

# **Synthesis and Reactivity of Chiral Hypervalent Iodine Compounds**

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

**By**

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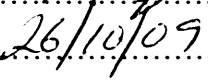
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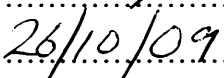
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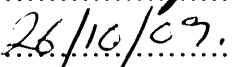
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## Abstract

Hypervalent iodine compounds are molecules of increasing interest to the synthetic chemist. Their low toxicity when compared to heavy metal reagents and their ease of use in the laboratory are helping to establish them into the armoury of the synthetic chemist. More recently, research into chiral hypervalent iodine compounds has been the main focus.

The work performed during this research tenure is based upon the development of new chiral hypervalent iodine reagents for use in stereoselective synthesis and this research can be summarised into three main sections:

- Synthesis of novel chiral iodine(III) compounds
- Reactivity of chiral iodine(III) compounds
- Novel oxidative procedure

The synthesis of new chiral iodine(III) compounds and their use in asymmetric oxidative functionalisations are described herein. The use of stoichiometric quantities of these iodine(III) reagents with 1 eq of *p*TsOH·H<sub>2</sub>O in the  $\alpha$ -oxytosylation of ketones and 2 eq of *p*TsOH·H<sub>2</sub>O in the dioxytosylation of alkenes, have given the corresponding products in good yields, 57-76% (3-12% *ee*) and 48-75% (9-16% *ee*) respectively.

Additionally, a new catalytic method is described in which the presence of a stoichiometric oxidant, 1 eq of *p*TsOH·H<sub>2</sub>O and only catalytic quantities of the chiral iodine(I) reagent is necessary to afford  $\alpha$ -oxytosylated ketones.

The final aspect of the research has dealt with the problems associated with oxidizing iodine(I) compounds to iodine(III) compounds. The development of a new method to oxidise iodine(I) compounds to [bis(trifluoroacetoxy)iodo]arenes through the use of urea-hydrogen peroxide adduct and trifluoroacetic anhydride is also described.

## Abbreviations

3c-4e	three centre four electron bond
$[\alpha]_D$	specific optical rotation
Ac	acetyl
APCI	atmospheric pressure chemical ionisation
Ar	aromatic
$\text{BF}_3 \cdot \text{OEt}_2$	boron trifluoride diethyl etherate
Bn	benzyl
BTI	[bis(trifluoroacetoxy)iodo]benzene
<sup>t</sup> Bu	tertiary-butyl
C/c	concentration
cat.	catalyst
column chromatography	flash column chromatography
d	doublet
DCM	dichloromethane
DIB	(diacetoxy)iodobenzene
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
Et	ethyl
EI	electronic ionisation
ES	electrospray
ether	diethyl ether
<i>ee</i>	enantiomeric excess
equiv. (eq.)	equivalent(s)
GC	gas chromatography
GP $n$	general procedure number
h	hour(s)
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HTIB	[hydroxy(tosyloxy)iodo]benzene (Koser reagent)

## Abbreviations

Hz	hertz
IBA	1-hydroxy-1,2-benziodoxole-3(1H)-one
IBX	<i>o</i> -iodoxybenzoic acid
(-)-Ipc <sub>2</sub> BCl	(-)- $\beta$ -chlorodiisopinocampheyl borane
IUPAC	international union of pure and applied chemistry
<i>i</i>	<i>iso</i>
IR	infra red
<i>J</i>	coupling constant
Lit.	literature
M	molar
<i>m</i> CPBA	<i>meta</i> chloroperbenzoic acid
<i>m</i>	mass
m	multiplet
Me	methyl
min.	minute(s)
MITB	[methoxy(tosyloxy)iodo]benzene
mmol	millimole(s)
MnTIB	[menthyloxy(tosyloxy)iodo]benzene
NMR	nuclear magnetic resonance
mol	mole(s)
mp	melting point
MHz	megahertz
MS	mass spectrometry
<i>n</i>	<i>normal</i>
n.d.	not determined
OAc	acetoxy
OCOCF <sub>3</sub>	trifluoroacetoxy
OH	hydroxy
OTs	oxytosylate
<i>p</i>	<i>para</i>
<i>p</i> TsOH·H <sub>2</sub> O	<i>para</i> toluenesulphonic acid monohydrate
p	pentet
PCC	pyridinium chlorochromate

## *Abbreviations*

Ph	phenyl
q	quartet
r.t.	room temperature
s	singlet
sept.	septet
<i>t</i>	tertiary
t	triplet
<i>tert</i>	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UHP	urea-hydrogen peroxide adduct
vol.	volume(s)
<i>z</i>	charge
$\sigma$	sigma
*	chiral



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## Chapter 1

# 1 Introduction

## 1.1 Hypervalency

Musher introduced the word ‘hypervalent’, and applied it to polyvalent molecules in 1969.<sup>1</sup> According to Musher, hypervalent compounds are ions or molecules of the elements of groups 15-18, bearing more than eight electrons in their valence shell.

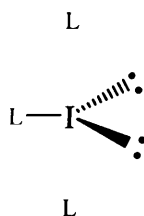
An atom has two ways of keeping electrons beyond the octet in its valence shell:

1. By hybridisation of higher energy d-orbitals, forming  $dsp^3$  or  $d^2sp^3$  hybrid-orbitals.
2. By forming highly ionic orbitals.

In 1951, Pimentel and Rundel published the idea of a three-centre, four-electron bond (3c–4e) using molecular orbital theory.<sup>2</sup> A more recent investigation by Schleyer on hypervalent bonding led to the rejection of the hybridisation concept.<sup>3</sup> Contribution of d-orbitals to hypervalent bonds seems not to be fundamental. The energy gap between sp- and d-orbitals in main group elements is too large to allow hybridisation. However, d-orbitals play an

important role in *ab initio* calculations. In these calculations, the stability of SF<sub>2</sub>, SF<sub>4</sub> and SF<sub>6</sub> increases in proportion with the d-orbitals. The central atom accepts electrons from ligands. This observation is explained with the back bonding model. Reed and Schleyer showed that, with an increasing d-orbital proportion, the  $\sigma^*$ -orbital of the central atom bond becomes more polarised and therefore the  $\pi$ -bonding between the two atoms is strengthened by a negative hyperconjugation.

The concept of a 3c–4e bond has been accepted to explain hypervalent bonding. One pair of bonding electrons from the central atom in hypervalent compounds is delocalised to the two substituents.



**Figure 1.1:** A 3c–4e hypervalent bond.

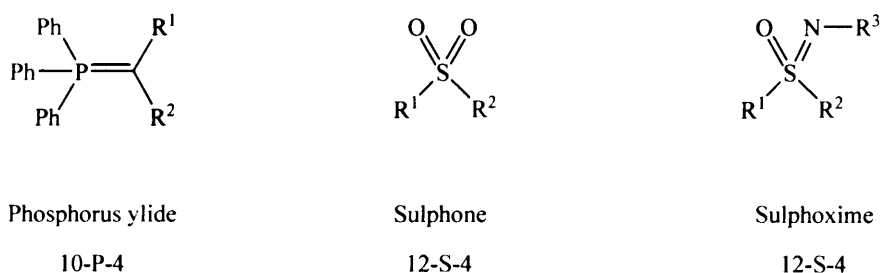
The 3c–4e bond leads to a charge distribution of almost  $-0.5$  charge on the ligands and about  $+1.0$  charge on the central atom. These linear bonds are electron-rich and the non-bonding molecular orbital becomes the highest occupied molecular orbital (HOMO). Therefore, in a 3c–4e bond, electrons are distributed to the ligands. The actual number of electron pairs in the valence shell of the central atom is less than four and the octet rule is not affected. Although there have been, and still are, discussions about whether one can use the expression “hypervalent” for these compounds, it is already accepted in chemical literature.

