Synthesis and Reactivity of Aryl Iodo Difluorides

Thesis submitted in accordance with the
requirements of the University of Cardiff
for the degree of Doctor in Philosophy
by

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Abstract

Organofluorine substrates are molecules of increasing demand in both academic and industrial settings. Organofluorine compounds are very rare in nature and therefore several approaches to their synthesis have been developed.

In the work performed during this research tenure, the approach towards the synthesis of organofluorine substrates is based on the use of hypervalent iodine reagents.

The structure of the research program can be summarized into three main sections:

- Synthesis of aryl iodo difluorides
- Reactivity of aryl iodo difluorides towards organoselenium substrates
- Approach toward stereoselective fluorinations with the synthesis of chiral iodo difluorides

Aryl iodo difluorides reagents have been known for more than a century but they have not been extensively used mainly due to their difficulty of synthesis, which require harmful and hazardous reagents. We have developed an alternative method for their preparation involving three synthetic steps: perborate oxidation of an aryl iodide, followed by basic hydrolysis and subsequent treatment with hydrofluoric acid. A number of aryl iodo difluorides were synthesized using this procedure and each of them is characterized by high purity and high yield.

The reactivity of (difluoroiodo)toluene (DFIT) as a fluorinating agent was tested on organoselenium substrates. α-Seleno esters, amide and nitriles undergo α-fluorination when treated with 2 equivalents of DFIT. Under these conditions, the monofluoro derivatives were obtained with yields ranging from 20% to 65%.
Additionally, (difluoroiodo)toluene can be employed in oxidative fluorinations. The exploitation of its oxidative nature produced tetraethyl ammonium iodo difluoride, and preliminary results indicate that it can be used as fluorinating agent, as well.

The third aspect of the research dealt with stereoselective fluorination reactions. The synthesis of an opportune chiral iodo difluoride can provide the further development of hypervalent iodine reagents as fluorinating reagents. Different substrates were used to reach this goal and the study conducted in this direction brought about the synthesis of a difluoride with the iodine atom in oxidation state V, which can be use as chiral fluorine transfer after a simple modification of its structure.

Microform

The synthetic importance of fluorinated organic compounds in the last decades has experienced rapid growth and increased interest from both academic and industrial points of view. Different approaches to their synthesis have been developed.

In this work, an alternative synthesis of aryl iodo difluorides involving three synthetic steps: perborate oxidation, basic hydrolysis and subsequent treatment with hydrofluoric acid is been reported. Reagents of this type have been known for more than a century but not extensively used, mainly due to their difficult and hazardous synthesis.

After an analysis of the synthesis of aryl iodo difluorides, the reactivity of (difluoroiodo)toluene with different classes of organoselenium substrates is presented. α-Seleno esters, amides and nitriles undergo α-fluorination when treated with (difluoroiodo)toluene. Additionally tetraethyl ammonium iodo difluoride was synthesised exploiting the oxidative nature of (difluoroiodo)toluene.

Chiral reagents are being synthesised for the further development of stereoselective fluorinations.

Dedico questa tesi a mio padre,
fonte di ispirazione e coraggio

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Contents

List of Abbreviations

$[\alpha]_D$	specific optical rotation
Ac	acetyl
Ar	aromatic substituent
C / c	concentration / concentrate
Δ	heating
DAST	(diethylamino) sulfur trifluoride
DCM	dichloromethane
DIP-Cl	(+)-B-chlorodiisopinocampheylborane
DFIT	(difluoroiodo)toluene
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethyl formamide
DMSO	dimethyl sulphoxide
4e-3c	four electrons- three centres bond
ee	enantiomeric excess
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride
EI	electronic ionisation
eq	equivalents
Et	ethyl
GC-MS	gas chromatograph-mass spectroscopy
GP n	general procedure number
h	hours
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hyp.	hypervalent
IBA	1-hydroxy-1,2-benziodoxol-3(1H)-one
IR	infrared spectroscopy
J	constant coupling
LHA	lithium aluminium hydride
MCPBA	*meta*-chloro perbenzoic acid
Me	methyl
MOM	methoxymethyl
mp	melting point

MPLC	medium pressure liquid chromatography
MS	mass spectroscopy
NMR	nuclear magnetic resonance
NFSI	*N*-fluoro benzene sulfonimmide
PET	positron emission tomography
2.2-PHANEPHOS	4,12-bis(diphenylphosphino)-[2.2]-paracyclophane
PIDA	(diacetoxyiodo)benzene
PPHF	polypyridinium hydrogen fluoride
PCC	pyridinium chloro chromate
i-PrOH	2-propanol
Py	pyridine
R_f	retention factor
rt	room temperature
Tf/ triflate	trifluoromethyl sulfonyl
TCA	tricarboxylic acid
TFA	trifluoro acetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TolI	*para*-iodo toluene
Tos/ tosyl	*para*-toluene sulfonyl
UHP	urea-hydrogen peroxide adduct

Chapter 1

1 Introduction

1.1 The element fluorine: a brief introduction

The most reactive and electronegative of all elements of the periodic table is fluorine. It is not a common element in the earth's crust, being only the 0.06% of the total composition and it is found mainly as a fluoride anion. Small amounts can be found in the rocks in which it substitutes for an oxygen atom in an isomorphic way. Its main mineral is Fluorspar (CaF_2), which constitutes the most important material for the extraction of fluorine and for the preparation of its derivatives. As a fluoride ion, it is also found as a trace element in animals and humans and between 0.3-0.5 mg/day is recommended for human diet. As a diatomic molecule F_2 is a pale yellow, corrosive gas, which reacts with most elements (including noble gases xenon, radon and krypton) and most organic and inorganic materials.

Fluorine (from latin ***Fluere*** meaning ***flow***) was first described in the sixteenth century for the use of Fluorspar, mineral used to promote the fusion of metals and minerals. The element was first isolated by Henry Moissan in 1886. After several years of continuous attempts, Moissan separated the element by electrolysis of a 1 to 12 mixture of KF and HF in a U shaped Pt tube cooled at –23°C. Prior to Moissan, many attempts to its isolation were made. The difficulty in isolating this element was due to the fact that, once separated, it immediately reacts with the surrounding materials. Fluorine was first used in the industrial process for the preparation of the atomic bomb in the Word War II. Uranium hexafluoride (UF_6) was used to separate the isotopes of uranium ($^{235}U/^{238}U$) by gas diffusion. This process is still in use today in nuclear power applications.

Today the main commercial applications of fluorine lie in the synthesis of organofluorine compounds that have found a variety of applications in our everyday life.

1.2 Organofluorine compounds

Although a great number (around 3500) of naturally occurring halogenated compounds are known,[1,2] only a dozen represents the fluorinated natural products,[3,4,5] most of which are highly toxic. Some of them are illustrated in Figure 1.1.

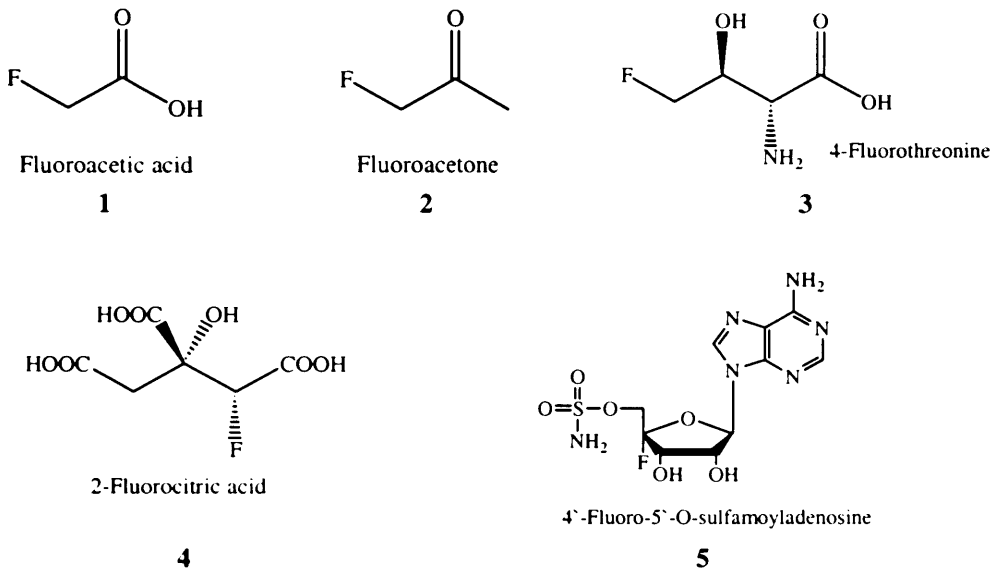


Figure 1.1: Naturally occurring organofluorine compounds.

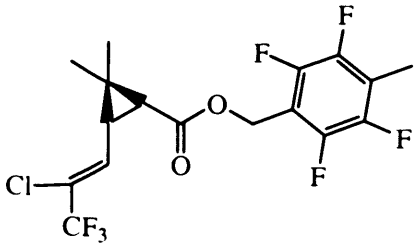
A biological system able to fluorinate organic substrates is the fluorinase enzyme from the bacteria Streptomyces cattleya.[4] This enzyme is able to bio-transform particular organic substrates into fluoroacetic acid,[4] a toxin found in more than 40 plant species. Fluoroacetic acid **1**, the smallest representative of the natural organofluorine compounds, is sadly famous because it blocks the tricarboxylic acid cycle (TCA) in humans and animals, killing the organism.[6,7] For this property, in the past it found industrial applications as a pesticide.

Despite this small number of natural organofluorine substrates, the fluorination of organic molecules has been of increasing interest to organic and medicinal chemists for the past 50 years[8] and the synthetic importance of fluorinated organic compounds has been growing in interest from both industrial and academic points of view.

From an industrial point of view, this importance is correlated with the use of the fluorinated compounds in several aspects of live. Fluorine-containing compounds have widely spread into our modern life with broad applications in electronic, agricultural and medicinal industries.[9]

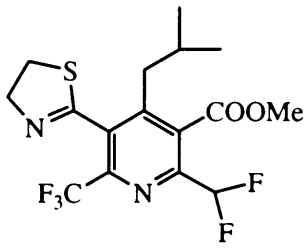
Fluorocarbon polymers such as Teflon® are used to make products like motor gaskets and dashboard accessories for the automobile industry. They are also used on the surface of frying pans and other kitchen utensils to reduce the need for fat in cooking, as well as in the textile industry to create wrinkle-free, stain resistant fabrics. Fluorochlorohydrocarbons are extensively used in air conditioning and in refrigeration, as well as anesthetics. Organofluorine compounds are used to manufacture semiconductors for a variety of the information and telecommunication equipment, and to manufacture microprocessors and data storage devices. In agriculture, more than 10% of commercial agrochemicals contains fluorine and are found in pesticides, herbicides and fungicide applications (Figure 1.2).

Fluorinated agrochemicals:



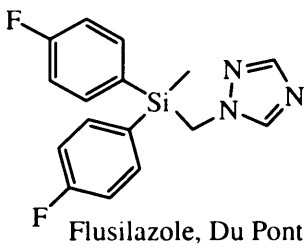
Tefluthrin, ICI
Insecticide

6



Thiazopyr, Monsanto
Herbicide

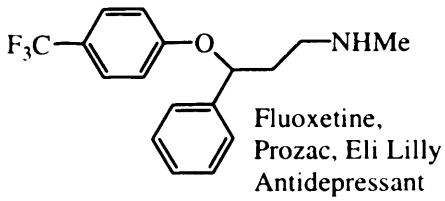
7



Flusilazole, Du Pont
Fungicide

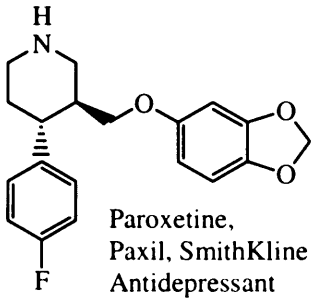
8

Fluorinated drugs:



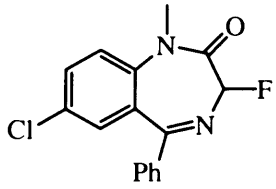
Fluoxetine,
Prozac, Eli Lilly
Antidepressant

9



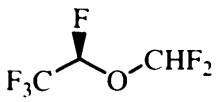
Paroxetine,
Paxil, SmithKline
Antidepressant

10



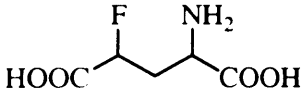
F-Diazepam
Anxiolytic

11



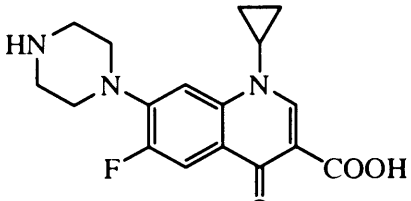
R-Desfluran
Anesthetic

12



4-F-glutamic acid
Antitumor, antiviral

13

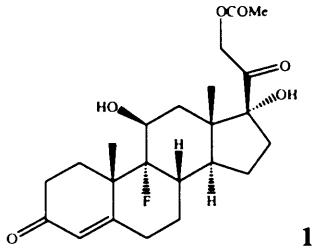


Ciprofloxacin, Bayer
Antibacterial

14

Figure 1.2: Examples of fluorinated agrochemicals and some best-selling drugs containing fluorine.

In medicinal industries, many fluorinated molecules are used to make anti-inflammatory, anti-cancer and anti-depressant medications, as well as antibiotics. Figure 1.3 shows the chemical structure of 9-fluorohydrocortisone acetate[10,11] which was the first example of a fluorinated drug and the first evidence of a positive biological effect due to the presence of fluorine atom. Other examples of fluorinated drugs are shown in Figure 1.2. Recent applications of fluorine substrates in medicinal chemistry are also found as blood substitutes.[12]



15

Figure 1.3: 9-Fluorohydrocortisone acetate: the first fluorinated cortisone.

From a chemical point of view, the reasons in synthesising organofluorine compounds can be introduced by the romantic sentence of Schlosser:[14] "Fluorine does not leave nobody indifferent, it inflames emotions be that affections or aversions. As a substituent, it is rarely boring, always good for a surprise, but often completely unpredictable".

1.2.1 Properties of fluorine compounds

The reasons behind the growing importance of organofluorine compounds lie in the properties of fluorine itself.[13,14] Some physical properties of fluorine and some other key elements (H and Cl) and the OH group are illustrated for comparison in Table 1.1.

Table 1.1: Physical properties of H, F, Cl and OH.

	EN[a] Pauling	VdW[b] radius Å	IP[c] kcal/mol	EA[d] kcal/mol	BE[e] CH_3-X kcal/mol	CH_3-X Å	X···H[f] kcal/mol	X···H[f] Å
H	2.1	1.20	313.6	17.7	99	1.09	/	/
F	4.0	1.35	401.8	79.5	116	1.39	2.38	1.9
Cl	3.0	1.80	299.0	83.3	81	1.77	/	/
OH	3.5	1.40	310.4	33.7	86	1.43	5	0.8

[a] EN = electronegativity. [b] VdW = Van der Waals. [c] IP = ionisation potential. [d] EA = electron affinity. [e] BE = bond energy. [f] X···H = hydrogen bond.

Fluorine is unique for its properties and differs from the others halogens. Chlorine for instance is bigger in size, less electronegative and more polarizable, properties that are reflected in the

correspondent organochloride derivatives. Despite the high electronegativity, fluorine is the only halogen able to donate its electrons by efficient overlap of the p-orbitals, a phenomenon that is less favourable or forbidden for the other halogens.

The fluorine atom is considered isosteric with hydrogen having a Van der Waals radius of fluorine 1.35 Å (hydrogen 1.20 Å). This implies that the resulting fluorinated substrate does not present appreciable steric differences than the corresponding hydrogen compound. At the same time, the presence of the most electronegative element changes the electronic density in the molecule, sometimes in a dramatic way. In fact, the joint effect of electron withdrawing over σ-bonds, a consequence of its electronegativity, and the electron donor effect by conjugation over π-bonds, derived from its electron pairs, changes the reactivity of the reaction centres in the molecule itself. Acidity and basicity of the molecule, for instance, are greatly influenced by the presence of fluorine substitution. As a consequence of these properties, the introduction of fluorine atoms in an organic substrate allows chemists to use the fluorine atom as a probe of reactivity and to synthesise compounds with important physical and biological properties of high value. Moreover, the elevated stability of the carbon-fluorine bond compared with the carbon-hydrogen bond (116 kcal/mol versus 99 kcal/mol) implies that these substrates can be employed in the study of metabolic transformations and in many cases they have been used as enzymatic inhibitors exploiting their biomimetic effect.[i]

Fluorine is not only important in the isosteric substitution of hydrogen, but it is also used as a substituent of other groups, shown in Figure 1.4.

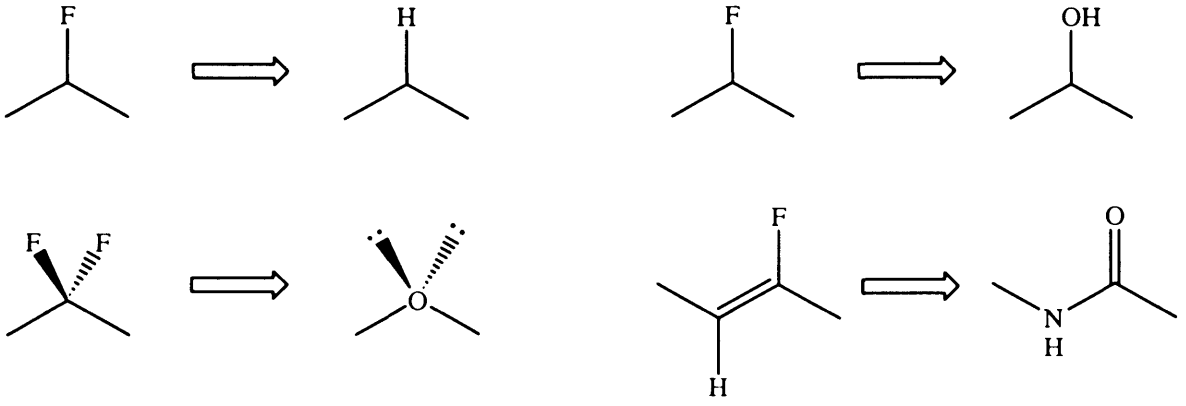


Figure 1.4: Mimetic effect of fluorine over different functional groups.

The small difference in Van der Waals radius between fluorine and oxygen (1.35 Å versus 1.40 Å) and the difference in stability of the correspondent bond with carbon reflect its mimetic effect, when the oxygen is substituted by fluorine in alcohols[15] and in amides[16] or by the CF_2

[i] Biomimetic effect is defined as the influence due to suitable substitute able to change the electronic structure of the molecule without appreciable alteration of the steric asset of the whole molecule.

group in ethers[15] (Figure 1.4). Once again, the bond energy of the carbon-fluorine bond compared to carbon- oxygen reflects a high stability towards oxidation processes. In this case, it has to be mentioned that fluorine has the possibility to act as hydrogen bond acceptor. Although the strength of the F···H bond is less relevant than the O···H (Table 1.1), it still remains another valid and biologically important characteristic exploited by the presence of fluorine.

Another useful characteristic of the fluorine derivatives is the increased lipophilicity compared with analogous hydrocarbons.[15] Therefore, the judicious placement of fluorine atoms on pharmaceutical targets allows the synthetic chemist to change the physical and metabolic properties of the target.

Apart from the traditional organic techniques for the analysis of organic molecules, fluorine-containing substrates can be studied by specific analysis. In fact fluorine-19 is a spin ½ nucleus and is the only natural isotope of fluorine. These properties imply that ^{19}F NMR spectroscopy can be use as a powerful tool to further investigate the effect of fluorine in the substrate. Additionally, positron emission tomography (PET) uses the isotope fluorine-18 (derived from the neutron bombardment of an ^{18}O-H_2O target) as a nuclide probe for medicine.[17]

Because these unique, unpredictable, and useful characteristics of fluorine-containing compounds are united with the numerous applications in a variety of research fields, different approaches to their synthesis have been developed.

The research developed in this work aims to contribute to the exciting and challenging field of fluorination using a particular method based on hypervalent iodine reagents. Before concentrating on the project, the methodologies, which are possible to use in the synthesis of these relevant and fascinating fluorinated substrates, are reviewed.

1.3 Fluorine transfer reactions: a background

The synthetic methodologies for the construction of fluorinated compounds can be subdivided in two groups: use of fluorinated species as building blocks and direct synthesis of fluorine-carbon bonds. The former is not widely used because of the limited number of natural organofluoro compounds or the high cost of the commercially available fluorinated precursors. Applications in this area include fluorinated ylides[18] and perfluoroalkylating agents.[19] For the direct synthesis of carbon-fluorine bonds, several methods of fluorination are possible which can be subdivided in two different routes:

- nucleophilic substitution reactions with a fluoride anion

- electrophilic addition.[ii]

The most straightforward method would be the anionic fluorination whereby fluoride ion from HF, from fluoride salts or from (diethylamino)sulfur trifluoride (DAST) displaces a leaving group on the substrate. A disadvantage of these methods is that the fluoride anion can react preferentially as a base instead as a nucleophile, due to the small size and low polarizability of the fluoride anion. The reagent polypyridinium hydrogen fluoride (PPHF),[20] belonging to this group, is quite important and increasingly used as fluorinating reagent. PPHF, commonly known as Olah's reagent, is a 1:9 mixture of pyridine in HF (30% Py: 70% HF w/w) and can fluorinate secondary and tertiary alcohols, alkenes and alkynes.[21] It is also employed in halogen exchange reactions[22,23] and in ring opening reactions of epoxides.[24]

Alternatively, electrophilic fluorination has become a useful method for the introduction of fluorine and is based on a reagent which has the fluorine atom bonded to a powerful leaving group. A variety of electrophilic fluorinating reagents have been developed over the last 40-50 years. Reagents such as molecular fluorine itself (F_2), acetyl hypofluorites and several N-F reagents belong in this category, the most important of them is Selectfluor[iii,25] **16**, from which stereoselective fluorinations were developed.[26]

In Table 1.2 some reagents belonging to the electrophilic class in both achiral and chiral form are shown. Through the development of the latter[26] is possible not only to insert the fluoride in a specific position of the molecule, but also to perform such reactions in an asymmetric way,[27] a task particularly valued in medicinal chemistry.

The electrophilic fluorinating reagents are mainly based on the N-F functional group as in the achiral reagents of Selectfluor and NFSI.[iv]

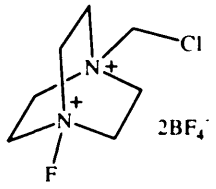
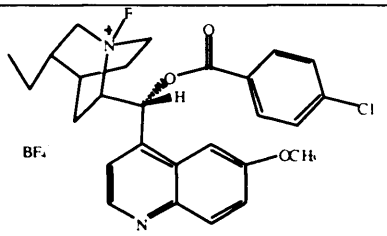
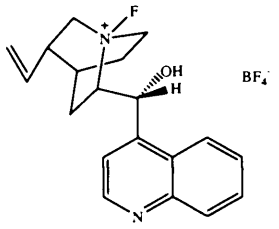
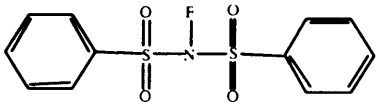
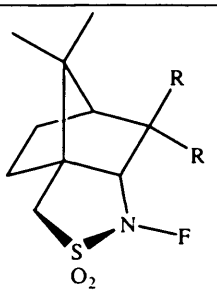
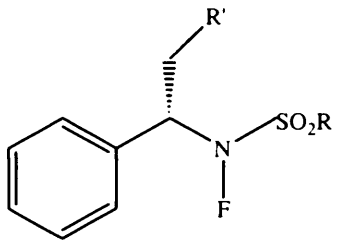
Differding and Lang,[26a] who synthesised the first camphor derived *N*-fluorosultam **19**, prepared the first example of electrophilic fluorinating reagent. The application of *N*-fluoro ammonium salts from chinchona alkaloids **17a** recently brought the first example of an α-fluoro α-amino acid.[28] These fluorinating reagents are quite versatile; they can be used as stoichiometric reagents (using the chiral forms) or in a catalytic way in the presence of Selectfluor or NFSI plus an opportune chiral catalyst based of titanium[29] or palladium.[26p-26q] Togni and co-workers,[29] using Selectfluor in conjunction with a titanium catalyst, performed the first enantioselective and catalytic fluorination.

[ii] The notion of electrophilic fluorination was a bit confusing in the beginning. This term means that the bond X-F is susceptible to nucleophilic attack from an electron rich centre. The whole process is aided by the fact that the adjacent group is usually a relatively good leaving group and is accepted to symbolise an electrophilic fluorine by the "F^+" symbol. $R\text{-}X + F\text{-}Y \rightarrow [R\text{-}X\text{-}F]^+ + Y^-$

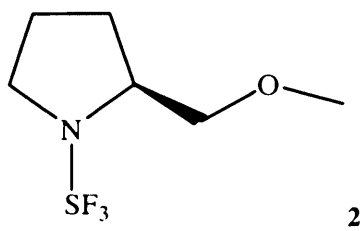
[iii] 1-(Chloromethyl)-4-fluoro-[1,4-diazoniabicyclo[2.2.2.]octane bis(tetrafluoroborate)]

[iv] *N*-Fluoro benzene sulfonimide

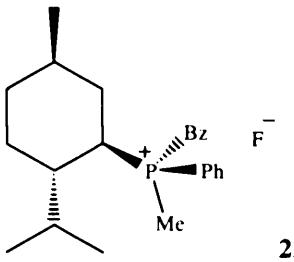
Table 1.2: Established N-F electrophilic fluorinating reagents: achiral and chiral.

Fluorinating reagent	**Chiral derivatives**
 **16** **Selectfluor**	 **17a**  **17b** *N*-Fluoro ammonium salts from cinchona alkaloids
 **18** **NFSI** *N*-Fluoro benzene sulfonimide	 **19** R = H, Cl, OCH_3  **20** R = CH_3, *p*-Tol R' = H, OAc ***N*-Fluoro sultams**

Examples of chiral fluorinating reagents belonging to the nucleophilic class (Figure 1.5) are known,[30,31] although they are not very commonly used, mainly due to the poor enantioselectivity observed. Only two examples of chiral nucleophilic fluorinating reagents are known: the proline derivative **21** synthesised by Hann and Sampson[30] and the more recent chiral quaternary phosponium fluoride[31] **22**.



21



22

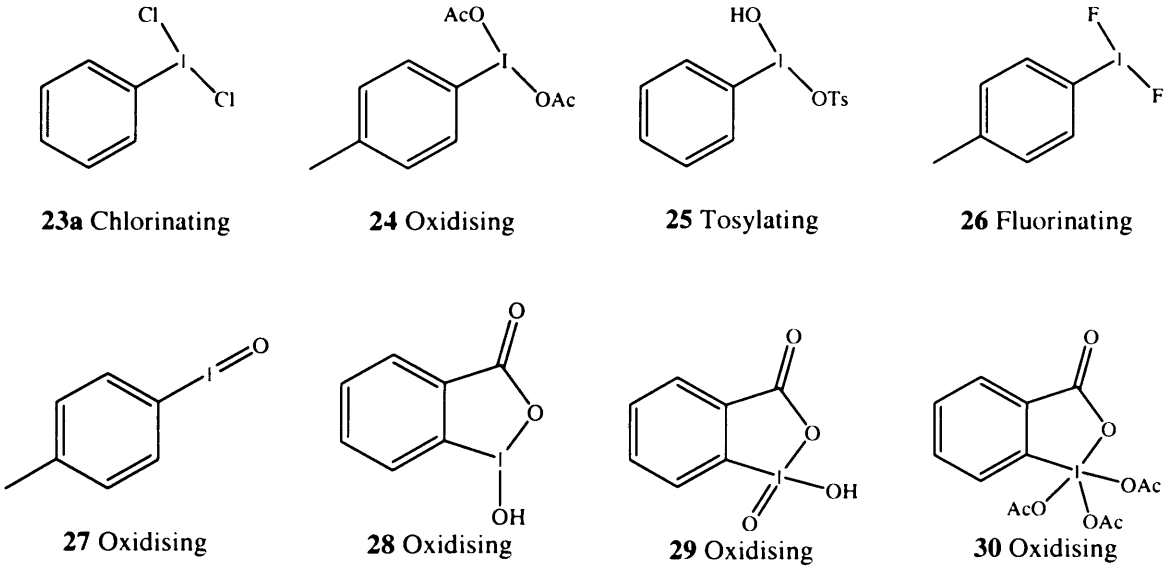
Figure 1.5: The proline derivate **21** and the more recent chiral quaternary phosphonium fluoride **22**.

An alternative fluorination method is based on the use of organoiodine (III) compounds.[32] Their application as reagents in organic synthesis is valuable and rich. Numerous transformations with these reagents have been developed and include oxidations, additions, lactonizations, cyclizations, and rearrangements. It should come as no surprise, given the breadth of reactivity

of these compounds, that a fluorinating reagent would be among them. In particular, the electrophilic molecule of (difluoroiodo)toluene (DFIT) has become a very useful reagent in the transfer of fluorine to several organic substrates. The use of DFIT allows one to avoid other harmful methods using reagents such as molecular fluorine (F_2), toxic fluoride salts or (diethylamino)sulfur trifluoride (DAST). Double bonds, α-position to carbonyl groups, triple bonds are some functionalities, which react with DFIT, allowing the synthesis of important fluorinated substrates. A very interesting recent paper reports the *ipso*-aromatic fluorination of *para*-substituted phenols done using (diacetoxyiodo)benzene (PIDA) in combination with PPHF,[33] revealing the wide applicability and the versatility of multivalent organoiodine reagents in organic synthesis. The hypervalent iodine reagents were selected as fluorine transfer reagents for this work. The following paragraph describes the general features of the hypervalent iodine reagents.

1.4 Hypervalent iodine compounds: general features

Iodine is the largest, most-easily polarizable, and least electronegative atom of the halogens group. Therefore, it is able to form stable polycoordinate organoiodanes violating the octet rule by expanding its valence. A wide variety of different classes of hypervalent iodine compounds are known. These multivalent organoiodides differ in oxidation state, which can be III, V or VII, in the nature of the ligand and, consequently, in their chemical applications. Figure 1.6 shows some key hypervalent iodine regents.



23a Chlorinating **24** Oxidising **25** Tosylating **26** Fluorinating

27 Oxidising **28** Oxidising **29** Oxidising **30** Oxidising

Figure 1.6: Established hypervalent iodine reagents. The main use for each of them is also reported.

The first polyvalent organic iodine compound was (dichloroiodo)benzene $PhICl_2$, which was synthesised by the German chemist Willgerodt one century ago. This was followed by the preparation of many others since 1960. This interest is mainly due to the similarity of chemical behaviour (reductive elimination and ligand exchange) with transition metals such as Hg(II) and Pb(IV). The total absence of environmental problems connected with the use of hypervalent iodine reagents is an advantage if compared with the toxic heavy metal reagents showing similar reactivity. Also some hypervalent reagents are commercially available and/or the synthetic steps for their preparation are straightforward.

1.4.1 The hypervalent bond

The structural features of the organic iodine (III) compounds are generally explained by Musher.[34] In the hypervalent model, the nonhybridized 5p orbitals of the iodine atom are participating in the bond with the ligands. The least electronegative ligand is bound to by a normal covalent bond to the single occupied equatorial 5p orbital where the other two ligands are bonding with the same axial doubly occupied 5p orbital. The result is a linear three center four electrons with an overall pseudotrigonal bipyramidal geometry. Such bonds, called hypervalent, are weaker and longer than covalent bounds. Such geometry was found correct also in describing the geometry for DFIT[8a] reported in Figure 1.7.

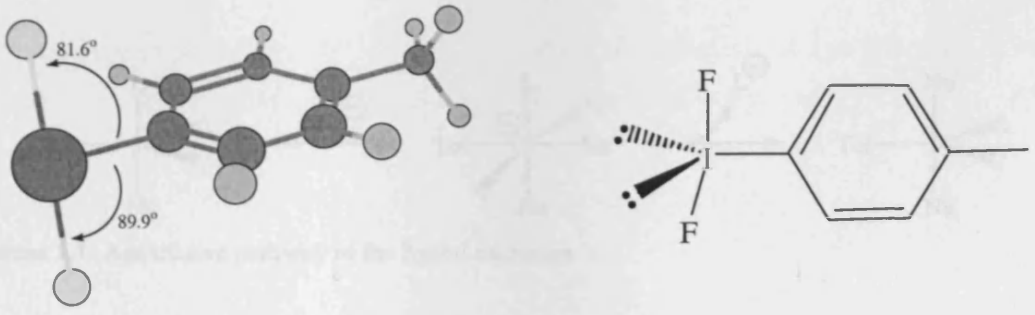


Figure 1.7: Pseudotrigonal bipyramid geometry associated with organoiodine DFIT **26**.

The general reactivity of these compounds is determined by the hypervalent nature of the I-X bond and by the electrophilic character of the iodine atom. These structural characteristics are responsible for their chemical behaviour.

Due to these properties, hypervalent compounds find their application in organic synthesis as selective oxidants and electrophilic ligand transfer reagents.

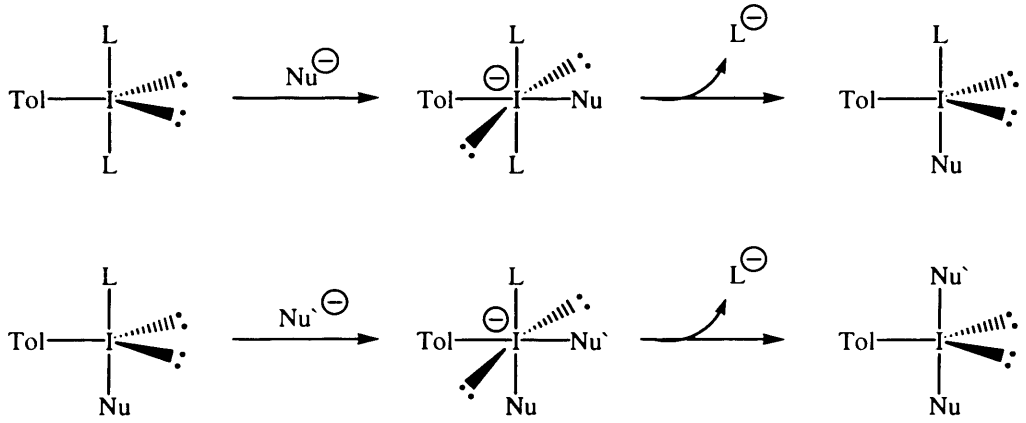
In the next paragraph an overview of the reactivity of the hypervalent iodine species, is reported.

1.4.2 General mechanistic pathways

The reactivity of the hypervalent iodine reagents could be explained by three main mechanisms,[32] often associated with the chemistry of transition metals. These main mechanisms, which can be operating, are:

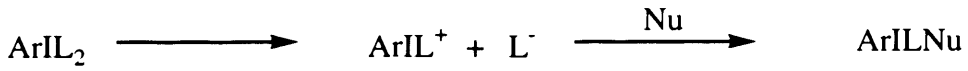
- ligand exchange
- reductive β-elimination
- reductive elimination with subsequent substitution.

The first mechanism involves an interconversion of the ligand bound to the iodine with an external nucleophile. This interconversion does not modify the oxidation state of the iodine atom and can occur by an associative (Scheme 1.1) or by a dissociative pathway (Scheme 1.2). The associative pathway involves a sequence of addition (with the formation of a tetracoordinate intermediate) and subsequent elimination of the first ligand. A second sequence of addition and elimination of TolI(L)Nu produces $TolINu_2$ or TolINuNu` when different nucleophiles are used.



Scheme 1.1: Associative pathway in the ligand exchange.

On the other hand, in the dissociative mechanism (Scheme 1.2) one ligand is first eliminated with consequent formation of a highly energetic iodine species $ArIL^+$, which can react with the nucleophile to produce ArILNu. Additional steps of elimination and addition afford the synthesis of $ArINu_2$ or ArINuNu`.



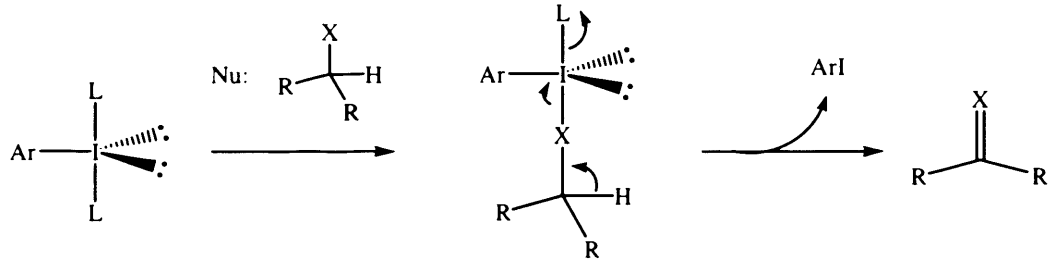
Scheme 1.2: Dissociative pathway in the ligand exchange.

The ligand exchange is normally used to synthesise a variety of polycoordinated iodine reagents. A typical example, shown in Scheme 1.3, is the preparation of (diacyloxyiodo)arenes reagents starting from (diacetoxyiodo)arenes such as for instance PIDA.

$$ArI(OAc)_2 + 2\,RCOOH \longrightarrow ArI(OOCR)_2 + 2\,AcOH$$

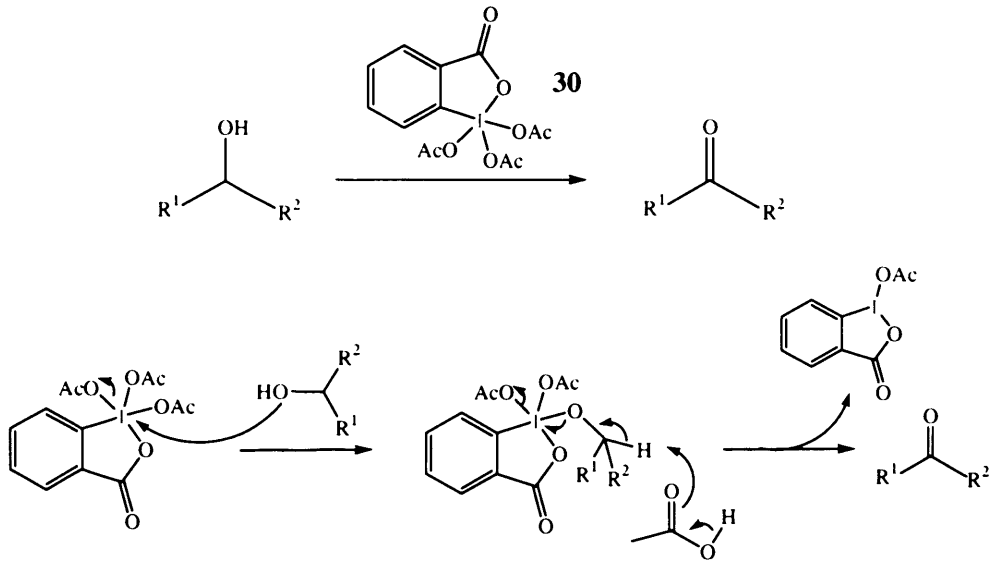
Scheme 1.3: Synthesis of (diacyloxyiodo)arenes from (diacetoxyiodo)arenes.

The second mechanism, shown in Scheme 1.4, involves a reductive β-elimination with formation of the oxidation product. In this case the hypervalent aryl iodo reagent is transformed into the reduced precursor. It has been proven[35] that the β-elimination occurs with *syn* stereochemistry. The combination of ligand exchange and β-elimination provides an excellent method widely used for oxidation of sulfides, alcohols and amines in the corresponding sulfoxides, carbonyl compounds and imines.



Scheme 1.4: Reductive β-elimination.

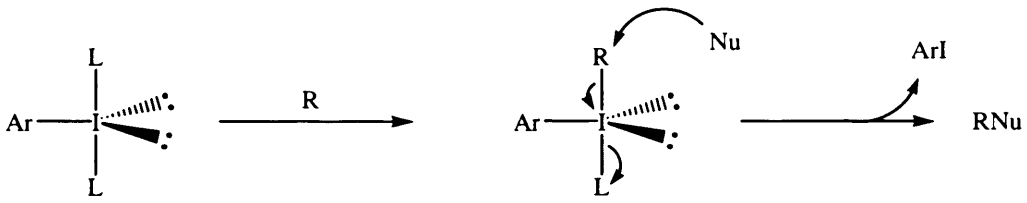
The Dess-Martin periodinane **30** is commonly used in oxidation rections. In Scheme 1.5 the mechanism of oxidation of a generic alcohol performed by **30** is reported.



Scheme 1.5: Oxidation of a generic alcohol performed by the Dess-Martin periodinane **30**.

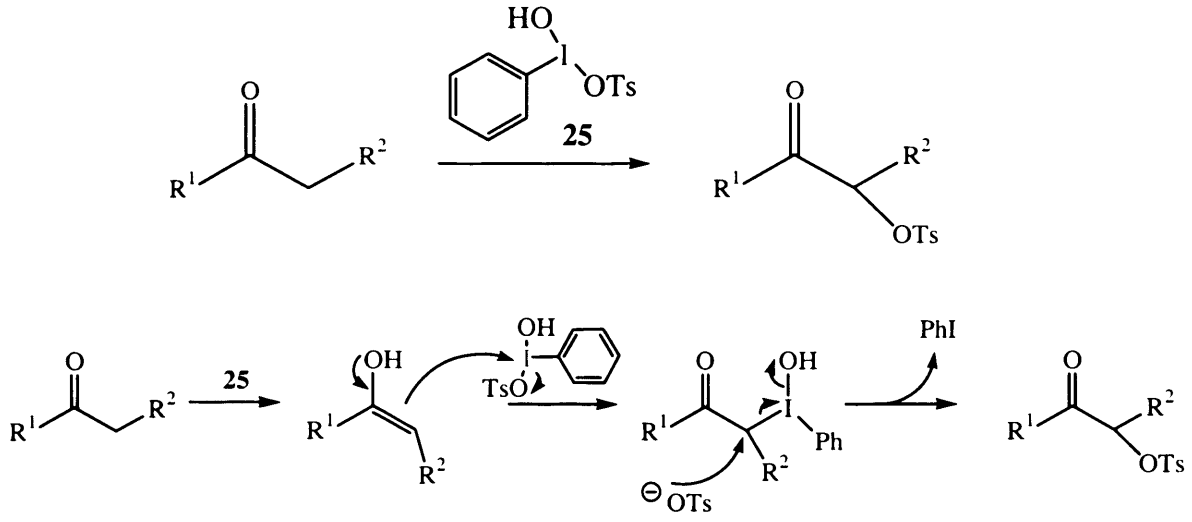
The electron pairs in alcoholic oxygen promote the first step of ligand exchange. At this point, reductive β elimination produces the formation of the carbonyl and the release of the reduced iodo reagent.

The third mechanism implies a reductive elimination with subsequent substitution (Scheme 1.6). The first step of ligand exchange is followed by nucleophilic attack on the carbon atom bounded to the iodine with consequent production of substituted products. When this mechanism is operating, the addition of several functionalities into a substrates is possible.



Scheme 1.6: General mechanism for the reductive elimination with substitution.

In this context, the α-oxidation of carbonyl substrates is perhaps the most important reaction performed by hypervalent iodine reagents. For instance, reactions of a generic carbonyl substrate with the Koser reagent **25** (Scheme 1.7) afford α-tosyloxy carbonyl products.

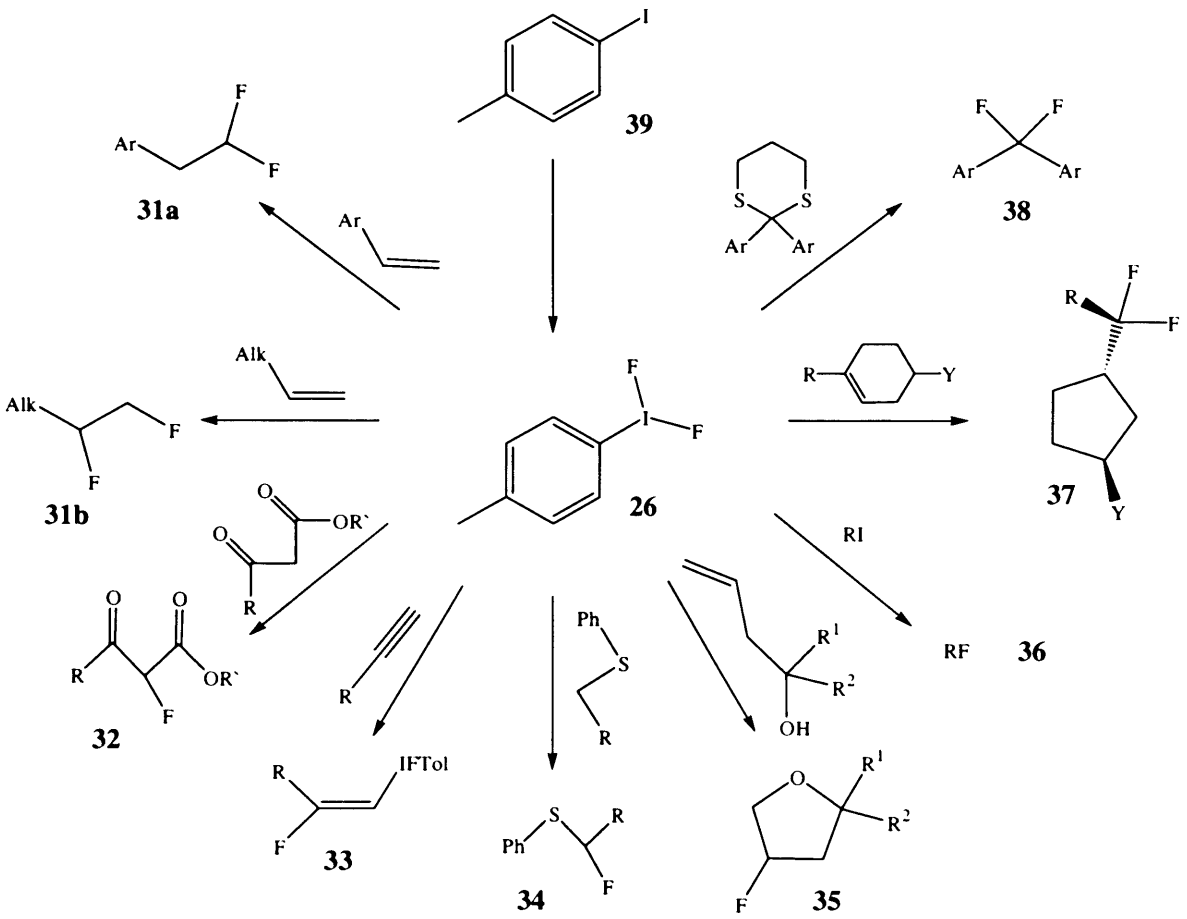


Scheme 1.7: α-Oxidation of a generic carbonyl substrate performed by the Koser reagent **25**.

1.4.3 (Difluoroiodo)toluene as fluorinating reagent

As briefly previously reported, this research exploits the chemical reactivity of hypervalent iodine reagents applied to the synthesis of fluorine-carbon bounds. Fluorination reactions performed by (difluoroiodo)arenes are usually rationalised by the mechanisms reported in the previous Section.

In particular, (difluoroiodo)toluene **26**, the most representative of the (difluoroiodo)arenes, has been successfully employed as a useful fluorinating reagents. The common fluorination reactions carried out with DFIT are shown in Scheme 1.8.

