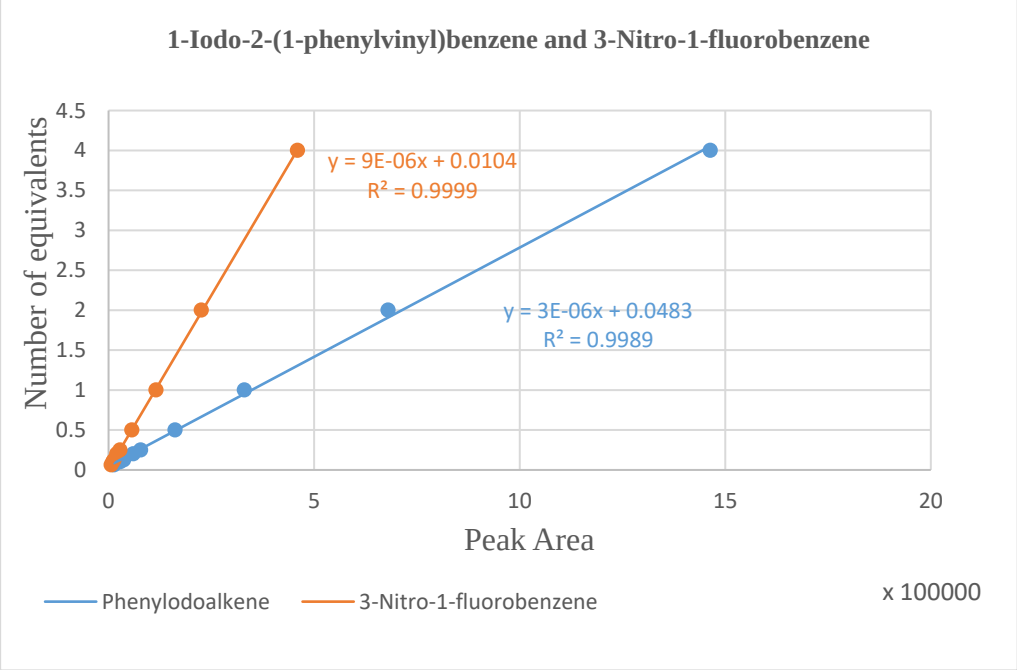

Figure A8: *Calibration plots of 1-iodo-2-(1-phenylvinyl)benzene* ***3.20***

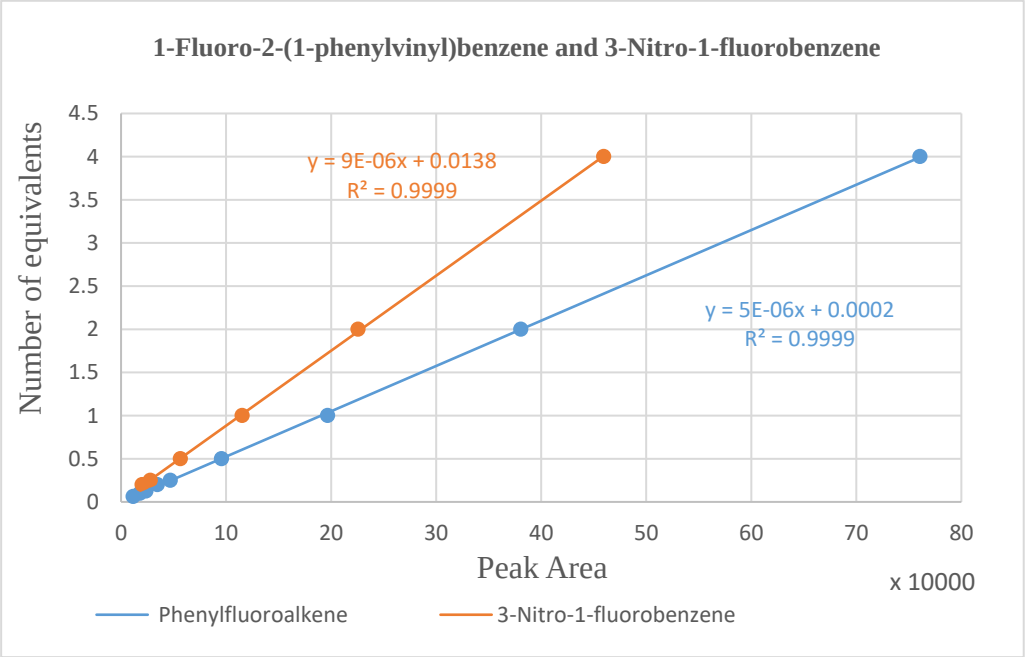

Figure A7: *Calibration plots of 1-fluoro-2-(1-phenylvinyl)benzene* ***4.6***

Conferences and Symposia Attended

- 50th annual meeting on ‘Modern Aspects of Steriochemistry, University of Sheffield, 10-01-2017: attended
- University of Leicester Department of Chemistry Postgraduate research day 04/7/2017: Poster presentation.
- 17th Annual RSC Fluorine Subject Group Postgraduate meeting, 17 – 18 September 2017, attended
- The 22nd International Symposium on Fluorine Chemistry, University of Oxford on the 22nd - 27th July 2018: Poster presentation.