The general definition of hypervalent compounds is given by Martin and Arduengo:<sup>4</sup>

*Hypervalent compounds are main group element compounds that contain a number ( $N$ ;  $N > 8$ ) of formally assignable electrons in the valence shell, directly associated with the central atom ( $X$ ) in directly bonding a number ( $N$ )*

of ligands (*L*). The designation *N-X-L* is conveniently used to describe hypervalent compounds (Martin-Arduengo nomenclature).

Hypervalency is not very common in organic chemistry, but there are a large number of hypervalent compounds that find application in organic synthesis. Sulphuric acid and phosphates belong to this class of compound as well as phosphorus ylides, sulphones and sulfoximines, as shown in Figure 1.2.



**Figure 1.2:** Hypervalent compounds using the Martin-Arduengo nomenclature.

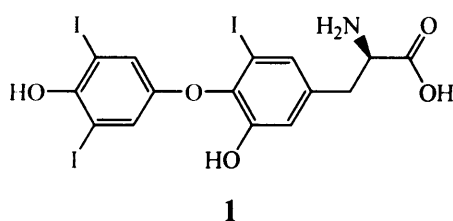
## 1.2 A Brief History of Iodine

In 1811 a French saltpetre manufacturer, Bernard Courtois, became the first person to isolate the element iodine. He was able to do so by treating the ash of seaweed (*Fucus*, *Laminaria* and other brown seaweed) with an excess of sulphuric acid, and collecting the violet crystals of the condensed iodine vapour. Courtois, unable to continue his research on the substance, passed his knowledge on to two Dijon chemists, Charles-Bernard Desormes and Nicolas Clement. Having acquired his permission, they announced his work to the Institut de Chemie de France in 1813, for which he was acknowledged with the discovery of iodine. However, it was another Dijon chemist Louis-Joseph Gay-Lussac, who gave iodine its name, referring to it as iode, from the Greek ιοειδής [ioeidès], meaning ‘violet coloured’.<sup>5</sup> The suffix -ine added in analogy with chlorine, the apparently similar element.



It is a group 17, fifth row element, with the electron configuration  $[\text{Kr}]d^{10}s^2p^5$ , having seven electrons in its valence shell. Therefore, the preferred oxidation state of iodine is  $-1$ .

Organoiodine compounds have long been known to play an important biological role in the function of many organisms. Thyroxine **1** (Figure 1.3) is a metabolism-controlling hormone that is produced naturally by the thyroid. Iodine-containing compounds have been used since 1819 as a remedy for thyroid disorders. Another well-known iodine compound is ‘Tincture of iodine’, which is widely used as an antiseptic.<sup>6</sup>



**Figure 1.3:** Thyroxine.

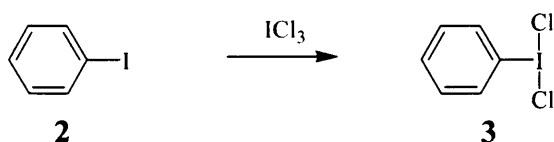
Although the first iodine-containing mineral ( $\text{AgI}$ ) was discovered in Mexico in 1825, the most industrially significant discovery was that of  $\text{IO}_3^-$  in Chilean saltpetre in 1840.<sup>7</sup>

Use of organoiodine compounds in synthesis began in the middle of the 19<sup>th</sup> century, most notably in reactions such as the Hoffmann alkylation of amines, Williamson’s ether synthesis and in Wurtz coupling reactions. Currently, one of the most important and common uses of organoiodine compounds involves various metal-mediated cross-coupling reactions where they serve as electrophilic partners in Heck, Negishi, Suzuki, Sonogashira, Stille, and similar cross-coupling reactions. These metal-catalysed cross-coupling reactions are extensively employed in preparative organic chemistry, the synthesis of complex natural products, and the manufacture of drugs, as well as in supramolecular and materials chemistry.

Iodine forms relatively weak bonds with first row elements, for example the bond dissociation energy of an iodine-carbon bond is typically about 55 kJ/mol. Because it is the largest, the most polarisable, and the least electronegative of the common halogens, it can readily bear a positive charge. Also, a very prominent feature resulting from these properties is its ability to form polycoordinated compounds with two to eight relatively weak bonds to mostly electronegative groups or elements such as oxygen, nitrogen, sulphur or a halide. In these compounds iodine can be in the following oxidation states: I, III, V, VII along with  $-I$  in iodate anions of the general formula  $IX_2^-$ .<sup>8</sup>

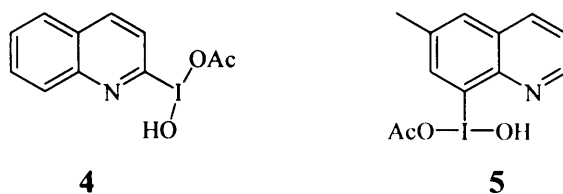
### 1.3 History of Hypervalent Iodine

A German chemist, Willergodt, was the first to discover iodine in its hypervalent form. He found that iodine had the ability to form organic compounds having a valency of 3 or 5, towards the end of the 19<sup>th</sup> century. Willergodt synthesised the first member of this class of compounds (dichloriodo)benzene **3**, by reacting iodobenzene **2** with  $ICl_3$ , in a cooled solution of chloroform in 1886 (Scheme 1.1).<sup>9</sup>



**Scheme 1.1:** Willergodt's synthesis of (dichloriodo)benzene **3**.

Subsequently, Willergodt discovered that by passing chlorine gas through a solution of iodobenzene in chloroform, he could obtain this iodine compound **3** in higher yields. This was rapidly followed by the synthesis of (diacetoxyiodo)benzene<sup>10</sup> **6** ( $PhI(OAc)_2$ ) and diphenyliodonium hydrogen sulphate<sup>11</sup> ( $Ph_2I^+HSO_4^-$ ), the first iodonium salt along with derivatives of iodoquinolines (Figure 1.4) containing both acetoxy and hydroxy moieties (**4**, **5**).

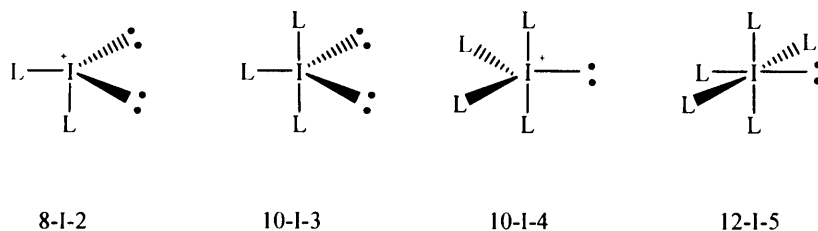


**Figure 1.4:** Willergodt's isoquinoline derivatives.

Since then, the interest in hypervalent iodine compounds in organic chemistry has risen and declined over the decades. The early 1970's saw a renaissance of hypervalent iodine compounds amongst synthetic chemists. This rise is attributed to the chemical properties and reactivity of iodine(III) compounds, being similar to those of heavy metal containing compounds such as Hg(II), Ti(II) and Pb(IV), but without the toxicity and environmental concerns associated with them.<sup>12</sup>

## 1.4 Structure, Bonding and Nomenclature

The various structural classes of hypervalent compounds known differ in three ways: The number of electrons (N) surrounding the central atom (X) and the number of ligands (L) that are bound to it. As described by the Martin-Arduengo designation,<sup>4</sup> there are four main structural types of hypervalent iodine compounds that play an important role in organic chemistry (Figure 1.5):

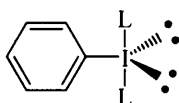


**Figure 1.5:** The four main structural types of hypervalent iodine compounds.

Following IUPAC rules, any compound with a non-standard bonding number, are denoted with a lambda notation. Therefore  $\text{H}_3\text{I}$  is referred to as a  $\lambda^3$ -iodane and  $\text{H}_5\text{I}$  a  $\lambda^5$ -iodane.