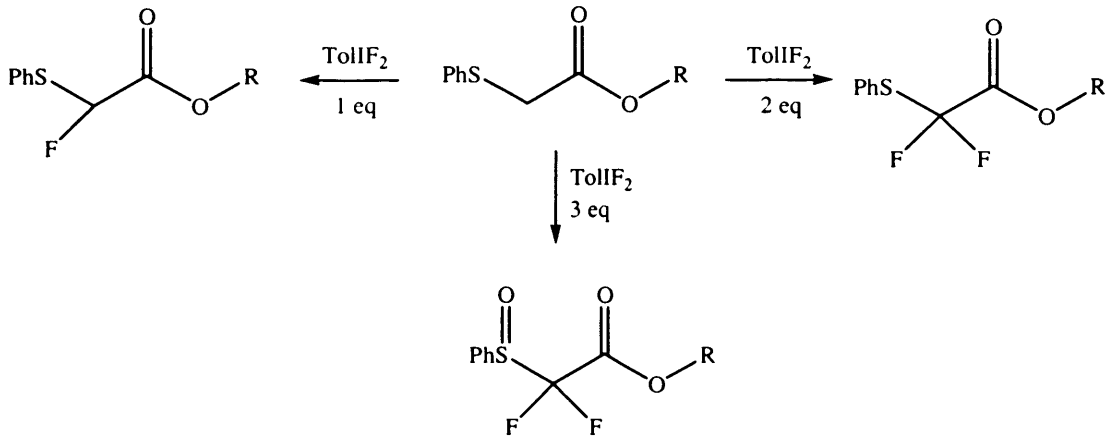


Scheme 1.8: Reaction of (difluoroiodo)toluene **26** with different functional groups.

This useful reagent can be used in the fluorination of linear and cyclic olefines producing difluoro-derivatives **31a**, **31b** and **37**.[36,37,38] The fluorination with DFIT provides gem-difluorides **31a** starting from aryl group substitued alkenes[37,38] and vic-difluorides **31b** starting from terminal alkenes.[36] In the case of cyclic olefins,[39] a rearrangement is operating with a consequent ring-contraction of for instance the six membered ring to the correspondent five membered ring **37**. When the olefin contains an internal nucleophile in a suitable position a ring closure with production of **35** is possible[40] due to the hypernucleofugicity of the iodonium group bond to the double bond of the olefin. Through a deiodofluorination the synthesis of fluoro organic substrate **36** became possible starting from the corresponding iodine precursor.[41,42,43,44,45,46] The use of triple bonds allows the construction of an iodonium salt **33** with simultaneous incorporation of the fluorine atom. The iodonium salt **33** can be employed in successive steps of regio and stereo-selective synthesis able to convert the iodononium group to several functionalities.[47,48,49,50] β-Dicarbonyl substrates **32**[51,52,53] undergo α-fluorination after

treatment with DFIT. All these reactions need acidic condition in order to work. In some cases, the presence of hydrofluoric acid is sufficient for a successful reaction, while in other reactions it is necessary to use a mixture of hydrofluoric acid in triethyl amine (1:3 or 1:5) or in pyridine (1:9) (Olah's reagent).

The presence of a mild nucleophile in the substrate allows the reaction to be free from the use of strong acidic conditions. This is the case for sulfur substrates,[54] which exhibit a particular affinity towards the fluorinating reagent with production of fluoro derivatives **34** and **38**. Motherwell et al. have demonstrated the high affinity of sulfur-containing substrates towards DFIT. The proposed mechanism involves a Pummerer-type reaction.[55] For instance, dithioketals[54a] are readily converted in diaryldifluoromethane **38**. By this procedure, the fluoride is also easily incorporated in the sulfur-containing molecule[54] such as phenylsulfanyl esters (Scheme 1.9) allowing for the synthesis of the corrisponding monofluorides, difluorides and fluoro-sulfoxides depending on the reaction conditions.



Scheme 1.9: Fluorination reaction of phenylsulfanyl esters by DFIT.

1.5 Task of the project

The work described in this thesis involves the concept of fluorination using the rich chemistry of hypervalent iodine reagents.

Hypervalent iodine reagents were chosen as fluorinating agent due to their good reactivity and mild and environmentally friendly reaction conditions often observed for this class of compounds.

The first aim was to improve the synthesis of the main fluorinating reagent used in this work, (difluoroiodo)toluene. This was previously prepared by the Carpenter method. In Chapter 2 an alternative route for its preparation is reported, which avoids the use of hazardous reagents. The applicability of this methodology is also discussed with the reported synthesis of analogous (difluoroiodo)aryl hypervalent reagents.

The reactivity and the capacity of operating as fluorine transfer was exploited towards different classes of seleno containing substrates for the preparation of the corresponding monofluoro-derivatives. The ability of DFIT to react in oxidative fluorinations with iodosubstrates was also considered with the synthesis of an interesting difluoro alkyl iodine. This part of the work, based on the reactivity of DFIT, is reported in Chapter 3.

Finally, research was conducted to synthesise a chiral aryliodo difluoride reagent (Chapter 4). The synthesis of such reagents is relevant because of the increasing demand of enantiopure organofluorine derivatives widely used in pharmaceutical and agrochemical industries.

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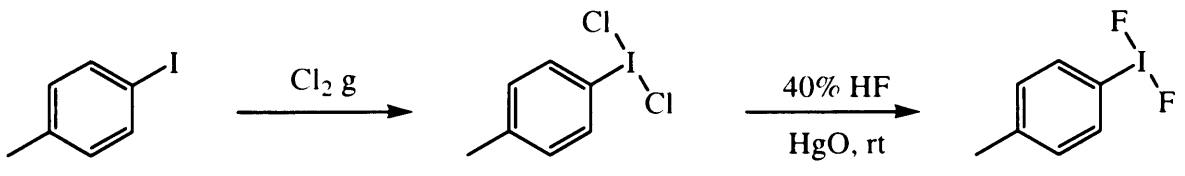
Chapter 2

2 Syntheses of aryl iodo difluoride reagents

2.1 Introduction

In this Chapter the synthesis of hypervalent iodine(III) difluorides will be reported. After a brief overview on the literature of known procedures for the synthesis of aryl iodine (III) difluorides, the new methodology adopted to prepare aryl iodo (III) difluorides with a particular emphasis on (difluoroiodo)toluene (DFIT) will be discussed. Subsequently, the applicability of the new route to the preparation of analogues hypervalent iodo difluoride reagents will be outlined.

Hypervalent iodine(III) difluorides were first synthesised in 1901 by Stille[1] and several methods for their preparation are known.[2] The most common method relies on the Carpenter method[3] involving two synthetic steps: the oxidation of the iodine atom realised with elemental chlorine (Cl_2) and subsequent ligand exchange of the resulting dichloride with HF in the presence of HgO (Scheme 2.1).



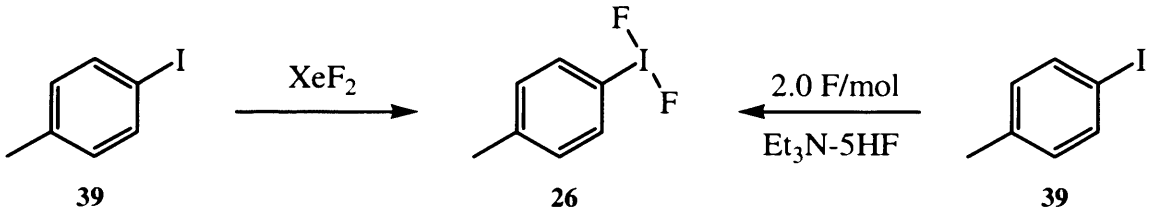
85% 95%

39 **23b** **26**

Scheme 2.1: The Carpenter method for the synthesis of DFIT.

The Carpenter method was first developed in 1966. After almost 50 years, this method is still the most commonly used in the synthesis of DFIT.

Other methods (Scheme 2.2) are possible for its synthesis but are less frequently used. The Zupan-Pollack[4] method is based on an oxidative fluorination with XeF_2. Also, the anodic oxidation,[5,6] using Et_3N-5HF[6] as an electrolyte, leads to DFIT in quite good yield, but requires special equipment such as Teflon® cells for the electrolysis. In fact, all preparation methods reported in the literature require the use of harmful and hazardous reagents making an alternative route highly desirable.



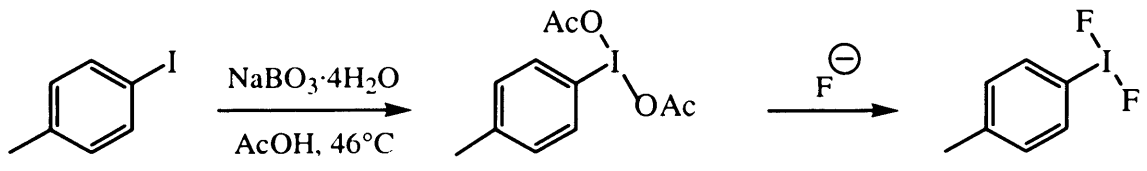
39 **26** **39**

Scheme 2.2: Zupan-Pollack (left) and electrochemical methods (right) used for the synthesis of DFIT **26**.

The synthesis of DFIT using an alternative route was the first aim of the research. In order to avoid reagents such as Cl_2 gas, XeF_2 or toxic heavy metal salts in the synthesis of DFIT, a different route has been devised.

2.2 Synthesis of (difluoroiodo)toluene 26

The synthesis of DFIT was first carried out using Carpenter's procedure to obtain DFIT as a reference sample. The new strategy (Scheme 2.3) for the synthesis of DFIT also involves two steps. First, it is necessary to oxidise the iodine atom. Secondly, a source of nucleophilic fluorine for the ligand exchange reaction must be used to complete the synthesis of DFIT.



39 **24** **26**

Scheme 2.3: New designeted route to the synthesis of DFIT **26**.

The synthesis of **24**, as described by the McKillop,[7] proceeds smoothly using $NaBO_3 \cdot 4H_2O$. To obtain DFIT by ligand exchange, the (diacetoxyiodo)toluene **24** was treated with different

sources of fluoride nucleophiles. Fluoride ion has been used from either alkaline metal or directly from hydrofluoric acid. The behaviour between MF (with M = Li, Na and Cs) and HF is quite different. Indeed using an alkaline fluoride, the formation of (difluoroiodo)toluene was not observed even when the time of reaction and/or the reaction temperature was increased. This is probably due to the low solubility of the metal fluorides in organic solvents and to the low nucleophilicity of the fluoride anion.

However, a completely different outcome was found when the reaction was performed in the presence of HF. In this reaction the (difluoroiodo)toluene is formed with different yields depending on the experimental conditions.

More experimental observations are reported.

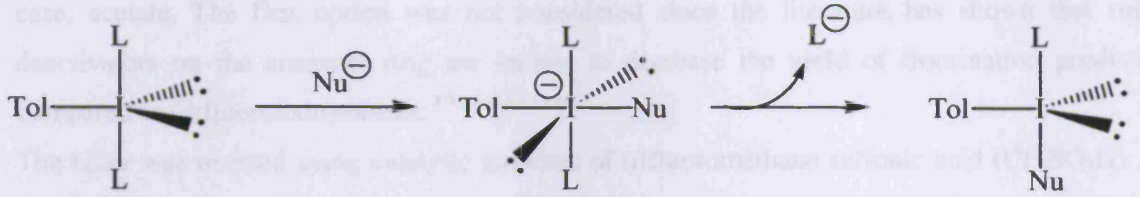
- Using an alkaline metal. The experiments performed with MF with M = Na, Li in aprotic solvents and polar solvents like DMSO/$CHCl_3$ or protic solvents like water or done in CH_2Cl_2 did not give any formation of DFIT. In such reactions mainly decomposition of diacetate **24** into iodotoluene was observed. The degree of the decomposition was correlated with the reaction time.

  Experiments performed with CsF in $MeO(CH_2)_2OMe$ at room temperature after one day showed the presence of roughly 50% starting material. In these conditions, at the end of the reaction, another component was found. That product, which was not identified, showed a completely different chemical shift in the ^{19}F NMR from DFIT. In addition, a small amount of iodotoluene was observed. After 6 days, a total decomposition of diacetate **24** into iodotoluene was observed. The same decomposition was also observed in the experiment performed with CsF at room temperature for 4 hours at room temperature plus 2 additionally hours at 60°C.

- Using HF. HF in CH_2Cl_2 produced (difluoroiodo)toluene in just 1 hour. From ^{19}F-NMR spectral analysis, it was possible to distinguish the presence of another two fluorinated compounds with peaks at -131ppm and -116 ppm. The peak at -131 ppm was a sharp singlet one-third the weight of the peak at -177 ppm attributed to DFIT, while the peak at -116 ppm appeared as a broad jagged singlet. The former may be attributed to partially fluorinated iodide (III), while the latter may be due to a coordination of the iodide(III) with traces of HF. The presence of the two components was also observed in the ^1H-NMR. The yield of DFIT obtained seems dependent on the reaction time. Indeed after 2 hours 46% of the (difluoroiodo)toluene was formed, while after three hours only 14% of DFIT was found (from NMR data) and the amount of the other two components increased.

From a mechanistic point of view, the ligand exchange involves an interconversion of the ligand already present on the I(III) with the a external nucleophile via a postulated addition-elimination sequence as reported in Scheme 2.4 for the first ligand exchange.[8] A detailed

mechanism for such a type of transformation is not known. Alternatively a dissociative pathway may be involved. Independent from the type of mechanism operating in the ligand exchange (associative or dissociative), the driving force of the reaction is the electrophilic nature of the iodine atom.



Scheme 2.4: Associative pathway involved in the ligand exchange.

The susceptibility of the iodine atom to a nucleophilic attack can be seen in the simulation model (Figure 2.1), obtained after optimisation of the steric contribution and considering the electronic density in the molecule. The presence of colours such as red and yellow in the iodine atom represents the high and medium electrophilicity of this centre, respectively.

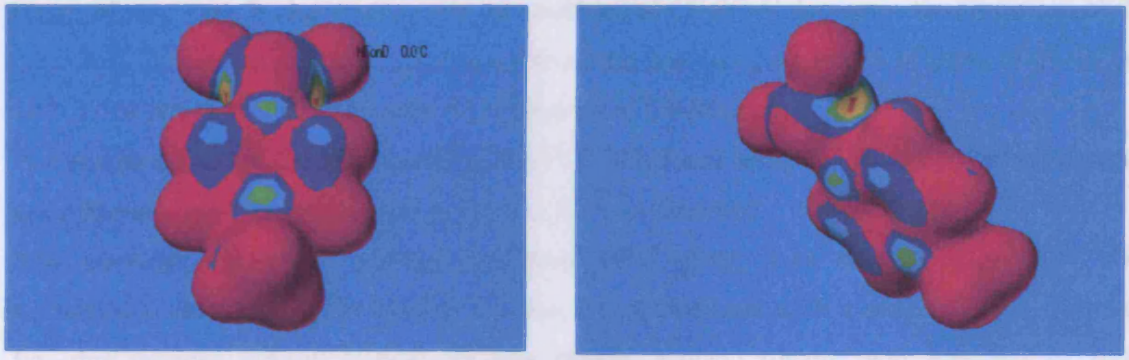


Figure 2.1: The susceptibility of **26** to a nucleophilic attack represented by colours on an electron density isosurface (generated using a MOPAC/PM3 wavefunction) using Quantum CAChe 5.04

The electrophilic nature of the iodine atom is due to the presence of a node in the filled non-bonding orbital as shown in Figure 2.2. The presence of the node implies a separation of charges with a consequent positive polarisation of the iodine atom.

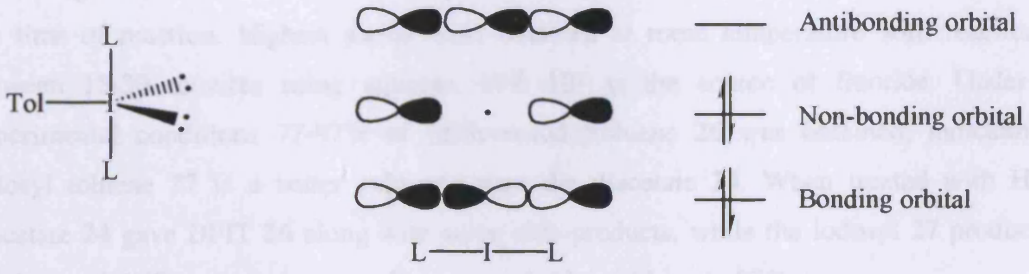


Figure 2.2: Orbital molecular involved in the 4e-3c bond over the hypervalent iodine substrates.

Having these concepts in mind, there are basically two possible ways to increase the nucleophilic attack of the fluorine on (diacetoxyiodo)toluene (Scheme 2.3). The first way is to increase the electrophilic nature of the iodine atom. This could be achieved by modifying the structure using an electron-withdrawing group on the aromatic ring. The second way would involve increasing the leaving group ability of the ligand on the I(III) atom, in this particular case, acetate. The first option was not considered since the literature has shown that ring deactivators on the aromatic ring are known to decrease the yield of fluorination products compared to (difluoroiodo)toluene.[3,9,10,11,12,13,14]

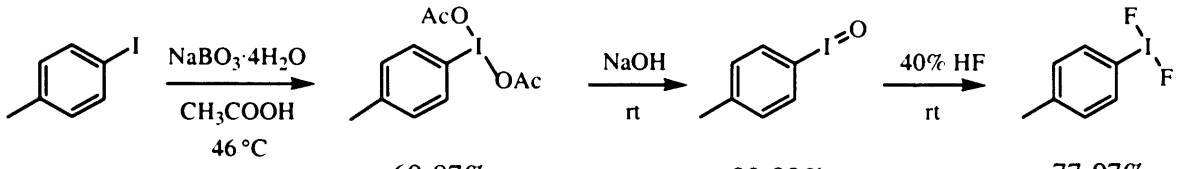
The latter was realised using catalytic amounts of trifluoromethane sulfonic acid (CF_3SO_3H): a strong acid with a weak conjugate base, which it is not able to act as a competitive nucleophile. The use of CF_3SO_3H helped indeed to increase the yield of DFIT. For the experiment carried out with diacetate **24** and CF_3SO_3H in presence of HF, the formation of DFIT was observed after 1 hour of reaction. Under these conditions, 72% yield of (difluoroiodo)toluene was obtained together with a small amount of two other unidentified components (the same components were also found for the reaction performed using only HF) and iodotoluene (respectively 1%, 14% and 13% from NMR data assuming that the aromatic ring is not the centre of reaction). It also appears that the presence of CF_3SO_3H decreases the formation of the other two fluorinated products. After three hours the reaction gave a 62% of yield of **26** instead 14% in the reaction conducted with HF in absence of CF_3SO_3H.

The results found working in the presence of CF_3SO_3H and using CsF as the source of fluoride are different as in this case no formation of DFIT was observed.

The reactions previously reported produced DFIT along with some side-products. The nucleophilic attack from the fluoride ion was then carried out with a parental I(III) substrate. For this purpose iodosyl toluene **27** was chosen. Iodosyl toluene was prepared by basic hydrolysis of (diacetoxyiodo)toluene **24** using 6 equivalents of aqueous 5M NaOH in a period of 45 minutes. Under these conditions iodosyl toluene **27** was obtained in 90-99% yield (Scheme 2.5).

In analogy with (diacetoxyiodo)toluene **24**, iodosyl toluene was treated with CsF and HF. Using CsF no formation of the desired difluoride was observed, in analogy with what found for (diacetoxyiodo)toluene **24**. With 40% HF, the amount of difluoride obtained was dependent on the time of reaction. Highest yields were obtained at room temperature with reaction time between 15-30 minutes using aqueous 40% HF as the source of fluoride. Under these experimental conditions 77-97% of (difluoroiodo)toluene **26** was obtained, indicating that iodosyl toluene **27** is a better substrate than the diacetate **24**. When treated with HF, the diacetate **24** gave DFIT **26** along with some side-products, while the iodosyl **27** produced the synthesis of DFIT in high purity and in a remarkable yield, up to 97%.

To summarise, an alternative synthesis of DFIT has been developed which involves the following three steps: perborate oxidation, basic hydrolysis and reaction with aqueous HF (Scheme 2.5). The oxidation of iodotoluene proceeds smoothly.[7] Basic hydrolysis with elimination allows for the conversion of the (diacetoxyiodo)toluene into iodosyltoluene **27**, which is then fluorinated using 40% HF.

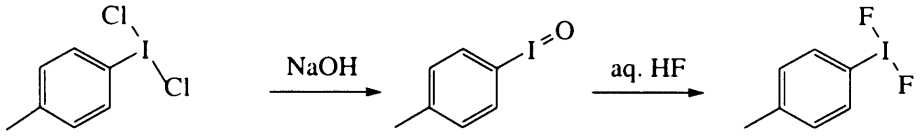


39 **24** **27** **26**

Scheme 2.5: Synthesis of DFIT **26** by basic hydrolysis of iodosyltoluene and successive treatment with hydrofluoric acid.

This alternative synthesis of DFIT avoids the use of harmful and hazardous reagent such as Cl_2 gas, XeF_2 or toxic heavy metal salts such as HgO.

Recently, an alternative synthesis[15] was published which involves the preparation of the dichloride **23b** as reported in Scheme 2.6.



23b **27** **26**

Scheme 2.6: Reported synthesis of DFIT **26** carried out by Hara and co-workers[15].

In our synthesis we avoided the synthesis of the dichloride, which is notoriously unstable and is light and heat-sensitive. On the other hand (diacetoxyiodo)toluene is a stable crystalline compound which can be stored for long periods of time. Furthermore, the overall yield reported by Hara and co-workers is around 80% starting from the dichloride while, in our procedure, the difluoride can be obtained in an overall yield of up to 97% starting from (diacetoxyiodo)toluene.

2.3 Application to new difluorides

The previous method was then also applied to various substrates allowing for the synthesis of other (difluoroiodo)aryl reagents. As reported below, the method appears to be general. In particular, new difluorides were obtained using iodo naphthalenes and 2-iodo benzoic acid.

These particular substrates were chosen because of the potential applicability in enantioselective fluorinations, a subject that will be developed in Chapter 4.

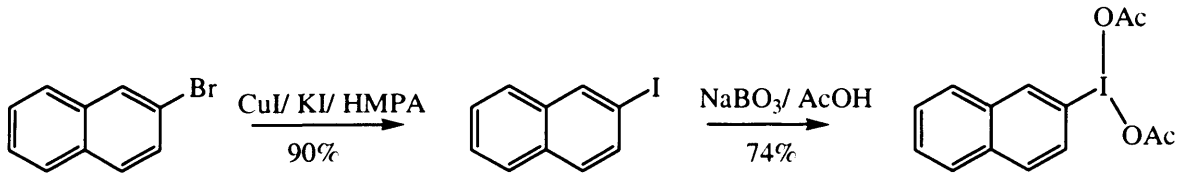
2.3.1 Naphthalene substrates

1-Iodo naphthalene **45** and 2-iodo naphthalene **41** were used as precursors in the synthesis of the corresponding difluorides. The first is commercially available while the second was synthesised from the 2-bromo naphthalene **40** using two different protocols of halogen exchange. The results, reported in Table 2.1, illustrate that the best yield was found using CuI[16,17] instead of Ni.[18] The synthesis of **41** by halogen exchange in presence of CuI was already described in the literature,[17] and the obtained yield is consistent with the literature data.

Table 2.1: Conditions used and yields in the halogen exchange

Substrate	Conditions	Yield
2-bromo-naphthalene	KI (10 eq), Ni (10 eq), I_2 (5 eq), DMF 170-180°C, 2 days	73%
2-bromo-naphthalene	KI (10 eq), CuI (5 eq), HMPA 170-180°C, 7h	90%

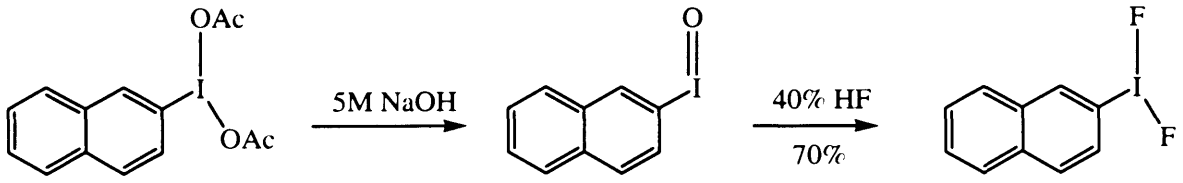
The oxidation of 2-iodo naphthalene **41** was straightforward as shown in Scheme 2.7.



40 **41** **42**

Scheme 2.7: Synthesis of 2-(diacetoxyiodo)naphthalene **42**.

Successive basic hydrolysis of the diacetate derivative **42** and addition of 40% HF gave the difluoride in 70% yield (Scheme 2.8).

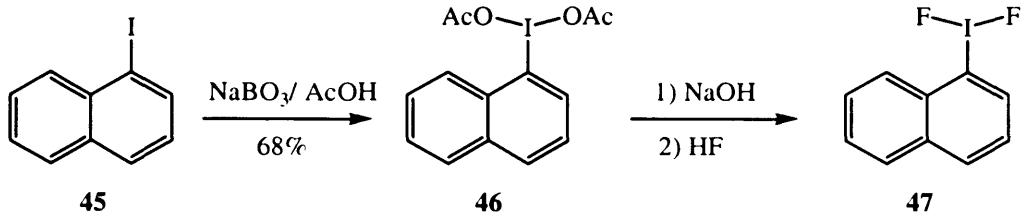


42 **43** **44**

Scheme 2.8: Synthesis of 2-(difluoroiodo)naphthalene **44**.

This difluoride **44**, at a first attempt, appeared to be unstable in the solid state, turning from crystalline yellow powder into a black material with fuming. However, in successive attempts, after washing it with hexane, the product could be isolated and its spectroscopic data were recorded.

The McKillop procedure was also applied to the synthesis of 1-(diacetoxyiodo)naphthalene **46** (Scheme 2.9).



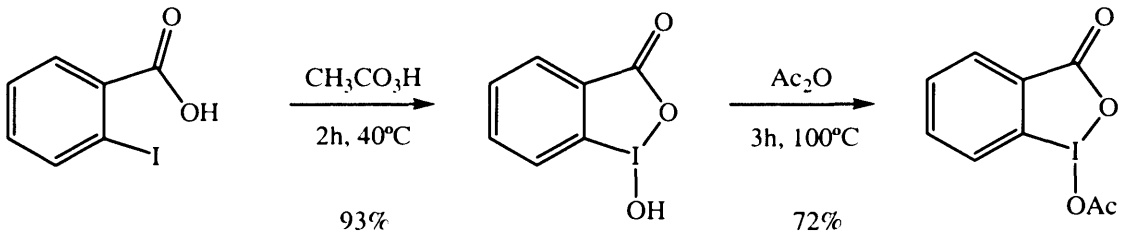
45 **46** **47**

Scheme 2.9: Synthesis of 1-(difluoroiodo)naphthalene **47**.

The consequent hydrolysis and reaction with HF was carried out. In analysing the crude reaction, the difluoride **47** could not be isolated by washing with hexane. A peak in the ^{19}F NMR was, however, found at -166.61 ppm as a sharp singlet. The peak is consistent with the presence of a hypervalent iodinedifluoride such as **47**.

2.3.2. Substrates from 2-iodo benzoic acid

We started with the synthesis of iodoso benzoic acid **28** (IBA) and the corresponding acetate derivative from the commercially available 2-iodobenzoic acid **48** following the protocol reported in the literature.[19] Oxidation with peracetic acid produced **28**, which was converted into the analogue acetate **49** refluxing the latter in acetic anhydride. These steps of reactions are summarised in Scheme 2.10.



48 **28** **49**

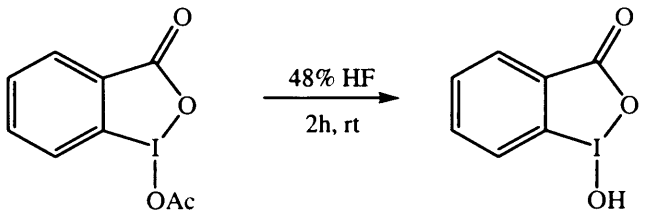
Scheme 2.10: Synthesis of IBA **28** and its acetate derivative **49**.

The presence of an electron withdrawing substituent in the *ortho* position to the iodine atom in IBA **28** should, as reported in the literature, inhibit the fluorination reaction. But the

incorporation of the iodine in a 5-membered ring is a more important feature because it increases the stability of the whole molecule. The high stability of the cyclic hypervalent iodine reagents made possible the isolation of unstable compounds, such for instance the bromo-benziodoxole.[20]

The synthesis of the corresponding fluoro-benziodoxole was performed starting not only from IBA **28** (corresponding to the iodsosyltoluene), but also from iodobenzoic acid **48** and from the acetate derivative **49**, applying for each one the opportune protocol.

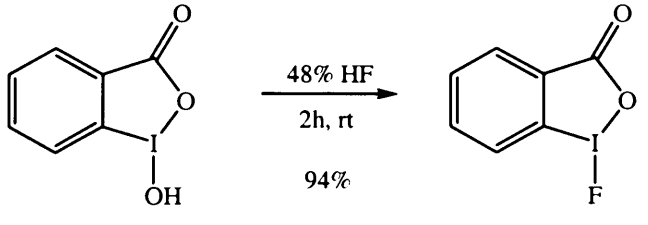
The insertion of fluoride was attempted letting benziodoxoles **28** and **49** react in the presence of HF. IBA **28** and the acetate **49** showed different behaviour when treated with HF. The substrate **49** after 2 hours stirring with HF gave IBA **28**. This could be due to the hydrolysable character of acetoxy benziodoxole **49**. The presence of water in the HF solution used would be a possible explanation for this result. In fact, IBA **28** can be obtained by a simple hydrolysis with water[21] of the corresponding acetate **49**.



49 **28**

Scheme 2.11: Hydrolysis of acetoxy benziodoxole **49** with aqueous hydrofluoric acid.

Different behaviour was observed for the hydroxyl compound, **28**. This compound, insoluble in the most organic solvent, reacted with HF. The compound obtained showed a fluorine peak at -171.16 ppm as a singlet. This value is typical for an I-F bond in a hypervalent iodine compound, in which iodine is in oxidation state III. These spectroscopic data and the microanalysis indicate that the synthesised compound is the fluoro benziodoxole derivative **50**. This white crystalline solid, obtained in 90-94% yield, is fairly stable as it starts to decompose at 180°C and completely melts at 232°C. It is worth mentioning that the yield of the fluorine derivative decreased when the reaction mixture was stirred for periods of time longer than 2 hours. For instance, after 3 hours a 83% yield was recovered.



28 **50**

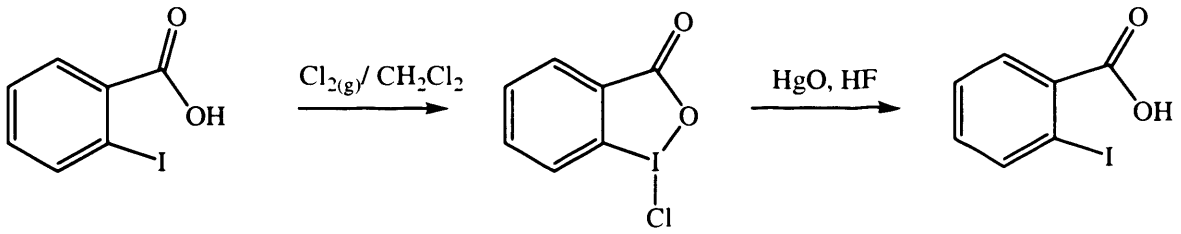
Scheme 2.12: Hydrolysis of IBA **28** with aqueous hydrofluoric acid.

IBA **28** and acetate **49** revealed to have different chemical reactivity when treated with HF as the acetate **49** produced IBA **28** while IBA gave the fluoro derivative **50**. Since the two reactions were performed using the same reaction time (2 hours) it could be possible that a longer reaction time is necessary to effect acetate **49** conversion to the fluoride **50** via the hydroxyl **28**.

As reported in Section 2.1, different routes for the synthesis of iodo difluorides are possible. In the next Sections, the traditional methods of Carpenter and the oxidative fluorination with XeF_2 of Zupan-Pollack were evaluated for the synthesis of fluoro benziodoxole **50**. The results obtained are then compared with the hydrolysis of IBA in hydrofluoric acid.

2.3.2.1 Carpenter method

Scheme 2.13 illustrates the synthetic steps in the attempt to synthesise fluoro benziodoxole **50** by applying the Carpenter method.



48 **51** **48**

Scheme 2.13: Carpenter method applied in the synthesis of fluoro benziodoxole **50**.

Initially, the oxidation over the monovalent iodine through chlorination led to a 1:1 mixture of chloro derivative **51** and starting material. The subsequent hydrolysis with hydrofluoric acid, in presence of mercuric oxide, did not lead to the fluorination of **51** but iodobenzoic acid **48** was recovered as the final product of reaction. This could be due either to a redox reaction in the reaction medium, or to a decomposition of the chloro-benziodoxole **51**.

2.3.2.2 Oxidative fluorination with XeF_2

The oxidative fluorination with XeF_2, a synthetic procedure used in the preparation of DFIT according to the Zupan-Pollack method,[4] was applied to obtain fluoro benziodoxole **50**. This method has general applicability since several oxidations using XeF_2 are reported in the literature not only to oxidise the iodine[4,22] but also other atoms such as phosphorus,[22] tellurium,[23,24] arsenic[22] and bismuth.[25]

Three different molecules were used as substrates for the oxidative fluorination: iodobenzoic acid, the isopropyl ester **52** and the amide derivative **53**. XeF_2 is stable in CH_3CN at -30°C or in

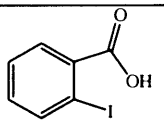
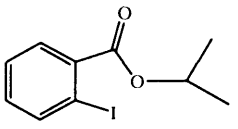
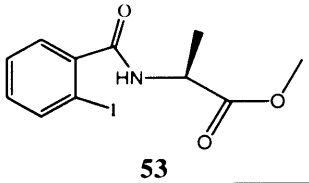
CH_2Cl_2 at -70°C while, in other solvents or at higher temperatures from those indicated decomposition results. It is also known that XeF_2 can react with carboxylic acids obtaining fluoro-decarboxylation as shown in Scheme 2.14. Patrick and co-workers[26] explained the several possible mechanisms operating in decarboxylation promoted by the formation of a xenon ester.

$$RCOOH + XeF_2 \longrightarrow RCOOXeF + HF$$
$$RCOOXeF + F^- \longrightarrow RF + CO_2 + Xe + F^-$$
$$RCOOXeF \longrightarrow R^{\bullet} + CO_2 + \dot{X}eF$$
$$R^{\bullet} + \dot{X}eF \longrightarrow RF + Xe$$
$$R^{\bullet} + \dot{X}eF \longrightarrow R^+ + Xe + F^-$$
$$R^+ + F^- \longrightarrow RF$$

Scheme 2.14: Possible mechanisms operating in the fluoro-decarboxylation in reactions conducted in presence of XeF_2.

Having concerns about this possible side reaction, the oxidative fluorination was performed with iodobenzoic acid **48**, the isopropyl ester **52** and the amide derivative **53**. The results of these experiments are summarised in Table 2.2. The reaction solvents used were either acetonitrile or dichloromethane (depending on the substrate) at -30°C, in round bottom flasks made of Teflon®. It is reported that for the reaction with XeF_2 not only the choice of the solvent can influence the success of the reaction but even the material of the reaction vessel is an important variable.[27]

Table 2.2: Oxidation of 2-iodo benzoic acid **48** and its derivatives **52** and **53** with XeF_2.

Entry	Substrates	Conditions[a]			Results
		Ratio[b]	Hours	Solvent	I(III): S.M.
1	 **48**	1:1	18h	CH_3CN	1:1
		1:1	2 days	CH_3CN	0:1
		1:2	6h	CH_3CN	0:1
		1:2	20h	CH_3CN	1:1
2	 **52**	1:1	18h	CH_2Cl_2	1:1
		1:1	2 days	CH_3CN	0:1
		1:2	4h	CH_3CN	0:1
		1:2	20h	CH_3CN	0:1
3	 **53**	1:1	6h	CH_3CN	0:1
		1:1	23h	CH_3CN	0:1
		1:2	6h	CH_3CN	0:1
		1:2	23h	CH_3CN	1:1

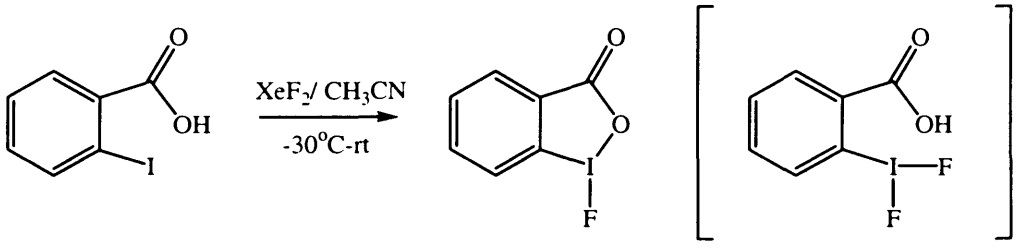
a) Temperature was -30°C for all the experiments.
b) Ratio refers to the used equivalents between substrate: XeF_2

With both substrates iodo benzoic acid and its isopropyl ester derivative, one equivalent of XeF_2 gave an oxidised compound deducible from the peak, in ^1H NMR, with chemical shift at around 8.2 ppm derived from the presence of hypervalent iodine (III) product. After 18 hours of reaction, the starting material was still present in both the experiments when a 1:1 equivalent ratio was used. For longer reaction time (2 days) and one equivalent of XeF_2, no oxidation took place and the iodobenzoic acid **48** or the isopropyl ester **52** were found to be the only constituents of the final reaction mixture. When 2 equivalents of XeF_2 were used for short periods of time (respectively 6 h for **48** and 4 h for **52** in Table 2.2) no trivalent species were detected. When 2 equivalents of XeF_2 were used with 2-iodo benzoic acid, a mixture 1:1 of trivalent and monovalent (starting material) iodine was observed.

With the amide **53** no oxidation was observed using 1 equivalent of XeF_2. For this substrate only the presence of 2 equivalents of the oxidising reagent led to a 1:1 mixture between monovalent and trivalent iodine derivatives after 23 h of reaction.

Under all the experimental conditions the reaction did not reach completion and only a partial oxidation was observed. This behaviour may be due to the presence of the electron withdrawing group *ortho* to the iodine. This group can be responsible for the reduced availability of the electron pairs of the iodine atom in the oxidation process.

It is worth mentioning that the resulting chemical shifts of the product derived from the oxidation of iodobenzoic acid with XeF_2 are very similar to those of fluoro benziodoxole **50** synthesised by simple ligand exchange of IBA with HF. This suggests that this oxidised species is fluoro benziodoxole **50**. When iodobenzoic acid is treated with XeF_2 the oxidation of the iodine might give a difluoride **54** as shown in Scheme 2.15.



48 **50** **54**

Scheme 2.15: Oxidation of 2-iodobenzoic acid **48** with XeF_2.

By general comparison with analogous benziodoxoles, it is reasonable to assume that the open difluoride **54** is less stable than the cyclic one **50**. Moreover, the analogous chloro benziodoxole **51** is formed first as an open dichloride and rapidly converts to the cyclic monochloride with loss of hydrochloric acid.[28,29] In analogy with the chloro derivative **51**, a similar mechanism can

also be assumed for the fluoro benziodoxole with consequent production of the cyclic form **50** rather than the open one **54**.

2.4. Conclusions

In this Chapter an alternative synthetic route for the preparation of DFIT, an hypervalent iodine (III) reagent used as a fluorine transfer reagent, has been reported. The classical methods for its preparation were developed by Carpenter and Zupan-Pollack. The alternative synthesis is realised by three synthetic steps: a perborate oxidation, basic hydrolysis and subsequent reaction with hydrofluoric acid. This alternative route offers the following advantages:

- it avoids the use of particular dangerous reagents such as XeF_2, strong oxidants like Cl_2 gas or heavy metal salts of mercury which are expensive to dispose
- remarkable purity and overall yield which was up to 97%
- general applicability to the synthesis of new difluoride reagents.

For this last point, the synthesis of new fluoride hypervalent reagents based on the naphthalene moiety and on the 2-iodobenzoic acid was reported. The synthesis of these new potential fluorinating reagents proceeded smoothly with high yields (70% for 2-(difluoroiodo)naphthalene and up to 94% for fluoro benziodoxole). In the case of fluoro benziodoxole, different routes were evaluated and compared. The Carpenter method failed in its preparation while the oxidative fluorination by XeF_2 produced a partial oxidation of the used precursor. In contrast with the previous methods, the reaction of IBA with aqueous hydrofluoric acid seems the only way to its preparation.

During this Chapter, it has been also reported that it is possible to interconvert the (diacetoxyiodo)toluene into DFIT using hydrofluoric acid (or hydrofluoric acid and trifluoromethyl sulfonic acid), although the difluoride is contaminated with other side-products.

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Chapter 3

3 Reactivity of (difluoroiodo)toluene with organoselenium substrates

3.1 Introduction

From analysing the number of publications (these numbers refer to December 2004 from SciFinder using the keywords "hypervalent iodine" and "difluoride iodides") is possible to see the growing interest in the field of hypervalent iodine chemistry. The graph shown in Figure 3.1 illustrates the research conducted during the decades in the general field of hypervalent iodine compared with the research involved for difluorides. Looking at the graph, the data reveal that the attention dedicated to the difluorides (first row) is only 8% of the total research conducted in the field of hypervalent iodine.[1]

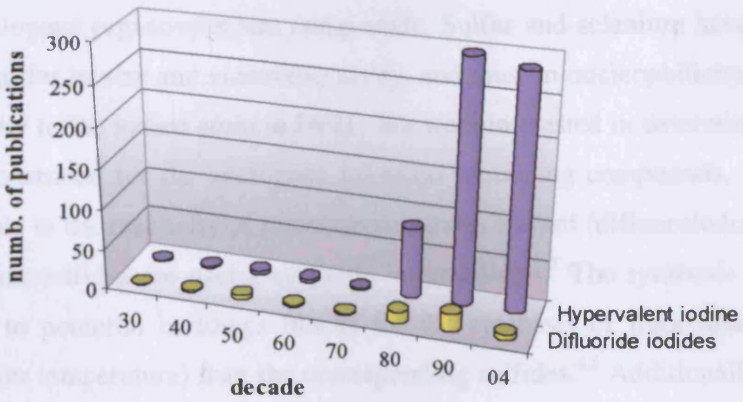
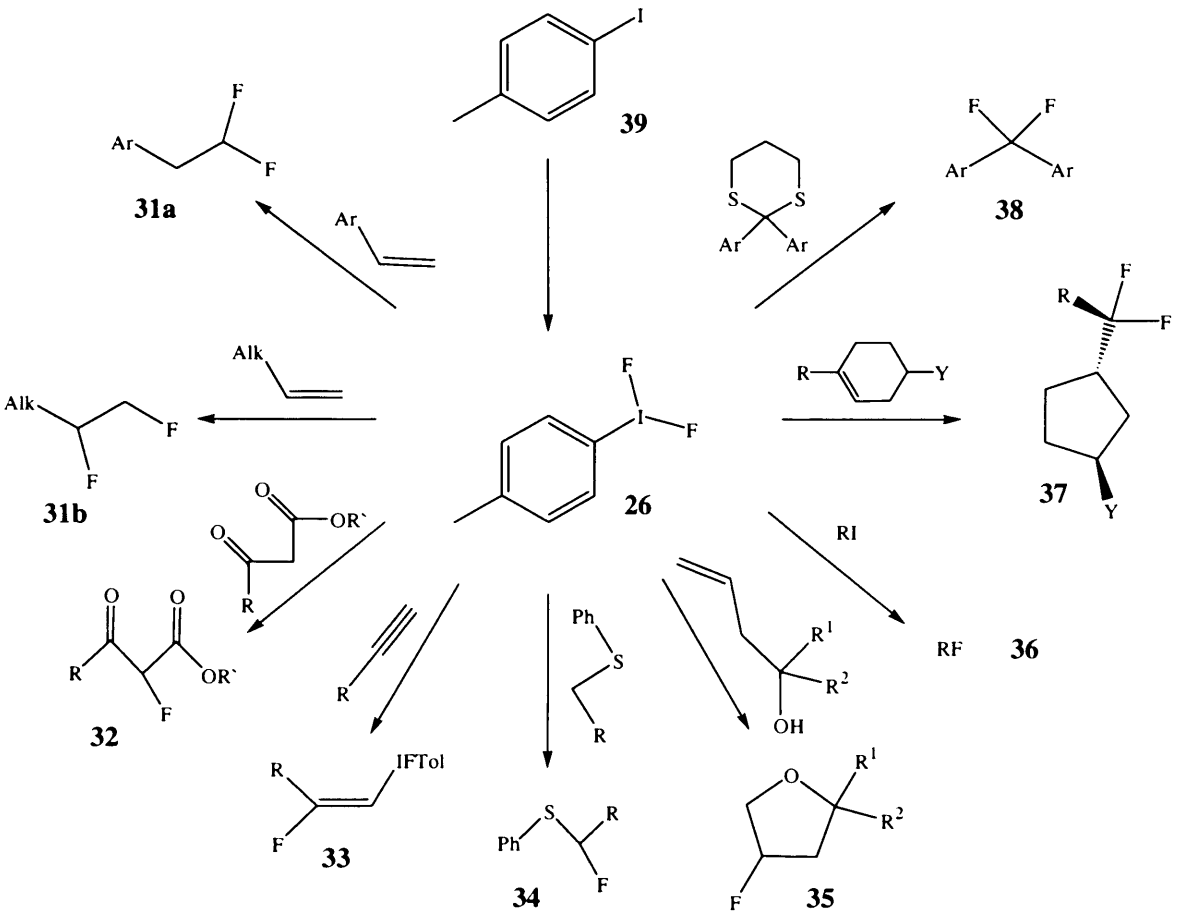


Figure 3.1: Number of publications on the field of hypervalent iodine and iodo-difluorides as a function of decades.

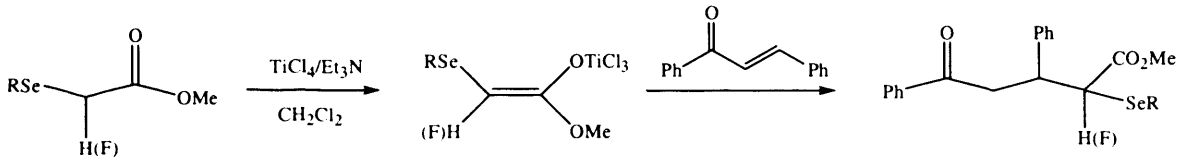
Although this limited research, the (difluoroiodo)toluene **26** has been proved to be as a versatile fluorinating reagents as shown in Scheme 3.1. These reactions have been previously discussed in Section 1.4.3.



Scheme 3.1: Reaction of (difluoroiodo)toluene **26** with different functional groups.

The fluorination reactions of different classes of sulfur containing molecules using DFIT have been investigated in details by Motherwell[2] et al. On the other hand very little attention has been paid to the analogous organoselenium compounds. Sulfur and selenium have similar chemical reactivity, but differ in size and electronegativity, and thus, in nucleophilicity. Sulfur exhibits a particular affinity to the iodine atom in DFIT. We were interested in determining if that affinity would be demonstrated for the analogous selenium-containing compounds, which would play an important role in the reactivity of selenium substrates toward (difluoroiodo)toluene. It is well known that fluorosulfides are useful synthetic intermediates.[3] The synthesis of fluoroselenides will also lead to potential buildings blocks for the synthesis of fluoroalkenes under milder conditions (lower temperature) than the corresponding sulfides.[4,5] Additionally, the synthesis of functionalised fluoro-selanyl esters **57** from fluoro-selanyl esters **55** can be used as a useful and

versatile method (Scheme 3.2). This synthetic step was already used without the presence of fluorine.[6]



55 56 57

Scheme 3.2: Synthesis of functionalized fluoro-selanyl esters **57** from fluoro selanyl esters **55**. These synthetic steps were already used without the presence of fluorine.

The selanyl substituent as an easily removable group can be used in subsequent synthetic steps exploiting the rich chemistry of selenium. As shown in Figure 3.2, the selanyl group can be easily removed in several ways.[7]

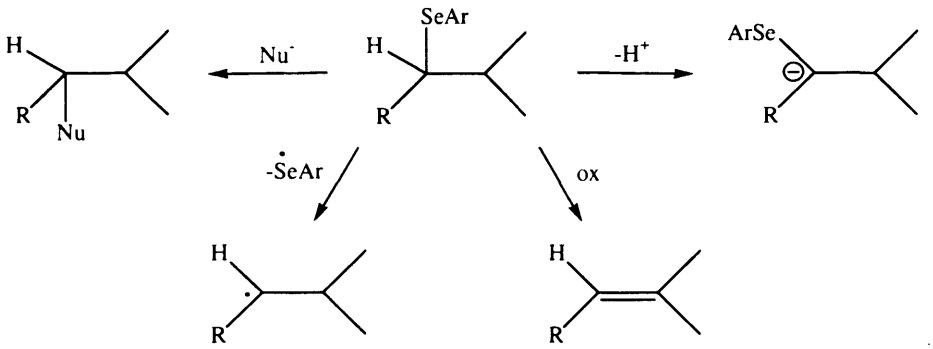


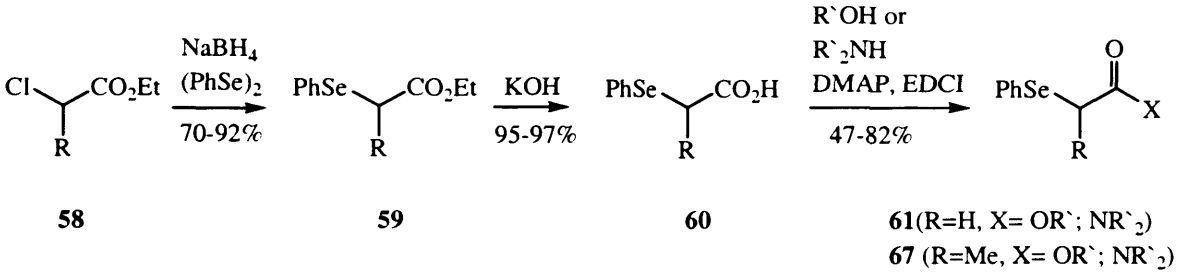
Figure 3.2: An overview of the reactivity of selanyl substrates.

Nucleophilic attack, homolytic radical cleaveage or oxidation to selenoxide and subsequent β-elimination with formation of the double bond are synthetic approaches widely use in organic synthesis. Additionally the use of organo-lithium compounds allows the synthesis of selenium carbanions, which can be used as valuable intermediates.

3.2 Reactivity of organoselenium substrates towards (difluoroiodo)toluene

3.2.1 Preparation of organoselenium substrates

Organoselenium substrates were easily prepared by α-selenenylation of commercially available α-chloro esters **58** using $(PhSe)_2/NaBH_4$ as shown in Scheme 3.2. Subsequent hydrolysis to the corresponding carboxylic acid **60** and reaction with the appropriate alcohol or amine after activation with DMAP and EDCI gave a range of organoselenium substrates **61** for the investigation of fluorinations with (difluoroiodo)toluene.



Scheme 3.2: Synthesis of α-selanylesters and α-selanylamides **61**.

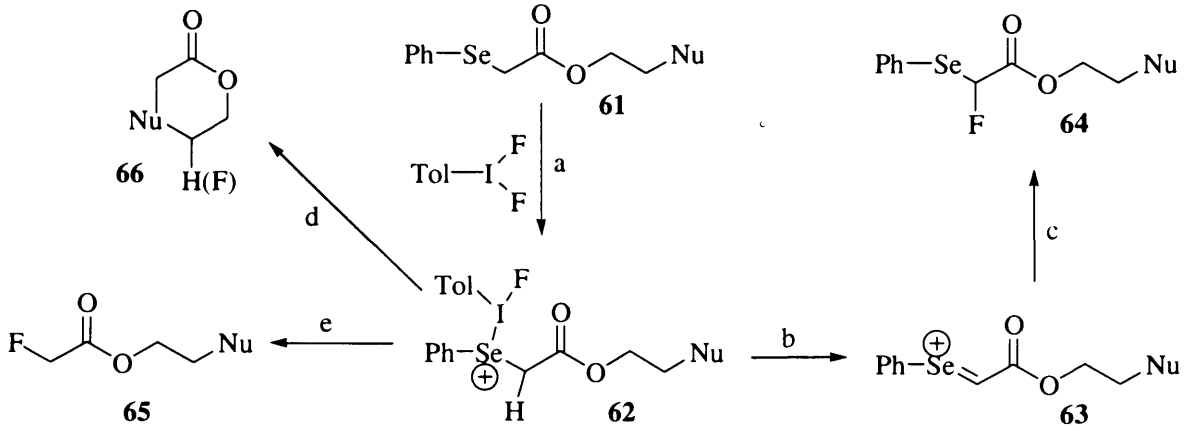
In Table 3.1 the yields of the synthesised organoselenium substrates from the acid **60** are reported.

Table 3.1: Yields of the α-phenylselanylesters and α-phenylselanylamides from the acid **60**

Substrate			Yield%	Substrate			Yield%
61a	R = H	X = OEt	92%	**61i**	R = H	X = $NHCH_3$	66%
61b	R = H	X = OPh	75%	**61l**	R = H	X = $N(CH_3)_2$	80%
61c	R = H	X = $OCH_2CH{=}CH_2$	72%	**61m**	R = H	X = NHPh	64%
61d	R = H	X = $OCH_2CH{=}C(CH_3)_2$	70%	**61n**	R = H	X = $N(CH_3)Ph$	45%
61e	R = H	X = (*E*)-$OCH_2CH{=}CHPh$	76%	**61o**	R = H	X = $NHCH_2Ph$	83%
61f	R = H	X = $OCH_2CH_2C(CH_3){=}CH_2$	70%	**67a**	R = Me	X = OEt	70%
61g	R = H	X = $OCH_2C{\equiv}CH$	76%	**67b**	R = Me	X = NHPh	79%
61h	R = H	X = OCH_2CH_2OH	47%	**67c**	R = Me	X = $N(CH_3)Ph$	82%

3.2.2 General mechanistic pathway of DFIT with seleno substrates

From a mechanistic point of view, the possibilities of reactivity of selanyl esters with DFIT are several as illustrated in Scheme 3.3.



Scheme 3.3: An overview of the possible operating mechanisms.

Attack of the hypervalent iodine by the selenium atom, with loss of fluoride will generate the selenium cation shown. Elimination and then fluorination would give the monofluorinated selanyl ester **64** (path a/b/c in Scheme 3.3). Alternatively, there is a possibility of displacing the selanyl group using a nucleophile. The C-Se bond (58 kcal/mol) is notoriously much weaker than the analogous C-S bond (73 kcal/mol). Additionally, the PhSe-ITol(F)$^+$ group exhibits hypernucleofugicity. These characteristics could lead, in principle, to the substitution of the phenylselanyl group in the same reaction pot by an internal nucleophile. This would lead to the formation of lactones **66** (path a/d in Scheme 3.3), or by reaction with fluoride to give fluoro esters **65** (path a/e in Scheme 3.3). The process of activation of selenides by electrophiles is a known mechanism and largely employed as a very efficient synthetic tool. In the presence of more than 1 equivalent of DFIT, it would be possible to obtain difluorides by a second Pummerer reaction. Moreover the fluorine transfer leading to fluorophenylselanyl esters **64** (path a/b/c in Scheme 3.3) may occur in a concerted or stepwise way.

In order to evaluate all these mechanistic possibilities, different substrates were tested. Some of them contain a nucleophile such as multiple bonds or a hydroxy group, in the hope of detecting products of a substitution reaction via the formation of a lactone.

3.2.3 Fluorinations of seleno esters and amides with DFIT

Before embarking on the reaction of different substrates **61**, we initially followed the reaction of some selected substrates and analysed their behaviour under different reaction conditions in order for finding optimal yields. Various temperatures (0°C → 25°C, 40°C) and different ratios of (difluoroiodo)toluene: substrate were investigated. In Figure 3.3, the separated yields for phenylselanyl ethyl acetate **61a** and phenylselanyl phenyl acetate **61b** in different experimental conditions are shown. The experiments were carried out in Teflon® vessels. The use of this material is of crucial importance for the success of the reaction. In fact, experiments performed in common glassware (Section 3.5) showed that the fluorination reactions did not occur.

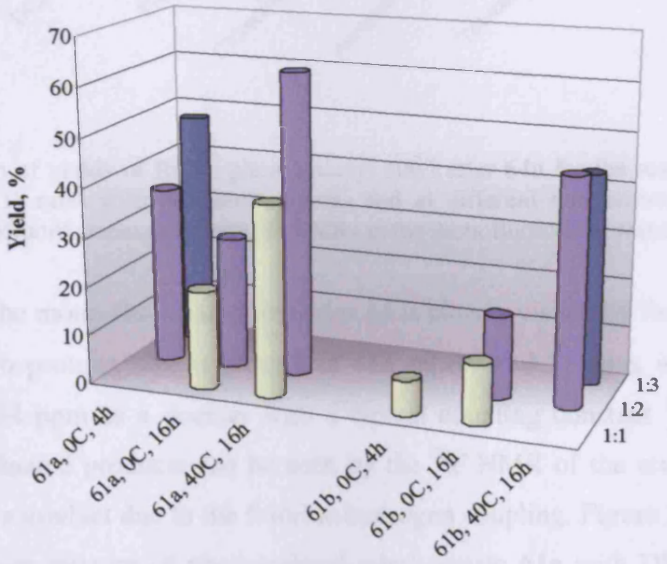


Figure 3.3: Isolated yields of monofluoro derivatives from $PhSeCH_2CO_2Et$ **61a** and $PhSeCH_2CO_2Ph$ **61b** under different experimental conditions.

Reactions employing a 1:1 molar ratio of **26**:**61** (either at 0°C or at 40°C) showed, after a reaction time of 16 hours, still significant amounts of starting material. For shorter reaction times (4 h), again with a 1:1 ratio of reagent:substrate at 0°C, the starting material was found to be the major component of the reaction mixture. Increasing the temperature and the reaction time until 16 hours and using an excess (2 equivalents) of (difluoroiodo)toluene, increased the yield of the monofluorinated product.

Several solvents differing in polarity and boiling points were also investigated. An increase in the reaction temperature affected positively the ratio between the monofluorinated product and the starting material, but even working at 100°C (e.g. toluene), a complete conversion was not observed with a 1:1 ratio of reagent to substrate. In Figure 3.4, the isolated yields of monofluoroderivate and the ratio between the monofluoro and the starting material for reactions

carried out with **61a** are reported. The ratios were deduced by ^{1}H NMR of the crude and inseparable mixture of the two components.

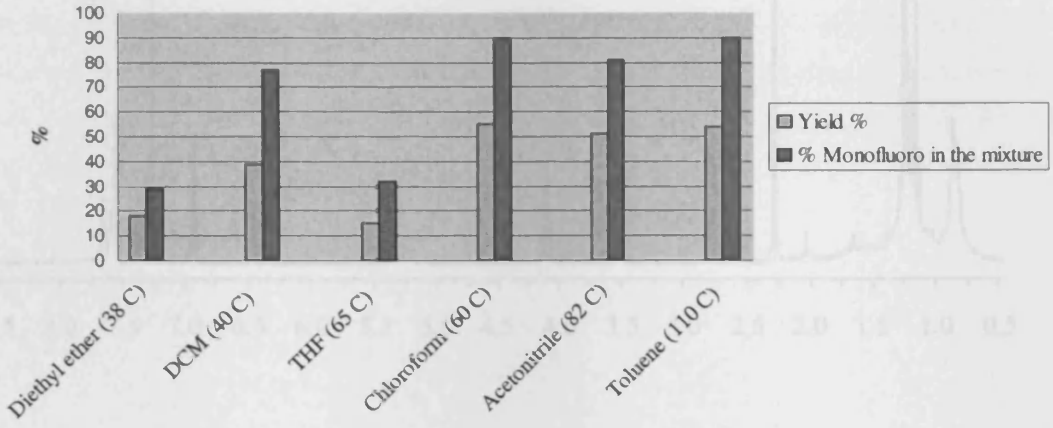


Figure 3.4: Diagram of yields of fluoro-phenylselanyl ethyl ester **64a** for the reactions carried out with DFIT and **61a** in 1:1 ratio with different solvents and at different temperatures. The corresponding percents of the monofluoro (measured from ^{1}H NMR) in the monofluoro:S.M.mixtures are also reported.

The formation of the mono-fluorinated selenides **64** is clearly visible by the ^{1}H NMR signal and integration of the α-protons. The α-protons of **61a** appear at 3.51 ppm, while the α-proton of **64a** appears at 6.34 ppm as a doublet with a typical coupling constant $^{1}J_{H,F}$ = 51.7 Hz. The absence of difluorinated products can be seen by the ^{19}F NMR of the crude reaction mixture, which shows only a doublet due to the fluorine-hydrogen coupling. Figure 3.5 shows the spectra of the crude reaction mixture of phenylselanyl ethyl acetate **61a** with DFIT (1:1 equivalents) carried out at 40°C for 16 hours. In the same Figure, the spectra of the pure starting material phenylselanyl ethyl acetate **61a** and the pure product fluoro phenylselanyl ethyl acetate **64a** are shown as well.

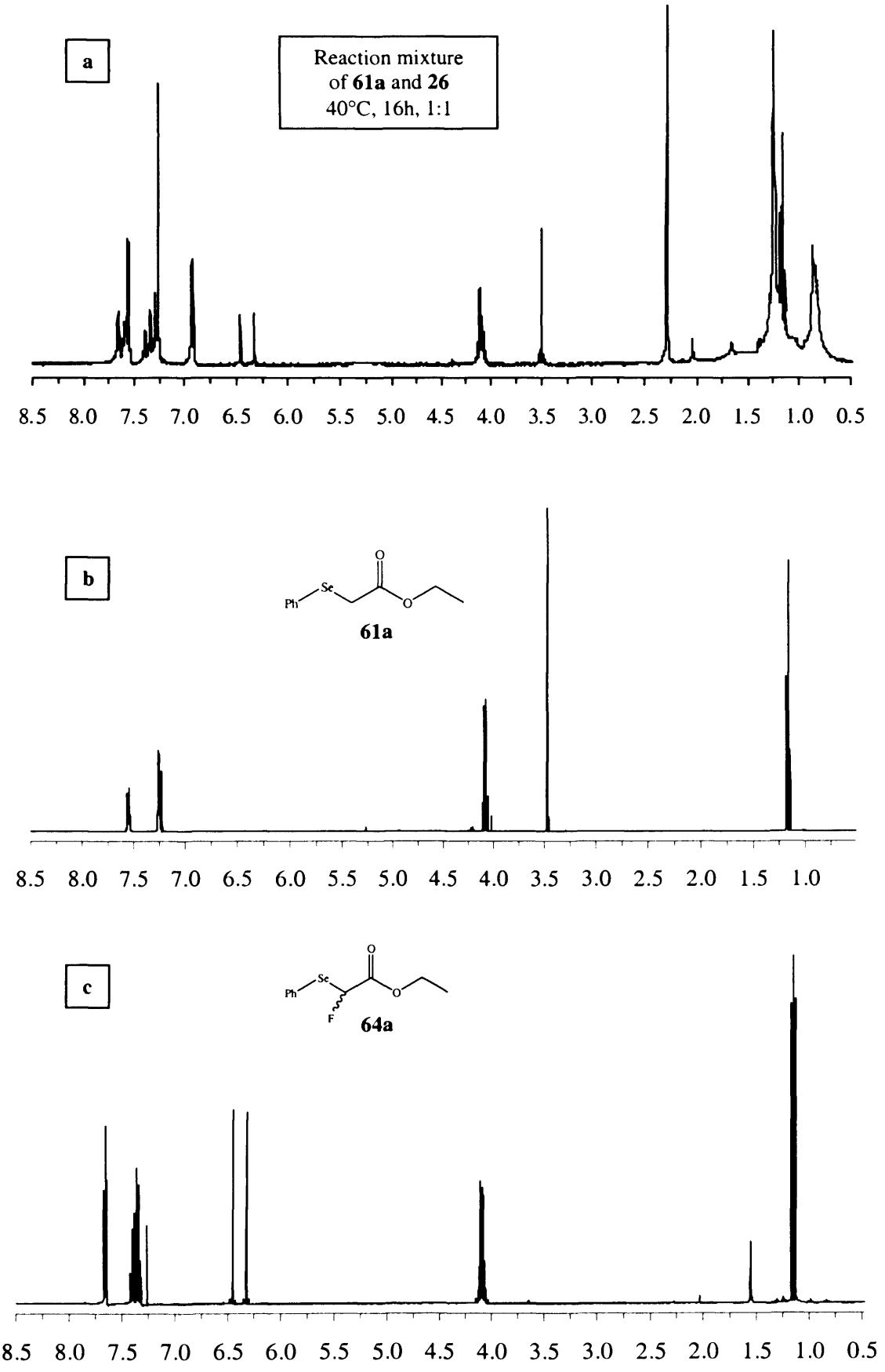


Figure 3.5: Spectra of (**a**) the crude of reaction in the reported experimental condition. Below are the spectra of (**b**) the pure starting material **61a** and (**c**) the pure product **64a**.

The mixtures of α-fluoro α-phenylselanyl esters **64** and their starting materials **61** are almost impossible to separate by flash chromatography. They displayed almost identical behaviour in all solvent systems investigated. Even the use of fluorinated solvents or MPLC failed to separate the mixtures. Separation of these mixtures could only be achieved by HPLC. The figure 3.6 shows the chromatogram of the mixture of phenylselanyl phenyl acetate **61b** and fluoro phenylselanyl phenyl acetate **64b**. It is interesting to highlight that the starting material is found between both the enantiomers of the product as a chiral HPLC column (Chiracel OD-H) was used for the analysis.

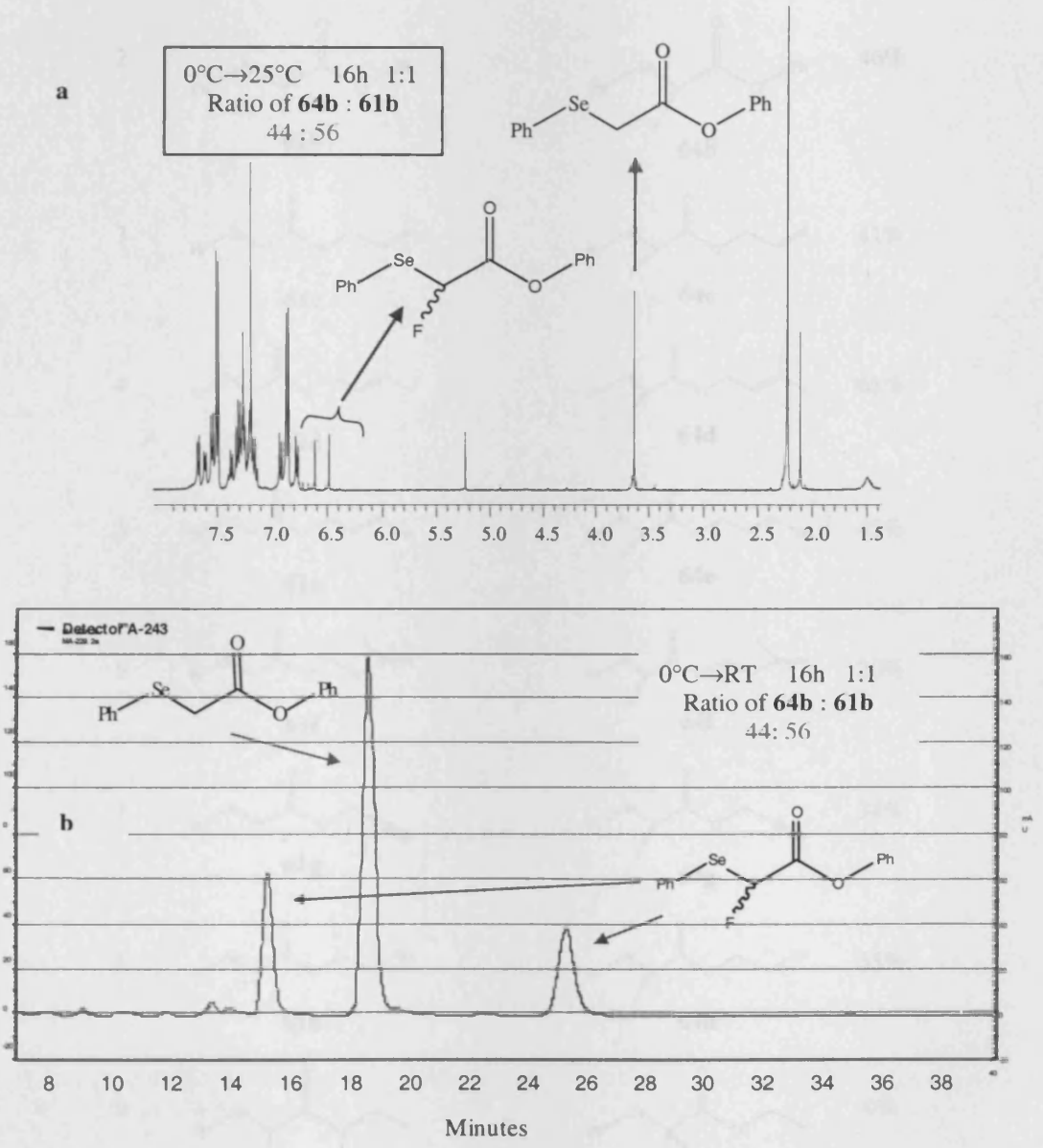
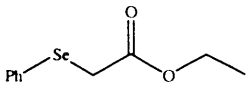
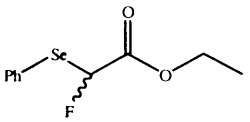
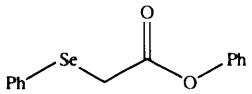
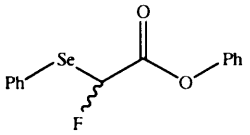
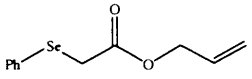
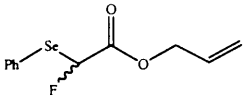
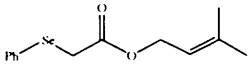
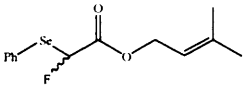
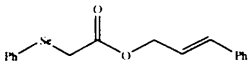
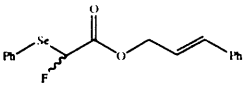
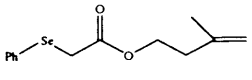
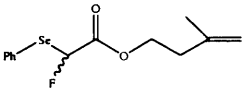
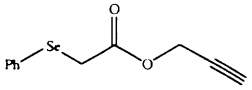
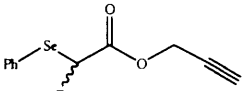
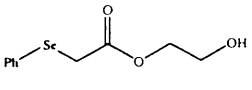
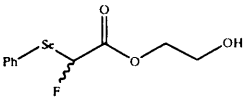
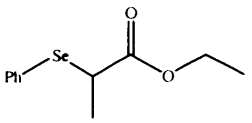
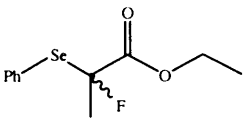


Figure 3.6: (**a**) The ^{1}H NMR of the reaction mixture composed from the enantiomeric couple of fluoro phenylselanyl phenyl acetate **64b** and phenylselanyl phenyl acetate **61b**. (**b**) Chromatogram of the products referred to the same reaction.

Unlike the fluorinated esters, the corresponding fluorinated amides were easily separated from their starting materials by column chromatography. In Table 3.2 the yields of the monofluoro esters **64** using an excess of (difluoroiodo)toluene (2 equivalents) are reported.

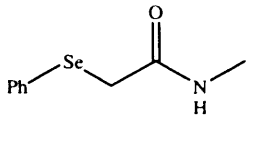
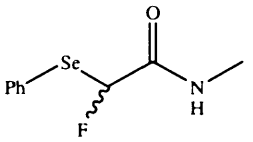
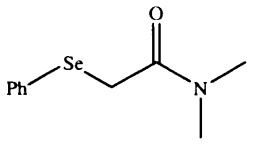
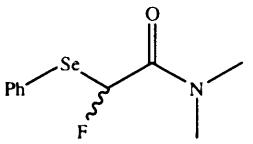
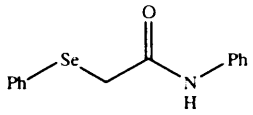
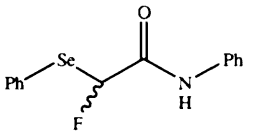
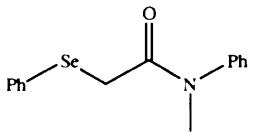
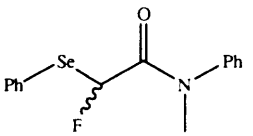
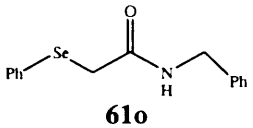
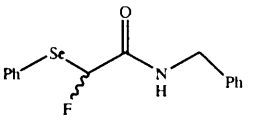
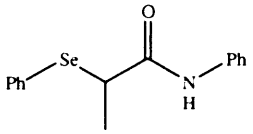
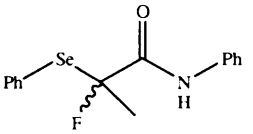
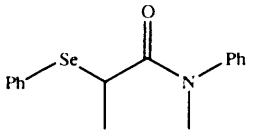
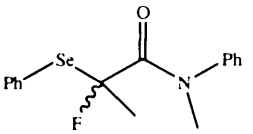
Table 3.2: Fluorination of esters **61** with (difluoroiodo)toluene **26**

Entry	Ester	Products	Yield[a)]
1	 **61a**	 **64a**	62%
2	 **61b**	 **64b**	46%
3	 **61c**	 **64c**	41%
4	 **61d**	 **64d**	65%
5	 **61e**	 **64e**	45%
6	 **61f**	 **64f**	20%
7	 **61g**	 **64g**	34%
8	 **61h**	 **64h**	38%
9	 **67a**	 **68a**	0%

a) Isolated yields for the corresponding monofluorides using 2 equivalents of DFIT versus the substrate, 40°C in CH_2Cl_2 as solvent

The results (Table 3.2 Entry 1-8 and Table 3.3 Entry 1-5) illustrate the formation of monofluorinated acyclic compounds with yields ranging from 20 to 65%.

Table 3.3: Fluorination of amides **61** with (difluoroiodo)toluene **26**

Entry	Amides	Products	Yield[a)]
1	 **61i**	 **64i**	31%
2	 **61l**	 **64l**	42%
3	 **61m**	 **64m**	31%
4	 **61n**	 **64n**	40%
5	 **61o**	 **64o**	53%
6	 **67b**	 **68b**	0%
7	 **67c**	 **68c**	0%

a) Isolated yields for the corresponding monofluorides using 2 equivalents of DFIT versus the substrate, 40°C in CH_2Cl_2 as solvent.

A typical aqueous work-up by extraction with an organic solvent resulted in a significant loss of material. The presence of hydrofluoric acid in the reaction can result in the hydrolysis of the ester. No loss of compound was observed by work-up just by evaporation of the solvent.

Additionally, decomposition of the product was detected in some cases during chromatography, while in other substrates the presence of monofluorinated phenylselanyl acetic acid was noticed probably due to hydrolysis of the ester.

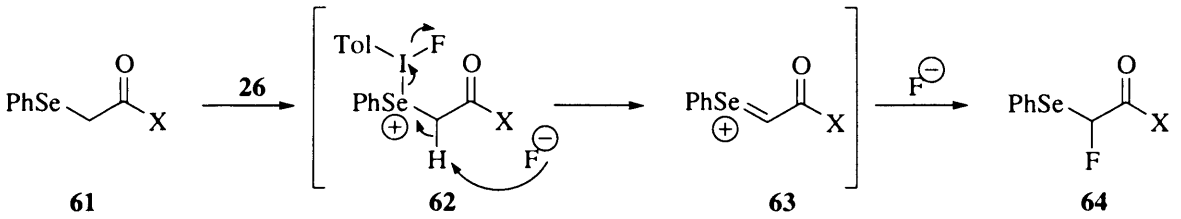
The reactivity of α-seleno esters did not change even when more than 2 equivalents of (difluoroiodo)toluene were used.

The same was observed for the corresponding amides, these results are summarized in Table 3.3.

Even with large excess of (difluoroiodo)toluene (3 equivalents), we have never observed any difluorinated products and it seems that a second fluorination reaction does not take place at all. This is probably due to the presence of the α-fluorine atom, which decreases the nucleophilicity of the selenium atom towards a second electrophilic attack by the iodine atom of (difluoroiodo)toluene. This is in contrast to some sulfur-containing substrates investigated by Motherwell, where difluorinations have been observed.[2c,d,e,f]

We thought that the hypernucleofugicity of the PhSe-ITol(F)$^+$ moiety could lead to the formation of fluoroesters **65** or, in the presence of an internal nucleophile as in substrate **61h**, the formation of lactone products **66**. In all substrates there was, however, no evidence for the formation of fluorinated products with loss of selenium. Additionally, reaction of esters containing a multiple bond showed no reaction with the hypervalent iodine compound and no evidence of lactone formation. Obviously groups such as double bonds, triple bonds or hydroxyl groups are not nucleophilic enough to carry out an attack on the activated selenium moiety.

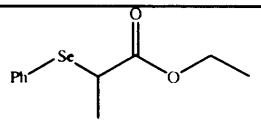
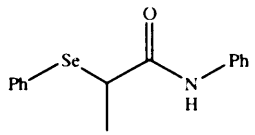
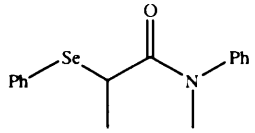
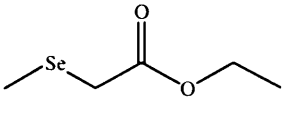
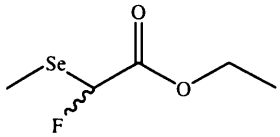
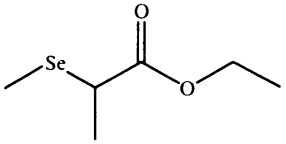
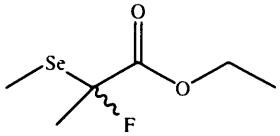
The reaction of selenide **61a** with (difluoroiodo)toluene **26** is believed to proceed in a similar way as the corresponding sulfides via a Seleno-Pummerer reaction. An interaction of the hypervalent iodine with the selenium atom leads to a ligand exchange on the iodine with loss of a fluoride and generates the cationic selenium intermediate **62** as shown in Scheme 3.4. Elimination to **63** and subsequent fluorination leads to the monofluorinated selanyl ester **64**.



Scheme 3.4: Fluoro-Pummerer reaction of substrates **61** with (difluoroiodo)toluene **26**.

The construction of quaternary carbon atoms using (difluoroiodo)toluene was also investigated (Table 3.4).

Table 3.4: Fluorination of α-methylated substrates **67** with (difluoroiodo)toluene **26**.

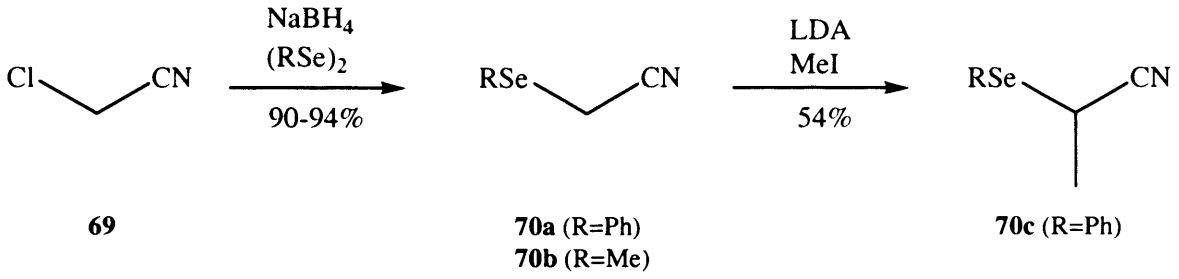
Entry	Ester/Amide	Product	Yield
1	 **67a**	---	---
2	 **67b**	---	---
3	 **67c**	---	---
4	 **67d**	 **68d**	25%[a] (+**67d**, 25%)
5	 **67e**	 **68e**	28%[a] (+**67e**, 37%)

[a] Product is very volatile and an accurate determination of the isolated yield is difficult.

Reaction of ethyl α-phenylselanyl-propionate **67a** failed to generate any fluorinated products and starting material was recovered. To investigate the steric and electronic contribution of the phenylselanyl moiety on the fluorination reaction, α-methylselanyl derivatives **67d** and **67e** were also synthesised. Higher reactivity of these substrates was expected with (difluoroiodo)toluene due to the greater localised positive charge of the selenium cation and due to the presence of the methyl group as a sterically less demanding moiety. The experimental results support this hypothesis. In contrast to **67a**, which did not react with (difluoroiodo)toluene, the corresponding methylselanyl propanoate **67e** was fluorinated to generate product **68e** with a quaternary carbon atom, although the conversion was not complete and unreacted starting material contaminated the product. The corresponding amide derivatives **67b** and **67c** did not react as all as shown in Table 3.4.

3.2.4 Fluorination of nitriles with (difluoroiodo)toluene

In order to compare the reactivities of acceptor-substituted α-seleno derivatives, we synthesized the corresponding α-selenonitriles as shown in Scheme 3.4.

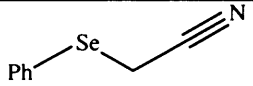
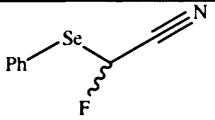
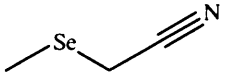
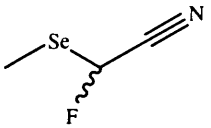
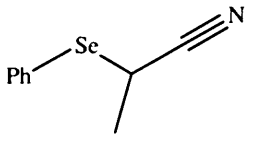


69 **70a** (R=Ph) **70b** (R=Me) **70c** (R=Ph)

Scheme 3.4: Synthesis of α-selenonitriles **70**.

Reaction of nitriles **70** with (difluoroiodo)toluene under the reaction conditions described above for ester and amides led to the formation of the α-fluoro substituted compounds. As with esters and amides **61** and **67**, only the unsubstituted α-phenylselanyl nitrile **70a** could be fluorinated, the α-methylated compound **70c** was unreactive. The low yields observed in the fluorination of nitrile **70b** are probably due to the high volatility of the fluorinated product. The results are summarized in Table 3.5.

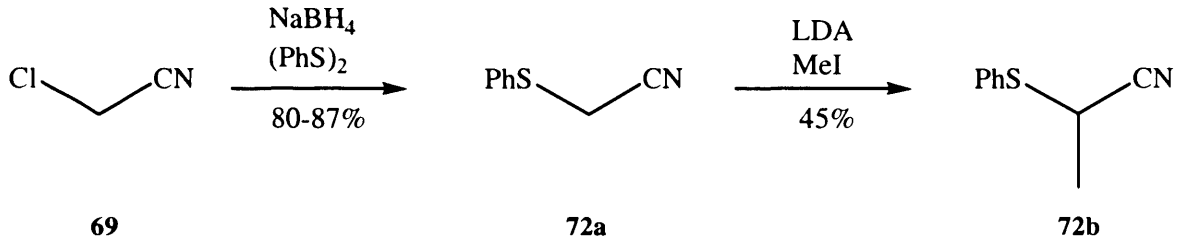
Table 3.5: Fluorination of α-selenonitriles **70** with (difluoroiodo)toluene **26**.

Entry	Nitrile	Product	Yield
1	 **70a**	 **71a**	50%
2	 **70b**	 **71b**	26%[a]
3	 **70c**	---	

[a] Product is very volatile and an accurate determination of the isolated yield is difficult.

The corresponding sulfur nitriles were synthesized and reacted with DFIT in order to compare the reactivities of nitriles bearing sulfur and selenium. Scheme 3.5 reports the procedure used in the synthesis of sulfur nitriles while Table 3.6 shows the results obtained using 2 equivalents of DFIT. Where the seleno nitrile produced monofluoro derivatives, the analogues sulfur reacted to

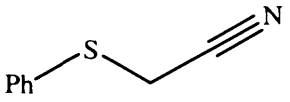
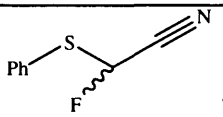
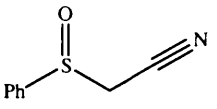
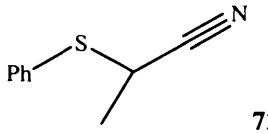
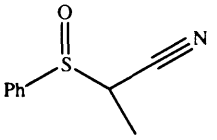
give a mixture of monofluoro derivatives **73** and sulfoxides **74**. The sulfoxide was found to be the main product of the reaction.



69 **72a** **72b**

Scheme 3.5: Synthesis of α-sulfurnitriles **72**.

Table 3.6: Fluorination of α-sulfurnitriles **72** with (difluoroiodo)toluene **26**[a)]

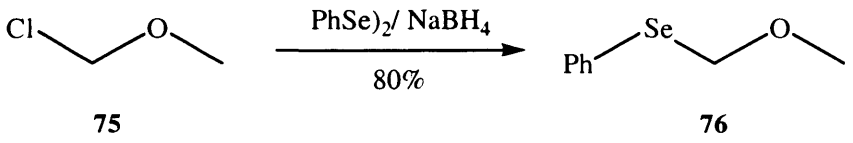
Entry	Nitrile	Products	Yield
1	 **72a**	 **73**	16%
		 **74a**	40%
2	 **72b**	 **74b**	72%

a) Yields refer to reactions carried out at 40°C in CH_2Cl_2 using 2 equivalents of DFIT towards the substrates.

A comparison between the reactivity of organoselenium substrates and their corresponding organosulfur analogues towards DFIT shows the following trend: selenium substrates are less reactive. This difference is seen in the quite dramatic difference in reaction of these two classes of compounds in their reactions performed using an excess of DFIT. Whereas the reaction of the organoselenium compounds only yield monofluorinated products regardless of the amount of DFIT used (Table 3.2, 3.3, 3.4 and 3.5), the corresponding organosulfur substrates give different products clearly dependent on the reaction conditions. For sulfanyl esters, Motherwell[2c] has established that a 2:1 ratio of DFIT: substrate, the difluorinated products are obtained, and fluorosulfoxides are produced using a 3:1 ratio. With organoselenium substrates the different experimental conditions used affected only the amount of monofluorinated product formed. An excess of (difluoroiodo)toluene does not lead to the formation of difluorinated product and no selenoxides have been observed. In particular, using the sulfanylnitriles **72** as substrates, the presence of sulfoxides **74** as products was detected already using 2:1 ratio of DFIT:substrate and the monofluorinated compound was observed as a minor product of the reaction.

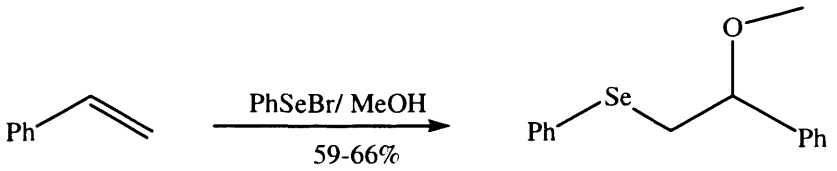
3.2.5 Fluorination of seleno acetals with (difluoroiodo)toluene

The investigation of the reactivity of seleno substrates was continued with the synthesis of seleno acetals. The synthetic procedure to obtain the mixed acetals is reported in Scheme 3.6 and in Scheme 3.7. The mixed acetal[8] **76** in Scheme 3.6 was prepared by α-selenylation of MOMCl, while methoxyselenenylation of styrene was performed to obtain the substrate[9] **78** in Scheme 3.7.



75 **76**

Scheme 3.6: Synthesis of methoxymethyl selanyl benzene **76**.



77 **78**

Scheme 3.7: Synthesis of (2-methoxy-2-phenyl)ethyl-seleno benzene **78**.

The seleno acetal **76** and the seleno substrate **78** were synthesised in order to analyse the mechanism of an eventual displacement of the phenylselanyl group by the fluorine atom. In this case the liberated fluorine generated from the nucleophilic attack of the selanyl moiety by DFIT cannot exploit its basic properties. Consequently, we would not expect the formation of fluorinated products bearing the phenylselanyl groups. Furthermore, the electron withdrawing effect created by the presence of the oxygen in alpha-position in methoxymethyl selanyl benzene **76,** would be responsible of a more accentuated positive polarization of the carbon interested to an eventual nucleophilic attack from the fluoride ion to the cationic selenium intermediate **62** in Scheme 3.4. For the seleno substrate **78** the destabilisation by the electronegative effect is less important due to a greater distance between the oxygen and the centre of the reaction. Unfortunately, the expected fluorination with consequent loss of selenide was not observed in these substrates.

However, an interesting feature of these experiments is that, at the end of the reaction, the hypervalent iodine is completely reduced to TolI.

3.2.6 The effect of the presence of the fluorine in the organoselenium substrates

In Section 1.2.1, the steric and electronic modifications caused by the presence of fluorine in an organic substrate were discussed. In this Section, the effect of fluorine in the fluoro-seleno substrates **64** will be described.

In particular, the NMR spectra (^{1}H, ^{13}C and ^{19}F) of the fluoro-seleno substrates **64** and their seleno precursors **61** were analysed.

2-Fluoro-propargyl-2-phenylselanyl acetate **64g** and its precursor **61g** are chosen as reference molecules for a common phenomenon valid for all the other molecule synthesised. Their ^{1}H NMR spectra are shown in Figure 3.7.

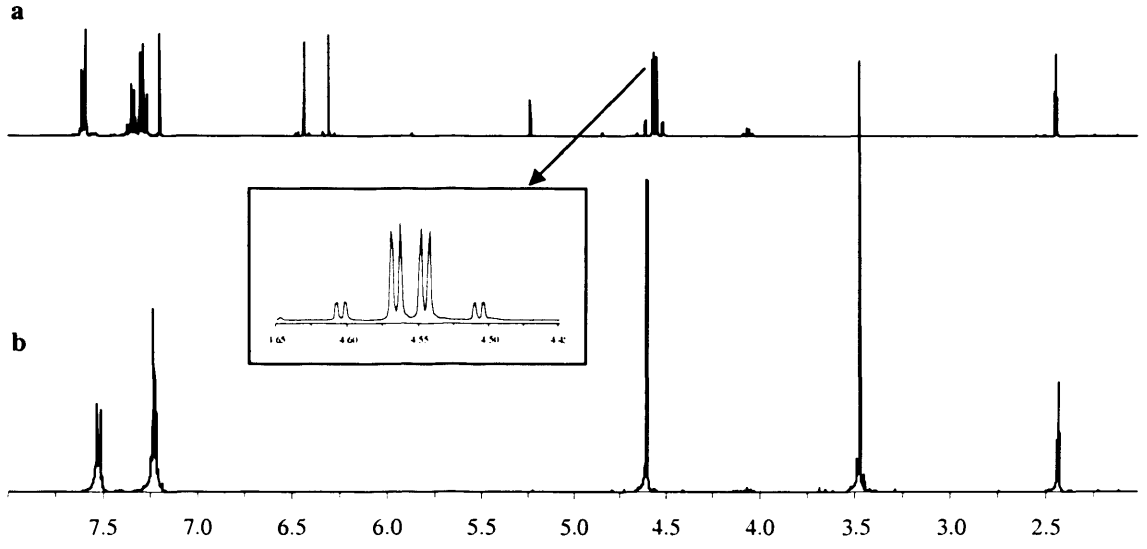


Figure 3.7: ^{1}H NMR of **a**) 2-fluoro-propargyl-2-phenylselanyl acetate **64g** and **b**) its seleno precursor **61g**. In the square, the particular of the splitting of the CH_2 group in 2-fluoro-propargyl-2-phenylselanyl acetate **64g** is shown.

In the NMR (^{1}H, ^{13}C and ^{19}F) it is possible to observe:

- the 2 protons in the CH_2 group, chemically and magnetically equivalent in the precursor, became diastereotopic in the fluorine derivative. The 2 protons in the CH_2 group are coupling with each other and each of them is interacting as well with the proton on the triple bond with a long range coupling $^{4}J_{H,H} = 2.5$ Hz.
- the presence of fluorine induces a splitting of the peak of the geminal protons due to the coupling of 2 nuclides with spin ½. A low field shift is also observed for this peak from 3.46 ppm in the precursor **61g** to 6.35 ppm in the fluorinated product **64g**. From this it was possible to distinguish and follow the ratio between the two components of the reactions

performed in different experimental conditions as previously reported (^{1}H NMR and ^{19}F NMR)

- a huge coupling between F and the carbon directly bonded to it, ^1J = 243 Hz (^{13}C NMR)
- a coupling of the carboxylic carbon with ^2J = 28.9 Hz (^{13}C NMR)

Most of these spectroscopic observations are directly correlated to the presence of fluorine in the molecule with a consequent coupling between the 2 nuclides (H and F or C and F). The presence of a chiral centre in the molecule induces a diastereotopic relationship in the methylene group. However this effect does not explain the strong coupling observed in the CH_2 group because of the large distance between the chiral centre and the methylene group. Therefore, the large splitting of the CH_2 group could be induced by the rigidity of the molecule due to the presence of the fluorine which can modify the electronic density of the whole molecule.

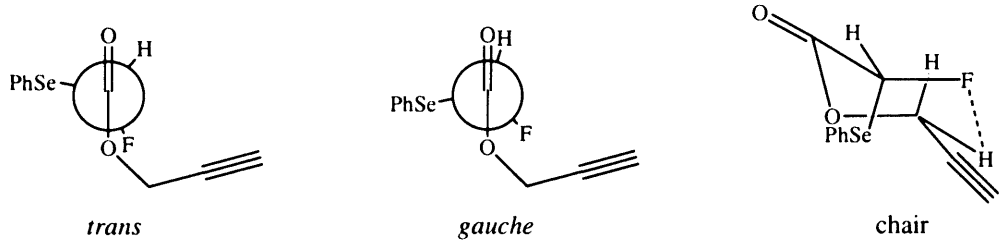
The electronic density in a molecule can be modified by fluorine in two different ways:

- via an electron withdrawing effect through the σ bonds, or
- via an electron donating effect through the π bonds.

The electron withdrawing effect cannot be directly responsible for the splitting of the 2 proton in the methylene group, as they are separated by a distance of 4 bonds from the fluorine. Additionally, if this effect was operating, it would possible to see a change in the chemical shift compared with the chemical shift for the same group of the precursor.

The electron donating effect by conjugation is not operating as well due to the lack of continuity of double bonds between fluorine and CH_2 group.