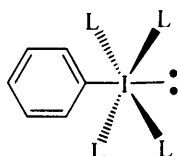
Aryl- $\lambda^3$ -iodanes ( $\text{ArIL}_2$ ) have a 10 electron, pseudotrigonal bipyramidal geometry with an aryl group and two lone pairs of electrons occupying equatorial positions with two heteroatom ligands (L) in apical positions. Bonding in  $\text{ArIL}_2$  uses an essentially pure 5p orbital in the linear L-I-L bond. This is a hypervalent three-centre four-electron bond (3c-4e) with two electrons from the doubly occupied 5p orbital on iodine and one electron from each of the ligands L. The aryl group is bound by a standard two-electron covalent bond with  $5sp^2$  hybridisation to form a  $\text{C}_{\text{Ar}}\text{-I}$   $\sigma$ -bond (Figure 1.6).<sup>13,14</sup>

The T-shaped structure, which stems from the stereoelectronic requirements of a 3-centre 4-electron system, is a typical feature of hypervalent iodine compounds.



**Figure 1.6:** An aryl-  $\lambda^3$ -iodane.

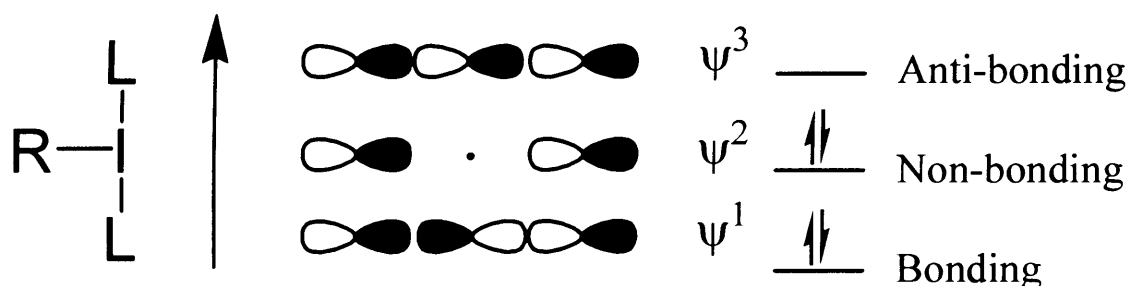
Aryl- $\lambda^5$ -iodanes ( $\text{ArIL}_4$ ) have a square pyramidal structure with an aryl group in an apical position and four heteroatom ligands in basal positions (Figure 1.7). Two orthogonal hypervalent 3c-4e bonds accommodate all of the heteroatom ligands and the apical aryl group has the character of a normal covalent bond using a hybridised 5sp orbital.<sup>15</sup>



**Figure 1.7:** An aryl-  $\lambda^5$ -iodane.

### 1.4.1 Orbitals

The two lower energy molecular orbitals, bonding and non-bonding, of the three required for hypervalent 3c–4e bond are filled (Figure 1.8). Partial positive charge develops on the central iodine atom, while partial negative charge develops on the axial heteroatom ligands, due to the fact that the filled non-bonding molecular orbital has a node at the central iodine. The presence of the node implies a separation of charges with a consequent positive polarisation of the iodine atom.



**Figure 1.8:** A 3c–4e orbital diagram.

The partial positive charge on the iodine of the highly polarised 3c–4e bond makes the aryl- $\lambda^3$ -iodane an electrophilic agent. The intrinsic nature of a 3c–4e bond explains the preferred orientation of more electronegative ligands in the apical positions. The presence of more electropositive central atoms is energetically favourable for hypervalent species, thus in general;  $\lambda^3$ -iodanes are more stable than analogous  $\lambda^3$ -bromanes and  $\lambda^3$ -chloranes.

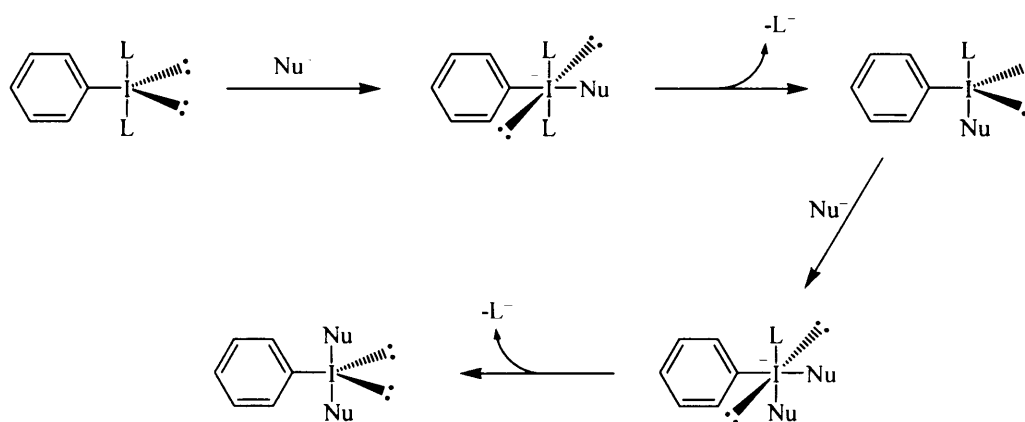
Aryl- $\lambda^5$ -iodanes  $\text{ArIL}_4$  have a 12-electron square pyramidal geometry with an aryl group in an apical position and four heteroatom ligands in basal positions. This species has two orthogonal hypervalent 3c–4e bonds, which accommodate all of the heteroatom ligands with the apical aryl group having the character of a standard covalent bond using a hybridised 5sp orbital.<sup>15</sup>

### 1.4.2 General Mechanistic Pathways

Once formed, hypervalent iodine compounds e.g.  $\lambda^3$ -iodanes and  $\lambda^5$ -iodanes can readily exchange their ligands with nucleophiles, in one of three ways;

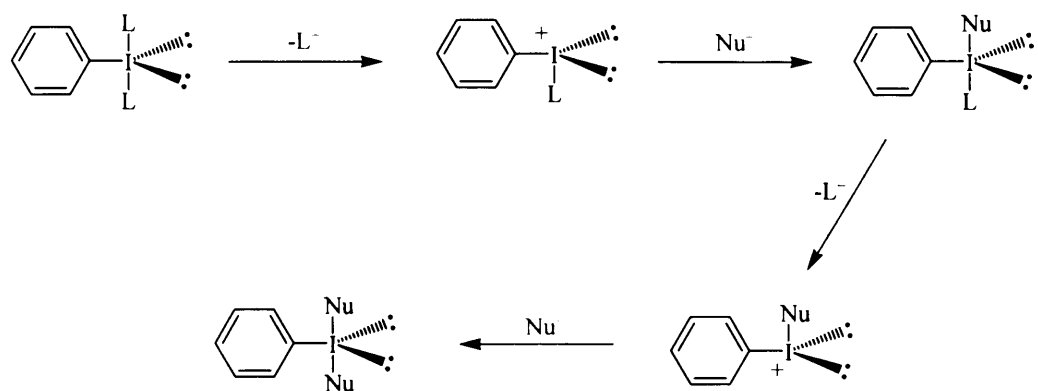
- Ligand exchange
- Reductive elimination
- Reductive elimination with subsequent substitution