A third possible way emerges from the research of O`Hagan[10] and Tormena.[11,12] O`Hagan and co-workers[10] demonstrated that the preferred conformation of α-fluoro amides is *trans*, whereas Tormena and co-workers,[11,12] from *ab-initio* calculations and experimental evidence, found that for α-fluoro-α-substituted amides the *gauche* form is preferred. Therefore, it is possible to assume that a *trans* or *gauche* conformation is also operating for the α-fluoro-α-phenylselanyl substrates **64** (Figure 3.8).



trans *gauche* chair

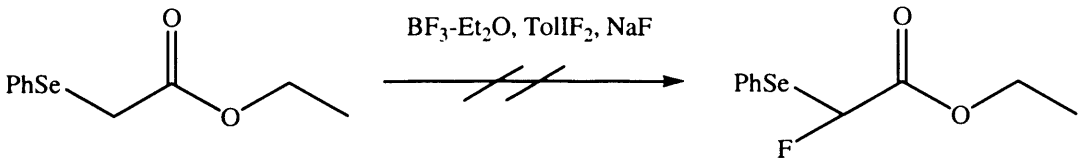
Figure 3.8: Possible conformers *trans* and *gauche* for 2-fluoro-propargyl-2-phenylselanyl acetate **64g**.

On the basis of these considerations, the splitting observed for the methylene group can be mainly derived from the proximity of fluorine to this group (either in *trans* or in *gauche*) with a consequent magnetic differentiation of the 2 protons. The stability of the conformation either *trans* or *gauche* (compared with the *cis*) can be influenced not only from a minor dipolar moment of the whole molecule but also from the possible hydrogen bonds which could be formed between fluorine and one of the 2 protons. This can be seen by arranging the molecule in a pseudo six-membered ring chair. As a consequence of the proximity of fluorine with the methylene CH_2, the 2 protons on this group would be affected differently by the presence of fluorine and therefore their magnetic equivalence disappears. In this situation each of them can give the doublet of doublet which was observed in the ^1H NMR.

3.3 The influence of an external nucleophile

3.3.1 Fluoride nucleophile

The idea was to shift the reaction towards a higher amount of fluorocompound using both internal and external source of fluorine. The internal source was as usual (difluoroiodo)toluene, while the external source was reached by adding a nucleophilic fluorine with the use of an external salt.[13] Additionally the electrophilic properties over the I(III) reagent **26** were increased using BF_3 as co-reagent.[14] In fact, the use of BF_3 on DFIT produces the formation of the corresponding iodonium reagent[14] $TolIF^+ \cdot BF_4^-$, complex that exhibits remarkable electrophilic properties. The experimental conditions are shown in Table 3.7. The reactions, carried out with different amount of external nucleophile, produced mainly starting material and the expected fluoroselenide **64a** was not detected at all (Scheme 3.8). Even when a large excess of external fluoride, introduced as NaF, was present there was no formation of fluoro-derivatives. The results of the experiments were not in accord with the theoretical idea.



61a **64a**

Scheme 3.8: Reaction scheme to attempt the fluorination of organoselenium substrate **61a** using an esternal source of fluorine.

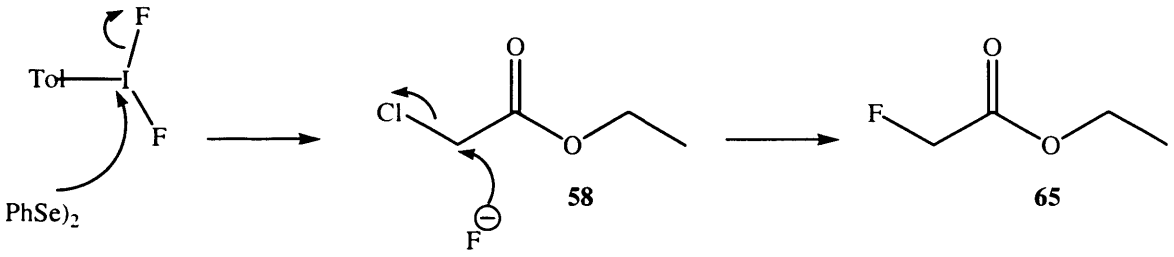
Table 3.7: Experimental conditions for the reaction in Scheme 3.7

Entry	Conditions*				
	T	Time	Equivalents of reagents		
			BF_3	DFIT	NaF
1	0°C→rt	16h	1.1	1	0
	0°C→rt	16h	1.1	1	1
	0°C→rt	16h	1.1	1	2
	0°C→rt	16h	1.1	1	5

*The term equivalents are referred to the ester.

3.3.2 Selenium nucleophile

A series of experiments (Table 3.8) were carried out trying to synthetise α-fluoro esters. In making the reaction independent from the presence of an internal heteroatom, either sulfur or selenium, in α position to the carbonyl, would give the reaction a more general feature. For such proposals, an external nucleophile is required which can attack the electrophilic iodine centre with subsequent release of a fluoride anion. The liberated fluoride would then act as a nucleophile and would be responsible for substitution reactions of, for instance, α-chloro esters **58** leading to α-fluoro esters **65** as reported in Scheme 3.9.



Scheme 3.9: Reaction scheme to attempt the halogen exchange using an external nucleophile and DFIT.

As a source of external nucleophiles $(PhSe)_2$, $(PhS)_2$ or $(CH_3Se)_2$ were used. α-Chloro ethyl acetate **58** was added in excess. The results obtained from these experiments showed no presence of fluorinated species. In every instance, α-chloro ethyl acetate **58** was recovered at the end of the reaction.

Table 3.8: Experimental conditions used for the reaction in Scheme 3.9

Entry	Nucleophile	Conditions*		
		T	Time	Ratio
A	$(PhSe)_2$	0°C→rt	16h	1:1
B	$(CH_3Se)_2$	0°C→rt	16h	1:1
C	$(PhS)_2$	0°C→rt	16h	1:1

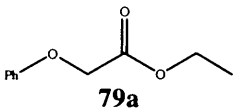
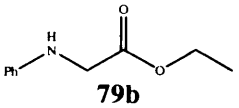
*The term ratio refers to the equivalents of nucleophile:DFIT used.

It is interesting to underline that the DFIT is completely converted in TolI at the end of the reaction. This fact may suggest that a concerted mechanism in the fluorine transfer is operating. This suggestion can be seen by combining the results obtained when an external source of nucleophile, be it fluoride or selenium. Using an external selenium or sulfur nucleophile, TolI was found at the end of the reaction but the fluorine transfer does not occur even when a large excess of fluoride from an external source is present. It is possible that the nucleophilic attack from the selenium atom is still operating, but the subsequent fluorine transfer does not occur probably because the fluorine is too far away from the molecule.

3.4 The influence of different heteroatoms in the alpha position

A series of experiments were carried out with α-oxo **79a** and α-azo **79b** esters with DFIT to establish the difference in reactivity derived from the presence of heteroatoms in alpha position to the carbonyl group. Examples of α-azo compounds with the nitrogen reacting as a nucleophile in a similar way to the Pummerer reaction are reported in literature. For instance, the Polonovsky reaction has a mechanism similar to the Pummerer reaction.
The experimental conditions with the α-oxo and α-azo esters with DFIT are summarised in Table 3.9.

Table 3.9: Reactivity of 2-phenoxy-ethyl acetate and phenylamino ethyl acetate.

Entry	Ester	Conditions*		
		T	Time	Ratio
1	 **79a**	0°C→rt	16h	1:1.1
		0°C→rt	16h	1:2
		40°C	16h	1:1.1
		40°C	16h	1:2
2	 **79b**	0°C→rt	16h	1:1.1
		0°C→rt	16h	1:2
		40°C	16h	1:1.1
		40°C	16h	1:2

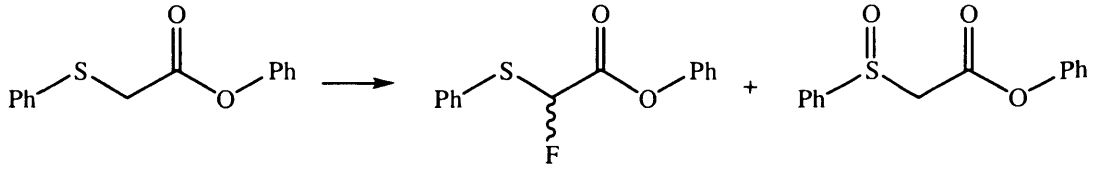
*The term ratio refers to the equivalents of ester: DFIT used.

In both cases the formation of expected fluoro derivatives was not observed. With the α-oxo (Entry 1 in Table 3.9), both starting materials were recovered, while with the α-azo (Entry 2 in

Table 3.9), a number of compounds were observed by TLC. The lack of reactivity of these compounds with DFIT could be a reflection of the participation of the d-orbitals during the path of reaction. Both sulfur and selenium have the possibility to stabilise the positive charge by themselves during the path of the reaction using the accessible d-orbitals, which is forbidden for both nitrogen and oxygen. This fact could have a major impact than the larger nucleophilicity of nitrogen and oxygen compared with sulfur and selenium.

3.5 The influence of the glassware

As briefly anticipated before, the material of the vessel in the fluorination reactions is very important for the success of this type of reactions. A series of reactions were performed in standard glassware and the results compared with those found using Teflon vessels. Phenylsulfanyl phenyl acetate **80a** and phenylselanyl allyl acetate **61c** were chosen as test substrates. Scheme 3.10 shows the general results when phenylsulphanyl ester **80a** is treated with DFIT in normal glassware. Table 3.10 reports the results obtained for the analysed substrates **80a** and **61c**. Fluoro derivative **81** and sulfoxide **82** were found as the main reaction products for phenylsulphanyl phenyl acetate **80a**.



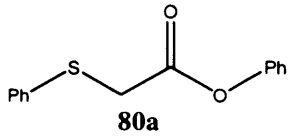
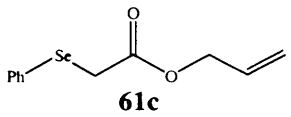
80a **81** **82**

Scheme 3.10: The general results when phenylsulfanyl phenyl acetate **80** is treated with DFIT in normal glassware.

As illustrated in Table 3.10, the main product results to be the sulfoxide **82**, where the monofluoro is present as a secondary product often detected only in trace amounts. In attempt to avoid the formation of sulfoxides, the reaction was carried out previously purifying the DFIT and degassing the solvent. The hypervalent reagent was purified because it was believed that the formation of sulfoxide was due to the trace amounts of iodosyl toluene, responsible for the oxidative reaction with consequent production of sulfoxide. In addition, the solvent of the reaction was degassed to lower the concentration of dissolved oxygen and thus to avoid the presence of sulfoxide. In order to avoid the contact with water, the work up was done by simple removal of the solvent. The results found for the reactions carried out in standard glassware were inconsistent and not uniform with each other. In particular reactions carried out with the

same experimental conditions using degassed CH_2Cl_2 or purified DFIT or both do not convey the same results.

Table 3.10: Results obtained treating esters **80a** and **61c** with DFIT in normal glassware.

Entry	Ester	Conditions[a]			Ratio of products[b]		
		T	Time	Ratio **80a**:**26**	**81**	**82**	**80a**
1	 **80a**	CH_2Cl_2 degassed					
		0°C→RT	4.3h	1:1.5	22%	78%	---
		0°C→RT	4.3h	1:1.5	30%	70%	---
		0°C→RT	3h	1:1.5	15%	85%	---
		DFIT purified + CH_2Cl_2 degassed					
		0°C→RT	2h,30m	1:1	Traces	---	98%
		0°C→RT	44h	1:1	Traces	---	98%
		0°C→RT	18h	1:1	Traces	95%	---
		0°C→RT	3h	1:1	---	---	100%
		0°C→RT	3h	1:1	Traces	96%	---
2	 **61c**	0°C→RT	17h	1:1	**64c** traces[c]	---	---
		0°C→RT	17h	1:2	**64c** traces[c]	---	---
		0°C→RT	17h	1:3	**64c** traces[c]	---	---

a) The term ratio refers to the equivalents of ester: DFIT used.
b) Ratios of the product were determined by ^1H NMR
c) Less than 5%

The same inconsistency occurs when phenylselanyl ester **61c** is treated with DFIT in standard glassware. In this case the monofluoro product **64c** was detected only in trace amounts and the starting material was found at the end of the reaction unreacted.

The absence of fluorinated products can be correlated with the material of the reaction vessel. In fact, an inverse trend was found using the two different materials. For sulfanyl esters **80**, Motherwell[2c,d] established that in the reactions carried out in Teflon vessels the monofluoro **81** is the main product of reaction, while with the same experimental conditions but using glassware vessels the correspondent sulfoxide **82** appeared to be the most preferred product. On the other end, the selanyl esters did not react in glassware vessels while in Teflon round bottom flask reacted with DFIT with consequent production of fluorinated derivatives **64**.

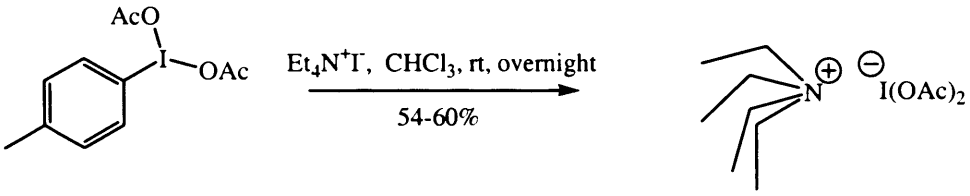
From a mechanistic point of view, the formation of sulfoxide in the reaction carried out in borosilicate vessel could be derived from an initial nucleophilic attack by the sulfur atom at the electrophilic centre of the hypervalent reagent. At this point it is possible that the fluoride anion, formed during the previous step, reacts as a nucleophile with the SiO_2 in the internal surface of the vessel of the reaction. The oxygen in the SiO_2 could be incorporated into the iodosulphonium salt with consequent production of sulfoxide. The presence of small amounts of

fluorosulphide may be explained by the competitive reaction of the fluoro anion as a base over the iodosulphonium salt.

3.6 Ligand exchange

(Difluoroiodo)toluene, being an hypervalent iodine (III) reagent, exhibits oxidative properties. This characteristic can be used in the synthesis of new difluorides through oxidation of iodides, at the iodine atoms, by a ligand transfer.[15] This characteristic feature of the hypervalent iodine reagents was, for instance, exploited by Koser. With the (hydroxy-tosyloxy)iodo benzene (Koser reagent) is indeed possible to oxidize different aryliodides obtaining new (hydroxy-tosyloxy)iodo arenes[15] analogous.

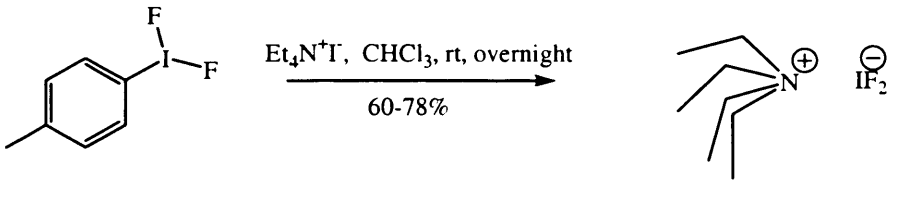
The possibility to use DFIT as a precursor in the synthesis of new difluorides was then investigated. Initially we exploited this possibility with the (diacetoxyiodo)toluene as shown in Scheme 3.11, transferring the diacetoxyl groups to tetraethyl ammonium iodide $Et_4N^+I^-$.



24 **83**

Scheme 3.11: Ligand transfer between (diacetoxyiodo)toluene **24** and (tetraethyl ammonium) iodide.

The corresponding diacetoxy iodide (III) **83** was obtained.[16,17] Then the same procedure was applied to DFIT as shown in Scheme 3.12.



26 **84**

Scheme 3.12: Ligand transfer between DFIT and (tetraethyl ammonium) iodide.

The latter reaction was performed in both, borosilicate and Teflon vessels. In both of the reactions a rapid change of color was observed from colorless to deep red. Using the borosilicate vessel a red-yellow solid start to precipitate. The analysis of the two reaction

mixtures revealed the presence of a singlet in the ^{19}F NMR at -152.31 ppm for the reaction carried out in normal glassware, while no peaks were found in the ^{19}F NMR when the reaction was performed in Teflon vessel. The value obtained in the ^{19}F NMR is characteristic of hypervalent iodine substrate and the elementary analysis indicated the presence of two fluoro atoms in the molecule as the theoretical ratio (C/F = 2.5) is in good agreement with the experimental ratio (C/F = 2.6).

The possible operating mechanism can be due to a dissociative pathway as shown in Scheme 3.13.

$$TolIF_2 \rightleftharpoons TolIF^+ + F^-$$

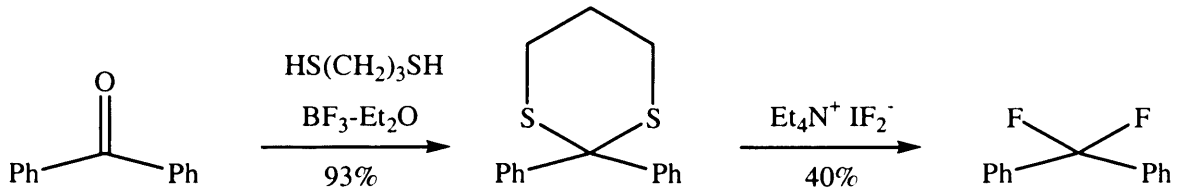
$$TolIF^+ + I^- \rightleftharpoons TolI + IF$$

$$Et_4N^+ + IF + F^- \rightleftharpoons Et_4N^+ IF_2^-$$

Scheme 3.13: Possible operating mechanism in the synthesis of **84**.

This compound was previously prepared by fluorination of $Et_4N^+ICl_2^-$ [18] and more recently by Naumann[19] in 37% yield by flushing IF over a pre-dried tretaethyl ammonium fluoride. However, this result is important for two reasons. The first lies in the specific context of synthesis of the difluoride **84** avoiding the use of reagents such IF. The second and more remarkable is that it is the first example of how DFIT can be used as a precursor in the preparation of new difluorides iodide (III) reagents by a simple oxidative fluorination.

The reactivity of this potential fluorinating agent was never studied. We started to investigate its ability to react as a fluorine transfer of some substrates. Preliminary experiments suggest that the substrate can indeed be used as fluorinating agent. As shown in Scheme 3.14, the difluoride **84** is indeed able of fluorine transfer over the dithioketal **86** with a yield of 40%.



85 **86** **87**

Scheme 3.14: Fluorination of the dithioketal **86** with the iodo difluoride **84**.

The direct transformation of the carbonyl group in aldeydes and ketones into the geminal difluoride is already described in literature with the use of reagents such as sulfur tetrafluoride[20] (SF_4) and DAST.[21] However extreme reaction conditions are necessary and low yields are often obtained. The geminal difluoride can be obtained indirectly by fluorination of carbonyl derivatives such as hydrazones (with halogen monofluorides[22] or fluorine[23]), diazocompounds

(with fluorine[24]) or by 1,3 dithiolanes. The last approach allows the synthesis of the CF_2 group from the parental carbonyl compound using reagents such as mixture of fluorine-iodine,[25] bromine fluoride[26] (BrF) generated *in situ*, $SOCl_2$-PPHF[27] and DFIT.[2a] Most of the previous methods require special equipment because of the presence of extremely corrosive fluorine gas or PPHF. On the other hand the use of DFIT or the difluoride **84** able the transformation of carbonyl group in CF_2 via the thioketal in an easy handle and safer way.

3.7 Conclusions

In this Chapter, the possibility of using hypervalent iodine (III) compound as fluorinating reagents was investigated. In particular DFIT, synthesised with the alternative route described in Chapter 2, was used as a fluorine transfer reagent.
Two types of reaction were studied:

- fluorination reaction of organoselenium substrates
- oxidative fluorination of iodides.

DFIT was found able to fluorinate seleno esters, amides and nitriles. The products of these reactions are α-fluoro selanyl derivatives which were obtained with yields ranging from 20% to 65%. The reactivity of organoselenium substrates was compared with the corresponding organosulfur substrates, which are generally more reactive. Additionally, we reported that the success of the fluorination reactions with DFIT depend on the material of the reaction vessel.

The oxidative fluorination of iodides by DFIT was also studied. Exploiting the oxidative nature of DFIT, the difluoride **84** was synthesized from tetraethylammonium iodide. This result casts new light on the possibility to synthesize new analogous difluorides using (difluoroiodo)toluene as a common precursor. The reactivity of tetraethyl ammonium iodate **84** ($Et_4N^+IF_2^-$) was tested and from preliminary experiments this compound is able to act as fluorinating agent.

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Chapter 4

4 Chiral hypervalent iodine difluorides

4.1 Introduction

The increasing demand for fluorinated compounds, often required as enantiopure products, led to investigation of the field of enantioselective fluorinations with the synthesis of chiral hypervalent iodo difluorides. Although hypervalent iodine reagents have been used in a large variety of reactions, only few chiral hypervalent reagents[1] have been synthesised and the lack of a chiral derivative obviously reduces their use in asymmetric organic synthesis.

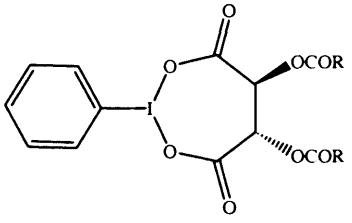
In particular, the present Chapter reports the attempts made towards the synthesis of chiral hypervalent iodo difluoride reagents.

Possible elements of chirality are centres, axes and planes of chirality. The first chiral hypervalent reagent synthesised (Figure 4.1) was derived from tartaric acid[1d] and it has axial symmetry C_2. This hypervalent I(III) reagent **88**, generated *in situ* in the work of Merkushev[1a] and Imamoto,[1b] was first isolated by Koser.[1d] Other chiral hypervalent reagents **89** were derived from chiral sulfonic acids. To introduce the chirality in this type of reagents, Varvoglis[1c] used the (+)-menthyl group whereas Koser[1f] utilised the (+)-10-camphoryl group. Others, formally structurally close to IBA, contain the iodine atom in a 5-membered ring, where the chirality is induced by the close tetrasubstituted carbon as in benziodoxole **90**[1g] (Figure 4.1) or by the presence of an aminoacid as in benziodazole **91**.[1r] The pseudo 5-membered ring reagent **92**, synthesised by Wirth[1n,o,q] is another example of chiral hypervalent compound with a structure similar to IBA. These last three reagents present the chiral centre in close proximity to the iodine compared with the first two. In all the previous examples of chiral hypervalent iodine, the stereogenic centre is localised on the oxygen or nitrogen ligand bound to the iodine atom.

Another example of chiral hypervalent iodine (Figure 4.1) is the binaphthyl[1e] **93**, where the chirality is induced by the axial symmetry of the carbon backbone.

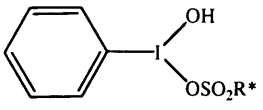
All the chiral polyvalent iodine (III) substrates were mainly used in oxidation of sulfides in sulfoxides, in stereocontrolled additions of acetoxy (AcO) and tosyloxy (TsO) groups to the double bonds in non symmetrical olefines, as well as in the stereocontrolled α-functionalization to carbonyl substrates.

It is important to note that no chiral hypervalent iodine difluorides are reported in the literature. The project aim was to investigate the synthesis of chiral iodo difluorides. The synthesised organoselenium compounds, reported in Chapter 3, could then have been used as substrates to test the chiral efficiency in the fluorine transfer promoted by the iodo difluorides.



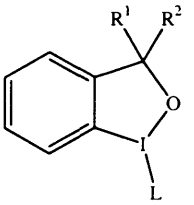
88

Koser (1990)



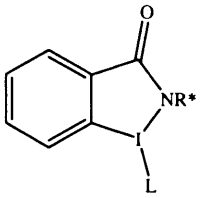
89

Varvoglis (1989)
Koser (1990)



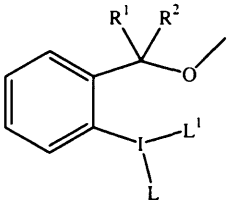
90

Koser (1996)



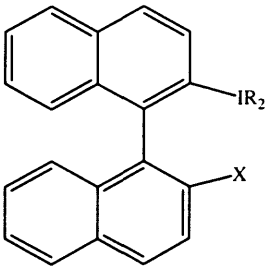
91

Zhdandkin (2003)



92

Wirth (1998)



93

Ochiai (1990)

Figure 4.1: Established chiral hypervalent reagents.

Basically two substrates with two different types of chirality were chosen for the development of stereoselective fluorinations.

The first substrate analysed was [2.2]-paracyclophane with planar chirality when a substituent is attached to one of the aromatic rings (Section 4.2).

The second type of molecules is based on the central chirality with the iodine being incorporated in a pseudo 5-membered ring (type **92** in Scheme 4.1) and will be discussed in Section 4.3.

4.2 Towards a chiral iodo difluoride with planar chirality: paracyclophane

[2.2]-Paracyclophane is a symmetrical molecule, which contains 2 face to face benzenic rings separated by two ethylene bridges in *para* position. The independent rotation of the benzenic rings around the ethylene bridges is limited to a few degrees. This implies that the molecule can be considered rigid and the presence of a substituent in one of the benzene rings makes the molecule chiral. The chiral form is stable with racemization process, which began operating at temperatures above180-200°C through a dibenzyl radical.[2]

Therefore, chirality and stability of the [2.2]-paracyclophane derivatives makes this molecule a powerful candidate in asymmetric synthesis. In fact opportune chiral substitued [2.2]-paracyclophane have been already used in enantioselective synthesis of β-hydroxy acids.[3] Disubstituted [2.2]-paracyclophanes were used as chiral N-O ligands in palladium catalysed allylic alkylation[4] and for enantioselective addition of diethylzinc to aldehydes.[5]

The overall plan was to use the planar chirality of the monosubstitued [2.2]-paracyclophane in the asymmetric development of fluorination reactions based on iodine hypervalent reagents.

4.2.1 Improved synthesis of 4-iodo-[2.2]-paracyclophane

Scheme 4.1 outlines the synthetic approach used for the synthesis of 4-iodo-[2.2]-paracyclophane, the key intermediate for the further construction of 4-difluoroiodo-[2.2]-paracyclophane, our first target as a chiral source of fluoride ions. [2.2]-Paracyclophane is commercially available and its bromination to the racemic mixture of 4-bromo-[2.2]-paracyclophane[6] is simple (Scheme 4.1). The direct transformation by metallation with *n*-butyllithium and successive reaction with I_2 gave **98** in low yield (path a in Scheme 4.1), yield which was consistent with the data already reported in the literature.[6] Indirect iodination was carried out using the procedure reported by Cipiciani[7] through amination with methoxyamine-methyllithium of the lithiated 4-bromo-[2.2]-paracyclophane and successive iodination via diazonium salt (path ii/iii in Scheme 4.1). The yields obtained were 40% in each step, also consistent with those found in the literature.

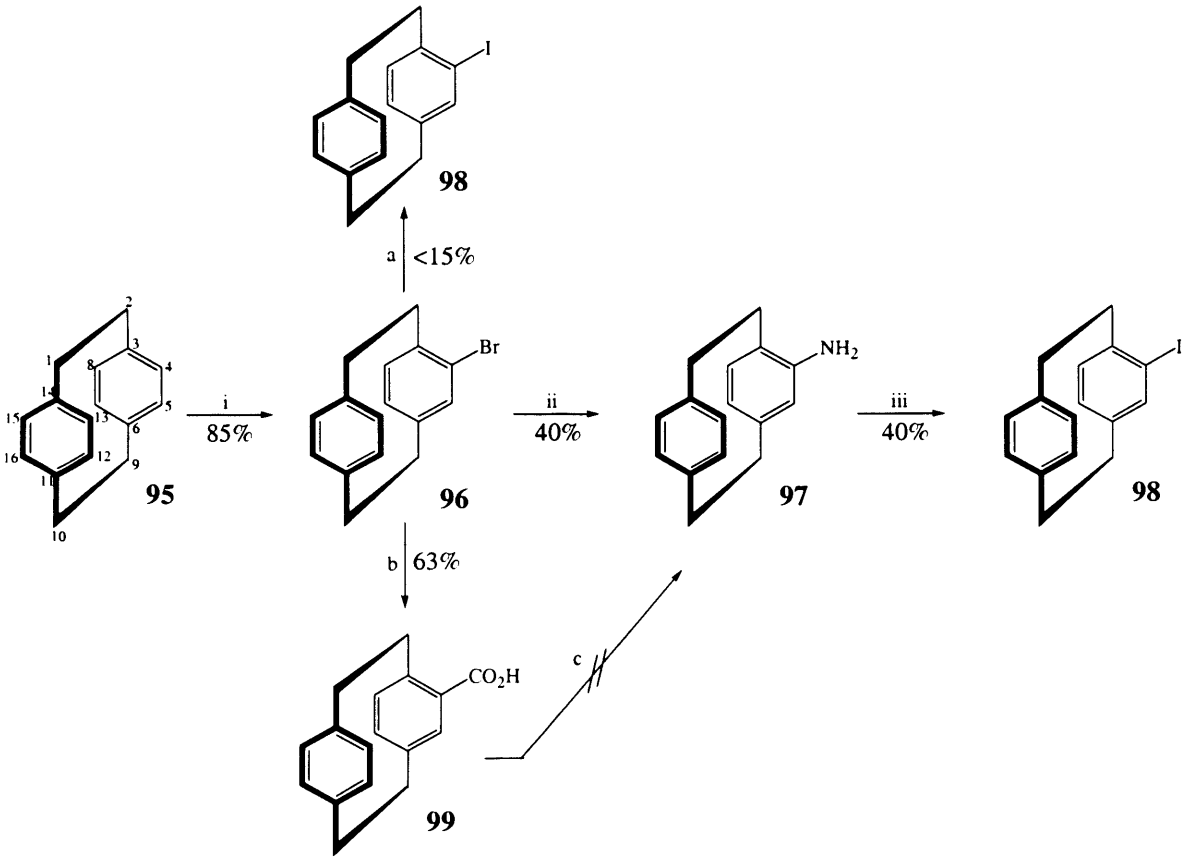
In Chapter 3 it has been reported that the fluorination reactions of the organoselenium substrates were performed using 2 equivalents of DFIT. Therefore the chiral difluorides must be accessible using a limited number of synthetic steps. Additionally, it would be advantageous to obtain the

iodo derivative in a high overall yield, due to the relatively high cost of the [2.2]-paracyclophane. Both strategies, previously reported, give yields that are quite low.

Firstly, in order to improve the preparation method, we attempted to increase at least the yield of one synthetic step in the reported procedure of Cipiciani. Leaving **97** in the procedure could be advantageous for the separation of the racemic mixture by formation of a diastereomeric salt as reported in literature.[7]

Consequently, in an attempt to increase the yield of **97**, the Schmidt rearrangement of the synthesised 4-carboxylic acid-[2.2]-paracyclophane **99** was performed, though failed to achieve great results (path b/c in Scheme 4.1).

The Curtius rearrangement[8] to synthesise **97** was not attempted even though the reported yields are high, because the overall procedure would involve three additional steps: synthesis of **99**, transformation into its acid chloride derivative and then synthesis of the amino group by sodium azide (NaN_3).



Scheme 4.1: *Reagents and conditions*: i, Br_2/Fe (85%); ii, *n*-BuLi/H_2NOCH_3-CH_3Li (40%); iii, $NaNO_2/H_2SO_4$/KI (40%); a, *n*-BuLi/I_2 (<15%); b, *n*-BuLi/CO_2 (63%); c, H_2SO_4/NaN_3, Δ.

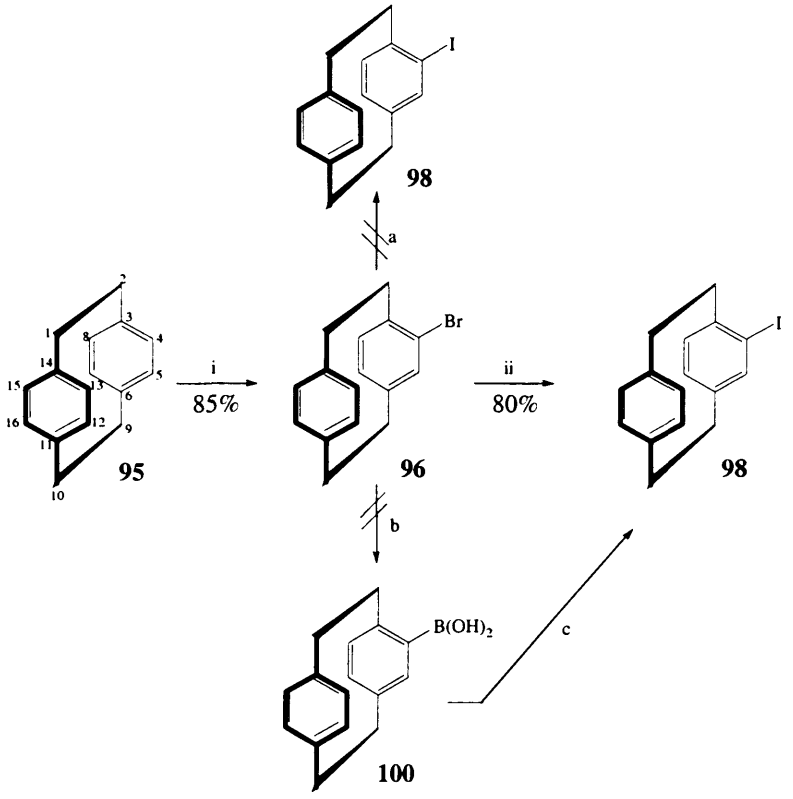
At this point, we concentrated on the synthesis of **98** using a short synthetic route, having in mind that the iodo or the bromo derivative could be subsequently separated using the HPLC

with a chiral column. Scheme 4.2 outlines the synthetic approach used to improve the synthetic pathway leading to 4-iodo-[2.2]-paracyclophane **98**.

In an effort to produce higher yield of **98**, experiments have been carried out in which different protocols were applied.

Particular emphasis was given in trying to convert the 4-bromo-[2.2]-paracyclophane **96** by boron activation and successive conversion of the aryl boronic acid in the iodo derivative with *N*-iodo-succinimide (path b/c in Scheme 4.2) without any success.[9,10]

Direct reaction with *n*-butyllithium (path a in Scheme 4.2) and successive reactions with different sources of iodine, such as ICl or *N*-iodo-succinimide, were tried. At the end of the reaction only paracyclophane was found as product.



Scheme 4.2: *Reagents and conditions*: a, *n*-BuLi/ICl (*N*-iodosuccinimide);b, Mg, BH_3-THF 0°C; i, Br_2/Fe (85%); ii, Ni, I_2, KI, DMF, Δ(80%).

Expectations were high following the protocol to synthesise aromatic iodides from bromides via the reverse halogen exchange using a metal[11,12] (path ii in Scheme 4.2). Using copper iodide (5 eq) in presence of potassium iodide (10 eq) in HMPA,[11] the conversion from bromide to iodide was around 50% after 3 days reflux at 170°C-180°C. Higher conversion was found using nickel (10 eq) in presence of a large excess of potassium iodide (10 eq) and iodine (5 eq)[12] and refluxing the mixture for 3 days at 170°C-180°C. In both cases, the analysis of the reaction mixtures with GC-MS revealed that no appreciable halogen exchange was operating during the

first 2 days. The use of this protocol not only makes a remarkable improvement in the yield (from 40% with the Sandmeyer[7] reaction applied to **97** to 80% by halogen exchange), but enabled us to gain a step of reaction by allowing the synthesis of **98** directly from **96**. In this manner, the 4-iodo-[2.2]-paracyclophane **98** was prepared using only 2 synthetic steps (bromination and halogen exchange) with each step characterised by high yield (85% and 80%). The synthesis of 4-iodo-[2.2]-paracyclophane **98** could be further developed by, for instance, a direct iodination of the paracyclophane. The improvement already achieved in the synthesis of **98**, involving two synthetic steps, was considered adequate and the analysis with HPLC commenced in order to find experimental conditions able to separate the racemic mixture of 4-iodo-[2.2]-paracyclophane **98**.

4.2.2 Separation of the racemic mixture of the (±)4-iodo-[2.2]-paracyclophane

The racemic mixture of 4-iodo-[2.2]-paracyclophane was analysed by chiral HPLC. Based on our knowledge, only the enantiomers of 4-F, 4-Cl, 4-Br were resolved by chiral HPLC.[13]
Several attempts were made using different chiral analytical columns and varying for each column temperature, ratios of the hexane : *i*-PrOH mixture and flow. Finally, the conditions for an adequate separation were found and the enantiomers of 4-iodo-[2.2]-paracyclophane **98** were resolved and separated by preparative chiral HPLC. The chromatogram is reported in Figure 4.2. The retention times of the two enantiomers are 49 and 54 minutes using OD as preparative column, hexane : *i*-PrOH (99 : 1) as solvent mixture, with 5°C as the temperature of the column, 6 ml/min as flow.

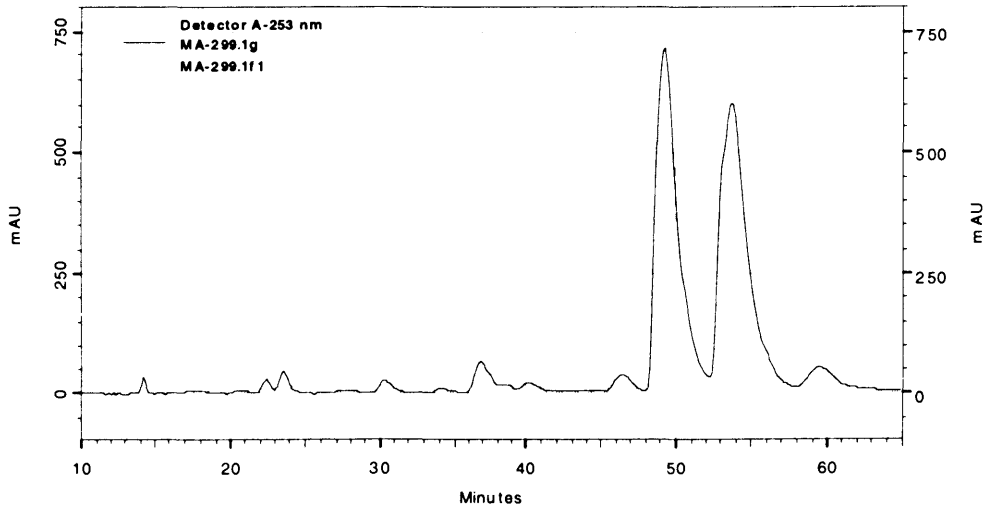


Figure 4.2: Chromatogram of the racemic mixture of (±)4-iodo-[2.2]-paracyclophane **98** done by chiral HPLC.

The practical separation of the racemic couple required a long time mainly due to solubility problems. In fact, the solubility of iodo-[2.2]-paracyclophane **98** in the solvent mixture used to resolve them is around 8 mg/ml at room temperature. Being necessary to use 5°C as column temperature, it follows that the solubility is even less at the operating conditions. Additionally only injections with a maximum of 250 µl were possible. Injections with a greater volume produced an undesired overlap of the two chromatographic peaks.

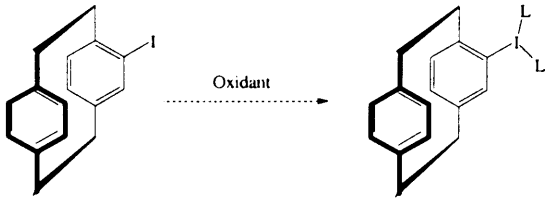
The time and solubility problems could be in principle solved trying an alternative method of separation of the racemate. According to the data in the literature,[14] the kinetic resolution of the racemic mixture of 4,12-dibromo-[2.2]-paracyclophane in presence of palladium-[2.2]-PHANEPHOS is indeed possible. Perhaps the same procedure applied to **96** could produce a kinetic resolution of the racemic mixture.

4.2.3 Oxidation of the iodine atom

Oxidation reactions of the 4-iodo-[2.2]-paracyclophane were performed to obtain 4-diacetoxyiodo-[2.2]-paracyclophane, the precursor needed to its further transformation in 4-difluoroiodo-[2.2]-paracyclophane. Unfortunately, the oxidation reaction of the iodine atom revealed to be particularly problematic.

The various oxidation reagents tried are summarized in Scheme 4.3.

The general route of oxidation developed by McKillop[15] ($NaBO_3 \cdot 4H_2O$) did not deliver the desired product. The oxidation reaction of the iodine did not take place under these experimental conditions and starting material was recovered at the end of the reaction. The reactions were performed for up to 3 days at 40°C. Increasing the temperature up to 80°C did not alter the result. The same behavior was found using peracetic acid generated in situ from acetic anhydride and 30% hydrogen peroxide.[1r,16] After 20 hours at 40°C the starting material was still present. Using commercially available peracetic acid (40% w/w), the result did not change.



98 **101**

Different oxidative reagents used:

- $NaBO_3$-$4H_2O$
- Ac_2O, 30% H_2O_2
- Peracetic acid
- CrO_3, AcOH, Ac_2O, H_2SO_4
- Koser reagent
- $Cl_{2(g)}$
- XeF_2
- $NaIO_4$, AcOH, AcONa, Ac_2O
- MCPBA, AcOH
- UPH

Scheme 4.3: Oxidative reagents used in the synthesis of the hypervalent I(III) reagent **101**, where L = OAc, OTs, Cl or F depending from the used experimental conditions.

The Jones reagent CrO_3,[17] an alternative oxidation reagent used in the synthesis of polyvalent iodine compounds, also failed as no oxidation was observed.

An attempt to oxidize the iodine atom in **98** using the Koser reagent[18] (hydroxy-tosyloxy-iodo-benzene) did not result in the expected ligand exchange with the consequent formation of the (4-hydroxy tosyloxy iodo)-[2.2]-paracyclophane. The reaction was monitored for 3 days.

Reaction with $Cl_{2(g)}$[19] produced a very complex mixture of several compounds, with probably products derived from the oxidation of the ethylenic bridges. Using this methodology, the 4-iodo-[2.2]-paracyclophane **98** was completely destroyed.

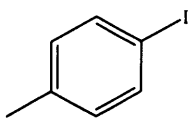
Oxidative fluorination with XeF_2[20] did not produce any oxidation of the substrate either when 1 equivalent was added to the reaction mixture in CH_2Cl_2 kept at -40°C or using 2 equivalents. Both reactions were monitored for 3 days.

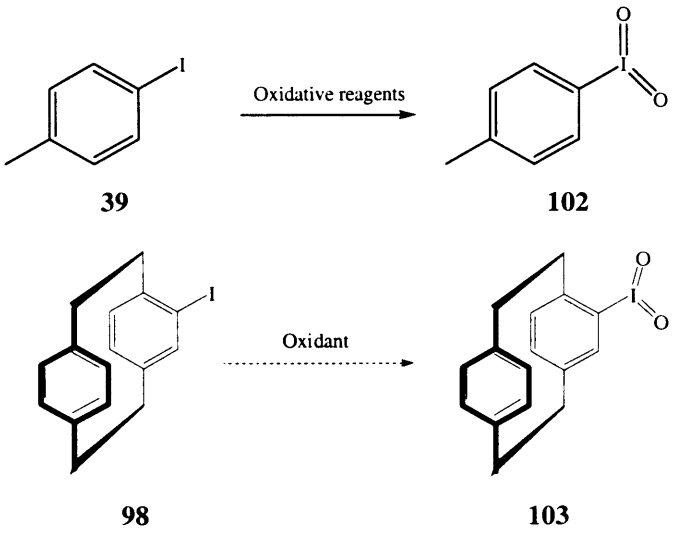
Sodium metaperiodate ($NaIO_4$) in acetic anhydride[21] left the 4-iodo-[2.2]-paracyclophane **98** unreacted and metachloroperbenzoic acid (MCPBA)[22] did not produce any visible oxidation of the iodine atom.

Urea-hydrogen peroxide adduct (UHP) in conjunction with HCl[23] did not produce formation of the correspondent dichloride via formation of the iodosyl derivative. At the end of the reaction performed at 90°C, starting material was recovered.

All the known procedures generally able to oxidise the iodine to I(III) proved to be inadequate. Therefore we attempted to use more powerful oxidants generally used in the synthesis of hypervalent iodine with oxidation state V. For this purpose different oxidants were tried but none of them led to the oxidation of the iodine atom. The accuracy of the used methodologies was compared with the use of iodotoluene (TolI) as a reference substrate. The reactions of 4-iodo-[2.2]-paracyclophane **98** and TolI **39** were performed with the same experimental conditions. Ozone monopersulfate,[24] a mixture of sodium metaperiodate ($NaIO_4$) in water[21] and a solution of bleach were used as oxidative reagents. These reagents were able to oxidize the iodine in TolI producing the correspondent and expected iodyl product **102** (Scheme 4.4) in yields dependent on the oxidant used (Table 4.4). The same reagents, unfortunately, were unable to oxidize the iodine atom present in **98**.

Table 4.1: Synthesis of iodyl toluene **102** from **39** under various experimental conditions.

Entry	Substrate	Conditions	Yield
1	 **39**	• Ozone monopersulfate ($KHSO_5$-$KHSO_4$-K_2SO_4), 6h 70°C	10%
2		• $NaIO_4$/ H_2O 7h 40°C	75%



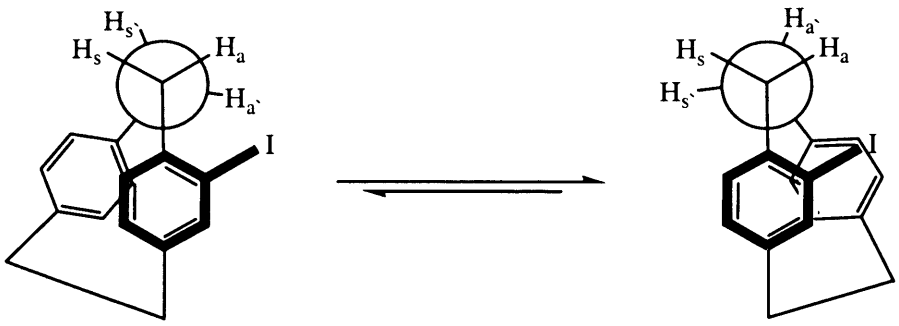
39 **102**

98 **103**

Scheme 4.4: Synthesis of iodyl toluene **102** from TolI **39** using the oxidative reagents in Table 4.1. The same reagents were also used in the attempts to oxidize the iodine in **98**.

The use of all the common oxidation methods for the synthesis of hypervalent iodine did not produce any oxidation in the iodine atom in **98**. This could be explained in two ways: steric impediment and thermodynamic factors.

From a steric point of view, the bulk iodine atom is in a close proximity to the methylene protons and the *ipso* proton on the other benzene ring. It is known that the enantiomers of monosubstitued [2.2]-paracyclophane exist in equilibrium between 2 conformers.[25] The 2 conformers for the R enantiomer are shown in Figure 4.3. The equilibrium between the 2 conformers is slightly in favour of the **b** for monosubstituted [2.2]-paracyclophane, conformer that became more energetically favourable as the size of the substituent on the benzenic ring increases.[25a] This equilibrium and the existence of a favoured conformer was deduced by the study of the variation of the J(Ha-Hs`) and J(Hs-Ha`), when different substituents were present on the benzenic ring.



R-98a **R-98b**

Figure 4.3: Equilibrium operating between the twisted conformation of the R enantiomer of 4-iodo-[2.2]-paracyclophane **98.**

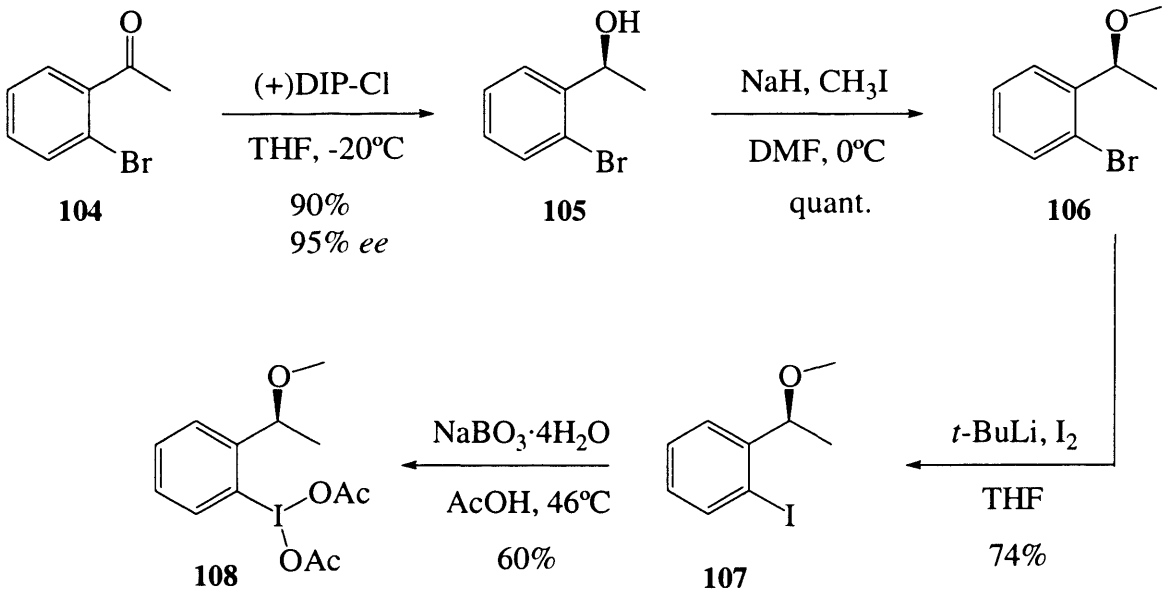
Thus, when a bulky iodine atom is present, it could be expected that the equilibrium shifts in favour of **98b**. As the equilibrium is in favour of **98b**, the unfavourable interactions between iodine and H_a diminished. Furthermore, structures, which contain a highly steric demanding substituent, based on the paracyclophane framework are known,[26] led to believe that the steric impediment is not the crucial point for the lack of the oxidation observed during the experiments.

From these facts, it seems more plausible that the lack of oxidisation of the iodine atom could be due to thermodynamic factors. Possibly the correspondent difluoride is less stable than its precursor or a very high energetic demand is required for the success of the reaction. This seems reasonable, considering that in most of the experiments performed the starting material was found unreacted at the end of the reaction.

4.3 Towards a chiral iododifluoride with central chirality: 1-iodo-2-(1-methoxyethyl) benzene

The second class of molecule considered for to the synthesis of a chiral difluoride was based on the central chirality like compound **92** in Figure 4.1. This type of reagents was already successfully used in the dioxytosylation of styrene and in the α-oxytosylation of propiophenone.[1q]

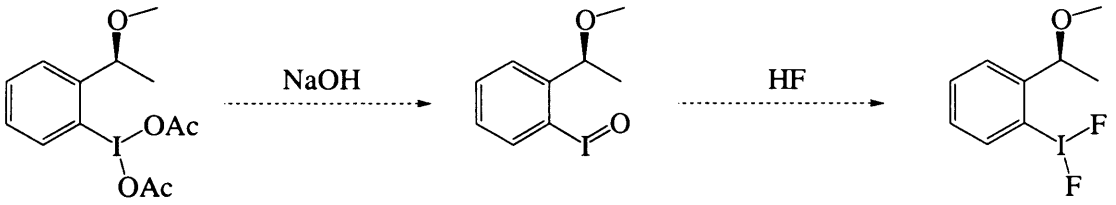
The synthesis started from 2-bromo-acetophenone **104** (Scheme 4.5).



Scheme 4.5: Synthesis of the aryl hypervalent reagent **108**.

Through an asymmetric reduction of the carbonyl group in **104** with DIP-Cl, it was possible to synthesise the enantiomeric pure alcohol derivative **105** (95% *ee*). Methylation of the hydroxy group and successive halogen exchange, produced 1-iodo-2-(1-methoxyethyl) benzene **107** in 74% yield. Standard conditions for the oxidation resulted in the synthesis of the I(III) **108** in 60% yield.[10]

At this stage, two additionally steps are necessary to convert the diacetate derivative **108** in the parental difluoride **110**: basic hydrolysis with NaOH and subsequent treatment with hydrofluoric acid (Scheme 4.6).

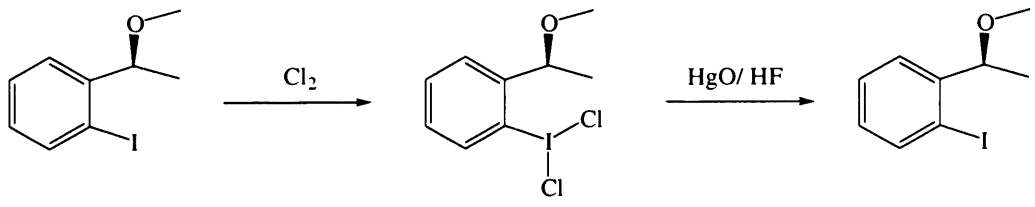


108 **109** **110**

Scheme 4.6: Additional steps required to the synthesis of the correspondent difluoride **110** from diacetate **108**.

During the basic hydrolysis, which should produce the synthesis of iodosyl derivative **109**, no precipitation was observed and the extraction of this reaction mixture revealed the unexpected presence of the iodo precursor **107**. Direct treatment of the diacetate **108** with aqueous HF produced the same result.

Chlorination[19] of the iodo precursor **107** produced a mixture 40:60 of dichloride derivative **111** and starting material. The dichloride **111** obtained in this reaction was quite unstable. In less than 12 hours it totally decomposes towards the iodo precursor **107**. On the previous mixture (dichloride: S.M 40:60) the Carpenter method was applied. The treatment of the mixture with mercuric oxide and HF produced, once again, the iodo precursor **107** (Scheme 4.7) and not the expected difluoride.



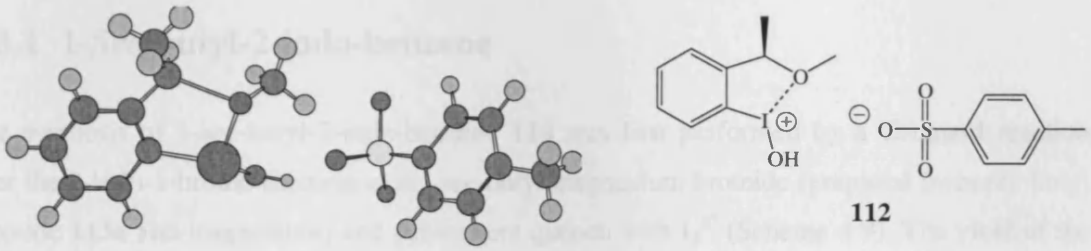
107 **111** **107**

Scheme 4.7: Carpenter method applied to 1-iodo-2-(1-methoxyethyl) benzene **107**.

Oxidative fluorination with XeF_2[20] (1 and 2 equivalents in CH_2Cl_2 at -40°C up to 3 days) did not result in any oxidation of the iodine.

In conclusion, the attempts made to interconvert the diacetate **108** or the dichloride **111** in difluoride **110** failed.

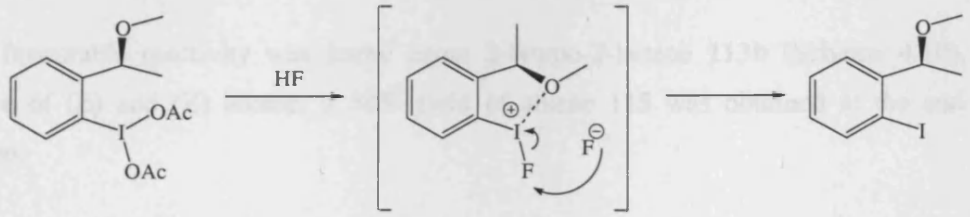
It is well known that in such kind of compounds there exists a coordination between the oxygen in the methoxy group and the iodine atom.[1o,1q] Figure 4.4 shows the analogous hydroxy tosyloxy reagent **112** synthesised by Hirt.[1o,1q] In particular, the crystal structure revealed that the distance between oxygen in the methoxy group and iodine is less than that of iodine and the tosyloxy ligand.



112

Figure 4.4: Three-dimensional structure of hydroxy tosyloxy [2-(methoxyethyl)phenyl]iodine **112**.

We believed that this coordination would be operating also in the analogous difluoride **110** and it could be responsible for the instability and therefore for the lack of preparation of the difluoride. Shown in square parenthesis in Scheme 4.8, is a possible mechanism acting over the probable intermediate difluoride **110**. The coordination between the oxygen and the iodine should produce an increased nucleophilic power over one fluorine atom that could be responsible for attacking the molecule with consequent release of the iodo precursor **107**.



108 **110** **107**

Scheme 4.8: Possible mechanism operating in the decomposition of the intermediate fluoride derivative **110**.

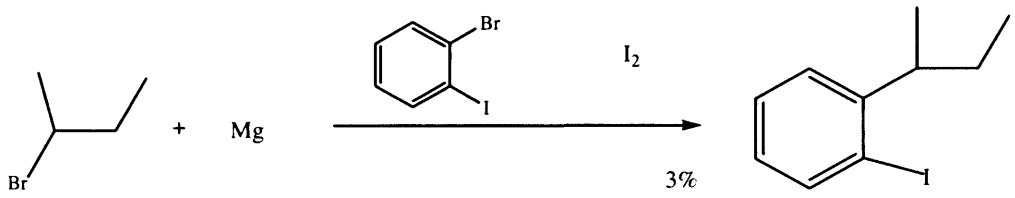
As a consequence of the previous experiments and in particular attributing to the coordination between oxygen and iodine the responsibility for the lack of synthesis of the difluoride derivative **110**, we found two possible ways to continue the research and produce supplementary information. The first way is to eliminate the coordination between iodine and oxygen with the synthesis of a compound, which does not contain heteroatoms. The second way

is to synthesise a compound with a covalent bond between the iodine and the heteroatom present.

We investigated both ways. 1-*Sec*-butyl-2-iodo-benzene **114**, structurally similar to 1-iodo-2-(1-methoxyethyl) benzene **107**, was chosen for the synthesis of the difluoride which does not contain heteroatoms able to coordinate the iodine. 1-Hydroxy-1,2-benziodoxol-3(1H)-one (IBA) was chosen as representative of the second way, having the iodine in a stable 5-membered ring and covalently bound to the oxygen of the carboxylic acid.

4.3.1 1-*Sec*-butyl-2-iodo-benzene

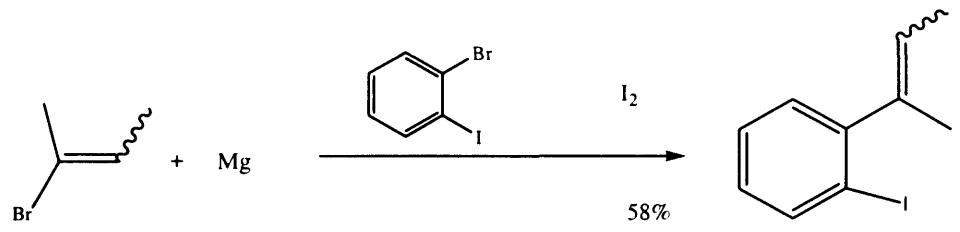
The synthesis of 1-*sec*-butyl-2-iodo-benzene **114** was first performed by a Grignard reaction over the 2-iodo-1-bromo benzene using *sec*-butyl magnesium bromide (prepared from *sec*-butyl bromide **113a** and magnesium) and subsequent quench with I_2[27] (Scheme 4.9). The yield of the recovered product **114** was 3%. Longer time of reaction or refluxing the mixture before quenching with I_2 did not increase the yield.



113a **114**

Schema 4.9: Synthesis of 1-sec-butyl-2-iodo-benzene **114**.

More favourable reactivity was found using 2-bromo-2-butene **113b** (Scheme 4.10). Using mixture of (E) and (Z) alkene, a 58% yield of alkene **115** was obtained at the end of the reaction.



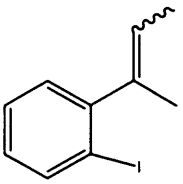
E/Z

113b **115**

Scheme 4.10: Synthesis of the iodo alkene **115** by Grignard reaction.

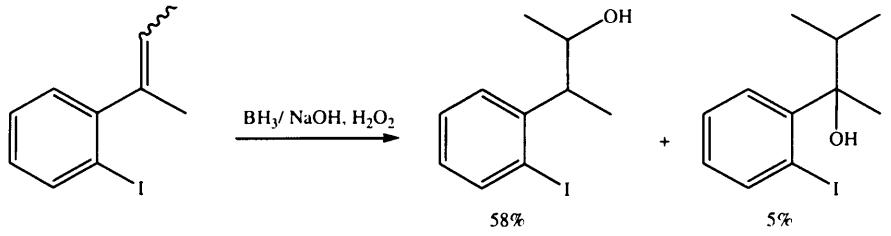
On the latter substrate we attempted unsuccessfully the hydrogenation reaction using either Wilkinson catalyst[28] (experimental conditions and results are reported in Table 4.2) or Ni and Pd as catalysts at atmospheric pressure. No hydrogenation of the double bond was observed.

Table 4.2: Experimental conditions and results with Wilkinson catalyst in the hydrogenation of **115**.

Substrate	Experimental conditions				Product
	Time	Solvent	Pressure	% mol catalyst	
 **115**	16h	i-PrOH/THF (1:1)	1atm	4%	S.M.
	10h	i-PrOH/THF (1:1)	20 bar	4%	S.M.
	12h	i-PrOH/THF (1:1)	20 bar	8%	S.M

An accurate literature research revealed that the hydrogenation of trisubstituted olefines requires particular strong pressure[29]conditions. For instance, (Z)-2-phenylbut-2-ene can be hydrogenated using a pressure of 100 atm and a temperature of 80°C.

At this point, hydroboration reactions were tried to functionalize the double bond in **115**. The hydroboration with subsequent acidic quench by acetic acid gave the iodo alkane **114** in low yield (3%). This is probably due either to a slow rate of hydrolysis of the two final alkyl groups in the trialkyl borane intermediate, or to the formation of boron acetate once the acid is added, as previously reported by Brown.[30] The hydroboration with subsequent oxidation by alkaline hydrogen peroxide produced the *anti*-Markovnikov alcohol **116** in 58% yield. Also the Markovnikov alcohol **117** was obtained in 5% yield as shown in Scheme 4.11.



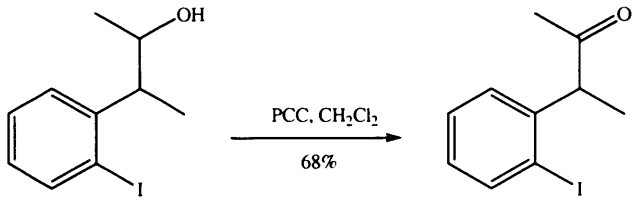
58% 5%

115 **116** **117**

Scheme 4.11: Synthesis of the *anti*-Markonivkov alcohol **116** by hydroboration with subsequent oxidation by alkaline hydrogen peroxide.

The reduction of the alcohol **116** was attempted under different reaction conditions using either triethylsilane and boron trifluoride[31] or triethylsilane and trifluoro acetic acid and resulted in no formation of the hydrocarbon or production of the olefin. A further fruitless attempt of reducing the alcohol was sought by converting the alcohol into tosylate and then reducing this group by $LiAlH_4$.

Therefore we thought to oxidise the alcohol **116** to ketone **118** and then decarbonylate the ketone. The ketone **118** was synthesised using PCC as shown in Scheme 4.12. Due to time constraints, the synthesis of 1-sec-butyl-2-iodo-benzene **114** could not be continued.



116 **118**

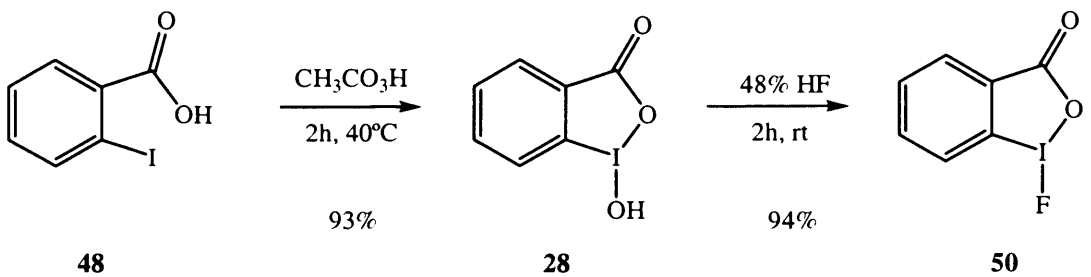
Scheme 4.12: Synthesis of 3-(2-iodo-phenyl)-butan-2-one **118**.

Starting from the ketone **118**, the synthesis of the butyl-iodo-benzene **114** requires one additionally step. That can be done either using the Clemmensen reduction (Zn in HCl) or the Wolff-Kishner (hydrazine NH_2NH_2) reaction.

Once the steps have been established for the synthesis of 1-sec-butyl-2-iodo-benzene, the oxidation reaction of the iodine, basic hydrolysis of the I(III) and subsequent reaction with HF should be able to give the correspondent iodo difluoride. The enantiopure iodo benzene substrate **114** could be obtained in different ways. Separation can be done by chiral HPLC. Another possibility would involve an asymmetric hydroboration of the double bond of the alkene. That could be realised using for instance catecolborane in the presence of a chiral catalyst.

4.3.2 1-Hydroxy-1,2-benziodoxol-3(1H)-one

1-Hydroxy-1,2-benziodoxol-3(1H)-one (IBA) **28**, with a covalent bond between the oxygen in the carboxylic group and the iodine, was chosen as a precursor to synthesise the corresponding fluoride **50**. The synthesis of the correspondent fluoro derivative has already been described in Chapter 2 and is shown again in Scheme 4.13.



48 **28** **50**

Scheme 4.13: Synthesis of fluoro derivate **50** from **48**.

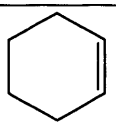
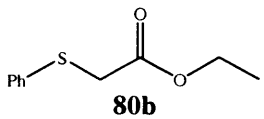
Its synthesis was performed by simple treatment of the IBA with hydrofluoric acid and **50** was isolated as moderately hygroscopic and thermally stable solid. Alternative routes for the synthesis of **50** were also reported in Chapter 2.

In this Section, we will firstly report on the experiments performed to study its reactivity as fluorine transfer reagent and secondly on the attempts made for the further development of the chiral analogue based on the structure of fluoro benziodoxole **50**.

4.3.2.1 Reactivity of fluoro-benziodoxole

The reactivity of this new potentially fluorinating agent was studied with different functionalities such as the double bond in cyclohexene and the carbonyl group in phenylsulfanyl ethyl acetate. The experimental conditions and the results obtained are summarised in Table 4.3.

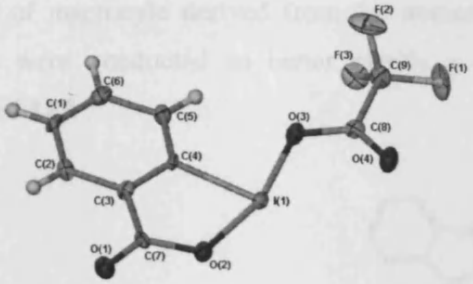
Table 4.3: Reactivity of fluoro-benziodoxole with different substrates

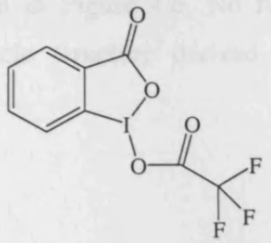
Entry	Substrates	Conditions[a]			Results
		Ratio	Time	Solvent	S.M.:product
1	 **119**	1:1	16h	CH_2Cl_2	1:0
		1:2	16h	CH_2Cl_2	1:0
		1:1	16h	CH_2Cl_2[b]	1:0
		1:1	16h	CH_2Cl_2[b]	1:0
2	 **80b**	1:1	16h	CH_2Cl_2	1:0
		1:2	16h	CH_2Cl_2	1:0
		1:1	16h	CH_2Cl_2[c]	1:0
		1:1	22h	$(ClCH_2)_2$	1:0
		1:1	16h	$(ClCH_2)_2$[d]	1:0

a Temperatures were 40°C with CH_2Cl_2 and 80°C with $(ClCH_2)_2$
b With the additional presence of 1 equivalent of $(PhSe)_2$
c With additional presence of few drops of HF 48%
d With additional 1equivalent of KF

In all cases no reactivity and no formation of fluorine products were observed and the unreacted starting material was recovered at the end of the reaction. The use of few drops of hydrofluoric acid, the presence of $(PhSe)_2$ or the addition of a external fluoride salt in the reaction mixture did not change the experimental results. In the reaction with the sulfanyl ester **80b**, when additional KF (last experimental condition for **80b**) was used, a trace amount of the correspondent sulfoxide was found in the reaction mixture.

We attempted to crystallise the new fluoro benziodoxole **50** in order to obtain further information about its structure. Several attempts with different solvents were made. In most cases, no crystals were obtained. Using toluene and a few drops of TFA, a suitable crystal was found and analysed (Figure 4.5). The analysis of the structure (Appendix 1) revealed that a ligand exchange occurred with a consequent formation of the trifluoroacetoxyl derivative **120**.





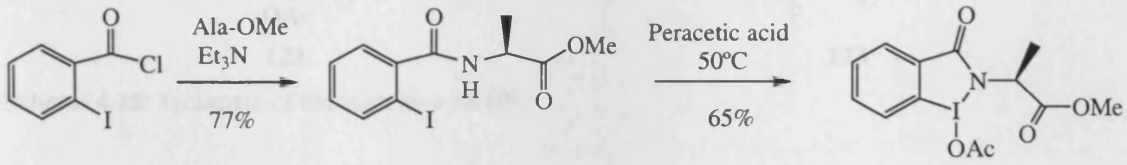
120

Figure 4.5: Crystal structure of 1-trifluoroacetoxy-benziodoxole **120**.

4.3.3.2 Towards to the chiral fluoride: benziodazole

The fluoro benziodoxole **50** was used as substrate for the further synthesis of a chiral hypervalent iodofluoride. Despite the fluoro benziodoxole **50** revealed not to be an efficient fluorinating agent, the structure of the correspondent benziodazole may modify the chemical reactivity and may be active as a fluorinating agent.

The following synthesis was performed through which it could be possible to construct a chiral difluoride based on the benziodazole moiety. Benziodazole **122** was prepared by amidation of **121** and successive oxidation of **53** with peracetic acid (Scheme 4.14).



121 **53** **122**

Scheme 4.14: Synthesis of acetoxy benziodazole **122**.

The amino acid alanine introduces directly the chirality into the substrate. The synthesis of the corresponding fluoride was attempted first trying to convert the acetate group in **122** in hydroxy and then performing the reaction with HF on the hydroxyl derivative.

The treatment with 10% NaOH produces a complete solubility of acetoxy benziodazole **122**. The subsequent acidification of the solution either with 10% HCl or with HF produced the precipitation of a white solid. The ^{1}H NMR spectra showed a peak at 8.6 ppm, indicative of the presence of hypervalent iodine species, the absence of methyl ester and the absence of the peak correspondent to the acetoxy group. The product of the reaction was still a hypervalent species. More than likely, an additional coordination between the oxygen in the free carboxylic acid and the iodine is present. The autoassembly of monomeric units of hypervalent iodine substrates with consequent formation of macrocycles is a phenomenon already known in literature.[32] An

example of macrocyle derived from the autoassembly[32] is shown in Figure 4.6. No further analyses were conducted to better clarify a possible macrocycle structure derived from compound **122**.

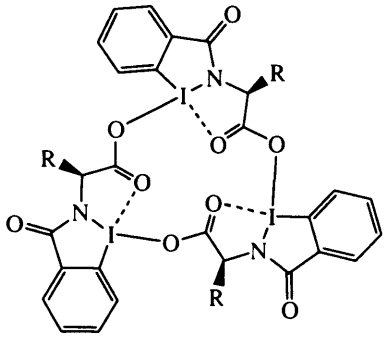
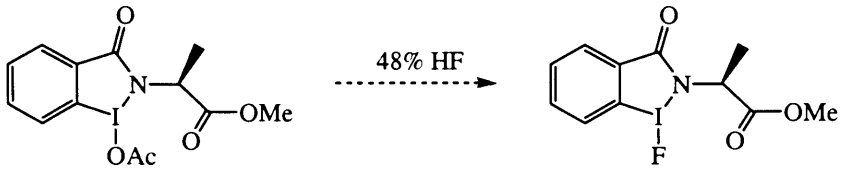


Figure 4.6: Macrocycle derived from the autoassembly of 3 monomers of hypervalent iodine species[32].

The synthesis of the fluoro derivative **123** was directly attempted from the acetoxyl substrate **122** and a hydrolysis with HF was performed (Scheme 4.15).



122 **123**

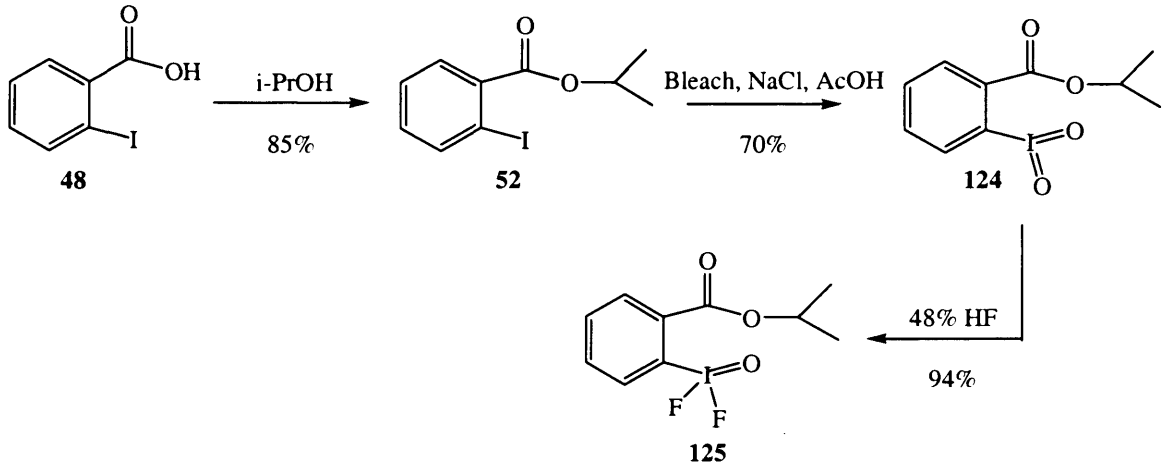
Scheme 4.15: Treatment of the acetoxy with HF.

A white crystalline solid was recovered after 2 hours of reaction. The ^{1}H NMR showed peaks which are consistent with structure **123**. The ^{19}F-NMR showed a peak at -109 ppm, suggesting also the presence of fluorine, but the elementary analysis gave values, which are in strong disagreement with the proposed structure **123**.

4.4 A new difluoride with hypervalent iodine in oxidation state V

4.4.1 Synthesis

To enhance the reactivity of fluoro benziodoxole **50**, we planned to increase the oxidation state of the iodine atom, trying to synthesise a pentavalent iodine bearing four fluorine atoms. To achieve this, the iodyl precursor **124** was synthesised by oxidation reaction with bleach of the isopropylic ester **52** (Scheme 4.16). The iodyl derivative **124** was then left to react with HF. The combined results derived from ^{1}H, ^{13}C, ^{19}F NMR showed the presence of a hypervalent species. The low field shift of the aromatic proton at 8.71 ppm and the presence of a quaternary carbon at 152 ppm indicated the formation of an hypervalent iodine species with the iodine in oxidation state V. Additionally the ^{19}F NMR indicated the presence of fluorine with a peak at –28.69 ppm as a sharp singlet. The elementary analysis and the mass spectroscopy were conclusive in the attribution of the right structure. The compound synthesised by hydrolysis of the iodyl **124** with HF presents 2 fluorine atoms and an oxygen atom bounded to the iodine atom.



Scheme 4.16: Synthesis of the difluoride iodo (V) hypervalent reagent **125**.

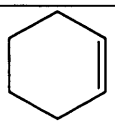
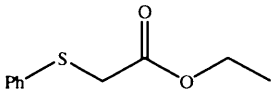
4.4.2 Reactivity

The reactivity of the new difluoride was tested with two different substrates: cyclohexene and sulfanyl ester **80b**. The experimental conditions and the results are summarised in Table 4.4.

No reactivity was observed with the double bond present in cyclohexene. The NMR analysis showed the presence of the starting material in the reaction mixture.

With the sulfanyl ester **80b**, no appreciable reactivity was observed when the reactions were performed using CH_2Cl_2 or acetonitrile as a solvent at room temperature. Under the previous conditions the starting material was recovered at the end of the reaction, together with a trace amount of the correspondent sulfoxide. Increasing the temperature at 80°C and using 1,2 dichloroethane as a solvent, the sulfanyl ester **80b** was converted into the sulphoxide (deduced from the presence of a doublet of doublets at 3.76 ppm in the ^1H NMR) and the difluoride (deduced from the peak at 108.42 ppm in the ^{19}F NMR) and the oxidation state of the hypervalent reagent changed during the path of reaction from pentavalent to monovalent. The ratio of the sulphoxide and the difluoride is around 1:1 from NMR data.

Table 4.4: Reactivity of the difluoride **125** with cyclohexene **119** and sulfanyl ester **80b**.

Entry	Substrates	Conditions[d]			Results
		Ratio	Time	Solvent	S.M.:product
1	 **119**	1:1	16h	CH_2Cl_2	1:0
		1:1	16h	CH_2Cl_2[a]	1:0
		1:1	16h	CH_3CN	1:0
		1:1	16h	CH_2Cl_2[b]	1:0
2	 **80b**	1:1	16h	CH_2Cl_2	1:0
		1:1	16h	CH_2Cl_2[a]	1:0
		1:1	16h	CH_3CN	1:0
		1:1	16h	$(ClCH_2)_2$[d]	c

a With the additional presence of few drops HF 48%
b With additional presence of $(PhSe)_2$
c Sulphoxide and difluoride were obtained as products of reaction.
d Temperature was 25°C in all experiments but the last one for ester **80b**

Despite the preceding result requiring further investigations, it suggests that this reagent can be used as fluorinating agent. The further chiral development could be performed by a simple introduction of chirality in the ester moiety.

4.5 Additional attempts

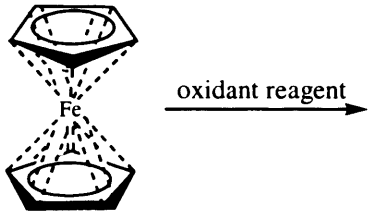
This Section reports two additional attempts made to synthesise chiral difluoride reagents. The planar chirality of the ferrocene and the accessible synthesis of chiral aminonaphthol were considered.

4.5.1 Ferrocene

A series of experiments were performed over the ferrocene to investigate its stability towards the most used oxidants used in the synthesis of hypervalent reagents.

The oxidants used to analyse the stability of the ferrocene are summarised in Scheme 4.17. Using either sodium perborate or sodium metaperiodate, a complete consumption of ferrocene was observed. Presumably, oxidation of the iron atom takes place instantaneously (a rapid change of colour takes place during the reaction) with the probable formation of ferrocinium and a complete destruction of the ferrocene structure.

When the Koser reagent[18] was used, the starting material was recovered at the end of the reaction, which lasted 3 days. This last experiment presented an opportunity in the aim of synthesising the hypervalent iodo over the ferrocene structure.



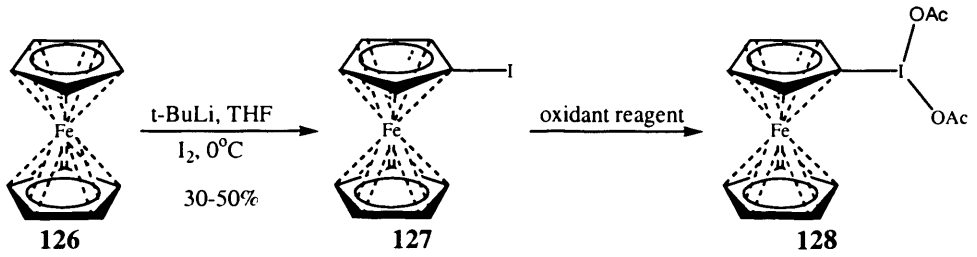
126

Different oxidant ragents used:

- $NaBO_3$ $4H_2O$, AcOH, 40°C, 3h
- $NaIO_4$, AcONa, AcOH, Ac_2O, rt, 5 h
- Koser reagent, rt, 3 days.

Scheme 4.17: List of oxidants used in the test of stability of the ferrocene **126** in oxidation reactions.

Iodo ferrocene[33] was then synthesised (Scheme 4.18) and let react with the Koser reagent.



126 **127** **128**

Scheme 4.18: Oxidation reactions using the iodoferrocene: a) $NaBO_3$ $4H_2O$, AcOH, 40°C, 48 h; b) Ac_2O, 30% H_2O_2, 40°C, 20h; c) CrO_3, AcOH, Ac_2O, H_2SO_4, 40°C, 5h; d) Koser reagent, rt, 2 days.

Unfortunately, the reactions performed with the iodoferrocene (Schema 4.18) destroyed the ferrocene structure, with the probable oxidation of the iron atom.

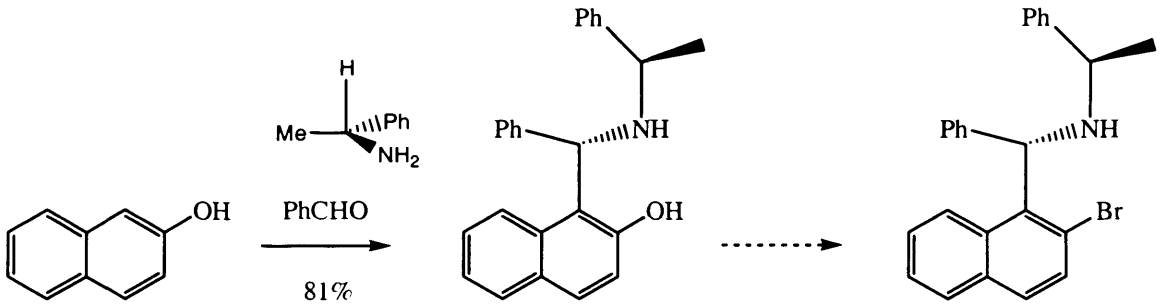
4.5.2 Amminonaphthol

The aminonaphthol was synthesized for its easy accessibility to chirality. This kind of compounds is normally used as chiral ligand in the asymmetric reduction of aldehydes with diethyl zinc.

According to data in the literature, the conversion of the phenolic group in bromide can be realised using triphenylphosphine. Once the halogen has been introduced, a halogen exchange reaction[11,12] will give the right iodine precursor for further oxidisation. The presence of the nitrogen group also presents the possibility to construct acyclic and cyclic iodo hypervalent reagents.

By protecting the nitrogen, it should be possible to generate hypervalent iodine with an open chain, and without its protection we should be able to synthesise the cyclic analogue. Furthermore, the presence of nitrogen allows for the possibility for interconversion into different functional groups without losing the information of chirality.

Scheme 4.19 reports the synthesis of the chiral aminonaphthol. The presence of the chiral amine produces the facial diastereodifferentation for the further attack from the 1 position in the naphthol.[34] With this methodology the synthesis of enantiopure (R,R) aminonaphthol **130** is straightforward.



129 **130** **131**

Scheme 4.19: Synthesis of the aminonaphthol **130**.

The limited experiments performed to interconvert the phenolic group in **130** into bromine (Table 4.5) failed. The use of PBr_3 was not able to produce the bromo derivative. Triphenyl phosphine in presence of Br_2 did not lead to the bromo derivative.

Table 4.5: Experimental condition for the conversion of the phenolic group into bromine.

Reagent	Condition
aminonaphthol	PBr_3
aminonaphthol	PPh_3, Br_2
Ts naphthol	I_2, KI, Ni, DMF
Tf naphthol	I_2, KI, Ni

Halogen exchange in presence of Ni was tried over the synthesised tosylate and triflate of the 2-napthol. In both cases no conversion was observed. The attempts to synthesise the bromo derivative **131** from the phenol **130** were ceased, due to the results found for the 1-iodo-2-(1-methoxyethyl) benzene **107**.

4.6 Conclusions

Enantiopure fluorinated products are substrates in increasing demand mainly from pharmaceuticals companies. In Chapter 1, examples of chiral fluorinating reagents based on different structures were reported.

The lack of chiral hypervalent reagents and in particular the absence of chiral polyvalent iodine (III) difluorides attracted our interest for the synthesis of a chiral iodo difluoride.

The research was mainly focused on:

1 The planar chirality of monosubstitued paracyclophane

2 The central chirality of 1-iodo-2-(1-methoxyethyl) benzene

For the paracyclophene the main results obtained can be summarised with the following points:

- improved synthesis of 4-iodo-[2.2]-paracyclophane which was synthesised in two steps
- the HPLC conditions for the separation of the racemic mixture of the 4-iodo-[2.2]-paracyclophane were found
- 4-iodo-[2.2]-paracyclophane was found to be stable in most of the oxidation reactions performed

The impossibility to interconvert the central chiral diacetate-1-iodo-2-(1-methoxyethyl) benzene led to the evaluation of similar compounds. In particular, the new fluoro benziodoxole and a new difluoride with the iodine in oxidation state V were synthesised. Preliminary experiments revealed the prospect of using the last substrate as a fluorinating agent. From this substrate the further development of chirality should be an achievable task, by the introduction of a chiral ester.

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Chapter 5

5 Conclusions

Fluoroorganic substrates are very extraordinary molecules extensively used in both academia and industrial companies. They are very rare as natural products and therefore a synthetic approach is necessary for their production. In the last 50 years, a variety of methodologies has been developed for the introduction of fluorine into organic substrates.

In this context, the work treated in this research is incorporated. In particular, the transfer of fluorine to organic substrates was investigated. Among the possible methodologies, this work developed the one based on hypervalent iodine reagents. Hypervalent iodine difluoride reagents have been known since a century but not extensively used possibly due to their synthesis, which require the use of harmful and hazardous reagents.

The research carried out can be summarised in three main points:

- Synthesis of aryl iodo difluorides
- Reactivity of aryl iodo difluorides
- Synthesis of chiral iodo difluorides for stereoselective fluorination reactions

Aims of the project and main results obtained during this research work are shown in the Figure 5.1.

The classical methods to synthesise aryliodo difluorides date back to the sixties and are mainly based on the Carpenter and Zupan-Pollack methods.

An alternative route has been developed (reported in Chapter 1) which involves three synthetic steps: perborate oxidation, basic hydrolysis and subsequent treatment with hydrofluoric acid. This methodology presents general applicability and allowed for the synthesis of different difluorides in high purity and remarkable yields. In particular (difluoroiodo)toluene was obtained with an overall yield up to 97% starting from the diacetoxy iodo substrate, difluoro iodo naphthalene was obtained in 70% and the fluoro benziodoxole in 94% from hydroxy benziodoxole (IBA). The hydrolysis of IBA in hydrofluoric acid revealed to be an efficient

strategy for the preparation of the correspondent fluoride. Alternative routes for its synthesis were also investigated. The Carpenter method did not produce the fluoride while the Zupan-Pollack method led to only partial oxidation of the iodine atom.

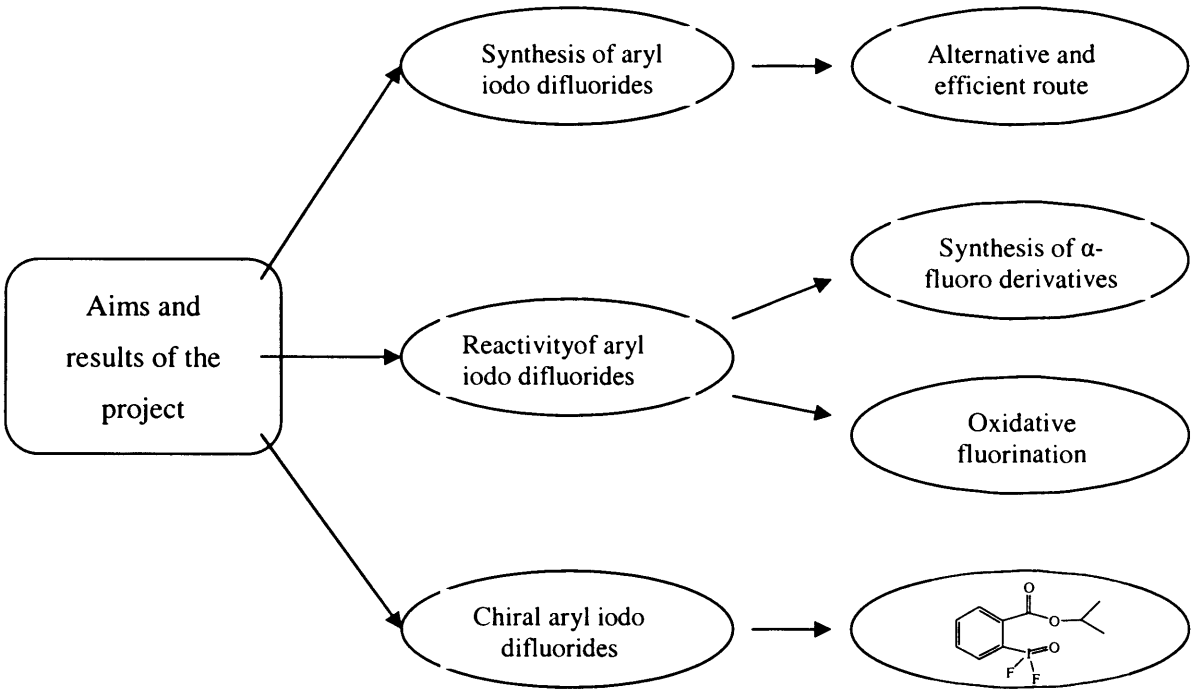


Figure 5.1: Aims and main results of the project.

The reactivity of the aryl iodo difluorides was tested on organic substrates. In particular, DFIT (2 equivalents) can α-fluorinate α-seleno esters, amides and nitriles. The monofluorinated products were obtained in yields ranging from 20% to 65%. Although the yields are only moderate, the reactions are usually very clean and, under the reaction conditions used no further oxidised products are observed.

The oxidative characteristic of DFIT was also exploited in the oxidative fluorinations of iodo substrates. Tetraethyl ammonium iododifluoride was synthesised by simple treatment of tetraethyl ammonium iodide with DFIT. Preliminary experiments showed the ability to react as a fluorine transfer reagent.

The enormous relevance of enantiopure fluorinated substrates led investigating the synthesis of chiral iodo difluorides. Different substrates were considered which can be divided into two groups depending on the type of chirality involved: planar and central chirality. For this purpose 4-iodo-[2.2]-paracyclophane was synthesised as a precursor of the difluoroiodo reagent . The synthesis of the 4-iodo-[2.2]-paracyclophane was developed respecting the methodology reported in the literature. The improvement of its synthesis, reported in Chapter 4, involved two

synthetic steps: bromination and halogen exchange. Each step is characterised by high yield (85% and 80%). Conditions for the separation by HPLC of the racemic mixture were discovered. The great stability of the iodo-[2.2] paracyclophane towards the oxidation reagents used to carry out the oxidation on the iodine atom was a surprise and prevented the synthesis of the correspondent iodo difluoride.

The impossibility to interconvert the diacetoxy iodo into difluoroiodo for the substrate 1-iodo-2-(1-methoxyethyl) benzene brought us to the synthesis of fluoro benziodoxole and difluoride with iodine in oxidation state V. Fluoro benziodoxole revealed to be unreactive as a fluorinating reagent. The lack of reactivity is possibly due to the high stability of the benziodoxole, in which the iodine is present in a 5-member ring. From preliminary experiments, the difluoride I(V) was found to be able to act as a fluorine transfer reagent. This result is encouraging and opens up a promising future for the possibility of its use as a chiral transfer regent of fluorine in stereocontrolled fluorinations.

Chapter 6

6 Experimental

6.1 General methods

Most reactions were carried out in standard borosilicate glassware of the appropriate size. The reactions performed in presence of hydrofluoric acid, either used as reagent either as expected side-product of the reaction itself, were carried out in special vessels made in Teflon purchased from Cowie®.

Experiments demanding water and/or oxygen exclusion were carried out under argon in pre-dried apparatus at 100°C in oven for an overnight period. Experiments demanding a precise and constant working temperature were performed using hot-plates with temperature probe control in silicon oil.

The solvents were usually removed in a Büchi R-124 rotation evaporator (final vacuum ca. 15 mbar). Further drying was realized in high vacuum at ca. 0.05 mbar.

Vacuum distillations were performed with a Büchi GKR-50 kugelrohr distillation apparatus.

Freezing baths were prepared from sodium chloride and ice-water (-20°C<T<0°C), acetone and carbon dioxide (-78°C) or from Trapp-mixture acetonitrile and liquid nitrogen (-40°C). Depending from availability and duration of the experiment a kryostate was used to reach the desired working temperature.

6.1.1 Solvents treatment

THF and diethyl ether were freshly distilled from sodium/benzophenone under inert gas atmosphere of N_2. Diisopropylamine and CH_2Cl_2 were distilled from CaH_2 under anhydrous atmosphere. All other high purity solvents used were bought from Fluka in septum bottles and handled under argon.
Solvents for chromatography and work-up were distilled, all other solvents were used as purchased from the company.

6.2 Physical data

6.2.1 ^{1}H NMR-spectroscopy

Jeol ECLIPSE+300 FT-NMR (300 MHz), Bruker DPX-400 (400 MHz), Varian EM-360 (300 MHz) (UMD, Duluth, US).
The chemical shifts δ are given in ppm relatively to an internal standard. Deuterated chloroform solutions containing tetramethylsilane were used to perform the analysis. Additionally the peak of the deuterated solvent was used as internal reference: $CDCl_3$ at δ = 7.26 ppm, MeOD at δ = 3.30 ppm, DMSO at δ 2.50 ppm. All coupling constant *J* are reported in Hertz. The multiplicity of the signal is abbreviated as follow: s = singlet, d = doublet, t = triplet, q = quadruplet, quin = quintuplet, sep = septet, m = unresolved multiplet, br = broad. Aromatic signals not specifically assigned at one particular position have been labeled as arom.

6.2.2 ^{13}C NMR-spectroscopy

Bruker DPX-400 (100.6 MHz), Varian EM-360 (75.5 MHz) (UMD, Duluth, US).
The chemical shifts δ are given in ppm relative to the solvent signals of deuterated chloroform (δ = 77.0 ppm, t), methanol (δ = 49.0 ppm, sep) or DMSO (δ = 39.5 ppm sep).

6.2.3 ^{19}F NMR-spectroscopy

Jeol ECLIPSE+300 FT-NMR (282.8 MHz), Varian EM-360 (282.8 MHz) (UMD, Duluth, US).