When only nucleophiles are involved, reactions follow an associative pathway (Scheme 1.2), in which an iodate(III) or (V) species is formed. The “mixed” tetracoordinated iodine intermediate is initially formed and is sometimes isolable but usually this procedure takes place with both ligands so that eventually the new species has two new ligands.<sup>16</sup>



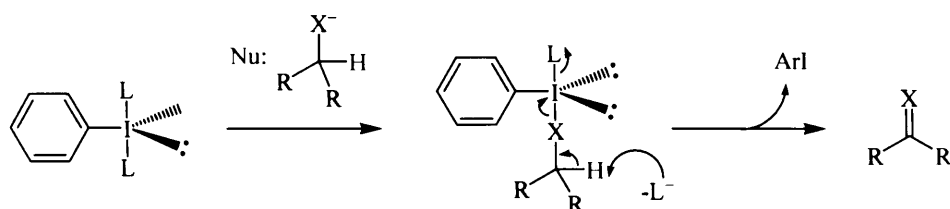
**Scheme 1.2:** Associative pathway in the ligand exchange.

The other pathway is dissociative and usually requires a good electrophile to help the removal of one ligand with formation of a high energy cationic iodonium species  $\text{PhI}^+\text{L}$ , which can react with the nucleophile to produce  $\text{ArILNu}$  (Scheme 1.3). Additional steps of elimination and addition afford  $\text{ArINu}_2$  or  $\text{ArINuNu}$ .<sup>16</sup>



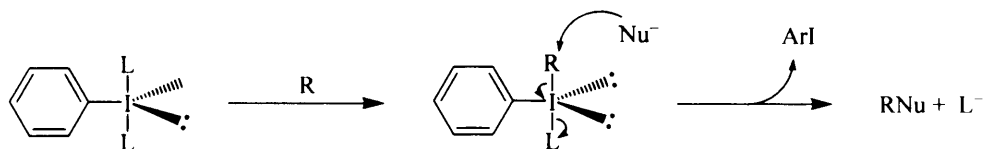
**Scheme 1.3:** Dissociative pathway in the ligand exchange.

The mechanism shown in Scheme 1.4 involves a reductive  $\beta$ -elimination with formation of the oxidised product. Here, the hypervalent aryl iodide is transformed into the reduced iodoarene. It has been shown<sup>17</sup> that the  $\beta$ -elimination occurs with *syn* stereochemistry. The combination of ligand exchange and  $\beta$ -elimination provides an excellent method widely used for oxidation of sulphides, alcohols and amines into the corresponding sulphoxides, carbonyl compounds and imines.



**Scheme 1.4:** Reductive  $\beta$ -elimination (shown in chapter 1.5.6).

A final mechanistic pathway follows a reductive elimination with subsequent substitution (Scheme 1.5). The first step of ligand exchange is followed by nucleophilic attack on the carbon atom bonded to the iodine, with subsequent production of substituted products. When this mechanism is in operation, the addition of several functionalities into a substrate is possible.



**Scheme 1.5:** General mechanism for the reductive elimination with substitution.

The displacement of heteroatom ligands in iodine(III) or iodine(V) species with external nucleophiles is a facile, low energy process. The high leaving group ability of iodine(III) ligands is amongst the most important features of hypervalent iodine compounds. This makes it possible to generate highly reactive species such as carbenes, nitrenes, cations and arynes under mild conditions as well as the possibility to oxidise a wide range of functionalities. The leaving process is referred to as reductive elimination, in which the iodine(III) species eliminates with the energetically preferable reduction to monovalent iodide.

## 1.5 Common Representatives of Hypervalent Iodine Compounds in Organic Chemistry

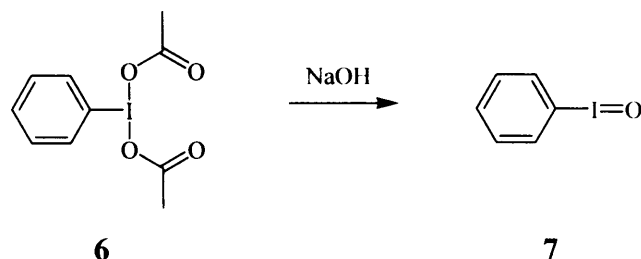
The general approach for preparation of the most common hypervalent iodine compounds is the initial oxidation of iodine(I) to iodine(III) or (V). This requires the correct choice of strong electrophilic reagents as well as conditions which will lead to the formation of either one, (for iodine(III)), or two, for (iodine(V)), hypervalent bonds.

### 1.5.1 Iodosobenzene

Of all the polycordinated iodine compounds known, one of the most important and thoroughly investigated I(III) reagents (ArIL<sub>2</sub>) is iodosobenzene **7** (PhIO). Although iodosobenzene is polymeric  $\{-(\text{Ph})\text{I}-\text{O}-\}_n$ , it is frequently written as monomeric PhIO. It is a yellow amorphous powder, which cannot be recrystallised due to its polymeric nature. It undergoes disproportionation to



iodobenzene **2** and explosive iodylbenzene  $\text{PhIO}_2$  on storage at room temperature. Iodosobenzene **7** is best synthesised by hydrolysis of (diacetoxyiodo)benzene **6** in aqueous  $\text{NaOH}$  (Scheme 1.6).<sup>15</sup>

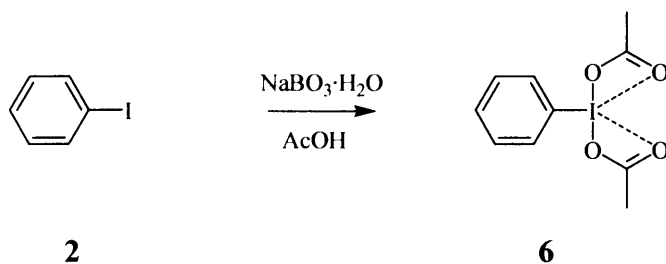


**Scheme 1.6:** Preparation of iodosobenzene **7**.

Iodosobenzene **7** can be applied to the synthesis of a wide range of other hypervalent iodine compounds. For example, iodonium salts, by reaction with the corresponding nucleophilic organic substrates. Practical usefulness in oxidation reactions is restricted due to its insolubility in most organic solvents. However, it can be activated by pulverisation of the polymer with an acid-treated silica gel by pestle and mortar or by ultrasonic irradiation.<sup>18</sup>

### 1.5.2 (Diacetoxyiodo)benzene (DIB)

Commercially available (diacetoxyiodo)benzene **6** (DIB) is one of the most common hypervalent iodine compounds in organic chemistry. It can easily be synthesised by several routes: Dissolving iodosobenzene **7** in acetic acid;<sup>10</sup> oxidation of iodobenzene **2** in peracetic acid at 40 °C;<sup>19</sup> treatment of iodobenzene **2** with sodium perborate in acetic acid (Scheme 1.7).<sup>20</sup>

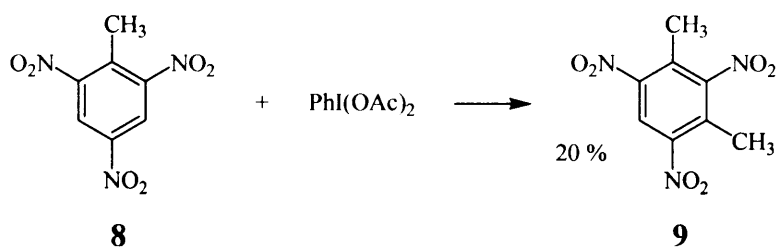


**Scheme 1.7:** Preparation of (diacetoxyiodo)benzene **6**.

Because of the acetoxy ligands ability to back-bond to the iodine atom, the molecule has a pentagonal plane shape. The free electron pairs of the carboxyl ligands overlap with the  $\sigma^*$  orbital of the iodine.