The chemical shifts δ are given in ppm relative to the external standard of BF_3-2EtOH (δ = -131.3 ppm) or $CFCl_3$ (δ = -28.1 ppm).

6.2.4 ^{77}Se NMR-spectroscopy

Jeol ECLIPSE+300 FT-NMR (57.3 MHz).

The chemical shifts δ are given in ppm relative to the external standard of diphenyl diselenide (δ = 463 ppm)

6.2.5 Mass spectroscopy

Mass spectroscopy analyses were performed either by atmospheric pressure chemical ionisation (APCI) or by GC-MS.

- Fisons VG Platform II. The analyses were performed in the mass spectrometry laboratory of the Chemistry Department, Cardiff University. Ions were generated by atmospheric pressure chemical ionisation (APCI).
- GC-MS (column: DB-5MS). If not otherwise specified, the following temperature conditions were used: from 70 to 200°C for 36 minutes, from 200 to 250°C for 4 minutes and 250°C for 5 minutes. In this case, electronical ionization (EI) was used as an ionisation method.

In both cases, the masses of the fragments are given in atomic mass unit per elementary charge (m/z). The intensity relative to the strongest signal (molecular peak) is quoted in brackets (in %).

Accurate high resolution mass spectral data were recorded by National Mass Spectrometry Service Centre at University of Swansea. The molecular formulae are given in molecular ion (M^+), molecular ion + hydrogen ($M+H^+$), molecular ion + ammonium ion ($M+NH_4^+$).

6.2.6 GC-MS combinations

Varian Sarturn 3400 GC/MS with column DB-5MS, 30 m. Ions were generated by EI and detected in a Varian Ultratrace ion trap.

6.2.7 IR-spectroscopy

All compounds were analysed on a Perkin-Elmer 1600 FTIR-spectrometer. The wave numbers are reported in cm^{-1}. Liquid samples were measured either as liquid film on sodium chloride pellets (NaCl), either as a solution in chloroform ($CHCl_3$) or as pressed pellets in previously flamed potassium bromide (KBr). Solid samples were analysed either as a film in nujol over sodium chloride pellets either as KBr pressed tablets.

6.2.8 Microanalysis

Microanalytical data were recorded either in the microanalytical laboratory at the Atlantic Microlab, INC, Norcross, Georgia,(USA) or in the Warwick Analytical Service Ltd, Coventry, (UK). The data are quoted as mass percentage.

6.2.9 Melting points

The melting points were measured in an open capillary tube with a Mel-temp II instrument and are uncorrected.

6.2.10 Optical rotation

Optical Activity Lts. AA-1000 Polarimeter. The samples were measured at 589 nm of wavelength at 25°C. The sample concentration is quoted in g/100 ml.

6.3 Chromatographic methods

6.3.1 Thin layer chromatography: analytical and preparative

Thin layer chromatography was performed with Merck silica gel 60 F254 precoated aluminium backed plates. Visualisation was achieved by UV-fluorescence, exposition to iodine vapour or heating after dipping in one of the following developing solutions:

1. 1 g potassium permanganate, 7 g potassium carbonate, 2 ml of a 5% solution of sodium hydroxide, 100 ml of water.
2. 1 g cerium(IV)sulfate-tetrahydrate, 2.5 g ammonium heptamolybdate tetrahydrate, 10 ml concentrated sulphuric acid, 90 ml water.

6.3.2 Flash chromatography

Fisher silica gel 60 (30-70 mesh). The solvent mixtures are quoted in volume percentage.

6.3.3 Medium pressure liquid chromatography

Solvent delivery system Büchi 681, column diameter 2.5 cm, column length 40 cm, packed with Merck silica gel LiChroprep Si 60 (15-25 μm), detection with Büchi UV-Vis-Filter-Photometer, Bio-Rad Model 2128 fraction collector.

6.3.4 High performance liquid chromatography

1. Merck-Hitachi L-6200 gradient pump with Merck-Hitachi L-4200 UV-Vis-Detector and Merck-Hitachi L-2500 integrator.
2. Shimadzu LC-10AT-VP solvent delivery system, Shimadzu SPD-M10A-VP DAD-detector, Shimadzu SCL-10A-VP controller, operated by Shimadzu Class VP-software

Analitical chiral columns used: OB, OD, OD-H from Daicel Chemical Industries, column length 25 cm, column diameter 0.46 cm.

Preparative chiral column used: OD from Daicel Chemical Industries, column length 25 cm, column diameter 2 cm.

6.5 General procedures

6.5.1 General procedure for the oxidation of iodine with chlorine gas[1,2] (GP1)

Under argon atmosphere, the aromatic iodine substrate (4 mmol) in a three neck round bottom flask was solubilised in CH_2Cl_2 anhydrous (3 ml). Chlorine (30 x 1 mmol) was generated from MnO_2 (30 mmol, 2.6 g) and concentrated hydrochloric acid (120 mmol, 10 ml) and dried by flushing it through a tube filled with $CaCl_2$. The bubbling of chlorine was realised by a Pasteur pipette directly put in the solution, previously cooled to 0°C. The third neck was connected with a vacuum bottle filled with 1M NaOH in order to quench the excess of chlorine gas.
The reaction mixture, protected from light sources, was then allowed to react at rt for 1 hour, then it was cooled to 0°C and fluxed several times with argon. The evaporation of the solvent produces a generally yellow solid, which can be contaminated from the starting material. The yellow solid obtained was washed with hexane to eliminate the starting material and dried on air, protected from light.

6.5.2 General procedure for the oxidation from iodo-arene to (diacetoxyiodo)arene (GP2)

Several procedures were used to oxidise the iodoaryl substrates to the correspondent diacetoxy derivative.

- **Oxidation with $NaBO_3 \cdot 4H_2O$[3] (GP2a)**

Sodium perborate $NaBO_3 \cdot 4H_2O$ (68 mmol, 10.46 g) was added portionwise to a stirred solution of aryl iodine (6.8 mmol) in glacial acetic acid (68 ml), previously heated to 40-46°C. The mixture was stirred at this temperature until TLC analysis indicated completion of reaction. Then the reaction mixture was concentrated by removal of acetic acid by evaporation under reduced pressure. Water was added to the residue. Extraction was made with choloroform (3 x 25 ml). The combined organic layer was then washed with brine and dried with $MgSO_4$.

Concentration on the rotary evaporator gave a solid, which was further purified by washing it with hexane or petrolether.

- **Oxidation with peracidic acid[4] (GP2b)**

The peracetic acid was prepared from acetic anhydride (60 ml) and hydrogen peroxide (16 ml) and refluxing the mixture for 4 hours at exactly 40°C. The aryl iodine substrate (10 mmol) was dissolved in peracetic acid (40 ml). The reaction mixture was stirred for 2-3 hours at 40°C. Then water was introduced and the mixture was put in the fridge at 0°C. The formed precipitate was collected by filtration and dried in the high vacuum pump.

- **Oxidation with chromium (VI) oxide[5] (GP2c)**

Powdered chromium oxide (CrO_3, 0.3 mmol, 29 mg) was slowly added to a stirred mixture of glacial acetic acid (0.2 ml) containing acetic anhydride (0.1 ml). The temperature was then raised to 40°C and kept at this temperature for 1 hour. The deep orange solution was then cooled down at 10°C and the iodo arene (0.45 mmol) was then introduced as a solid. The temperature was then raised once more to 40°C. At this temperature, concentrated H_2SO_4 (0.06 ml) was added to the reaction mixture and the reaction mixture was stirred for 1 hour at 40°C. Once the reaction mixture was cooled at 0°C, 20% aqueous solution of ammonium acetate was added to the deep-green mixture. The flask was kept in the fridge for few hours and the obtained precipitate was filtrate with cold 10% acetic acid (2 x 5 ml). The crude product was then purified by recrystallization.

- **Oxidation with $NaIO_4$[6] (GP2d)**

Sodium periodate (0.45 mmol, 96 mg) and sodium acetate (0.8 mmol, 70 mg) were suspended in a solution of glacial acetic acid (0.6 ml) in presence of acetic anhydride (0.06 ml). The aromatic iodo substrate (0.4 mmol) was the introduced. The resulting mixture was refluxed for 2 hours, cooled at room temperature and poured in water. Extraction was done with CH_2Cl_2 (3 x 10 ml). The collected extracts were dried over $MgSO_4$, the solvent was removed in the rotary evaporator. The obtained crude was purified washing it with hexane or petrolether.

- **Oxidation with Koser reagent[7] (GP2e)**

A solution of iodo-arene (1 mmol) in CH_2Cl_2 (10 ml, 0.1 M) was mixed with Koser reagent (1.2 mmol) added as a solid. The mixture was stirred at room temperature up to 3 days. The progress

of the reaction was monitored by ^1H NMR over small portion from the reaction mixture. The solvent was then removed in the rotary evaporator and the crude solid was further analysed.

6.5.3 General procedure to obtain the iodosyl substrates (GP3)

The (diacetoxyiodo)-substrate (7 mmol) was stirred in a 5M solution of NaOH (10 ml). This mixture was let stirred for 1-2 hours at room temperature. The yellow solid was collected by suction and washed first with water (500 ml) and then with $CHCl_3$ (100 ml). The solid was allowed to dry by suction and use immediately in the next step.

6.5.4 General procedure to obtain the iodo-difluorides (GP4)

Different procedures were used to obtain the difluorides depending from the particular substrate. For some substrates more than one method was used.

- **Carpenter method[8] (GP4a)**

In a Teflon round bottom flask, the iodo-dichloride substrate (2 mmol) was dissolved in CH_2Cl_2 (4 mL, 0.5M). Mercury oxide (yellow phase, 2.5 mmol) was added at rt and stirred for a few minutes. Then hydrofluoric acid 48% (1.6 ml) was added to the mixture of reaction. After 1 hour, the white precipitate of mercury dichloride ($HgCl_2$) was removed by filtration on paper. The filtrate was extracted with CH_2Cl_2 in a Teflon separating funnel, dried with $MgSO_4$ to obtain a yellow solid.

- **Hydrolysis with HF (40% or 48%) over the iodosyl substrates (GP4b)**

In a round bottom flask made of Teflon, a slurry of iodosyl-substrate (8.6 mmol) in CH_2Cl_2 (30 mL, 0.3M) was prepared. Hydrofluoric acid 40% was added (16 x 8.6 mmol) and the reaction mixture was allowed to stir for half hour. The mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed several times with small portions of water, dried with molecular sieves and the solvent was removed at atmospheric pressure through nitrogen flow to obtain a pale yellow solid, which was used without further purification.

- **XeF_2 over the iodo arene substrates[9] (GP4c)**

In a Teflon round-bottom flask, to a solution of iodo-arene (0.1 mmol) in acetonitrile or CH_2Cl_2 (2 ml) at -30°C, was added XeF_2 (0.1 or 0.2 mmol depending from the experiment). The mixture was let stirred up to 3 days. The progress of the reaction was monitored by ^1H NMR. The reaction mixture was then poured in 5% sodium bicarbonate, extracted with CH_2Cl_2 (2 x 5 ml) and dried over magnesium sulfate. All the reactions using XeF_2 were carried out in a well ventilated hood since solid XeF_2 is toxic and has a vapor pressure of 4.6 mm at 25°C.

6.5.5 General procedure to oxidise the iodo arene to the corresponding iodyl (GP5)

- **Oxidation with $NaIO_4$[6] (GP5a)**

Sodium periodate (2 mmol, 431 mg) was suspended in water (2 ml). The chosen iodo arene (0.92 mmol) was then introduced as a solid. The mixture was refluxed for 8-16 hours. Ice water was then added to the reaction mixture and the solid formed was collected by suction. The solid was then washed with hexane or chloroform (depending from the iodo arene used).

- **Oxidation with oxone monopersulfate[10] (GP5b)**

Ozone monopersulfate (1.3 mmol, 817 mg) was suspended in concentrated sulfuric acid (2.8 ml). The iodoarene (0.9 mmol) was then introduced as a solid and the temperature was raised to 70°C. The reaction mixture was stirred for 4-6 hours. The reaction mixture was cooled down to room temperature. Ice water was then added to the reaction mixture and the solid formed was collected by suction. The solid was then washed with hexane or chloroform (depending from the iodo arene used).

6.5.6 General procedure to prepare the phenylselnayl substrates (GP6)

The diselenide (diphenyl diselenide or dimethyldiselenide) (1 mmol) was dissolved in ethanol (2 ml) and cooled at 0°C. Sodium borohydride was added portionwise until the solution became colourless. Stirring was continued for 30 minutes at room temperature. At this stage the chosen

chloro substrate (α-chloro-ester, α- chloro-nitrile or chloromethyl methyl ether) (4 mmol) was added and the stirring continued for 3 hours. In case of chloromethyl methyl ether, the excess of alkylating agent was destroyed by quenching with concentrate ammonia solution (1ml), while in the other cases the reaction was quenched with water. Extraction was made with dichloromethane. The collected organic layer were washed with water, dried with $MgSO_4$, the solvent was removed. The products were purified by flash chromatography on silica gel.

6.5.7 General procedure to synthesise the phenylselanyl acid from the correspondent ester (GP7)

To a solution of ester (1.69 mmol) in EtOH (10 ml) was added a solution of KOH 30% (10 ml). The mixture was stirred until completion and monitored by TLC. Water and diethyl ether were added. The basic layer was acidified with HCl_c and extracted with diethyl ether. The organic layer was washed, dried over $MgSO_4$ and the solvent was evaporated. The crude was then purified by flash chromatography when necessary.

6.5.8 General procedure to obtain the phenylselanyl derivatives from the corresponding acid (GP8)

To a solution of phenylselanyl acid (7 mmol) in dry dichloromethane (40 ml) was added the proper alcohol or amine (10 mmol), DMPA (8 mmol) and EDCI (8 mmol). The mixture was stirred at room temperature overnight. Water was then added and the extraction was made with dichloromethane. The organic solution was washed with 1M NaOH to eliminate any traces of acid, and 1M HCl, dried and concentrated. The crude oil was then purified by flash chromatography on silica gel.

6.5.9 General procedure to fluorinate the seleno substrates with (difluoroiodo)toluene (GP9)

Under inert atmosphere of argon, (difluoroiodo)toluene (0.8 mmol, 204 mg) was dissolved in dry dichloromethane (7 ml) in a round bottom flask made in Teflon. The chosen substrate (0.4 mmol) in dichloromethane (1 ml) was added to the previous solution previously cooled at 0°C or warm up to the working temperature (usually 40°C). The reaction mixture was allowed to

react overnight (16 hours) at the chosen temperature. The solvent was removed and the obtained crude was further purified by flash chromatography on silica gel or by preparative TLC.

6.5.10 General procedure of alkylation (GP10)

At -78°C, under inert and anhydrous atmosphere, a solution of nitrile or ester (3 mmol) in THF (6 ml) was added to a solution of LDA (0.5 M in THF) freshly prepared. This mixture was allowed to react for about 30 minutes, then methyl iodide (4 mmol) was added as electrophile. The resulting solution was kept a -78°C for 1 hour and warmed to room temperature slowly. The solution was poured into a saturated solution of ammonium chloride and extracted with dichloromethane (3 x 10 ml). The combined organic portions were dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash chromatography on silica gel.

6.5.11 General procedure for aromatic bromination reactions (GP11)

Under inert atmosphere of argon, iron powder (0.4 mmol, 30 mg) was stirred in dichloromethane (20 ml). A portion (3 ml) of a solution of bromine (0.6 ml) in carbon tetrachloride (40 ml) was added to the previous solution and stirred for 2 hours at 25°C. After addition of more dichloromethane (165 ml), the aromatic substrate (9.6 mmol) was added. The remaining amount of the bromine solution (37 ml) was then added dropwise. The resulting solution was stirred under reflux for 14 hours (or 3 days at room temperature 25°C). The reaction mixture was then washed with sodium bisulfite solution, then water was added. Extraction was done with chloroform (3 x 25 ml). The collected organic portions were washed with water and brine. The organic solution was dried over $MgSO_4$ and the solvent was evaporated. The crude residue was purified by flash chromatography on silica gel.

6.5.12 General procedure for halogen exchange reactions (GP12)

- **Using Ni (GP12a)**[11]

Under argon atmosphere, the aryl bromide (5 mmol) was dissolved in DMF (71 ml). Potassium iodide (30 mmol, 4.9 g), nickel powder (50 mmol, 2.9 g), and iodine (30 mmol, 7.6 g) were subsequently introduced as solids. The mixture was then allowed to reflux until completion of

the reaction. The progress of the halogen exchange was monitored by GC-MS. Then the mixture was cooled, quenched with 10% sodium tiosulphite and filtrated from the nickel powder. Water was added and the extraction was done with dichloromethane (3 x 25 ml). The collected organic layers were washed with water, brine and dried over magnesium sulfate. Evaporation on the rotary evaporator give a crude residue, which was further purified by flash chromatography on silica gel.

- **Using CuI (GP12b)[12]**

A mixture of aryl bromide (1 mmol), potassium iodide (15 mmol, 2.49 g), copper iodide (18 mmol, 3.4 g) in HMPA (3 ml) as a solvent was prepared. Under argon, the mixture was vigorously stirred and allowed to reflux for the opportune time. The progress of the reaction was followed by GC-MS. When a good percent of exchange was reached, the reaction mixture was quenched by addition of dilute hydrochloric acid followed by dichloromethane. The organic phase was separated, washed with aqueous sodium sulphite and water, dried and evaporated from the solvent. The pasty brown solid obtained was purified by flash chromatography.

6.5.13 General procedure for Grignard reactions (GP13)[13]

Under Argon, a solution of alkyl or alkenyl magnesium bromide was prepared from alkyl or alkenyl bromide (14 mmol) and magnesium (15 mmol, 361 mg) in dry THF (35 ml). Few iodine crystals were added to accelerate the initial formation of the Grignard reagent. A solution of 1-iodo-2-bromo benzene (7 mmol, 0.9 ml) in THF (20 ml) was added dropwise to the Grignard reagent already prepared. The reaction mixture was stirred for 4-6 hours at room temperature. After that the reaction was quenched with iodine (11 mmol, 2.6 g) at 0°C. The mixture was vigorously stirred and warm up to room temperature. Aqueous Na_2SO_3 was then added and the mixture was extracted with diethyl ether (3 x 25 ml). The combined organic extracts were washed with water, brine, dried with magnesium sulfate and concentrated. The residue was then purified by flash chromatography.

6.5.14 General procedure for hydroboration (GP14)

To a solution of alkene (1 mmol) in THF freshly distilled (13 ml), diborane in THF (1 mmol, 1 ml) was added dropwise at 0°C. Once all the diborane solution was added, the reaction mixture was warm to room temperature. The progress of the reaction was followed by ^1H NMR. When

the typical peaks for the double bond disappeared, the reaction was quenched with one of the following methods.

- **Quenching with acetic acid (GP14a)[14]**

Protonolysis of the organoborane was realised adding acetic acid (5 ml) and refluxing the reaction mixture overnight (16 h). Water was added and the extraction was done with diethylether (3 x 10 ml). The organic layers were collected, washed with water and brine, dried with magnesium sulfate and the solvent was evaporated. The crude was analysed by flash chromatography.

- **Quenching with sodium hydroxide and hydrogen peroxide (GP14b)[15]**

Oxidation of the organoborane was made by adding 1M NaOH (2 ml), followed by H_2O_2 30-vol. (3 ml) at 0°C. The mixture was stirred for 30 minutes. After that the organic phase was separated from the aqueous. Extraction was done with diethyl ether (3 x 10 ml). The collected organic fractions were washed with water, dried over magnesium sulfate. The solvent was removed by rotary evaporator and the residue was purified by flash chromatography on silica gel.

6.5.15 General procedure of tosylation (GP15)[16]

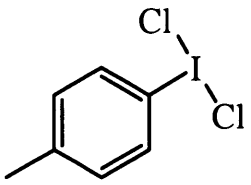
To a solution of the chosen alcohol (1 mmol) in dry chloroform (3 ml) was added dry pyridine (1.1 mmol, 0.08 ml) at 0°C. Tosyl chloride (1 mmol, 190 mg) was added to the previous solution as a solid. The mixture was stirred at room temperature until completion of the reaction followed by TLC. Water was then added and the extraction was done with CH_2Cl_2 (3 x 10 ml). The organic layers were washed with water and brine, dried over magnesium sulfate and the solvent was removed. The crude was then purified by flash chromatography.

6.5.16 General procedure for hydrogenation (GP16)

To a solution of the substrate (2 mmol) in degassed solvent (THF:MeOH 1:1, 12 ml) and saturated by hydrogen was added 4% mol of Wilkinson`s catalyst (0.07 mmol, 70 mg). The solution was stirred under hydrogen pressure (atmospheric pressure and 20 bar) at room temperature up to 16 hours. The reaction mixture was then filtered trough a short pad of alumina and washed with diethyl ether. The crude of reaction was then analysed.

6.6 Compounds

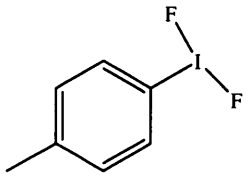
(Dichloroiodo)toluene[17] 23b



Synthesised according GP1 as a yellow solid. Yield was between 60 % (2.5 mmol, 0.72g) - 86% (3.5 mmol, 1.0 g). Spectroscopic data agree with those in literature.[17]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (3H, s; *CH_3*); 7.27 (2H, d, *J* = 8.3 Hz, arom); 8.04 (2H; d, *J* = 8.3 Hz, arom).

(Difluoroiodo)toluene[1] 26



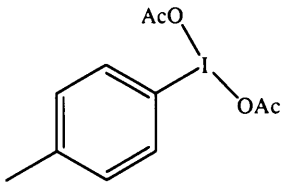
Synthesised according Carpenter method GP4a with yields ranging from 50% (1 mmol, 256 mg) to 60% (1.2 mmol, 310 mg). It was also prepared according GP4b. In this case yield was up to 97% (8.35 mmol, 2.14 g). Spectroscopic data agree with those in literature.[1,17]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (3H, s, *CH_3*), 7.40 (2H, d, *J* = 8.5 Hz, arom), 7.84 (2H, d, *J* = 8.5 Hz, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.2, 120.8, 130.2, 132.1, 142.3;

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = –177.33 (Lit.[1]: δ = –147.30; Lit.[18]: δ = –174.30; Lit.[17]: δ = –177.10).

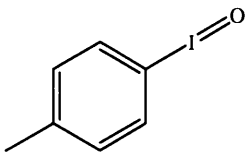
(Diacetoxyiodo)toluene[3] 24



It was prepared according to the procedure developed by McKillop GP2a. Yield ranging from 60% (4.1 mmol, 1.4 g) to 87% (5.9 mmol, 2.0 g). Spectroscopic data are in agreement with those in literature.[6]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (6H, s, CH_3COO); 2.47 (3H, s, CH_3); 7.22 (2H, d, J = 8.3 Hz); 7.91 (2H, d, J = 8.3 Hz).

Iodosyltoluene 27

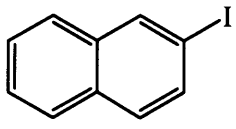


It was synthesised according GP3. Yield was from 90% (6.3 mmol, 1.4 g) to 99% (6.9 mmol, 1.6 g). mp = 175-180°C (Lit.[19]: mp = 177-180°C).

This compound is insoluble in non-reactive NMR solvents and a full characterisation was impossible.

IR (KBr pellets): ν = 3056, 1634, 1604, 1368, 800, 750 cm^{-1}.

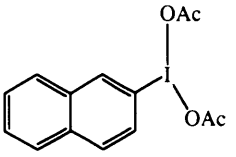
2-Iodo naphthalene[20] 41



Prepared according GP12a. After 3 days refluxing it was obtained in 73% (3.65 mmol, 927 mg) as brown solid after purification by flash chromatography in Petrol. Using GP12b, after 3 days refluxing the yield obtained was 90%. Spectroscopic data are in agreement with those in literature.[20]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.53 (2H, m, arom); 7.53 (1H, d, *J* = 8.6 Hz, arom); 7.62-7.68 (2H, m, arom); 7.77 (1H, dd, *J* = 6 Hz, *J* = 3.5 Hz, arom); 8.20 (1H, d, *J* = 1.5 Hz, arom).

2-(Diacetoxyiodo)naphthalene 42



Synthesis performed according GP2a. Obtained in 60% (4.0 mmol, 1.5 g) - 74% yield (5.0 mmol, 1.87 g) as yellow-orange solid. mp = 106-115°C

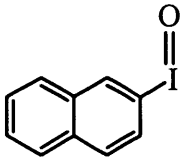
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95 (6H, s, *CH*$_3$); 7.54-7.60 (2H, m, arom); 6.82-7.89 (3H, m, arom); 8.04 (1H, dd, *J* = 9.1 Hz, *J* = 2.0 Hz,); 8.60 (1H, d, *J* = 2.0 Hz);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.4 (*C*H$_3$), 118.6, 127.6, 128.0, 128.5, 128.8, 130.3, 130.8, 133.96, 134.0, 136.0, 176.5 (CH$_3$*C*OO);

IR (KBr): ν = 1649, 1365, 1270, 1008, 807, 760, 671 cm^{-1};

Anal. Calcd. for $C_{14}H_{13}IO_4$: C, 45.18; H, 3.52; I, 34.10. Anal. Found: C, 44.63; H, 3.37; I, 34.74.

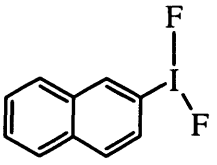
2-(Iodosyl)naphthalene 43



Prepared according GP3. Yield was quantitative. This compound is insoluble in non-reactive NMR solvents and a full characterisation was impossible.

IR (KBr): ν = 3045, 1573, 1125, 829, 738 cm^{-1}.

2-(Difluoroiodo)naphthalene 44



Synthesised according GP4b starting from **35** (0.67 mmol, 236 mg). Obtained in 70% yield (4.65 mmol, 236 mg) as yellow-orange solid after purification by washing in hexane. This compound appeared to be unstable for a full characterisation.

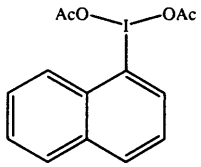
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.60 (2H, m, arom); 7.80-7.90 (3H, m, arom); 7.93-7.81 (1H, m, arom); 8.40 (1H, d, *J* = 2.0 Hz);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 120.7, 125.11, 127.6, 127.9, 128.3, 128.6, 130.7, 131.2, 134.0, 134.5;

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -176.78;

IR (KBr): ν = 1522, 1343, 1256, 1130, 933, 859, 811, 745 cm^{-1}.

1-(Diacetoxyiodo)naphthalene[3] 46



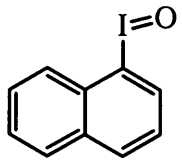
Synthesis performed according GP2a. Obtained in 60% (4.0 mmol, 1.50 g) - 68% yield (4.6 mmol, 1.72 g) as pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.87 (6H, s, CH_3); 7.47 (1H, t, *J* = 7.5 Hz, arom); 7.55-7.70 (2H, m, arom); 7.84 (1H, d, *J* = 8.0 Hz, arom); 8.04 (1H, d, *J* = 8.0 Hz, arom); 8.00-8.09 (2H, m, arom); 8.42 (1H, dd, *J* = 7.0 Hz, *J* = 1.0 Hz);

IR (KBr): ν = 1650, 1277, 1007, 925, 799, 733, 666 cm^{-1};

Anal. Calcd. for $C_{14}H_{13}IO_4$: C, 45.18; H, 3.52; I, 34.10. Anal. Found: C, 44.70; H, 3.37; I, 34.62.

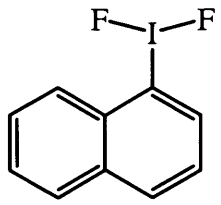
1-(Iodosyl)naphthalene



Prepared according GP3. Yield was quantitative.

IR (KBr): ν = 3050, 1573, 1130, 830, 748 cm^{-1}.

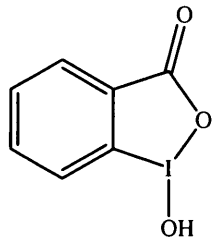
1-(Difluoroiodo)naphthalene 47



Obtained as a product, which could not be isolated, in the reaction mixture performed from the 1-(iodosyl)naphtalene according GP4b.

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -166.61

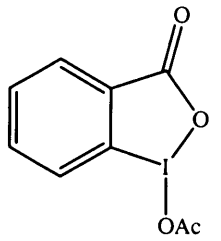
1-Hydroxy-1,2-benziodoxol-3(1H)-one[21] 28



Prepared according GP2b. The collected solid is insoluble in the most organic solvent, except in DMSO. Yield was 93% (9.8 mmol, 2.59 g) of white solid. Spectroscopic data are in agreement with those in literature.[21]

^1H NMR (300 MHz, DMSO): δ = 7.77 (1H, t, J = 7.5 Hz, arom); 7.80 (1H, d, J = 7.5 Hz, arom); 8.00-8.30 (2H, m, arom).

1-Acetoxy-1,2-benziodoxol-3-one[22] 49

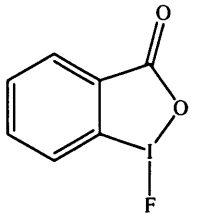


Hydroxy benziodoxole (4 mmol, 1 g) was stirred at 100°C with 15 ml of acetic anhydride for 1-2 hours, until the reaction mixture became clear. The solution was allowed to cool at room temperature. Then diethyl ether was added. The formed solid was collected by filtration and

dried in vacuum. Obtained as colourless crystals in 72% yield (2.9 mmol, 887 mg). Spectroscopic data are in agreement with those in literature.[22]

^{1}H NMR (300 MHz, $CDCl_3$): δ= 2.27 (3H, s, CH_3); 7.78 (1H, t, J = 7.5 Hz, arom); 7.87-8.10 (2H, m, arom); 8.21 (1H, d, J = 7.8 Hz).

1-Fluoro-1,2-benziodoxol-3-one 50



Synthesised according GP4b starting from **28** (0.4 mmol, 106 mg). Obtained in 90% (0.36 mmol, 95 mg) - 94% yield (0.37 mmol, 98 mg) as a white solid. Note: in $CHCl_3$ after a perfect solubility the solution became cloudy with formation of precipitate after half hour.

The synthesis using XeF_2 (GP4c) produced a mixture 1:1 between product and starting material.

mp = 230-232°C. Note: start to decompose (becoming brown at 180°C), turn in a brown liquid at 230°C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (1H, td, J = 7.1 Hz, J = 1.2 Hz); 7.94-8.05 (2H, m, arom); 8.25 (1H, dt, J = 7.3 Hz, J = 1.4 Hz, arom);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 120.4 (q), 127.9 (q), 128.1, 131.7, 133.2, 136.8, 192.3;

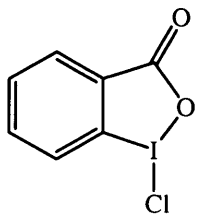
^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -171.160;

IR (KBr): ν = 1685, 1123, 842, 749, 704 cm^{-1};

HRMS for [M+Na] $C_7O_2H_4IF$+Na: calcd: 288.913; found: 288.916;

Anal. Calcd. for $C_7H_4FIO_2$: C, 31.61; H, 1.52; F, 7.14; I, 47.71; O, 12.03. Anal. Found: C, 31.69; H, 1.58; F, 6.66; I, 46.75; O, 13.42.

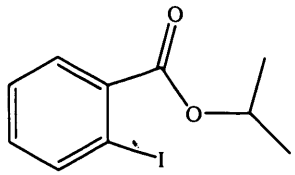
1-Chloro-1,2-benziodoxol-3-one [23] 51



Synthesised according GP1 as a yellow solid. Obtained as a mixture 1:1 with the starting material 2-iodo benzoic acid. Spectroscopic data are in agreement with those in literature.[23]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90-8.10 (2H, m, arom); 8.18-8.30 (2H; m, arom).

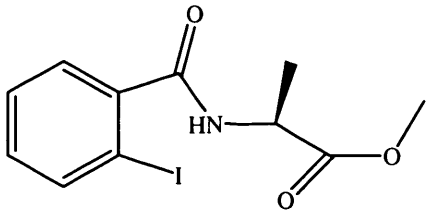
2-Iodo benzoic acid isopropyl ester[24] 52



It was synthesised from 2-iodo benzoic acid and isopropyl alcohol according GP8. Yield was 85% (5.95 mmol, 1.7 g). Spectroscopic data agree with those in literature.[24]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (6H, d, *J* = 6 Hz, $(CH_3)_3CH$); 5.29 (1H, sept, *J* = 6 Hz, $(CH_3)_3CH$); 7.15 (1H, td, *J* = 7.8 Hz, *J* = 1.9 Hz, arom); 7.41 (1H, td, *J* = 7.5 Hz, *J* = 1.0 Hz, arom); 7.77 (1H, dd, *J* = 7.7 Hz, *J* = 1.6 Hz, arom); 8.99 (1H, dd, *J* = 7.9 Hz, *J* = 1.0 Hz, arom).

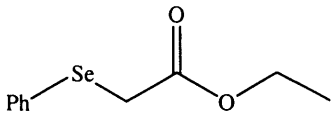
N-(2-iodobenzoyl) alanine methyl ester[25] 52



To the commercially available alanine methyl ester hydrochloride (18 mmol, 2.5 g) in CH_2Cl_2 (80 ml) was added triethylamine (5 ml) at 0°C and then the 2 iodo benzoyl chloride (18 mmol, 5 g). The reaction mixture was allowed to stir for 2 hours at rt. The organic layer was separated from the aqueous and the first was washed with 10% NaOH and 10% HCl. Evaporation of the solvent give a white solid recrystallised from EtAcO and hexane to afford 77% of N-(2-iodobenzoy)-alanine methyl ester (14 mmol, 4.75 g). Spectroscopic data agree with those in literature.[25]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (3H, d, *J* = 6.0 Hz, CH_3CH); 3.84 (3H, s, OCH_3); 4.85 (1H, q, *J* = 7.0 Hz, CH_3CH); 6.44 (1H, broad s, NH); 7.30-7.40 (1H, m, arom); 7.40-7.50 (2H, m, arom); 7.80-7.95 (1H, m, arom).

Ethyl phenylselanylacetate[26] 61a

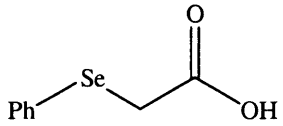


Obtained with 92% yield as yellow oil according to GP6. Spectroscopic data agree with the literature.[26]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (3H, t, *J* = 7.0 Hz, CH_2CH_3); 3.51 (2H, s, $PhSeCH_2$); 4.13 (2H, q, *J* = 7.0 Hz, CH_2CH_3); 7.20-7.30 (3H, m, arom); 7.57-7.61 (2H, m, arom);

^{77}Se NMR (57.3 MHz, $CDCl_3$): δ = 333.25

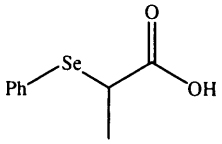
Phenylselanyl acetic acid[27] 59a



Prepared according GP7. Obtained in 95% yield (1.61 mmol, 345 mg) as pale yellow liquid. Spectroscopic data agree with the literature.[27]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (2H, s, $PhSeCH_2$); 7.24-7.32 (3H, m, arom); 7.58-7.64 (2H, m, arom).

2-Phenylselanyl-propionic acid 59b



Synthesis was performed according GP7. Obtained in 97% yield (1.64 mmol, 375 mg) as pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (3H, d, *J* = 7.2 Hz, CH_3CH); 3.77 (1H, q, *J* = 7.2 Hz, CH_3CH); 7.30-7.40 (3H, m, arom); 7.65 (2H, dd, *J* = 7.8 Hz, *J* = 1.6 Hz, arom);

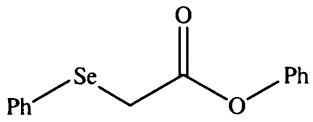
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.4, 36.9, 127.4, 128.8, 129.1, 135.8, 179.8;

IR (nujol): ν = 2923, 2852, 1687, 1450, 1377, 1329, 1298, 1243, 1162, 1078, 737, 667 cm^{-1};

MS (EI): *m/z* (%) = 230 (32) $[M]^+$, 185 (16), 157 (73), 105 (54), 77 (100), 51 (65), 45 (94);

HRMS for $[M+NH_4]$ $C_9H_{10}O_2Se+NH_4$: calcd 248.0184, found 248.0184.

Phenyl phenylselanylacetate 61b



Prepared according GP8. Obtained in 75% yield (5.25 mmol, 1.53 g) as a pale yellow solid after flash chromatography petrolether: EtOAc 9:1. mp: 44-46°C

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63 (2H, s, PhSe*C*H_2); 6.89-6.95 (2H, m, arom); 7.12-7.33 (6H, m, arom); 7.57-7.63 (2H, m, arom);

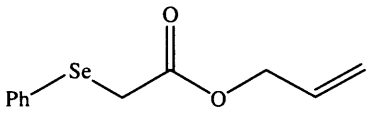
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.4, 121.3, 125.9, 128.2, 128.7 (q), 129.3, 129.4, 133.9, 150.6 (q), 169.5;

IR (film in nujol): ν = 2922, 1738, 1590, 1458, 1377, 1246, 1195, 1163, 1096, 934, 735, 688 cm^{-1};

MS (APCI): *m/z* (%) = 292 (13) $[M]^+$, 198 (36), 170(100), 123 (8), 83 (12), 71 (50);

HRMS for $[M+NH_4]$ $C_{14}H_{12}O_2Se+NH_4$: calcd 310.0341, found 310.0343.

Allyl phenylselanylacetate 61c



Prepared according GP8. Obtained with 72% yield (5.04 mmol, 1.29 g) as oil after flash chromatography petrolether: EtOAc 9:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (2H, s, PhSe*C*H_2); 4.59 (2H, d, *J* = 5.5 Hz, *C*H_2CH=CH_2); 5.24 (1H, dd, $^3J_{Cis}$ = 10.5 Hz, ^2J = 2.4 Hz, CH_2CH=C*H*H); 5.31 (1H, dd, $^3J_{Tans}$ = 17.0 Hz, ^2J = 1.0 Hz, CH_2CH=C*H*H); 5.85 (1H, m, CH_2CH=CH_2); 7.28-7.32 (3H, m, arom); 7.58-7.63 (2H, m, arom);

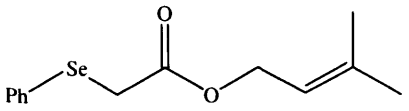
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.4, 65.8, 118.4, 127.9, 129.1, 129.1, 131.6, 133.4, 170.5;

IR: ν = 3057, 2935, 1730, 1648, 1578, 1478, 1438, 1410, 1261, 1107, 989, 931, 690 cm^{-1};

MS (APCI): *m/z* (%) = 256 (58) $[M]^+$, 196 (30), 170 (40), 122 (25), 83 (41), 70 (100);

HRMS for $[M+NH_4]$ $C_{11}H_{12}O_2Se+NH_4$: calcd 274.0341, found 274.0339.

3-Methyl-2-butenyl phenylselanylacetate 61d



Synthesised according GP8. Obtained with 70% yield (4.9 mmol, 1.4 g) after flash chromatography on silica gel (Petrolether: EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (3H, s, CH_3CH_3=); 1.70 (3H, s, CH_3CH_3=); 3.45 (2H, s, PhSeCH_2); 4.50 (2H, d, *J* = 7.2 Hz, CH_2CH); 5.15-5.25 (1H, m, CH_2CH); 7.18-7.22 (3H, m, arom); 7.46-7.54 (2H, m, arom);

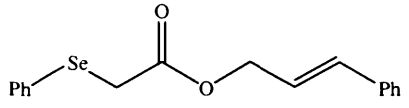
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.9, 25.7, 27.5, 27.9, 62.3, 118.1, 127.7, 129.1, 133.3, 139.5, 170.8;

IR (as a film):ν = 690, 735.8, 962, 1105, 1260, 1438, 1478, 1578, 1726, 2969, 3005 cm^{-1};

MS (APCI): *m/z* (%) = 285 (9) $[M]^+$, 216 (17), 198 (16), 170 (9), 69 (100);

HRMS for [M+H] $C_{13}H_{16}O_2Se$+H: calcd 285.0388, found 285.0388.

Cinnamyl phenylselanylacetate 61e



Synthesised according GP8. Obtained as pale yellow oil with 76% yield (5.3 mmol, 1.7 g) after flash chromatography on silica gel (Petrolether: EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.49 (2H, s, PhSeCH_2); 4.65 (2H, d, *J* = 6.5 Hz, OCH_2CH); 6.10 (1H, td, *J* = 15.8 Hz, *J* = 6.45 Hz, OCH_2CH); 6.50 (1H, d, *J* = 15.9 Hz, PhC*H*); 7.18-7.31 (8H, m, arom); 7.49-7.54 (2H, m, arom);

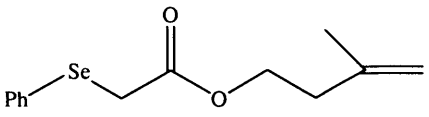
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.5, 65.8, 122.6, 126.6, 127.9, 128.1, 128.6, 128.9, 129.2, 133.6, 134.4, 136.1, 170.7;

IR (as a film): ν = 3056, 2956, 1729, 1573, 1473, 1443, 1257, 1106, 966, 740, 690 cm^{-1};

MS (EI): *m/z* (%) = 332 (8) $[M]^+$, 171 (12), 131 (12), 117 (100), 91 (29), 77 (12), 51 (16);

HRMS for $[M^+]$: $C_{17}H_{16}O_2Se$: calcd 332.0310, found 332.0315.

3-Methyl-3-butenyl phenylselanylacetate 61f



Synthesised according GP8. Obtained with 70% yield (4.9 mmol, 1.39 g) after flash chromatography on silica gel (Petrolether: EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (3H, s, *CH*$_3$); 2.19 (2H, t, *J* = 6.8 Hz, *CH*$_2$CH$_2$O); 3.40 (2H, s, PhSe*CH*$_2$); 4.10 (2H, t, *J* = 6.9 Hz, CH$_2$*CH*$_2$O); 4.62 (1H, s, =C*H*H); 4.71 (1H, s, =CH*H*); 7.15-7.25 (3H, m, arom); 7.40-7.60 (2H, m, arom);

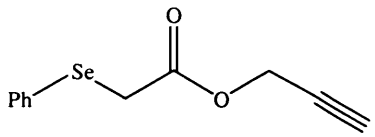
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.4, 27.4, 36.3, 63.4, 112.3, 127.7, 129.1, 129.2, 133.3, 141.2, 170.8;

IR:ν = 735, 891, 1106, 1262, 1473, 1579, 1649, 1724, 2955, 3066 cm^{-1};

MS (APCI): *m/z* (%) = 284 (45) [M]$^+$, 216 (12), 145 (38), 122 (18), 108 (18), 82 (30), 71 (100);

HRMS for [M+NH$_4$]: $C_{13}H_{16}O_2Se$+NH$_4$: calcd 302.0654, found 302.0655.

Propargyl phenylselanylacetate 61g



Prepared according GP8. Obtained with 76% yield (5.32 mmol, 1.35 g) after flash chromatography on silica gel (Petrolether: EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (1H, s, C*H*); 3.46 (2H, s, PhSe*CH*$_2$); 4.55 (2H, s, *CH*$_2$O); 7.15-7.25 (2H, m, arom); 7.48-7.58 (3H, m, arom);

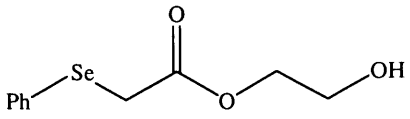
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.9, 52.5, 75.1, 127.9, 128.6, 129.0, 133.5, 169.9;

IR: ν = 3287, 3056, 2935, 2122, 1734, 1573, 1473, 1438, 1247, 1096, 1021, 996, 730, 695 cm^{-1};

MS (APCI): *m/z* (%) = 254 (17) [M]$^+$, 199 (31), 171 (42), 145 (18), 123 (26), 105 (29), 83 (25), 71 (100);

HRMS for [M+NH$_4$] $C_{11}H_{14}O_2Se$+NH$_4$: calcd 272.0184, found 272.0180.

2-Hydroxy-ethyl phenylselanylacetate 61h



Synthesised according GP8. Obtained in 47% yield (3.29 mmol, 855 mg) as pale yellow liquid after purification by flash chromatography in Petrol:EtOAc 1:1 (R_f: 0.31).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (1H, s broad, OH); 3.48 (2H, s, PhSeCH_2); 3.65 (2H, t, *J* = 4.0 Hz, CH_2CH_2OH); 4.11 (2H, t, *J* = 4.0 Hz, CH_2CH_2OH); 7.20-7.30 (3H, m, arom); 7.48-7.60 (2H, m, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.3, 61.0, 66.8, 128.1, 129.0, 129.3, 133.6, 171.1;

^{77}Se NMR (57.3 MHz, $CDCl_3$): δ = 340.8688;

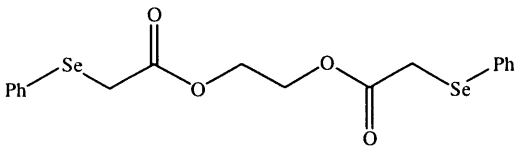
IR: ν = 3385 (broad), 3030, 2957, 1725, 1578, 1478, 1438, 1410, 1264, 1110, 1074, 1022, 960, 886, 739, 690 cm^{-1};

GC-MS (DB5). Retention time: 23.27 minutes;

MS (EI): *m/z* (%) = 260 (100) $[M]^+$, 243 (10), 216 (20), 171 (45), 157 (35), 91 (90), 77 (43), 51 (50);

HRMS for $[M^+]$ $C_{10}H_{12}O_3Se$: calcd 259.9946, found 259.9944.

Phenylselanyl-acetic acid 2-(2- phenylselanyl-acetoxy)-ethyl ester



Obtained as sideproduct of the reaction to obtain phenylselanyl-acetic acid 2-hydroxy-ethyl ester. Purification by flash chromatography in Petrol:EtOAc 1:1 (R_f: 0.79) give a pale yellow liquid in 10% yield (7 mmol, 320 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.40 (4H, s, CH_2Se), 4.10 (4H, s, CH_2O), 7.20-7.30 (6H, m, arom), 7.40-7.50 (4H, m, arom);

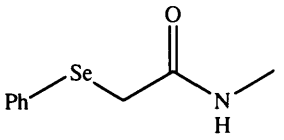
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.1, 62.7, 127.9, 129.0, 129.2, 133.4, 170.6;

IR: ν = 3030, 2959, 1731, 1578, 1477, 1437, 1248, 1102, 1022, 972, 911, 735, 689 cm^{-1};

MS (APCI): *m/z* (%) = 457 (8) $[M]^+$, 243 (100);

HRMS for $[M^+]$ $C_{18}H_{18}O_4Se_2$: calcd 457.9530, found 457.9523.

N-Methyl-2-phenylselanyl-acetamide 61i



Prepared according GP8. Obtained in 66% yield (4.62 mmol, 1.1 g) as pale yellow solid after purification by flash chromatography in Petrol:EtOAc 1:1 (R_f: 0.4). mp : 27-30°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.70 (3H, d, *J* = 4.9 Hz, CH_3NH); 3.52 (2H, s, CH_2SePh); 6.40 (1H, s broad, CH_3NH); 7.17-7.25 (3H, m, arom); 7.25-7.55 (2H, m, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.8, 30.2, 127.6, 129.1, 129.4, 131.9, 169.0;

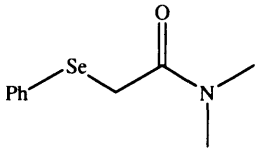
IR: ν = 3347, 3066, 2935, 1644, 1584, 1478, 1408, 1307, 1162, 1021, 740 cm^{-1};

GC-MS (DB5). Retention time: 13.03 minutes;

MS (EI): *m/z* (%) = 229 (100) [M]$^+$, 224 (10), 107 (53), 91 (10), 77 (5);

HRMS for [M$^+$] $C_9H_{11}NOSe$: calcd 229.0000, found 229.0004.

N, N-Dimethyl-2-phenylselanylacetamide 61l



Synthesis performed according GP8. Obtained in 80% yield (5.6 mmol, 1.36 g) as white oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.81 (3H, s, CH_3N); 2.82 (3H, s, CH_3N); 4.61 (2H, s, CH_2SePh); 7.17-7.26 (3H, m, arom); 7.45-7.59 (2H, m, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.2, 35.6, 37.9, 127.9, 129.2, 131.3, 133.2, 169.3;

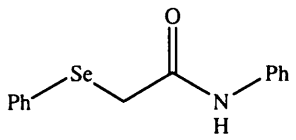
IR: ν = 3066, 2925, 1639, 1579, 1473, 1433, 1388, 1262, 735 cm^{-1};

GC-MS (DB5). Retention time: 23.27 minutes (70/200 5m; 200/250 13m; 250 5m);

MS (EI): *m/z* (%) = 243 (100) [M]$^+$, 121 (24), 72 (55), 58 (40);

HRMS for [M+H$^+$] $C_{10}H_{13}NOSe$+H$^+$: calcd 244.0235, found 244.0236.

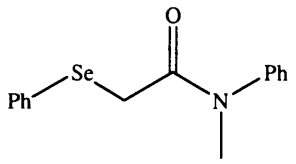
N-Phenyl-2-phenylselanylacetamide[28] 61m



Synthesised according GP8. Obtained in 64% yield (4.48 mmol, 1.3 g) as pale yellow solid after purification by flash chromatography in Petrol:EtOAc 8:2 (R_f: 0.2). mp: 73-75°C. The spectroscopic data are in agreement with those in literature.[28]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60 (2H, s, CH_2Se); 6.90-7.50 (10H, m, arom); 8.02 (1H, s broad, PhN*H*).

N-Methyl-*N*-Phenyl-2-phenylselanylacetamide 61n



Synthesis performed according GP8. Obtained in 45% yield (3.15 mmol, 961 mg) as pale yellow solid after purification by flash chromatography in Petrol:EtOAc 7:3 (R_f: 0.4). mp: 75-77°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.22 (3H, s, CH_3N); 3.40 (2H, s, CH_2Se); 7.02 (2H, d, arom); 7.10-7.18 (3H, m, arom); 7.20-7.30 (3H, m, arom); 7.32-7.44 (2H, m, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.7, 37.8, 127.3, 127.5, 128.0, 129.0, 129.7, 129.8, 133.3, 143.6, 169.9;

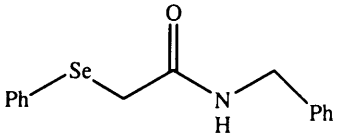
IR (film in nujol): ν = 2923, 1644, 1594, 1568, 1462, 1376, 1113, 722, 738, 694 cm^{-1};

GC-MS (DB5). Retention time: 30.26 minutes;

MS (EI): *m/z* (%) = 305 (54) $[M]^+$, 107 (100);

HRMS for $[M+H^+]$ $C_{15}H_{15}NOSe+H^+$: calcd 306.0392, found 306.0392.

N-Benzyl-2-phenylselanylacetamide 61o



Prepared according GP8. Obtained in 83% yield (5.81 mmol, 1.77 g) as white solid after purification by flash chromatography in Petrol:EtOAc 7:3 (R_f: 0.2). mp: 70-71°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.54 (2H, s, CH_2Se); 4.43 (2H, d, *J* = 5.8 Hz, CH_2NH); 6.65 (1H, s broad, CH_2NH); 7.03-7.40 (10H, m, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 30.2, 44.0, 127.5, 127.6, 127.7, 128.7, 128.8, 129.5, 132.2, 137.7, 168.3;

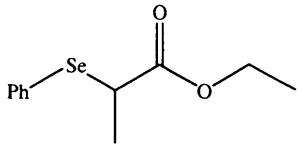
IR: ν = 2921, 2852, 1639, 1461, 1377, 1262, 743 cm^{-1};

GC-MS (DB5). Retention time: 32.02 minutes;

MS (EI): *m/z* (%) = 306 (30) [M]$^+$, 224 (10), 148 (100), 107 (25), 91 (24), 77 (8), 65 (8), 51 (8);

HRMS for [M$^+$] $C_{15}H_{15}NOSe^+$: calcd 305.0313, found 305.0316.

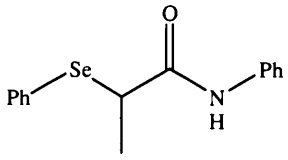
Ethyl 2-phenylselanylpropanoate[26] 67a



Synthesised according GP6. Obtained with 70% yield as yellow oil. Spectroscopic data agree with those in literature.[26]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (3H, t, *J* = 7.1 Hz, CH_2CH_3); 1.54 (2H, d, *J* = 7.0 Hz, CH_3CH); 3.77 (1H, q, *J* = 7.0 Hz, CH_3CH); 4.09 (2H, q, *J* = 7.1 Hz, CH_2CH_3); 7.27-7.36 (3H, m, arom); 7.57-7.63 (2H, m, arom).

N-Phenyl-2-phenylselanylpropionamide 67b



Synthesis performed according GP8. Obtained in 79% yield (5.53 mmol, 1.68 g) as white solid after crystallisation from CH_2Cl_2 and petrolether. mp: 121-124°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58 (3H, d, *J* = 7.1 Hz, CH_3CH); 3.76 (1H, q, *J* = 7.1 Hz, CH_3CH); 7.02 (1H, m, arom); 7.20-7.30 (7H, m, arom); 7.52 (2H, d, *J* = 7.1, arom); 7.63 (1H, s broad, NH);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.0, 41.4, 119.7, 124.4, 127.8, 128.7, 128.9, 129.5, 135.2, 137.6, 170.5;

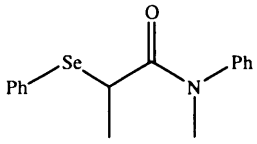
IR (film in nujol): ν = 3437, 1639, 1458, 1378, 720 cm^{-1};

GC-MS (DB5). Retention time: 30.31 minutes (50-250/250 10m);

MS (EI): *m/z* (%) = 305 (67) $[M]^+$, 212 (30), 185 (20), 169 (24), 157 (27), 120 (70), 105 (81), 93 (100), 77 (71), 65 (46), 51 (39);

HRMS for $[M+H^+]$ $C_{15}H_{15}NOSe+H^+$: calcd 306.0392 , found 306.0392.

N-Methyl-*N*-Phenyl-2-phenylselanylpropionamide 67c



Synthesised according GP8.Obtained in 82% yield (5.74 mmol, 1.83 g) as white solid after purification by flash chromatography in Petrol:EtOAc 6:4 (R_f: 0.75). mp: 64-66°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (3H, d, *J* = 6.5 Hz, CH_3CH); 3.18 (3H, s, CH_3N); 3.66 (1H, q, *J* = 6.6 Hz, CH_3CH); 7.01 (2H, d, *J* = 6 Hz, arom); 7.10-7.30 (8H, m, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.9, 37.3, 37.7, 127.2, 127.9, 128.2, 128.3, 128.8, 129.7, 135.6, 143.5, 172.8;

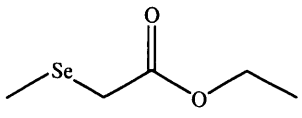
IR (film in nujol): ν = 2925, 1644, 1589, 1458, 1378, 1112, 625 cm^{-1};

GC-MS (DB5). Retention time: 29.54 minutes (50-250/250 10m);

MS (EI): *m/z* (%) = 319 (59) $[M]^+$, 162 (54), 134 (46), 107 (100), 77 (55), 65 (100), 51 (25);

HRMS for $[M+H^+]$ $C_{16}H_{17}NOSe+H^+$: calcd 320.0548, found 320.0549.

Ethyl methylselanylacetate 67d



Synthesis performed according GP6. Obtained in 98% yield as colourless liquid.

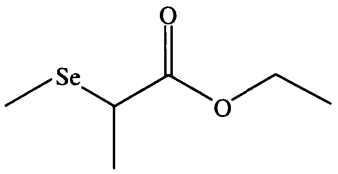
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (3H, t, *J* = 7.1 Hz, CH_3CH_2); 2.19 (3H, s, CH_3Se); 3.15 (2H, s, CH_2Se); 4.19 (2H, q, *J* = 7.1 Hz, CH_3CH_2);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 5.9, 14.1, 23.7, 61.2, 171.5;

^{77}Se NMR (57.3 MHz, $CDCl_3$): δ = 135.85;

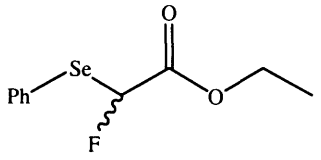
IR (liquid film): ν = 2927, 2853, 1727, 1458, 1419, 1365, 1263, 1109, 1031, 935, 737, 668 cm^{-1};
MS (EI): *m/z* (%) = 182 (57) $[M]^+$, 109 (100), 88 (71);
HRMS for $C_5H_{10}O_2Se$: calcd 181.9841, found 181.9842.

Ethyl 2-methylselanylpropionate 67e



Synthesis performed according GP6. Obtained as colourless liquid in 92% yield.
^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (3H, t, *J* = 7.0 Hz, CH_3CH_2); 1.46 (3H, d, *J* = 7.0 Hz, CH_3CH); 2.05 (3H, s, CH_3Se); 3.36 (1H, q, *J* = 7.0 Hz, C*H*Se); 4.12 (2H, q, *J* = 7.0 Hz, CH_3CH_2);
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 3.9, 14.2, 17.0, 32.1, 60.9, 173.7;
IR (liquid film): ν = 2985, 1722, 1450, 1368, 1326, 1257, 1208, 1147 cm^{-1};
GC-MS (DB5). Retention time: 5.45 minutes;
MS (EI): *m/z* (%) = 196 (80) $[M]^+$, 123 (100), 102 (51), 74 (11), 55 (22), 41 (70);
HRMS for $[M^+]$ $C_6H_{12}O_2Se$: calcd 195.9997, found 195.9994.

Ethyl 2-fluoro-2-phenylselanylacetate 64a



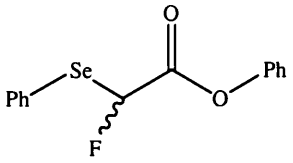
Synthesis performed according GP9. Obtained in 62% yield (0.25 mmol, 66 mg), as yellow oil after purification by flash chromatography in Petrol:EtOAc 9:1 (R_f: 0.4).
^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (3H, t, *J* = 7.0 Hz, CH_3CH_2); 4.01 (2H, q, *J* = 7.0 Hz, CH_2CH_3); 6.34 (1H, d, J_{HF} = 51.7 Hz, C*H*F); 7.20-7.40 (3H, m, arom); 7.63 (2H, dd, *J* = 7.9 Hz, *J* = 1.2 Hz, arom);
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.9, 62.1, 88.9 (d, $^1J_{CF}$ = 244 Hz, *C*FHSeC=O), 125.6, 129.3, 129.4, 135.9, 166.5 (d, $^2J_{C\text{-}F}$ = 26.8 Hz, C*F*HSe*C*=O);
^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -166.50 (1F, d, J_{HF} = 55.6 Hz, C*FH*SeC=O);
^{77}Se NMR (57.3 MHz, $CDCl_3$): δ = 509.96;

IR (film in nujol): ν = 2975, 1744, 1579, 1473, 1433, 1363, 1327, 1267, 1227, 1157, 1051, 1016, 855, 735, 695 cm^{-1};

MS (EI): *m/z* (%) = 262 (37) $[M]^+$, 188(12), 156 (34), 109 (100), 77 (45), 51 (30);

HRMS for $[M+NH_4^+]$ $C_{10}H_{11}O_2SeF+NH_4^+$: calcd 280.0247, found 280.0247.

Phenyl 2-fluoro-2-phenylselanylacetate 64b



Synthesis performed according GP9. Obtained in 46% yield (0.18 mmol, 57 mg) as red solid after purification by flash chromatography in Petrol:EtOAc 9:1 (R_f: 0.26). mp = 72-76 °C

^1H NMR (400 MHz, $CDCl_3$): δ = 6.54 (1H, d, $^2J_{HF}$ = 51.2 Hz, C*H*F); 6.78 (2H, d, *J* = 8.5 Hz, arom); 7.10-7.40 (6H, m, arom); 7.66 (2H, d, *J* = 7.0 Hz, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 88.3 (d, $^1J_{CF}$ = 283 Hz, *C*FHSeC=O), 120.9, 125.1, 126.3, 129.5, 129.6, 136.2, 136.2, 149.8, 165.0 (d, $^2J_{CF}$ = 28.2 Hz, C*F*HSe*C*=O);

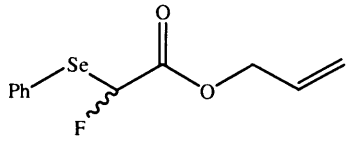
^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -166.75 (1F, d, J_{HF} = 52.19 Hz, C*FH*SeC=O);

IR (KBr pellet): ν = 3045, 2955, 1739, 1649, 1579, 1493, 1438, 1237, 1026, 931, 840, 735, 685 cm^{-1};

MS (EI): *m/z* (%) =310 (42) $[M]^+$, 156 (25), 109 (48), 77 (91), 65 (59), 51 (46), 39 (100);

HRMS for $[M+NH_4^+]$ $C_{14}H_{11}O_2SeF+NH_4^+$: calcd 328.0247, found 328.0252;

Allyl 2-fluoro-2-phenylselanylacetate 64c



Synthesis performed according GP9. Obtained in 41% yield (0.16 mmol, 45 mg) as yellow oil after purification by flash chromatography in Petrolether:EtOAc 9:1 (R_f: 0. 6).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.45 (1H, qt, ^2J =1.3 Hz , ^3J = 11.3 Hz); 4.47 (1H, qt, ^2J = 1.3 Hz , ^3J = 11.3 Hz); 5.17 (1H, dq, ^2J = 1.3 Hz, $^3J_{Cis}$ = 10.0 Hz, ^4J = 1.0 Hz); 5.23 (1H, dq, ^2J = 1.4 Hz, $^3J_{Tans}$ = 17.0 Hz, ^4J = 1.4 Hz); 5.62-5.78 (1H, m); 6.34 (1H, d, $^2J_{HF}$ = 51.2 Hz, C*H*F); 7.25-7.40 (3H, m, arom); 7.57 (2H, dd, *J* = 8.5, *J* = 1.5, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 66.4, 88.9 (d, $^1J_{CF}$ = 242 Hz, *C*FHSeC=O), 119.4, 125.5, 129.3, 129.4, 130.9, 135.9, 165.8 (d, $^2J_{CF}$ = 26.3Hz, C*F*HSe*C*=O);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -166.59 (1F, d, J_{HF} = 55.17 Hz, C*FH*SeC=O);

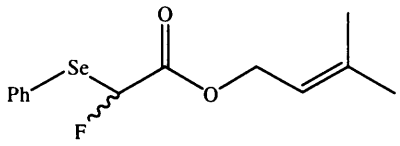
IR (film): ν=3059, 2950, 1754, 1648, 1578, 1477, 1439, 1272, 1226, 1156, 1049, 740, 691 cm^{-1};

GC-MS (DB5). Retention time: 18.36 minutes (70-200(26m)/200-250(4m)/250 (5m));

MS (EI): *m/z* (%) = 274 (19) $[M]^+$, 189 (12), 157 (19), 109 (100), 77 (25);

HRMS for $[M+NH_4^+]$ $C_{11}H_{11}O_2SeF+NH_4^+$: calcd 292.0247, found 292.0250.

3-Methyl-but-2-enyl 2-fluoro-phenylselanylacetate 64d



Synthesis performed according GP9. Obtained in 65% yield (0.26 mmol, 78 mg) as yellow oil after purification by flash chromatography in Petrol:EtOAc 9:1 (R_f: 0.4).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.60 (3H, s, C*H*$_3$); 1.67 (3H, s, C*H*$_3$); 4.40-4.52 (2H, m, *CH*$_2$CH); 5.14 (1H, m, CH$_2$C*H*); 6.35 (1H, d, $^2J_{HF}$ = 53.2 Hz, C*HF*); 7.25-7.40 (3H, m, arom); 7.58 (2H, d, *J* = 7.6 Hz, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.0, 25.8, 62.8, 88.9 (d, $^1J_{CF}$ = 243 Hz, *C*FHSeC=O), 117.4, 125.6, 129.3, 129.4, 135.9, 140.4, 166.5 (d, $^2J_{CF}$ = 27.2 Hz, C*F*HSe*C*=O);

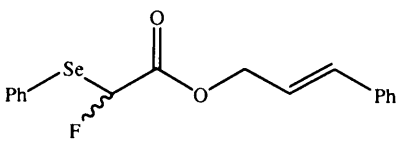
^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -166.26 (1F, d, J_{HF} = 58.94 Hz, C*FH*SeC=O);

IR (liquid film): ν = 2915, 1744, 1645, 1599, 1579, 1438, 1262, 1222, 1152, 1041, 740 cm^{-1};

MS (EI): *m/z* (%) = 302 (4) $[M]^+$, 234 (10), 157 (11), 109 (25), 77 (27), 69 (100), 41 (72);

HRMS for $[M+NH_4^+]$ $C_{13}H_{15}O_2SeF+NH_4^+$: calcd 320.0560, found 320.0563.

Cinnamyl 2-fluoro-2-phenylselanylacetate 64e



Synthesised according GP9. Obtained in 45% yield (0.18 mmol, 63 mg) as yellow oil after purification by flash chromatography in Petrol:EtOAc 9:1 (R_f: 0. 6).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.60 (1H, dd, *J* = 6.5 Hz, *J* = 1 Hz, OC*H*HCH); 4.63 (1H, dd, *J* = 7.0 Hz, *J* = 1.0 Hz, OCH*H*CH); 6.04 (1H, dt, *J* = 16.0 Hz, *J* = 7.1 Hz, OCHHC*H*); 6.35

(1H, d, $^2J_{HF}$ = 52.3 Hz, C*H*F); 6.54 (1H, d, *J* = 16.0 Hz, PhC*H*); 7.20-7.30 (8H, m, arom); 7.57 (2H, dd, *J* = 8.5 Hz, *J* = 1.5 Hz, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 66.5, 88.7 (d, $^1J_{CF}$ = 242 Hz, *C*FHSeC=O), 121.7, 126.7, 128.3, 128.6, 128.7, 129.2, 129.4, 135.4, 135.8, 136.1, 166.3 (d, $^2J_{CF}$ = 25.3 Hz, C*F*HSe*C*=O);

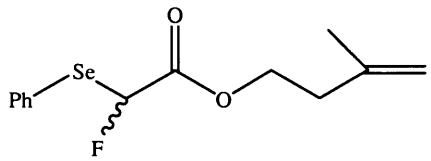
^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -166.59 (1F, d, $^2J_{HF}$ = 51.51 Hz, C*FH*SeC=O);

IR (as a film): ν = 3030, 1753, 1653, 1438, 1263, 1225, 1156, 966, 740 cm^{-1};

MS (EI): *m/z* (%) = 350 (3) [M]$^+$, 157 (22), 117 (100), 109 (65), 91 (53), 77 (63), 51 (41);

HRMS for [M$^+$] $C_{17}H_{15}O_2SeF^+$: calcd 350.0216, found 350.0224.

3-Methyl-but-3-enyl 2-fluorophenylselnylacetate 64f



Synthesised according GP9. Obtained in 20% yield (0.08 mmol, 24 mg) as yellow oil after purification by flash chromatography in Petrol:EtOAc 9:1 (R_f: 0. 6).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (3H, s, CH_3); 2.18 (2H, t, *J* = 6.9 Hz, OCH_2CH_2); 4.09 (2H, dt, *J* = 6.9 Hz, J_{AB} = 2.2 Hz, OCH_2CH_2); 4.64 (1H, s, =C*H*H); 4.74 (1H, s, =CH*H*); 6.33 (1H, d, $^2J_{HF}$ = 51.8 Hz, C*H*F); 7.23-7.38 (3H, m, arom); 7.59 (2H, dd, *J* = 8.0 Hz, *J* = 1.2 Hz, arom);

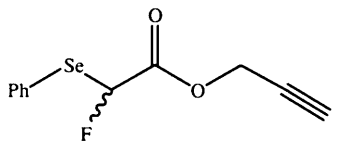
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.5, 36.3, 64.2, 88.9 (d, $^1J_{CF}$ = 244 Hz, *C*FHSeC=O), 112.7, 125.7, 129.3, 129.4, 135.9, 140.9, 166.5 (d, $^2J_{CF}$ = 27.3 Hz, C*F*HSe*C*=O);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -166.48 (1F, d, $^2J_{HF}$ = 51.48 Hz, C*FH*SeC=O);

IR (liquid film): ν = 3075, 2966, 1753, 1651, 1578, 1477, 1439, 1377, 1329, 1269, 1229, 1158, 1051, 895, 740, 690 cm^{-1};

MS (EI): *m/z* (%) = 302 (8) [M]$^+$, 234 (26), 157 (28), 109 (53), 77 (61), 51 (44), 41 (100).

Propargyl 2-fluoro-2-phenylselanylacetate 64g



Synthesised according GP9. Obtained in 34% yield (0.14 mmol, 38 mg) as yellow oil after purification by flash chromatography in Petrol:EtOAc 9:1 (R_f: 0.4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (1H, t, *J* = 2.6 Hz, C*H*); 4.53 (1H, dd, J_{AB} = 23.7 Hz, *J* = 2.5 Hz, OC*H*H); 4.58 (1H, dd, J_{AB} = 23.7 Hz, *J* = 2.5 Hz, OCH*H*); 6.35 (1H, d, $^2J_{HF}$ = 51.7 Hz, C*H*F); 7.20-7.40 (3H, m, arom); 7.59 (2H, dd, *J* = 8.5 Hz, *J* = 1.5 Hz, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 53.1, 75.9, 76.3, 88.4 (d, $^1J_{CF}$ = 243 Hz, *C*FHSeC=O), 125.2, 129.4, 129.6, 136.1, 165.8 (d, $^2J_{CF}$ = 28.9 Hz, C*F*HSe*C*=O);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -167.40 (1F, d, J_{HF} = 55.19 Hz, C*FH*SeC=O);

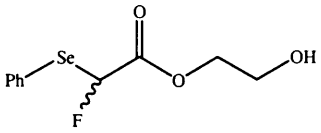
IR (film): ν = 3293, 3056, 2935, 2360, 1760, 1476, 1438, 1220, 1153, 1050, 740 cm^{-1};

GC-MS (DB5). Retention time: 18.56 minutes [70-200(26m)/200-250(4m)/250 (5m)];

MS (EI): *m/z* (%) = 272 (30) [M]$^+$, 189 (13), 157 (23), 109 (100), 77 (35), 51 (27);

HRMS for [M+NH_4^+] $C_{11}H_9O_2SeF$+NH_4^+: calcd 290.0090, found 290.0089.

2-Hydroxy-ethyl 2-fluoro-phenylselanylacetate 64h



Synthesised according GP9. Obtained in 38% yield (0.15 mmol, 42 mg) as pale yellow oil after purification by flash chromatography in Petrol:EtOAc 1:1 (R_f: 0.26).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (1H, s broad, OH); 3.55-3.69 (2H, m); 3.97-4.19 (2H, m); 6.37 (1H, d, $^2J_{HF}$ = 51.0 Hz, C*FH*SeC=O); 7.20-7.30 (3H, m, arom); 7.59 (2H, dd, *J* = 7.0 Hz, *J* = 1.0 Hz, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 60.6, 67.4, 88.5 (d, $^1J_{CF}$ = 244 Hz, *C*FHSeC=O), 125.3, 129.4, 129.6, 136.1, 167.7 (d, $^2J_{CF}$ = 27.2 Hz, C*F*HSe*C*=O);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -167.975 (1F, d, J_{HF} = 55.2 Hz, C*FH*SeC=O);

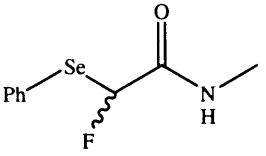
^{77}Se NMR (57.3 MHz, $CDCl_3$): δ = 512.4982;

IR (as a film): ν = 3427 (broad), 3056, 2945, 1744, 1579, 1473, 1433, 1373, 1327, 1277, 1232, 1162, 1051, 740, 685 cm^{-1};

MS (EI): *m/z* (%) = 278 (43) [M]$^+$, 157 (72), 109 (100), 77 (74), 45 (47);

HRMS for [M+NH_4^+] $C_{10}H_{11}FO_3Se$+NH_4^+: calcd 296.0196, found 296.0199.

N-methyl 2-fluoro-2-phenylselanylacetamide 64i



Synthesised according GP9. Obtained in 31% yield (0.12 mmol, 31 mg) as brown solid after purification by flash chromatography in Petrol:EtOAc 1:1 (R_f: 0.4). mp: 60-64°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59 (3H, d, *J* = 4.9 Hz, *CH*$_3$NH); 5.89 (1H, s broad, N*H*); 6.39 (1H, d, $^2J_{HF}$ = 52.3 Hz, C*FH*SeC=O); 7.20-7.40 (3H, m, arom); 7.45-7.53 (2H, m, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.9 (*C*H$_3$), 92.9 (d, $^1J_{CF}$ = 245.9 Hz, *CF*HSeC=O), 125.4, 129.2, 129.4, 136.3, 167.0 (d, $^2J_{CF}$ = 22.4 Hz, C*F*HSe*C*=O);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -163.5 (1F, d, $^2J_{HF}$ = 55.2 Hz, C*FH*SeC=O);

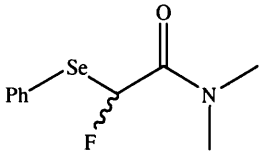
IR: ν = 3447, 2925, 2855, 1664, 1458, 1376, 1263, 743 cm^{-1};

GC-MS (DB5). Retention time: 12.06 minutes;

MS (EI): *m/z* (%) = 247 (100) [M]$^+$, 157 (25), 109 (81), 77 (33), 58 (58), 42 (19);

HRMS for [M+H$^+$] $C_9H_{10}NOFSe$+H$^+$: calcd 246.9906, found 246.9904.

N, *N*-Dimethyl 2-fluoro-2-phenylselanylacetamide 64l



Synthesised according GP9. Obtained in 42% yield (0.17 mmol, 44 mg) as yellow oil after purification by flash chromatography in Petrol:EtOAc 1:1 (R_f: 0.4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.88 (3H, s, *CH*$_3$); 2.98 (3H, s, *CH*$_3$); 6.51 (1H, d, $^2J_{HF}$ = 54.5 Hz, C*FH*SeC=O); 7.20-7.30 (3H, m, arom); 7.50-7.60 (2H, m, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 36.2, 37.1, 92.9 (d, $^1J_{CF}$ = 241 Hz, *CF*HSeC=O), 127.3, 129.1, 129.4, 135.1, 165.8 (d, $^2J_{CF}$ = 21.4 Hz, C*F*HSe*C*=O);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -160.8 (1F, d, $^2J_{HF}$ = 58.9 Hz, C*FH*SeC=O);

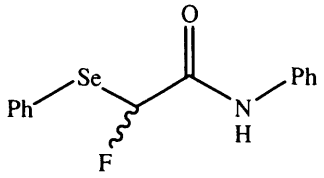
IR: ν = 3057, 2936, 1657, 1576, 1479, 1399, 1262, 1130, 1027, 741, 678 cm^{-1};

GC-MS (DB5). Retention time: 13.17 minutes;

MS (EI): *m/z* (%) = 261 (75) [M]$^+$, 214 (22), 104 (23), 72 (100), 42 (11);

HRMS for [M+H$^+$] $C_{10}H_{12}NOFSe$+H$^+$: calcd 261.0063, found 261.0059.

N-Phenyl 2-fluoro-2-phenylselanylacetamide 64m



Prepared according GP9. Obtained in 31% yield (0.12 mmol, 38 mg) as brown-red solid after purification by flash chromatography in Petrol:EtOAc 7:3 (R_f: 0.7). mp : 99-104°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.47 (1H, d, $^2J_{HF}$ = 51.7 Hz, C*F*H*S*eC=O); 7.00-7.12 (1H, m, arom); 7.20-7.30 (7H, m, arom); 7.42 (1H, s broad, N*H*); 7.60 (2H, dd, *J* = 7 Hz, *J* = 1.6 Hz, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 92.6 (*CF*HSeC=O, d, $^1J_{CF}$ = 248 Hz), 120.1, 124.8, 125.2, 128.9, 129.3, 129.6, 136.1, 136.5, 164.0 (d, $^2J_{CF}$ = 21.4 Hz, C*F*HSe*C*=O);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -162.2 (1F, d, $^2J_{HF}$ = 55. 8 Hz, C*F*H*S*eC=O);

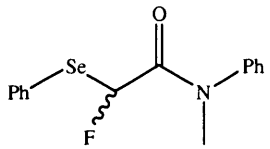
IR: ν = 3200, 1664, 1599, 1523, 1006, 730 cm^{-1};

GC-MS (DB5). Retention time: 29.18 minutes;

MS (EI): *m/z* (%) = 309 (100) $[M]^+$, 208 (10), 132 (20), 109 (50), 93 (16), 77 (10);

HRMS for $[M+H^+]$ $C_{14}H_{12}NOFSe+H^+$: Calcd 310.0141, Found 310.0146.

N-Methyl-*N*-phenyl 2-Fluoro-2-phenylselanylacetamide 64n



Synthesis performed according GP9. Obtained in 40% yield (0.16 mmol, 52 mg) as brown solid after purification by flash chromatography in Petrol:EtOAc 7:3 (R_f: 0.6). mp: 75-77°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.24 (3H, s, CH_3N); 6.11 (1H, d, J_{HF} = 54.1 Hz, C*H*F*S*e); 7.03-7.42 (10H, m, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 37.9, 92.1 (d, $^1J_{CF}$ = 245 Hz, *CF*HSeC=O), 127.4, 127.5, 128.6, 128.7, 128.9, 129.9, 134.7, 141.8, 165.6 (d, $^2J_{CF}$ = 21.5 Hz, C*F*HSe*C*=O);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = –162.9 (d, $^2J_{HF}$ = 55.8 Hz, 1F, C*F*H*S*eC=O);

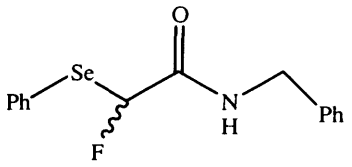
IR: ν = 3206, 3056, 2985, 1664, 1594, 1493, 1413, 1267, 725 cm^{-1};

GC-MS (DB5). Retention time: 20.10 minutes (50-250/250 10m);

MS (EI): *m/z* (%) = 323 (94) $[M]^+$, 146 (93), 134 (100), 109 (84), 77 (32), 51 (21);

HRMS for [M+H$^+$] $C_{15}H_{14}NOFSe+H^+$: Calcd 324.0297, Found 324.0300.

N-Benzyl 2-fluoro-2-phenylselanylacetamide 64o



Synthesised according GP9. Obtained in 53% yield (0.21 mmol, 68 mg) as brown solid after purification by flash chromatography in Petrol:EtOAc 7:3 (R_f: 0.5). mp : 57-61°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.19 (1H, dd, $J_{Ha\text{-}Hb}$ = 6.5 Hz, PhCH_aH_bNH, $J_{Ha\text{-}NH}$ = 14.5 Hz, PhCH_aH$_b$N*H*); 4.20 (1H, dd, $J_{Ha\text{-}Hb}$ = 6.5 Hz, PhCH_aH_bNH, $J_{Ha\text{-}NH}$ = 14.5 Hz, PhCH$_a$$H_b$N*H*); 6.08 (1H, s broad, N*H*); 6.37 (1H, d, $^2J_{HF}$ = 51.7 Hz, C*FH*SeC=O); 6.88-7.96 (2H, m, Ph); 7.20-7.40 (6H, m, arom); 7.59 (2H, dd, *J* = 8.0 Hz, *J* = 1.0 Hz, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 43.5 (*C*H$_2$NH), 92.6 (d, $^1J_{CF}$ = 245 Hz, *C*FHSeC=O), 125.1, 127.7, 127.8, 128.7, 129.3, 129.4, 136.5, 136.8, 166.4 (d, $^2J_{CF}$ = 22.3 Hz, CFHSe*C*=O);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -163.7 (1F, d, J_{HF} = 55. 8 Hz, C*FH*SeC=O);

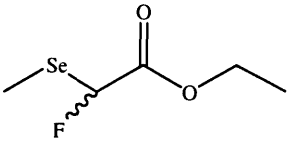
IR: ν = 3337, 1664, 1518, 1453, 1378, 1262, 735 cm^{-1};

GC-MS (DB5). Retention time: 30.51 minutes;

MS (EI): *m/z* (%) = 323 (7) [M]$^+$, 166 (100), 109 (37), 91 (39), 77 (11);

HRMS for [M$^+$] $C_{15}H_{14}NOFSe^+$: calcd 323.0219, found 323.0216.

Ethyl 2-fluoro-methylselanylacetate 68d



Synthesised according GP9 starting from **67d** (0.3 mmol, 58 mg). Obtained in 25% yield (0.075 mmol, 16 mg) as yellow oil after purification by preparative TLC in Petrol:EtOAc 9:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (3H, t, *J* = 7.2 Hz, *C*H$_3$CH$_2$); 2.14 (3H, s, *C*H$_3$Se); 4.20-4.28 (2H, dq, *J* = 7.1 Hz, J_{AB} = 2.9 Hz, CH$_3$*C*H$_2$); 6.15 (1H, d, $^2J_{HF}$ = 47.7 Hz, C*H*FSe);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 3.3, 14.1, 62.1, 84.4 (d, $^1J_{CF}$ = 239 Hz, *C*FHSeC=O), 167.1 (d, $^2J_{CF}$ = 28.1 Hz, C*F*HSe*C*=O);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -173.82 (1F, d, J_{HF} = 51.5 Hz, C*FH*SeC=O);

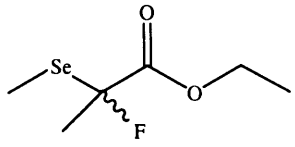
^{77}Se NMR (57.3 MHz, $CDCl_3$): δ = 291.87;

IR: ν = 2983, 1747, 1446, 1370, 1329, 1268, 1234, 1161, 1049, 912, 733 cm^{-1};

MS (EI): *m/z* (%) = 200 (62) [M]+, 127 (93), 106 (100), 78 (36);

HRMS for $C_5H_9O_2FSe$: calcd 199.9746, found 199.9748.

Ethyl 2-fluoro-methylselanylpropanoate 68e

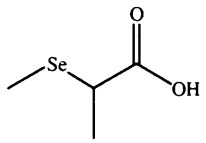


Synthesised according GP9. The solvent was carefully removed by nitrogen flow. Obtained in about 40% yield, which could be not purified from the starting material.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (3H, t, *J* = 7.1 Hz), 1.90 (3H, d, *J* = 19.25, CH_3CF), 2.10 (3H, s, CH_3Se), 4.20 (2H, dq, *J* = 7.1 Hz, *J* = 1.99 Hz,);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -137.44 (1F, q, J_{HF} = 18.5 Hz, $CFHSeC{=}O$).

2-Methylselanyl propionic acid



Synthesised according GP7. Obtained in 90% yield as white liquid.

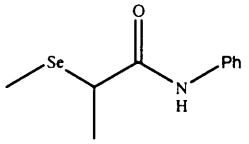
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (3H, d, *J* = 7.0 Hz, CH_3CH); 2.11 (3H, s, CH_3Se); 3.41 (1H, q, *J* = 7.0 Hz, CH_3CH);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 4.5, 16.6, 31.7, 179.6;

MS (EI): *m/z* (%) = 168 (86) $[M]^+$, 123 (100), 107 (22), 93 (42), 74 (59), 55 (29), 45 (84);

HRMS for [M] $C_4H_8O_2Se$: calcd 167.9684, found 196.9682.

N-Phenyl 2-methylselanylpropionamide



Synthesised according GP8 from 2-methylselanyl propionic acid (2.56 mmol, 428 mg). Obtained in 60% yield (1.50 mmol, 364 mg) as colourless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.60 (3H, d, *J* = 7.2 Hz, *CH*$_3$CH); 2.03 (3H, s, *CH*$_3$Se); 3.64 (1H, q, *J* = 7.2 Hz, CH$_3$C*H*); 6.97-7.09 (1H, m, arom); 7.28-7.40 (2H, m, arom); 7.50-7.60 (2H, m, arom); 8.04 (1H, s broad, PhN*H*);

^{13}C-NMR (400 MHz, $CDCl_3$): δ = 3.6, 18.0, 36.8, 119.5, 124.3, 129.0, 137.8, 172.1;

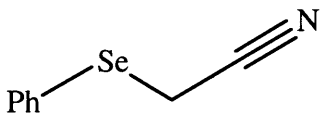
IR: ν = 3500, 1644, 1594, 1533, 1453, 1373, 715 cm^{-1};

GC-MS (DB5) Retention time: 13.25 minutes;

MS (EI): *m/z* (%)=243 (100) [M]+, 149 (43), 120 (20), 93 (54);

HRMS for [M+H$^+$] $C_{10}H_{12}NOSe+H^+$: calcd 243.0157, found 243.0154.

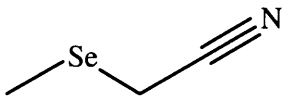
Phenylselenylacetonitrile[29] 70a



Synthesised according GP6 from diphenyldiselenide and α-chloro acetonitrile. Obtained in 90-94% yield as colourless liquid. The spectroscopic data are in agreement with those in literature.[29]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.30 (2H, s, *CH*$_2$Se); 7.30 (3H, m, arom); 7.60 (2H, m, arom).

Methylselanylacetonitrile 70b



Synthesised according GP6 from dimethyldiselenide and α-chloro acetonitrile. Obtained in 67% yield as pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (3H, s, *CH*$_3$Se); 3.18 (2H, s, *CH*$_2$Se);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 6.12 (*C*H$_3$), 30.92 (*C*H$_2$), 117.12;

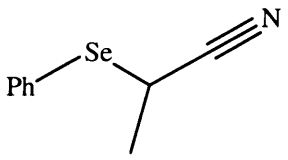
IR: ν = 2985, 2928, 2245, 1421, 1401, 1281, 1189, 923 cm^{-1};

GC-MS (DB5). Retention time: 3.14 minutes;

MS (EI): *m/z* (%) = 135 (70) [M]$^+$, 84 (100), 45 (70);

HRMS for [M+H$^+$] $C_3H_5NSe+H^+$: calcd 134.9582, found 134.9585.

2-Phenylselanyl-propionitrile 70c



Synthesised according GP10. Obtained in 54% yield as pale yellow liquid after purification by flash chromatography in Petrol:EtOAc 9:1 (R_f: 0.4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (3H, d, *J* = 7.0 Hz, CH_3CH); 3.70 (1H, q, *J* = 7.0 Hz, CH_3CH,); 7.20-7.30 (3H, m, arom); 7.50-7.70 (2H, m, arom);

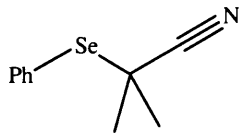
^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 19.5, 120.8, 125.8, 129.5, 129.7, 136.5;

IR: ν = 3045, 2985, 2925, 2222, 1579, 1478, 1438, 1338, 1302, 1162, 1086, 1016, 976, 730, 700 cm^{-1};

MS (EI): *m/z* (%) = 210 (38) $[M]^+$, 157 (100), 116 (18), 77(88), 51 (72);

HRMS for $[M+NH_4^+]$ $C_9H_9NSe+NH_4^+$: calcd 229.0238, found 229.0241.

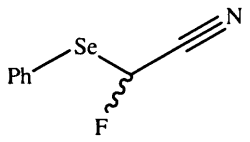
2-Methyl-2-phenylselanyl-propionitrile[30]



Obtained as sideproduct during the synthesis of 2-phenylselanyl-propionitrile in 28% yield GP10. Purified by flash chromatography in Petrol:EtOAc 9:1 (R_f: 0.5). The spectroscopic data are in agreement with those in literature.[30]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (6H, s, CH_3CCH_3); 7.20-7.40 (3H, m, arom); 7.61-7.82 (2H, m, arom).

Fluoro phenylselanylacetonitrile 71a



Synthesised according GP9. Obtained in 50% yield (0.2 mmol, 43 mg) after purification by flash chromatography petroether:EtOAc 9:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41 (1H, d, $^2J_{HF}$ = 50.2 Hz, C*H*F); 7.25-7.55 (3H, m, arom); 7.52-7.73 (2H, m, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 76.3 (d, $^1J_{CF}$ = 253.6 Hz, *C*HFSe), 113.8 (d, $^2J_{CF}$ = 36.1 Hz, CH*F*Se*C*N), 124.6, 129.8, 130.5, 136.4;

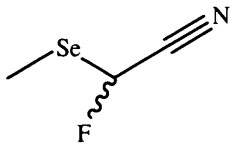
^{19}F NMR (282.8 MHz, $CDCl_3$): δ = 164.42 (1F, d, $^2J_{HF}$ = 52.2 Hz);

IR: ν = 3056, 2955, 2353, 1573, 1478, 1438, 1302, 1011, 926, 740, 680, 660 cm^{-1};

MS (EI): *m/z* (%) =215 (80) [M]$^+$, 157 (100), 116 (17), 77(78), 51 (43);

HRMS for [M$^+$] $C_8H_6NFSe^+$: calcd 214.9644, found 214.9645.

Fluoro methylselanylacetonitrile 71b



Prepared according GP9. Obtained in 26% yield (0.10 mmol, 16 mg) as pale yellow liquid by preparative TLC (petrolether: EtOAc 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (3H, s, CH_3Se); 6.3 (1H, d, $^2J_{HF}$ = 49.7 Hz, C*H*FSe);

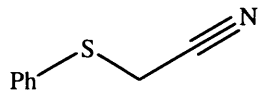
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 53.4, 72.8 (d, $^1J_{CF}$ = 235.2 Hz, *C*HF), 113.9 (d, $^2J_{CF}$ = 39.8 Hz, *C*NCH*F*Se);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = 168.61 (1F, d, $^2J_{HF}$ = 52 Hz);

IR: ν = 2984, 2359, 1374, 1248, 1045, 908 cm^{-1};

MS (EI): *m/z* (%) = 153 (61) [M]$^+$, 95 (100), 58 (19).

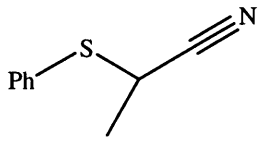
Phenylsulfanylacetonitrile[31] 72a



Synthesised according GP6 from diphenyldisulphide and α-chloro acetonitrile. Obtained in 80-87% yield as pale yellow liquid. The spectroscopic data are in agreement with those in literature.[31]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.71 (2H, s, CH_2S); 7.30-7.50 (3H, m, arom); 7.54-7.65 (2H, m, arom).

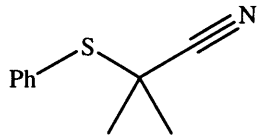
2-Phenylsulfanylpropionitrile[32] 72b



Synthesised according GP10. Obtained in 45% yield (1.35 mmol, 220 mg) as pale yellow liquid after purification by flash chromatography in Petrol:EtOAc 9:1 (R_f: 0.4). The spectroscopic data are in agreement with those in literature.[32]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (3H, d, CH_3CH, J = 7.0 Hz); 3.70 (1H, q, CH_3CH, J = 7.0 Hz); 7.15-7.45 (3H, m, arom); 7.36-7.65 (2H, m, arom).

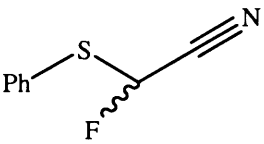
2-Methyl-2-phenylsulfanylpropionitrile[33]



Obtained as sideproduct during the synthesis of 2-phenylsulfanyl-propionitrile in 32% yield (0.96 mmol, 170 mg) GP10. Purified by flash chromatography in Petrol:EtOAc 9:1 (R_f: 0.5). The spectroscopic data are in agreement with those in literature.[33]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (6H, s, CH_3CCH_3); 7.25-7.56 (3H, m, arom); 7.61-7.81 (2H, m, arom).

Fluoro-phenylsulphanylacetonitrile[34] 73

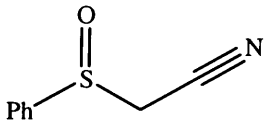


Synthesised according GP9. Obtained in 16% yield (0.06 mmol, 11 mg) as yellow oil after purification by flash chromatography in Petrol:EtOAc 9:1 (R_f: 0.6).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.18 (1H, d, ^2J = 49.3 Hz, CHF); 7.39-7.60 (3H, m, arom); 7.53 (2H, dd, J = 7.6 Hz, J = 1.9 Hz, arom);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -152.41 (1F, d, $^2J_{HF}$ = 55.3 Hz).

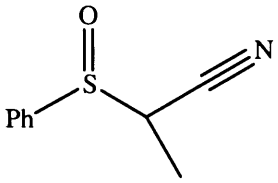
Benzenesulfinyl-acetonitrile[35] 74a



Obtained as side product during the synthesis of fluoro-phenylsulphanyl-acetonitrile (GP9) in 40% yield (0.16 mmol, 26 mg) after flash chromatography in petrolether: EtOAc 1:1 R_f: 0.4.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (1H, d, *J* = 15.7 Hz, *CH*HCN); 3.54 (1H, d, *J* = 15.7 Hz, *CH*HCN); 7.50-7.54 (3H, m, arom); 7.66-7.71 (2H, m, arom).

2-Benzenesulfinyl-propionitrile 74b



Synthesised according GP9. Obtained in 70% yield (0.28 mmol, 50 mg) as yellow oil after purification by flash chromatography in Petrol:EtOAc 6:4 (R_f: 0.4). The data refers to a mixture 1:1 of the 2 diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 (3H, d, *J* = 7.3 Hz, *CH*$_3$CHCN); 1.54 (3H, d, *J* = 7.2 Hz, *CH*$_3$CHCN); 3.57 (1H, q, *J* = 7.2 Hz, CH$_3$C*H*CN); 3.65 (1H, q, *J* = 7.2 Hz, CH$_3$C*H*CN); 7.51-7.56 (3H, m, arom); 7.63-7.67 (1H, m, arom); 7.68-7.72 (1H, m, arom);

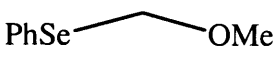
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 9.5 (11.0), 50.1 (50.8), 113.8 (114.3), 123.6 (123.8), 128.4 (128.5), 131.4 (131.5), 137.8 (138.9). The peaks of one diastereomer are in bracket;

IR: ν = 3056, 2962, 2239, 1477, 1444, 1090, 1054, 998, 915, 750, 690 cm^{-1};

MS (CI): *m/z* (%) = 197 (100), $[M+NH_4]^+$, 181 (8), 126 (22), 94 (9), 52 (28);

HRMS for $[M+NH_4^+]$ $C_9H_9NSO+NH_4^+$: calcd 197.0743, found 197.0744.