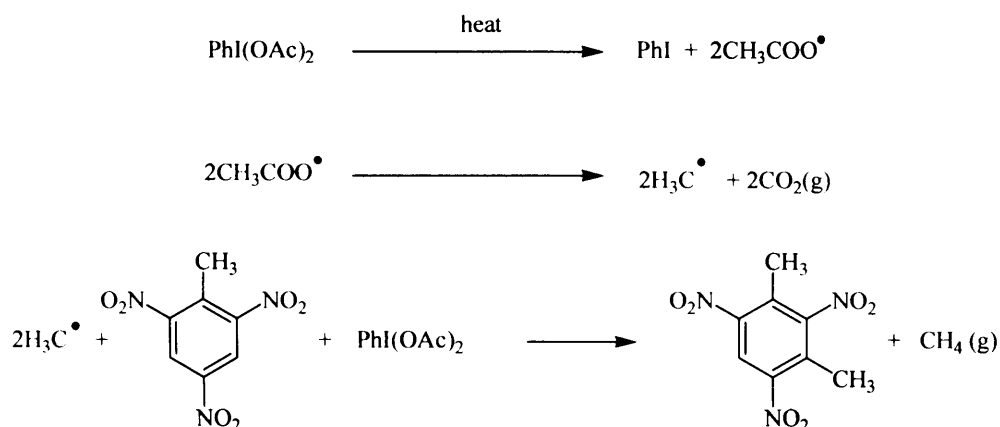
(Diacetoxyiodo)benzene **6** has found application in various transformations, including oxidations and substitutions with organic substrates, are the most widely observed reactions performed with hypervalent iodine diacetates.

Use of lead tetra-acetate allowed Fiseur and co-workers to convert trinitrotoluene **8** into trinitro-*m*-xylene **9** with yields of up to 32%. As early as 1945 Sandin and McCormack<sup>21</sup> rationalised that since tetra-lead esters were similar to some iodoso compounds, DIB may produce similar results (Scheme 1.8).



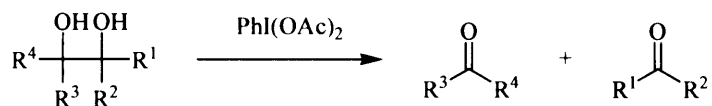
**Scheme 1.8:** PhI(OAc)<sub>2</sub> as a methylating agent.

When they applied (diacetoxyiodo)benzene to the above reaction they found that they obtained a 20% yield of trinitro-*m*-xylene **9**. To account for the formation of the product they proposed a free radical mechanism, shown in Scheme 1.9.



**Scheme 1.9:** Free radical mechanism for the formation of trinitro-*m*-xylene **9**.

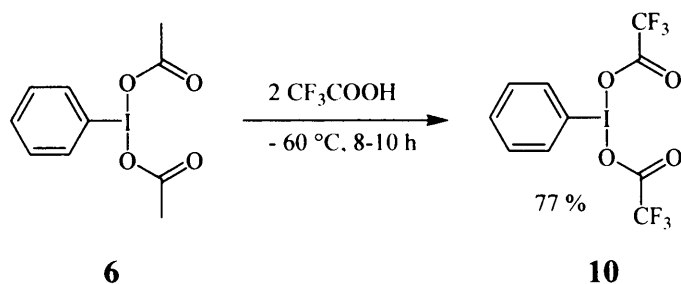
Acetic acid solutions of (diacetoxyiodo)benzene **6** may also be used to cleave 1,2-diols to form ketones or aldehydes (Scheme 1.10). Within this transformation, introduction of electron-withdrawing substituents on the iodoaryl ring increases the rate of reaction, while electron-donating substituents decrease it.<sup>22</sup>



**Scheme 1.10:** Glycol cleavage with (diacetoxyiodo)benzene **6**.

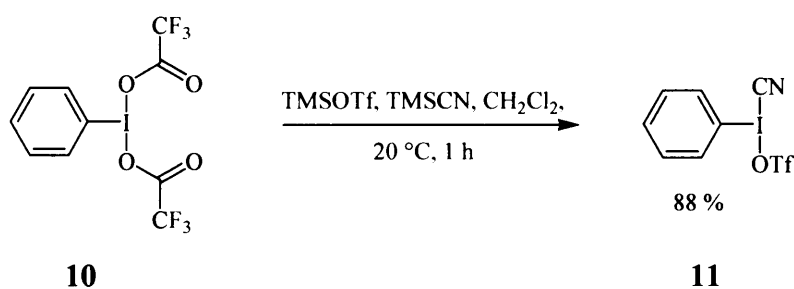
### 1.5.3 [Bis(trifluoroacetoxy)iodo]benzene (BTI)

Bis(trifluoroacetates), in the form of  $\text{ArI}(\text{CO}_2\text{CF}_3)_2$ , originally synthesised by Yagupolskii *et al.*<sup>23</sup> (Scheme 1.11), have been applied as potent and often chemoselective oxidants, which have a broad appeal throughout organic synthesis. They are easily prepared through a ligand exchange reaction between (diacetoxyiodo)benzene **6** and trifluoroacetic acid (scheme 1.11).



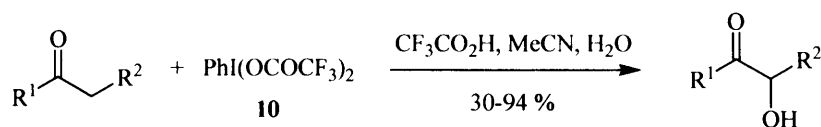
**Scheme 1.11:** Preparation of [bis(trifluoroacetoxy)iodo]benzene **10**.

[Bis(trifluoroacetoxy)iodo]benzene **10**, also known as BTI or PIFA, is an useful precursor in the generation of new iodine(III) compounds (Scheme 1.12). For example, the reaction of [bis(trifluoroacetoxy)iodo]benzene **10**, trimethylsilyl triflate and cyano trimethylsilane produces (cyano)aryliodonium triflate **11** in high yields (scheme 1.12).<sup>24</sup>



**Scheme 1.12:** [Bis(trifluoroacetoxy)iodo]benzene **10** as a precursor for new iodine(III) compounds.

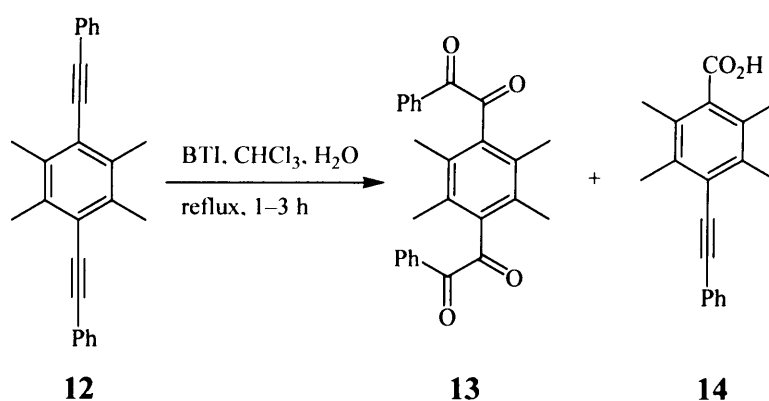
Under acidic conditions, [bis(trifluoroacetoxy)iodo]benzene **10** may be used to  $\alpha$ -hydroxylate enolisable ketones.



**Scheme 1.13:** Hydroxylation of ketones with [bis(trifluoroacetoxy)iodo]benzene **10**.

After initial attack of the enol tautomer of the ketone on the [bis(trifluoroacetoxy)iodo]benzene **10**, and nucleophilic substitution of the iodonium intermediate, results in the  $\alpha$ -hydroxy-substituted ketone observed.<sup>25</sup>

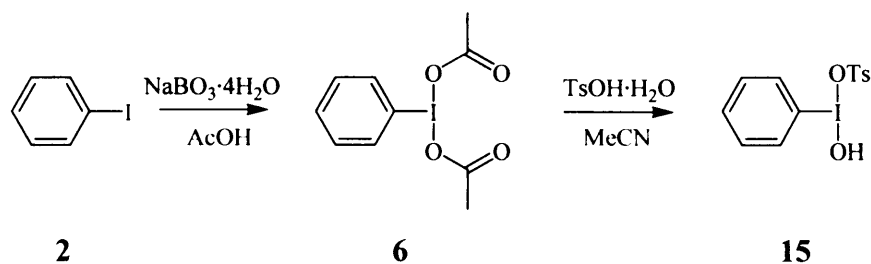
Alkynes can also be oxidised with [bis(trifluoroacetoxy)iodo]benzene (Scheme 1.14), giving the corresponding 1,2-diones. In many cases, the oxidative cleavage reaction breaks the triple bond on the alkyne, to form carboxylic acids. The following reaction (Scheme 1.14) shows the oxidation of bisphenylethynyl durane **12** with [bis(trifluoroacetoxy)iodo]benzene **10** to give two products: a carboxylic acid **14** and a 1,2-dione **13**.<sup>25</sup>



**Scheme 1.14:** Oxidative cleavage of bisphenylethynyl durane **12** with [bis(trifluoroacetoxy)iodo]benzene **10**.

#### 1.5.4 [Hydroxy(tosyloxy)iodo]benzene (HTIB)

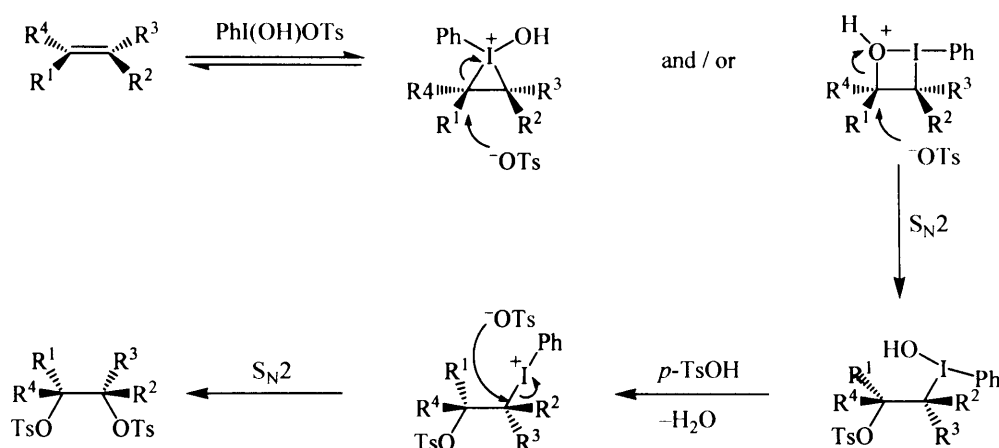
Another high profile aryl- $\lambda^3$ -iodane is [hydroxy(tosyloxy)iodo]benzene **15** (HTIB). It is more commonly known as Koser's reagent, although it was originally prepared by Nieland and Karele<sup>26</sup> in 1970 (Scheme 1.15).



**Scheme 1.15:** Preparation of Hydroxy(tosyloxy)iodobenzene **15**.

Koser's name is synonymous with [hydroxy(tosyloxy)iodo]benzene **15** as it was he who realized its synthetic potential and therefore investigated its reactivity.<sup>27</sup> Around the same time, Stang reported that the chemical properties and reactivity of iodine(III) compounds was similar to those of heavy-metal containing compounds (Hg(II), Ti(II) and Pb(IV)), but without the toxicity and environmental concerns associated with them.<sup>25</sup> In addition, it was also noted that the iodoarene by-product of these reactions is relatively environmentally friendly, as it may be recovered, oxidised and reused in later synthesis.

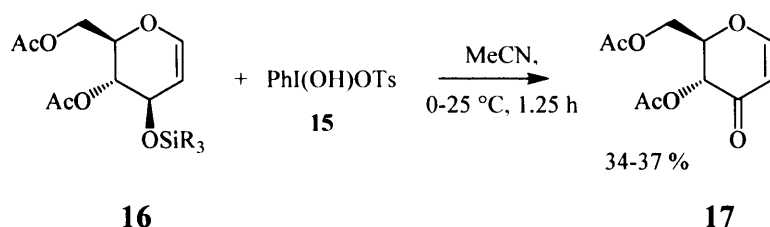
Analysis of the reaction pathways of various alkenes with [hydroxy(tosyloxy)iodo]benzene was carried out by Koser and Rebrovic,<sup>28</sup> in which they proposed (Scheme 1.16) a mechanism for the conversion of alkenes into vic-bis(tosyloxy)-alkanes with HITB.



**Scheme 1.16:** Reaction mechanism for bis oxytosylation of alkenes.

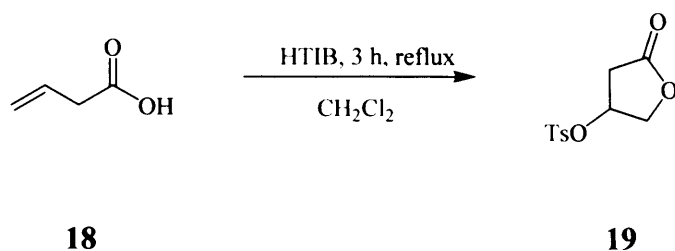
In order to account for the *cis*-stereochemistry of the addition of the tosyloxy ligands to the carbon-carbon double bond, Koser and Rebrovic concluded that some type of cyclic organoiodine intermediate formed, by electrophilic addition to the double bond of the alkene. Collapse of the intermediate, nucleophilic substitution with the tosylate followed by displacement of iodobenzene with a second tosylate ion, leads to the final product of *syn* dioxytosylation.

[Hydroxy(tosyloxy)iodo]benzene **15** is reactive toward many nucleophilic organic substrates. These include alkenes, alkynes, ketones, enol ethers and aromatic compounds.<sup>24</sup> It can form alkynyl- and alkenyl-iodonium tosylates as well as transform ketones and ethers into tosyloxy ethers. **15** also dioxytosylates alkenes and converts sulphides to sulphoxides. It is also widely used as an effective oxidising agent. [Hydroxy(tosyloxy)iodo]benzene **15** has been used by Kirschning<sup>29</sup> as a reagent for the chemoselective oxidation of protected glycals (Scheme 1.17). In this reaction other hypervalent iodine reagents such as (diacetoxyiodo)benzene **6** and [bis(trifluoroacetoxy)iodo]benzene **10** showed no oxidizing power.