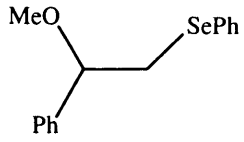
Methoxymethyl selanyl benzene[36] 76



It was synthesised according to the procedure GP5. Purification by flash chromatography (petrolether:EtOAc 9:1) to obtain a yellow oil in 80% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.34 (3H, s, CH_3OMe); 5.18 (2H, s, CH_2OMe); 7.20-7.24 (3H, m, arom); 7.48-7.52 (2H, m, arom).

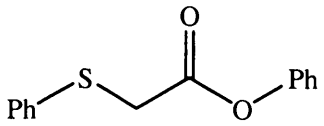
(2-Methoxy, 2-phenyl)ethyl-seleno benzene[37] 78



Phenyl selenyl bromide (0.068 g, 0.02 mmol) was dissolved in dry diethyl ether (4 ml, 0.05M) under argon, cooled at -78°C and left stirring until complete dissolution of the reagent. To the reaction mixture silver triflate (0.02 mmol, 80 mg) in methanol (0.1 ml) was added. The reaction was stirred for 15 minutes and subsequently was treated with styrene (20 µl). After stirring for 4 hours, the reaction was quenched with collidine (0.1 ml) and water (4 ml). The mixture was extracted 3 times with *tert*-butyl methyl ether. The organic layer was washed with water and brine and dried with $MgSO_4$. Concentration on the rotatory evaporator gave a yellow liquid which was purified by column chromatography on silica gel (Petrol: EtOAc 9:1) to obtain a yellow oil (34 mg). Yields obtained were between 59-66%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.97 (1H, dd, *J* = 12.2 Hz, *J* = 4.7 Hz, C*H*HSe); 3.17 (3H, s, CH_3O); 3.24 (1H, dd, *J* = 12.2 Hz, *J* = 6.2 Hz, CH*H*Se); 4.25 (1H, dd, *J* = 6.5 Hz, *J* = 5.0 Hz, C*H*OCH$_3$); 7.00-7.40 (5H, m, arom).

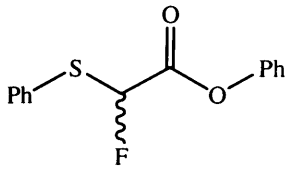
Phenyl phenylsulphanylacetate[38] 80a



Prepared according GP8 from commercially available phenylthio acetic acid. Obtained in 75% yield (5.25 mmol, 1.28 g) as colourless oil. Spectroscopic data agree with those in literature.[38]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (2H, s, PhSCH_2); 7.02 (2H, dd, *J* = 7.0 Hz, *J* = 1.0 Hz, arom); 7.20-7.55 (6H, m, arom); 7.60 (2H, dd, *J* = 7.0 Hz, *J* = 1.0 Hz, arom).

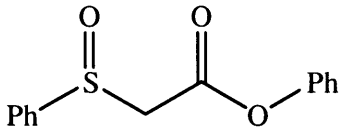
Phenyl 2-fluoro-2-phenylsulphanyl acetate[38] 81



Synthesised according GP9 in normal glassware. Obtained in 17-42% yield as a solid after purification by flash chromatography in Petrol:EtOAc 9:1 (R_f: 0.55). Spectroscopic data agree with those in literature.[38]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.28 (1H, d, $^2J_{HF}$ = 51.2 Hz, C*H*F); 6.78 (2H, d, *J* = 8.5 Hz, arom); 7.10-7.40 (6H, m, arom); 7.66 (2H, d, *J* = 7.0 Hz, arom).

Phenyl benzenesulfinylacetate 82



Synthesised according GP9 in normal glassware. Obtained in 33-48% yield as yellow oil after purification by flash chromatography in Petrol:EtOAc 6:4 (R_f: 0.4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (1H, d, *J* = 13.5 Hz, PhS(O)C*H*H); 4.03 (1H, d, *J* = 13.5 Hz, PhS(O)CH*H*); 6.91 (2H, d, *J* = 8.1 Hz, arom); 7.19 (1H, d, *J* = 8.7 Hz, arom); 7.25-7.33 (2H, m, arom); 7.45-7.55 (3H, m, arom); 7.64-7.75 (2H, m, arom);

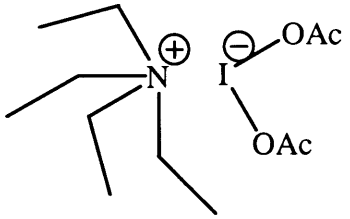
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 61.3, 121.2, 124.4, 126.4, 129.5, 129.6, 132.1, 142.8, 149.9, 163.2;

IR: ν = 3076, 1749, 1589, 1493, 1438, 1252, 1192, 1157, 1086, 1046, 911, 725 cm^{-1};

MS (CI) for $[M+NH_4^+]$: *m/z* (%) = 278 (47) $[M+NH_4^+]$, 262 (50), 154 (100), 94 (21), 77 (19), 52 (44);

HRMS for $[M+NH_4^+]$ $C_{14}H_{12}O_3S+NH_4^+$: calcd 278.0845, found 278.0850.

Bis(acetato-O) tetraethylammonium iodine[39] 83

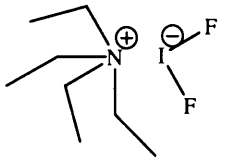


To a solution of tetraethylammonium iodide (0.9 mmol, 240 mg) in dry chloroform (1.5 ml, 0.7M) (diacetoxyiodo)toluene (0.9 mmol, 325 mg) was added as a solid. The resulting mixture was allowed to stir at room temperature for an overnight period. The formed solid was collected by filtration, washed with diethyl ether and dried over $CaCl_2$. Yield was 54-60% (0.54 mmol, 202 mg). Spectroscopic data agree with literature[39]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (12H, t, *J* = 7.2 Hz, CH_3CH_2); 1.91 (6H, s, CH_3COO); 3.37 (8H, q, *J* = 7.2 Hz, CH_3CH_2);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 7.8, 52.9.

Tetrabutilammonium iodo difluoride[40] 84



In normal borosilicate glassware and under inert atmosphere of argon, to a solution of tetraethylammonium iodide (0.93 mmol, 238 mg) in dry chloroform (6 ml, 0.15M) was added DFTI (0.97 mmol, 248 mg). The mixture was stirred overnight at room temperature. After addition of dry diethyl ether the mixture was cooled at 0°C. The red-brown solid was collected by filtration, washed with dry diethyl ether to eliminate the iodo toluene and dried over $CaCl_2$. Yield was up to 78% (0.74 mmol, 217mg).

mp = 145-150°C with decomposition (Lit.[40] mp = 140-160°C)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (12H, td, *J* = 7.2 Hz, *J* = 1.7 Hz); 3.40 (8H, q, *J* = 7.3 Hz);

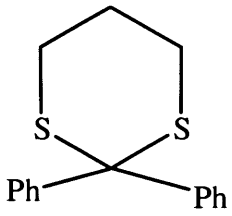
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 7.7, 52.8;

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -152.31 (s, 2F);

IR (KBr pellets): ν = 1483, 1443, 1393, 1363, 1172, 1056, 996, 790, 740 cm^{-1};

Anal. Calcd. for $C_8H_{20}NF_2I$: C, 32.55; H, 6.83; N, 4.75; F, 12.87. Anal. Found: C, 30.13; H, 6.32; N, 4.12; F, 11.32.

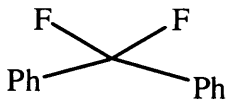
2,2-Diphenyl-[1,3] dithiane[41] 86



A chloroform solution (5 ml) of benzophenone (2 mmol, 370 mg) was mixed with propane-1,3-propanedithiol (0.20 ml, 2 mmol) and boron trifluoride BF_3-2EtOH (0.1 ml). The mixture was allowed to reflux for three days. After being cooled to room temperature, the solution was washed with 1M NaOH. The chloroform layer was dried over $MgSO_4$, the solvent was then evaporated in vacuum. The residue was purified by column chromatography to obtain a white solide which was used without further purification (93% yield, 514 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88-2.00 (2H, m, $SCH_2CH_2CH_2S$); 2.66-2.77 (4H, m, $SCH_2CH_2CH_2S$); 7.10-7.25 (6H, m, arom); 7.56-7.67 (4H, m, arom)

Difluorodiphenyl methane[41] 87

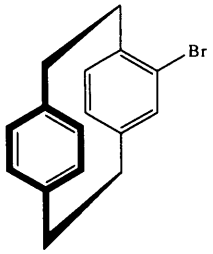


To a solution of 2,2-diphenyl-[1,3]dithiane (0.1 mmol, 29 mg) in CH_2Cl_2 (1 ml, 0.1M) was added at 0°C tetrabutilammonium iodo difluoride (0.1 mmol, 30 mg) dissolved in 0.5 ml of CH_2Cl_2. The solution was stirred for overnight period. Water was added and extraction was made with CH_2Cl_2. The organic layer was dried over $MgSO_4$, the solvent was removed and the crude residue was purified by flash chromatography on silica gel (Petrolether: EtOAc 9:1). The correspondent difluoride was obtained in 42% yield (0.042 mmol, 9 mg) as pale yellow oil. The spectroscopic data agree with those in literature.[41]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.70 (10H, m, arom);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -89.4 (2F, s).

(±)-4-Bromo[2.2] paracyclophane[42] 96



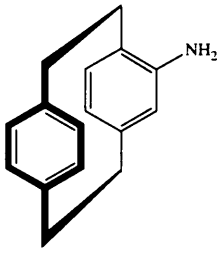
It was synthesized from [2.2] paracyclophane and bromine according to the procedure reported by Cram (GP11). The spectroscopic data are according to the literature[42]. Yield was 88% (8.7 mmol, 2.5 g) when the mixture was refluxed for 18 hours and 85% (8.2 mmol, 2.3 g)when the mixture was stirred at room temperature for 3 days. In both cases no evident formation of dibrominated products was observed by GC-MS.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73-3.53 (8H, m), 6.38-6.60 (6H, m, arom); 7.16 (1H, dd, *J* = 7.8 Hz, *J* = 1.8 Hz, arom);

GC-MS (DB5). Retention time: 27.37 minutes;

MS (EI): *m/z* (%) = 287 (40), 286 (40) $[M]^+$, 104 (100).

(±)-4-Amino [2.2] paracyclophane[43] 97



Under inert atmosphere, to a stirred solution of methoxyamine (18 mmol, 1.5 g) in dry diethyl ether (18 ml) was added at -78°C a solution of methyllithium (1.6 M in diethyl ether, 36 mmol). Then a solution of 4-lithium-[2.2]-paracyclophene, prepared from 4-bromo-[2.2]-paracyclophene (9 mmol, 2.6 g) in dry diethy ether (125 ml) and *n*-BuLi (14 mmol, 5.7 ml), was added to the previous mixture at -78°C. The resulting mixture was kept at -78°C for half hour and then at -20°C for 2-3 hours. Water was added, and the mixture was extracted with diethyl ether (3 x 25 ml). The collected organic fractions were washed with water and dried over magnesium sulfate. After evaporation of the solvent the crude was purified by flash chromatography on silica gel with a mixture 1:1 of petrolether and diethyl ether. Yield was from

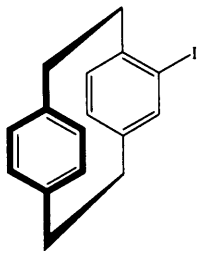
20 to 40% (3.6 mmol, 803 mg). The spectroscopic data are in agreement with those in literature.[43]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45-3.10 (8H, m), 3.30 (2H, s broad, NH_2); 5.36 (1H, d, *J* = 1.4 Hz, arom); 6.00-6.60 (5H, m, arom); 7.15 (1H, dd, *J* =7.8 Hz, *J* = 1.7 Hz, arom);

GC-MS (DB5). Retention time: 27.58 minutes;

MS (EI): *m/z* (%) = 223 (100), 119 (78), 104 (9), 91 (16).

(±)-4-Iodo-[2.2] paracyclophane[43] 98



- Sandemayer procedure starting from 4-amino [2.2] paracyclophane.

4-Amino [2.2] paracyclophane (0.56 mmol, 127 mg) was added to a mixture of 96% H_2SO_4 (0.5 ml) in water (6 ml). The mixture was then heated to 85°C, until the solution became clear. The solution was then cooled down to 0°C and an aqueous solution of $NaNO_2$ (1 mmol, 72 mg in 1.5 ml H_2O) was added dropwise. After 30 minutes a solution of KI (1.8 mmol, 309 mg) in water (1 ml) was added at 0°C. The mixture was allowed to react for 30 minutes at 0°C and then at room temperature. The solution was then quenched with $NaHSO_3$ and extracted with $CHCl_3$. The organic phase was dried with brine and $MgSO_4$ and evaporated. The crude product was then purified by flash chromatography in petrolether as eluent to obtain a 40% yield (0.23 mmol, 76 mg) of the product.

- Halogen exchange using CuI. (GP12b). The progress of the reaction was monitored by GC-MS. After 3 days refluxing yield was 50% (0.05 mmol, 17 mg).
- Halogen exchange using Ni. (GP12a). The progress of the reaction was followed by GC-MS. After 3 days yield was between 68 and 86% (4.3 mmol, 1.4 g).

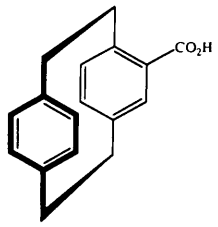
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.85-3.45 (8H, m), 6.38-6.60 (5H, m, arom); 6.82 (1H, d, *J* = 1.7 Hz, arom); 7.24 (1H, dd, *J* = 7.8 Hz, *J* = 1.8 Hz, arom);

GC-MS (DB5). Retention time: 29.07 minutes;

MS (EI): *m/z* (%) = 334 (52) $[M]^+$, 230 (21), 104 (100), 77 (22), 51 (13);

Separation of the racemic mixture was done by HPLC, Daicel OD, *n*-hexane: *i*-PrOH (99 : 1), 6 ml/min, T = 5°C, $R_f(1)$ = 49 min, $R_f(2)$ = 54 min.

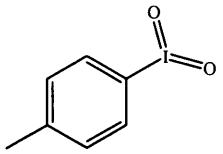
(±)-4-Carboxy[2.2] paracyclophane[42] 99



Was synthesised from 4-bromo-[2.2]-paracyclophane, *n*-BuLi and dry ice. The spectroscopic data agree with the literature.[42]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.70-3.20 (8H, m), 6.20-6.70 (5H, m, arom); 7.10-7.30 (2H, m, arom).

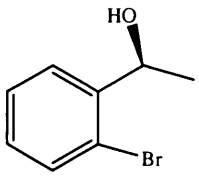
4-Iodyl toluene[6] 102



Synthesised according GP5a. Obtained as white solid in 75% yield (0.68 mmol, 172 mg). Using ozone monopersulfate (GP5b) the yield was 10% (0.08 mmol, 20 mg). mp = 215-223°C (Lit.[6]: 226°C).

^{1}H NMR (400 MHz, DMSO): δ = 2.13 (3H, s, CH_3); 7.33 (2H, d, J = 7.9 Hz, arom); 7.83 (1H, d, J = 8.0 Hz, arom).

(S)-1-(2-Bromo-phenyl)-ethanol[44] 105

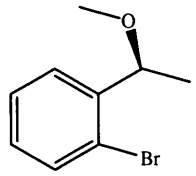


1-(2-Bromo-phenyl)-ethanone (5 mmol, 1 g) was dissolved in 5 ml of THF and slowly added to a solution of (+)-DIP-Cl (6 mmol, 1 M in THF) at -25°C. After the reaction completed (15-25 hours) the solution was allowed to warm up to room temperature and the solvent was removed in vacuo. The residue was quickly dissolved in diethyl ether (10 ml) and diethanol amine (10.2

mmol) was added. The mixture was stirred for 2 hours and then was filtered through celite and concentrated. The oil was then purified by flash chromatography over petrol ether: EtOAc 8:2. Yield was 90% (4.5 mmol, 0.9 g); 95% ee (HPLC, Daicel OD-H, n-hexane: 2-propanol 99:1, 0.5 ml/min, T = 25°C, R_f(S) = 25.4 min, R_f(R) = 28.5 min).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.41 (3H, d, *J* = 6.5 Hz, CH_3CHOH); 5.18 (1H, q, *J* = 6.4 Hz, CH_3CHOH); 7.06 (1H, td, *J* = 7.7 Hz, *J* = 1.6 Hz, arom); 7.27 (1H, td, *J* = 7.7 Hz, *J* = 1.0 Hz, arom); 7.44 (1H, dd, *J* = 8.0 Hz, *J* = 1.1 Hz, arom); 7.53 (1H, dd, *J* = 7.8 Hz, *J* = 1.7 Hz, arom).

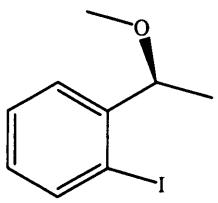
(S)-1-Bromo-2-(1-methoxyl-ethyl)-benzene[45] 106



Sodium hydride (20 mmol, 55% dispersion in mineral oil), was washed with hexane and then suspended in DMF (25 ml). After cooling at 0°C, the alcohol solution (5 mmol, in 12 ml DMF) was added. The reaction mixture was allowed to react at room temperature for half hour and then methyl iodide (6 mmol) was added at 0°C. After a further 3 hours at room temperature, water was added. The mixture was extracted with diethyl ether, dried and concentrated. The product was used in the next step without further purification. The yield was quantitative.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (3H, d, *J* = 6.4 Hz, CH_3CHOH); 2.74 (3H, s, CH_3O); 4.54 (1H, q, *J* = 6.4 Hz, CH_3CHOMe); 7.15 (1H, td, *J* = 7.7 Hz, *J* = 1.6 Hz, arom); 7.35 (1H, td, *J* = 7.7 Hz, *J* = 1.0 Hz, arom); 7.49-7.51 (2H, m, arom).

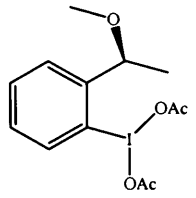
(S)-1-Iodo-2-(1-methoxyl-ethyl)-benzene[45] 107



The bromo precursor (6.9 mmol, 1.48 g) was dissolved in dry THF (35 ml). At -20°C, a solution 1.5 M of *tert*- BuLi (8 mmol, 5.3 ml) was dropwise added. The solution was allowed to react for half hour and then iodine was added (8 mmol, 2 g). The reaction was slowly let warm up to room temperature and let stir for additionally 3 hours. Water was carefully added and the

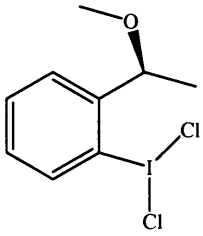
mixture was then extracted with diethyl ether. The yellow residue was purified by flash chromatography on silica gel using petrolether: EtOAc 9:1. Yield was 74% (5.1 mmol, 1.34 g).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (3H, d, *J* = 6.4 Hz, CH_3CHOMe); 3.18 (3H, s, CH_3OCH); 4.46 (1H, q, *J* = 6.4 Hz, CH_3CHOMe); 6.89 (1H, td, *J* = 7.5 Hz, *J* = 1.9 Hz, arom); 7.28-7.38 (2H, m, arom); 7.73 (1H, dd, *J* = 7.9 Hz, *J* = 1.0 Hz, arom).

(S)-Bis(acetato-O)[2-(1-methoxyethyl)-benzyl]-iodine[45] 108



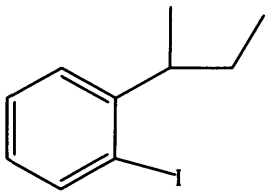
Synthesised with the McKillop procedure GP2a. Yield was 60% (4.08 mmol, 1.55 g).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (3H, d, *J* = 6.3 Hz, CH_3CHOMe); 1.97 (6H, s, CH_3COO); 3.24 (3H, s, CH_3OCH); 4.67 (1H, q, *J* = 6.4 Hz, CH_3CHOMe); 7.38 (1H, td, *J* = 7.1 Hz, *J* = 2.1 Hz, arom); 7.68-7.73 (2H, m, arom); 8.19 (1H, dd, *J* = 7.9 Hz, *J* = 0.8 Hz, arom).

(S)-Bis(chloro)[2-(1-methoxyethyl)-benzyl]-iodine 111



Synthesised according GP1. Obtained as a mixture 2:3 with the precursor 1-iodo-2-(1-methoxyl-ethyl)-benzene. This compound was found to be too unstable for a full characterisation.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55 (3H, d, *J* = 6.5 Hz, CH_3CHOMe); 3.24 (3H, s, CH_3O); 4.73 (1H, q, *J* = 6.4Hz, CH_3CHOMe); 7.32-7.38 (1H, m, arom); 7.58-7.68 (2H, m, arom); 8.16 (1H, dd, *J* = 8.7 Hz, *J* = 0.8 Hz, arom).

1-Sec-butyl-2-iodo-benzene 114



Its synthesis was performed according GP13. Obtained in 3% yield (0.2 mmol, 50 mg) after flash chromatography in petrolether. Also obtained in 3% yield (0.03 mmol, 8 mg) when synthesised according GP14a.

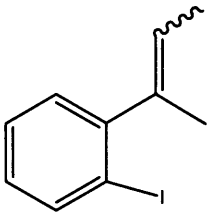
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (3H, t, *J* = 7.0 Hz, CH_3CH_2); 1.09 (3H, d, *J* = 7.0 Hz, CH_3CH); 1.40-1.62 (2H, m, CH_3CH_2); 2.91 (1H, ses, *J* = 7.0 Hz, CH_3CH); 6.8 (1H, td, *J* = 8. Hz, *J* = 1.1 Hz, arom); (1H, dd, *J* = 8.0 Hz, *J* = 1.0 Hz, arom); 7.2 (1H, td, *J* = 8.1 Hz, *J* = 1 Hz, arom); 7.80 (1H, dd, *J* = 7.6 Hz, *J* = 1.0 Hz, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12, 21, 30.4, 44.8, 104.2, 126.5, 127.6, 128.41, 139.4, 149.4;

MS (EI): *m/z* (%) = 260 (34) $[M]^+$, 231 (100), 217 (8), 104 (48), 77 (13), 51 (9);

HRMS for $[M^+]$ $C_{10}H_{13}I$: calcd 260.0056, found 260.0054.

1-Iodo-2-(1-methyl-propenyl) benzene 115



Prepared according GP13. Obtained in 58% yield (4.06 mmol, 1.05 g) after flash chromatography in petrol.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (3H, dd, *J* = 6.5 Hz, *J* = 1.5 Hz, CH_3CH); 1.90 (3H, s, CH_3); 5.45-5.55 (1H, m, CH_3CH); 6.82 (1H, td, *J* = 7.0 Hz, *J* = 2.0 Hz, arom); 7.01 (1H, dd, *J* = 8.0 Hz, *J* = 1.5 Hz, arom); 7.30 (1H, td, *J* = 7.5 Hz, *J* = 1.1 Hz, arom); 7.8 (1H, dd, *J* = 8.2 Hz, *J* = 1.1 Hz, arom);

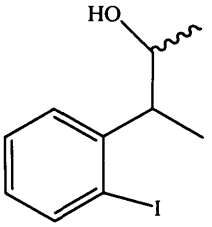
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.6, 24.5, 98.3, 122.9, 128, 128.8, 132.7, 138.9, 139.9;

IR: ν = 3045, 2966, 2905, 1579, 1558, 1463, 1418, 1373, 1006, 820, 755, 725 cm^{-1};

MS (EI): *m/z* (%) = 258 (100) $[M]^+$, 131 (48), 116 (78), 91 (76), 64 (58), 51 (25);

HRMS for [M^+] $C_{10}H_{11}I$: calcd 257.9900, found 257.9896.

3-(2-Iodo-phenyl)-butan-2-ol 116



Synthesised according GP14b. Obtained in 45-58% yield (0.58 mmol, 159 mg) after flash chromatography in petrolether:EtOAc 8:2 (R_f = 0.4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (3H, d, *J* = 6.2Hz, CH_3CH); 1.22 (3H, d, *J* = 6.9 Hz, CH_3CH); 3.00-3.14 (1H, m, CH_3CH); 3.83-3.94 (1H, m, CH_3CH)); 6.83 (1H, td, *J* = 7.3 Hz, *J* = 1.5 Hz, arom); 7.12 (1H, dd, *J* = 7.7 Hz, *J* = 1.6 Hz, arom); 7.20-7.28 (1H, m, arom); 7.79 (1H, dd, *J* = 8.0 Hz, *J* = 1.2 Hz, arom);

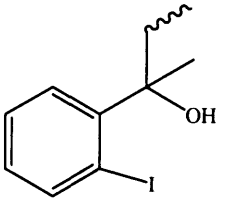
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.0, 21.3, 49.8, 71.2, 102.1, 127.6, 128.1, 128.4, 139.8, 146.9;

IR (as liquid film): ν = 3385 (broad), 2969, 2928, 1583, 1560, 1465, 1433, 1374, 1088, 1007, 910, 753, 653 cm^{-1};

MS (CI): *m/z* (%) = 294 (100) [$M+NH_4^+$], 194 (46), 178 (38), 168 (97), 150 (51), 136 (70), 112 (57), 98 (88), 86 (80), 72 (83);

HRMS for [$M+NH_4^+$] $C_{10}H_{13}OI+NH_4^+$: calcd: 294.0349, found: 294.0353.

2-(2-Iodo-phenyl)-butan-2-ol 117



Synthesised according GP14b. Obtained in 5-13% yield (0.13 mmol, 35 mg) after flash chromatography in petrolether:EtOAc 8:2 (R_f = 0.5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72 (3H, t, *J* = 7.5 Hz, CH_3CH_2); 1.64 (3H, s, CH_3COH); 1.86-1.97 (1H, m, CH_3CHH); 2.18 (1H, s broad, CH_3COH); 2.20-2.32 (1H, m, CH_3CHH); 6.82

(1H, td, J = 7.4 Hz, J = 1.8 Hz, arom); 7.28 (1H, td, J = 8.3 Hz, J = 1.4 Hz, arom); 7.56 (1H, dd, J = 8.0 Hz, J = 1.6 Hz, arom); 7.89 (1H, dd, J = 8.0 Hz, J = 1.6 Hz, arom);

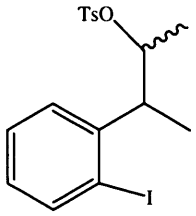
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 8.4, 27.6, 33.4, 76.0, 92.9, 127.8, 127.9, 128.5, 142.7, 147.5;

IR (liquid film): ν = 3438 (broad), 2967, 2929, 2876, 1582, 1559, 1459, 1427, 1374, 1270, 1160, 1004, 914, 755 cm^{-1};

MS (CI): *m/z* (%) = 294 (29) [M+NH_4^+], 276 (30) [M]$^+$, 166 (45), 150 (100), 138 (94), 112 (54), 98(86), 86 (78), 72 (82), 63 (59);

HRMS for [M+NH_4^+] $C_{10}H_{13}OI+NH_4^+$: calcd: 294.0349, found: 294.0350.

Toluene-4-sulfonic acid 2-(2-iodo-phenyl)-1-methyl-propyl ester



Prepared according GP15. Obtained in 50% yield (0.5 mmol, 21 mg) after flash chromatography in petrolether: EtOAc 9:1 (R_f = 0.4), mp = 85-90°C

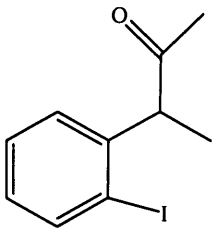
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.67 (3H, d, J = 7.0 Hz, CH_3CH); 1.50 (3H, d, J = 6.3 Hz, CH_3CH); 2.35 (3H, s, CH_3); 3.16 (1H, quint, J = 6.8 Hz, CH_3CHOTs); 4.66 (1H, quint, J = 6.4 Hz, CH_3CHPh); 6.78 (1H, td, J = 7.9 Hz, J = 1.5 Hz, arom); 6.99 (1H, dd, J = 7.9 Hz, J = 1.6 Hz, arom); 7.10-7.20 (3H, m, arom); 7.53 (1H, dd, J = 6.6 Hz, J = 1.7 Hz, arom); 7.64 (1H, dd, J = 8.0 Hz, J = 1.3 Hz, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ =14.3, 18.2, 20.4, 46.9, 81.4, 100.5, 126.3, 126.9, 127.2, 127.3, 128.4, 132.4, 138.4, 142.8, 143.0;

MS (EI): *m/z* (%) = 430 (6) [M]$^+$, 258 (12), 230 (45), 155 (49), 104 (32), 91 (100), 77 (41), 65 (47), 39 (24);

HRMS for [M$^+$] $C_{17}H_{19}IO_3S$: calcd 430.0094, found 430.0095.

3-(2-Iodo-phenyl)-butan-2-one 118



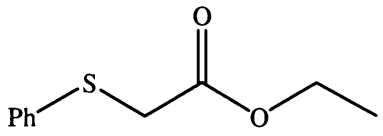
To a solution of PCC (4.35 mmol, 937 mg) in CH_2Cl_2 (30 ml) was added the alcohol (2.9 mmol, 795 mg) dissolved in CH_2Cl_2 (5 ml) at -10°C. The reaction mixture was stirred for overnight, then was filtered through celite and the solvent was removed. Purification was done by flash chromatography petroether: EtOAc 9:1 (R_f = 0.4) to obtain the pure product. Yield was 68% (1.97 mmol, 520 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (3H, d, *J* = 7.0 Hz, *CH*$_3$CH); 2.01 (3H, s, *CH*$_3$); 4.11 (1H, q, *J* = 6.9 Hz, CH$_3$C*H*); 6.89 (1H, td, *J* = 7.4 Hz, *J* = 1.6 Hz, arom); 7.02 (1H, dd, *J* = 7.8 Hz, *J* = 1.7 Hz, arom); 7.26 (1H, td, *J* = 7.4 Hz, *J* = 1.1 Hz, arom); 7.82 (1H, dd, *J* = 7.9 Hz, *J* = 1.2 Hz, arom);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.6, 28.9, 57.2, 101.7 (q), 127.4, 128.7, 128.8, 139.7, 143.4 (q), 208.2;

IR: ν = 3056, 2975, 1709, 1579, 1558, 1463, 1433, 1353, 1172, 1071, 1011, 760 cm^{-1}.

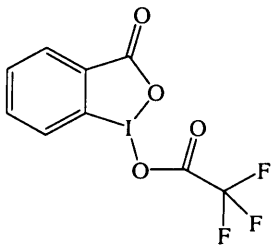
Ethyl phenylsulphanyl acetate[38] 80b



Prepared according GP6 from commercially available diphenyldisulphide. Obtained in 90% yield as colourless oil. Spectroscopic data agree with those in literature[38].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (3H, t, *J* = 7.1 Hz, CH$_2$*CH*$_3$); 3.66 (2H, s, PhS*CH*$_2$); 4.19 (2H, q, *J* = 7.1 Hz, *CH*$_2$CH$_3$); 7.23-7.35 (3H, m, arom); 7.30-7.50 (2H, m, arom).

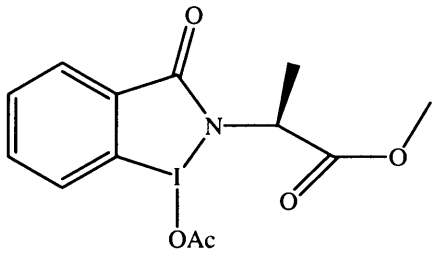
1-Trifluoroacetoxy-1,2-benziodoxol-3(1H)-one[46] 120



Obtained as product during the crystallisation of fluoro benziodoxole **42** using as solvent toluene and a few drops of TFA. Crystal data are reported in Appendix 1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (1H, t, *J* = 7.4 Hz, arom); 7.90 (1H, d, *J* = 8.3 Hz, arom); 7.90-8.10 (1H, m, arom); 8.23 (1H, dd, *J* = 7.6 Hz, *J* = 1.5 Hz, arom).

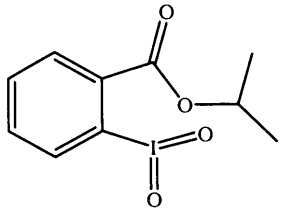
N-Alanine methyl ester-1-acetoxy-3-(1H)-1,2-benziodazole-3-one[25] 122



Prepared according GP2b. Obtained as a solid in 65% yield (6.5 mmol, 2.5 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (2H, d, *J* = 6.6 Hz, CH_3CH); 3.18 (3H, s, CH_3CO); 3.87 (3H, s, CH_3O); 5.12 (1H, q, *J* = 7.0 Hz, CH_3CH); 7.65 (1H, td, *J* = 7.4 Hz, *J* = 1.8 Hz, arom); 7.77 (1H, td, *J* = 7.8 Hz, *J* = 1.8 Hz, arom); 8.20-8.25 (1H, m, arom).

Isopropyl-2-iodyl-benzoate[24] 124

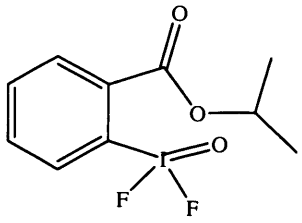


2-Iodo benzoic acid isopropyl ester (9 mmol, 2.74 g) was dissolved in CH_2Cl_2 (10 ml). A solution of 6% bleach (35 ml) containing of NaCl (8 g) was then added in the previous solution. Acetic acid (0.1 ml) was added in catalytic amount. The mixture was stirred for 2 hours. Then

$NaHCO_3$ (1 g) was added and left for 30 minutes. The solution was filtered through $MgSO_4$ and the solvent was removed by rotary evaporator. Yield was 70% (6.3 mmol, 1.9 g).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (6H, d, *J* = 6.3 Hz, *$(CH_3)_3$*CH); 5.31 (1H, sept, *J* = 6.3 Hz, $(CH_3)_3C$*H*); 7.58 (1H, t, *J* = 7.3 Hz, arom); 7.84 (1H, t, *J* = 7.3 Hz, arom); 8.00 (1H, d, *J* = 7.6 Hz, arom); 8.35 (1H, d, *J* = 7.8 Hz, arom).

Isopropyl 2-(difluoro-iodyl)benzoate 125



In Teflon round bottom flask, isopropyl-2-iodosyl-ester (0.3 mmol, 100 mg) was introduced. Hydrofluoric acid 48% (16 x 0.3 mmol) and CH_2Cl_2 (0.5 ml) were added. The reaction mixture was vigorously stirred for 2 hours. Using a Teflon separating funnel, the organic layer was separated from the aqueous and washed several times with small portions of water. Evaporation of the solvent under atmospheric pressure gave a white crystalline solid in 94% yield (0.31 mmol, 110 mg). Melting point = 168-171°C. Note: start to become brown at 124°C, turn in a colourless liquid at 168°C.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (6H, d, *J* = 6.0 Hz, *$(CH_3)_2$*CH); 5.44 (1H, sept, *J* = 6.0 Hz, $(CH_3)_2C$*H*); 7.81 (1H, t, *J* = 7.2 Hz, arom); 8.13 (1H, t, *J* = 7.2 Hz, arom); 8.23 (1H, d, *J* = 8.4 Hz, arom); 8.71 (1H, d, *J* = 8.1 Hz, arom);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.8, 73.7, 120.3, 123.5, 130.5, 133.5, 135.9, 152.7, 167.9;

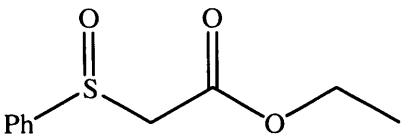
^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -28.697;

IR (KBr): ν = 1663, 1373, 1308, 1232, 1153, 1101, 906, 831, 755 cm^{-1};

MS for [M+Na] $C_{10}H_{11}F_2IO_3$+Na = 367;

Anal. Calcd. for $C_{10}H_{11}F_2IO_3$: C, 34.91; H, 3.22; F, 11.04; I, 36.88; O, 13.95. Anal. Found: C, 35.00; H, 3.20; F, 10.13; I, 36.65; O, 14.85.

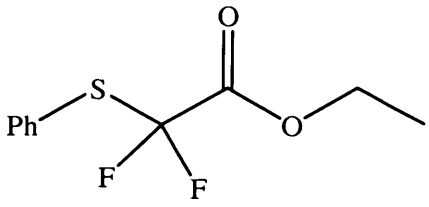
Benzenesulfinyl-ethyl acetate[47]



Obtained as a product (not isolated) in the reaction between the difluoride **125** and the sulphanyl ester **80b** according to GP9. The spectroscopic data are in agreement with the literature.[47]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (3H, t, *J* = 7.1 Hz, CH_2CH_3); 3.66 (2H, dd, *J* = 7.1 Hz, *J* = 1.4 Hz, $PhSCH_2$); 4.19 (2H, q, *J* = 7.1 Hz, CH_2CH_3); 7.42-7.55 (3H, m, arom); 7.58-7.64 (3H, m, arom).

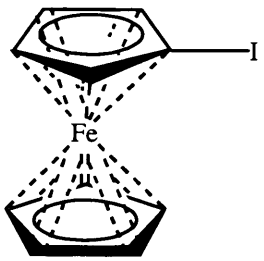
Difluoro-phenylsulphanyl ethyl acetate[38]



Obtained as a product (not isolated) in the reaction between the difluoride **125** and the sulphanyl ester **80b** according to GP9.

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -108.42 ppm.

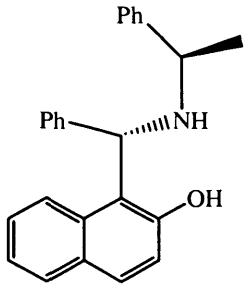
Iodo-ferrocene[48] 127



Synthetized with *t*-BuLi and iodine.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.04-4.12 (2H, m,); 4.13 (5H, s); 4.27-4.34 (2H, m).

1-((R)-phenyl-{[(1`R)-1`-phenyl-ethyl]amino}-methyl)- 2-naphthol[49] 130

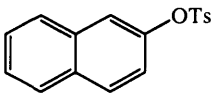


Under argon atmosphere, a mixture of 2-naphthol (3.5 mmol, 5 g), benzaldehyde (4.2 mmol, 4.2 ml) and R-(+)-1 phenylethylamine (3.6 mmol, 4.4 g) was stirred at 60°C for 8 hours. The reaction mixture was triturated at room temperature with EtOH. The crystals obtained were further washed with EtOH to give the pure product in 81% yield (2.8 mmol, 10 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (3H, d, *J* = 6.9 Hz, *CH*$_3$CH); 2.35 (1H, s broad, N*H*); 3.92 (1H, q, *J* = 6.9 Hz, CH$_3$C*H*); 5.47 (1H, s, PhC*H*NH); 7.15-7.83 (16H, m, arom); 13.70 (1H, s broad, O*H*);

$[\alpha]_D$ = -214.7 (c = 0.03 g/ml $CHCl_3$) ($[\alpha]_D$ = -220.7 from lit.[49]).

Toluene-4-sulphonic acid 2-naphthalenyl ester[50]

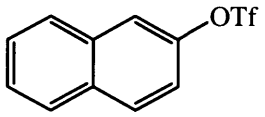


Synthesised according GP15. Obtained in 65% yield (0.65 mmol, 194 mg) as white solid after purification by flash chromatography in Petrol:EtOAc 7:3. Spectroscopic data are in agreement with the literature.[50]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38 (3H, s); 7.02 (1H, dd, *J* = 8.9 Hz, *J* = 2.5 Hz); 7.23 (2H, d, *J* = 8.1 Hz); 7.40-7.46 (3H, m); 7.60-7.80 (5H, m);

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.72, 119.95, 121.2, 126.4, 126.82, 127.7, 127.86, 128.55, 129.72, 129.75, 129.84, 132.31, 133.38, 145.36, 147.13.

Trifluoro-methanesulphonic acid 2-naphthalenyl ester[51]



Obtained in 70% yield as white solid after purification by flash chromatography in Petrol:EtOAc 8:2 (R_f: 0.8).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (1H, dd, J = 9.0 Hz, J = 2.5 Hz); 7.45-7.57 (2H, m); 7.69 (1H, d, J = 2.5 Hz); 7.80-7.92 (3H, m);

^{19}F NMR (282.8 MHz, $CDCl_3$): δ = -72.64 (3F, s).

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Appendix 1

Crystallographic data of substrate 120

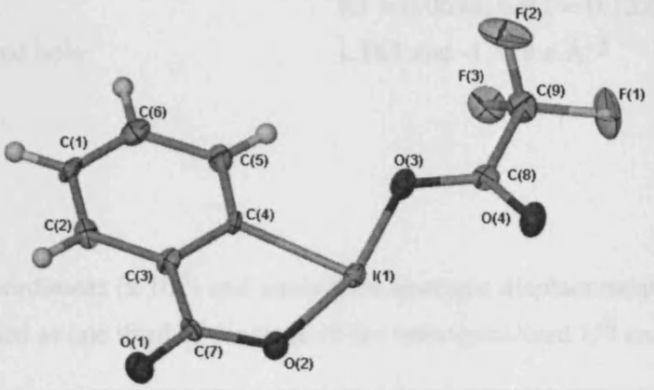

Table 1: Crystal data and structure refinement.

Empirical formula	C9 H4 F3 I O4	
Formula weight	360.02	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 5.0187(3) Å	a= 90°.
	b = 28.2432(17) Å	b= 107.842(2)°.
	c = 7.5547(4) Å	g = 90°.
Volume	1019.33(10) $Å^3$	
Z	4	
Density (calculated)	2.346 Mg/m^3	
Absorption coefficient	3.187 mm^{-1}	
F(000)	680	
Crystal size	0.38 x 0.25 x 0.08 mm^3	
Theta range for data collection	2.92 to 27.43°.	
Index ranges	-6<=h<=6, -28<=k<=36, -9<=l<=9	
Reflections collected	3846	
Independent reflections	2008 [R(int) = 0.0953]	

Completeness to theta = 27.43°	86.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7846 and 0.3773
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2008 / 0 / 154
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0473, wR2 = 0.1123
R indices (all data)	R1 = 0.0674, wR2 = 0.1222
Largest diff. peak and hole	1.163 and -1.318 e.Å^{-3}

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(6)	8023(15)	5913(2)	8341(9)	24(2)
C(7)	4659(14)	7306(2)	8062(8)	18(1)
C(8)	-2454(15)	5940(2)	3185(8)	21(2)
C(9)	-3033(16)	5418(3)	2583(10)	28(2)
F(1)	-5415(10)	5377(2)	1231(7)	51(1)
F(2)	-3205(13)	5167(2)	4039(7)	54(1)
F(3)	-1010(10)	5231(2)	2013(6)	37(1)
O(1)	5777(11)	7643(2)	9030(7)	29(1)
O(2)	2156(10)	7343(2)	6803(6)	23(1)
O(3)	120(10)	6010(2)	4189(6)	25(1)
O(4)	-4299(11)	6234(2)	2746(7)	31(1)
C(1)	9531(14)	6257(2)	9516(8)	22(2)
C(2)	8475(16)	6714(2)	9484(9)	21(2)
C(3)	5913(14)	6828(2)	8205(8)	17(1)
C(4)	4445(13)	6473(2)	7016(8)	15(1)
C(5)	5424(15)	6014(2)	7035(8)	21(2)
I(1)	651(1)	6731(1)	5259(1)	19(1)

Table 3: Bond lengths [Å] and angles [°].

C(6)-C(1)	1.376(9)
C(6)-C(5)	1.403(9)
C(6)-H(6)	0.9500
C(7)-O(1)	1.225(7)
C(7)-O(2)	1.327(8)
C(7)-C(3)	1.481(9)
C(8)-O(4)	1.212(8)
C(8)-O(3)	1.297(8)
C(8)-C(9)	1.543(9)
C(9)-F(1)	1.319(8)
C(9)-F(3)	1.328(8)
C(9)-F(2)	1.333(8)
O(2)-I(1)	2.092(4)
O(3)-I(1)	2.179(4)
C(1)-C(2)	1.393(9)
C(1)-H(1)	0.9500
C(2)-C(3)	1.389(10)
C(2)-H(2)	0.9500
C(3)-C(4)	1.396(9)
C(4)-C(5)	1.383(9)
C(4)-I(1)	2.091(6)
C(5)-H(5)	0.9500
C(1)-C(6)-C(5)	121.2(6)
C(1)-C(6)-H(6)	119.4
C(5)-C(6)-H(6)	119.4
O(1)-C(7)-O(2)	121.8(6)
O(1)-C(7)-C(3)	123.9(6)
O(2)-C(7)-C(3)	114.3(5)
O(4)-C(8)-O(3)	126.6(6)
O(4)-C(8)-C(9)	121.0(6)
O(3)-C(8)-C(9)	112.4(6)
F(1)-C(9)-F(3)	108.4(5)
F(1)-C(9)-F(2)	108.6(7)
F(3)-C(9)-F(2)	107.8(6)
F(1)-C(9)-C(8)	110.9(6)
F(3)-C(9)-C(8)	112.4(6)

F(2)-C(9)-C(8)	108.5(5)
C(7)-O(2)-I(1)	115.8(4)
C(8)-O(3)-I(1)	110.3(4)
C(6)-C(1)-C(2)	120.8(7)
C(6)-C(1)-H(1)	119.6
C(2)-C(1)-H(1)	119.6
C(3)-C(2)-C(1)	119.5(6)
C(3)-C(2)-H(2)	120.2
C(1)-C(2)-H(2)	120.2
C(2)-C(3)-C(4)	118.4(6)
C(2)-C(3)-C(7)	123.0(6)
C(4)-C(3)-C(7)	118.7(6)
C(5)-C(4)-C(3)	123.4(6)
C(5)-C(4)-I(1)	125.8(5)
C(3)-C(4)-I(1)	110.8(5)
C(4)-C(5)-C(6)	116.7(6)
C(4)-C(5)-H(5)	121.6
C(6)-C(5)-H(5)	121.6
C(4)-I(1)-O(2)	80.3(2)
C(4)-I(1)-O(3)	83.8(2)
O(2)-I(1)-O(3)	164.11(18)

Symmetry transformations used to generate equivalent atoms:

Table 4: Anisotropic displacement parameters ($Å^2 x\ 10^3$). The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(6)	30(4)	25(4)	18(4)	2(3)	8(3)	6(3)
C(7)	17(3)	17(4)	18(3)	-4(2)	4(3)	-6(3)
C(8)	29(4)	26(4)	10(3)	-1(3)	8(3)	-4(3)
C(9)	32(4)	29(4)	24(4)	-7(3)	7(3)	-3(4)
F(1)	32(3)	50(3)	58(3)	-31(2)	-6(2)	-2(2)
F(2)	90(4)	38(3)	46(3)	-3(2)	41(3)	-20(3)
F(3)	42(3)	32(3)	42(3)	-10(2)	19(2)	2(2)
O(1)	29(3)	22(3)	32(3)	-8(2)	4(2)	-3(2)
O(2)	25(3)	22(3)	20(3)	-4(2)	2(2)	0(2)
O(3)	24(3)	27(3)	20(2)	-3(2)	2(2)	5(2)
O(4)	29(3)	34(3)	24(3)	-6(2)	-2(2)	2(3)
C(1)	21(4)	30(4)	12(3)	9(2)	1(3)	3(3)
C(2)	19(3)	30(4)	16(3)	-6(3)	9(3)	-4(3)
C(3)	22(4)	24(4)	7(3)	-3(2)	5(3)	2(3)
C(4)	12(3)	19(4)	11(3)	1(2)	-2(2)	0(3)
C(5)	22(4)	25(4)	15(3)	-5(3)	4(3)	-4(3)
I(1)	19(1)	21(1)	14(1)	0(1)	2(1)	0(1)

Table 5: Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$).

	x	y	z	U(eq)
H(6)	8755	5601	8415	29
H(1)	11315	6182	10359	26
H(2)	9499	6946	10331	25
H(5)	4387	5780	6205	25