**Scheme 1.17:** Oxidation of protected glycal **16** with HTIB **15**.

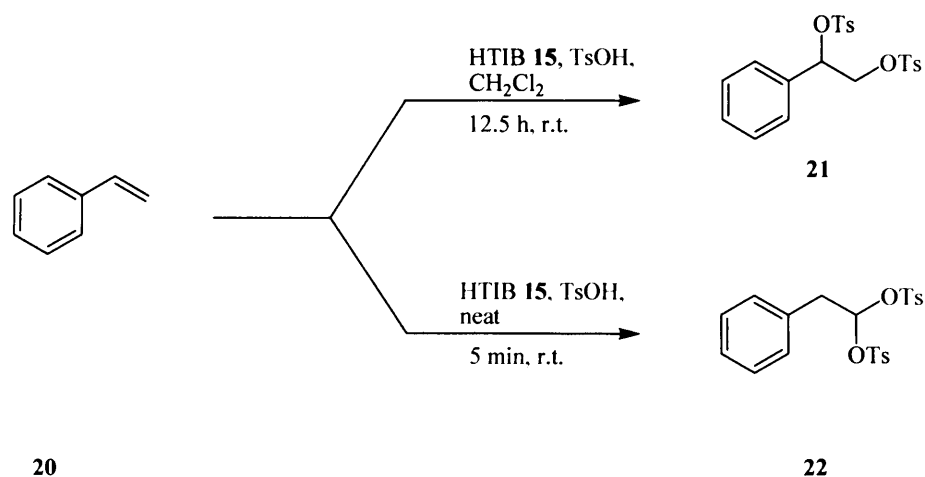
Additionally, [hydroxy(tosyloxy)iodo]benzene may be used to facilitate the tosyloxylactonisation reactions of various alkenoic acids<sup>30</sup>, as shown in Scheme 1.18.



**Scheme 1.18:** Tosyloxylactonisation of alkenoic acid **18**.

Koser and Rebrovic showed a remarkable solvent effect in the reactions of phenyl-substituted alkenes with [hydroxy(tosyloxy)iodo]benzene **15** (Scheme 1.19). When styrene **20** was reacted with [hydroxy(tosyloxy)iodo]benzene in the presence of solvent, 1-phenyl-1,2-bis(tosyloxy)ethane **22** was obtained in a 63% yield, but when the reagents were mixed in the absence of solvent, 1,1-bis(tosyloxy)-2-phenylethane **21** (63%) was formed.

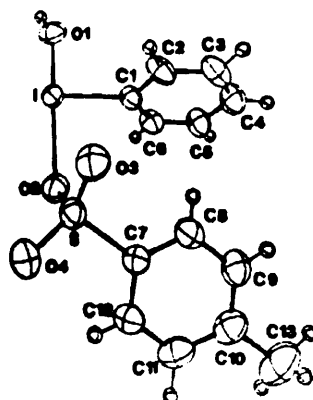
Unfortunately, there was no stereospecificity observed during the oxytosylation in the neat reaction. In order to prevent the migration of the phenyl moiety, this reaction is best done slowly in  $\text{CH}_2\text{Cl}_2$ .<sup>28</sup> A similar phenyl migration was noted by Moriarty.<sup>31</sup>



**Scheme 1.19:** Solvent effect on the reaction of styrene **20** with [hydroxy(tosyloxy)iodo]benzene **15**.



Like (diacetoxyiodo)benzene **6**, [hydroxy(tosyloxy)iodo]benzene **15** is an aryl- $\lambda^3$ -iodane with a T-shape structure. Its hydroxy and tosyloxy ligands are in the axial position of the trigonal bipyramid. The phenyl ligand builds up a trigonal plane with the two free electron pairs of the iodine atom.



**Figure 1.9:** The X-ray crystal structure of [hydroxy(tosyloxy)iodo]benzene.<sup>32</sup>

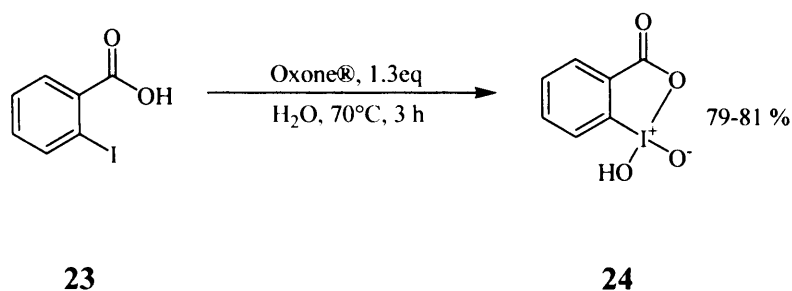
The I-O bond length between the central iodine atom and the coordinating tosyloxy oxygen atom (O2) is 2.47Å. This is much longer than the usual covalent bond length and the I-OTs bond is considered to be ionic.

### 1.5.5 *o*-Iodoxybenzoic acid (IBX)

From the range of I(V) reagents that have been synthesised, *o*-iodoxybenzoic acid or IBX **24**, has had use by the synthetic chemist for many years. Although, its synthetic usefulness has been limited due to its low solubility in most organic solvents along with practical problems associated with its synthesis.<sup>33</sup>

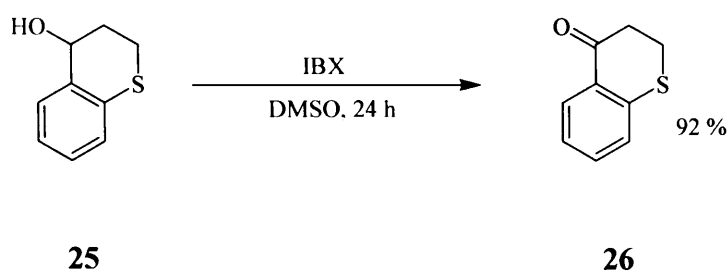
It was first obtained by reacting *o*-iodobenzoic acid **23** with nitric acid and then further oxidizing this compound with  $\text{KMnO}_4$ . In most instances, the synthesis of IBX was difficult for synthetic chemists. An alternative method for its preparation introduced by Meyer, used 2-iodobenzoic acid **23** as a starting

material. This transformation requires several steps of purification and is extremely low yielding. More recently using Oxone® (potassium monopersulphate) as the oxidant of 2-iodobenzoic acid **23**, has allowed for a more practical method for the preparation of IBX **24** (Scheme 1.20).<sup>34</sup>



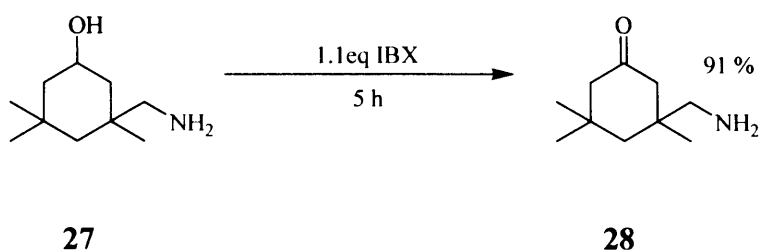
**Scheme 1.20:** Preparation of IBX **24** from 2-iodobenzoic acid **23** using Oxone®.

In contrast to other oxidizing agents, IBX is relatively inexpensive to prepare, easy to handle, moisture tolerant and isolated in high yield. Recently IBX has been used successfully in the chemoselective oxidation of alcohols. In the presence of sulphides, alcohols have been cleanly oxidised, with no sulfoxide or sulphone by-products being produced (Scheme 1.21).<sup>33</sup>



**Scheme 1.21:** Oxidation of alcohol **25** with IBX **24** in the presence of a sulphide.

Additionally, IBX **24** may be used for the oxidation of amino alcohols into amino ketones (Scheme 1.22) without the use of protecting groups or the anhydrous/low temperature conditions necessary for the more frequently used Swern oxidation.<sup>35</sup>

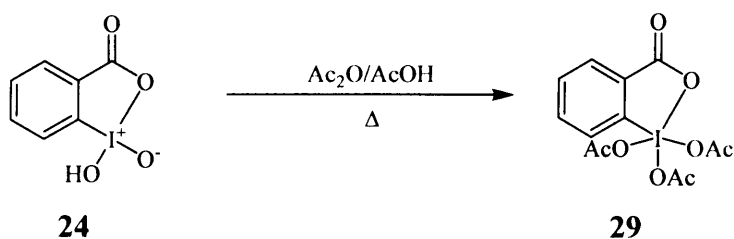


**Scheme 1.22:** Conversion of amino alcohol to amino ketone.

IBX **24** may also be used for the oxidation of benzylic carbons. It is not affected by the presence of halogens or *ortho*-substituents and over-oxidation to the corresponding carboxylic acid is not observed. Although IBX **24** can only be fully dissolved in the DMSO, it has been found that, despite its insolubility in most organic solvents, IBX **24** is able to oxidize alcohols without complete dissolution within the solvent.<sup>36</sup>

### 1.5.6 1,1,1-Tris-acetoxy-1,2-benziodoxolin-3(1*H*)-one (DMP)

The pentacoordinate iodine reagent 1,1,1-tris-acetoxy-1,2-benziodoxolin-3(1*H*)-one, better known as the Dess-Martin periodinane **29** (DMP) has been prepared (Scheme 1.23) by warming a mixture of IBX **24** in acetic anhydride/acetic acid.<sup>37</sup>

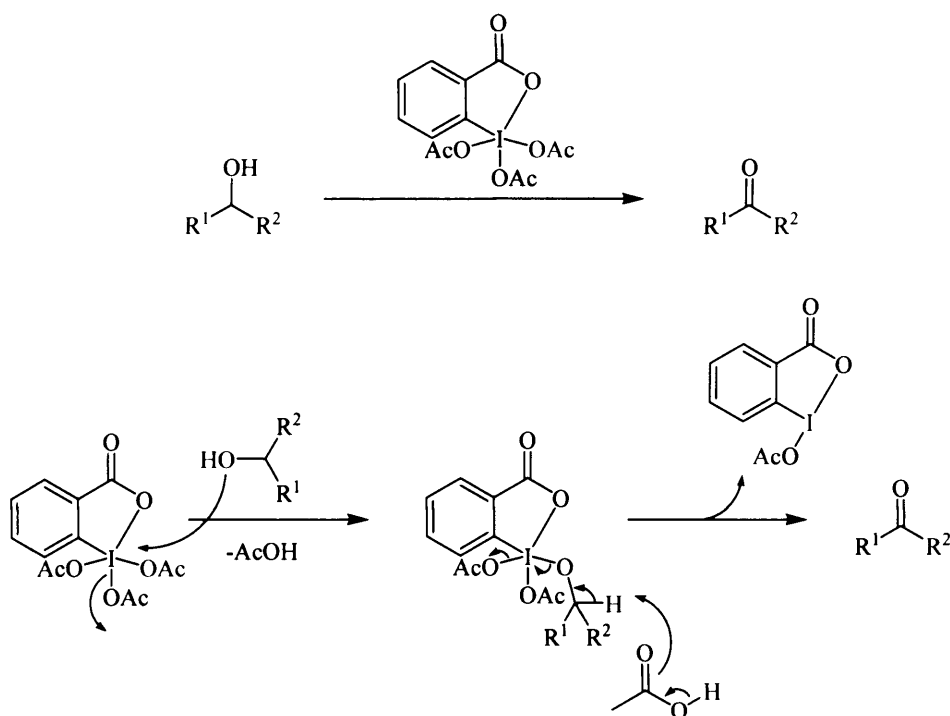


**Scheme 1.23:** Preparation of Dess-Martin periodinane **29**.

The Dess-Martin periodinane has been used effectively to convert primary alcohols to aldehydes (Scheme 1.25) and secondary alcohols to ketones (Scheme

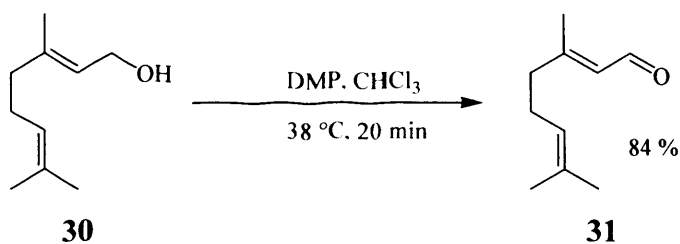
1.24) under mild conditions,<sup>38</sup> even in the presence of sensitive functional groups such as sulphides, enol ethers, furans and secondary amines.

Mechanistically, the reaction proceeds as shown in Scheme 1.24. A lone pair of electrons from the alcohol substrate promotes the first step of the ligand exchange. Subsequent reductive  $\beta$ -elimination results in the formation of the carbonyl product and the release of the reduced iodo reagent.



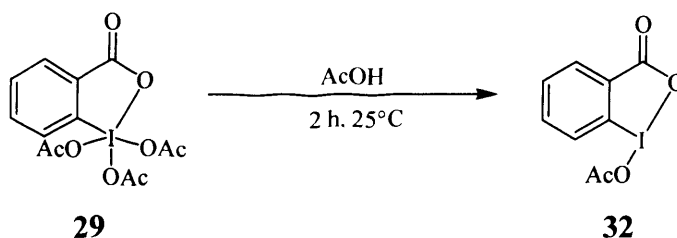
**Scheme 1.24:** Oxidation of a generic secondary alcohol performed by DMP **29**.

DMP **29** is favoured both to chromium(VI) reagents and dimethyl sulphoxide-derived reagents, which are some of the most common oxidizing agents used in organic synthesis. Reactions with DMP have shorter reaction times than most chromium(VI) reagents and usually do not require an excess of reagent to push a reaction to completion. Work-up of DMP **29** reactions is relatively easy compared to that of chromium(VI) derived reagents and it is neither toxic nor a known carcinogen like the chromium(VI) containing compounds. In contrast to dimethyl sulphoxide derived reagents, which have to be prepared at low temperatures *in-situ*, DMP **29** is storable and relatively easy to prepare.<sup>36</sup>



**Scheme 1.25:** Oxidation of a geraniol **30** with DMP **29**.

DMP **29** is an important precursor to many other hypervalent iodine reagents. Decomposition or ligand exchange with this reagent yields several useful compounds including benziiodoxole **32** (Scheme 1.26).



**Scheme 1.26:** Preparation of benziiodoxole **32** from DMP **29**.

The hypervalent iodine chemistry discussed within this section has only scratched the surface for uses of these safer, cleaner, heavy metal alternatives. The reactions have stimulated the application of hypervalent iodine reagents in synthesis. The discovery of new transformations with these compounds will certainly be the basis for future improved synthetic strategies and concepts. The subsequent chapters within this thesis will discuss the synthesis and application of a new range of chiral hypervalent iodine compounds.

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## Chapter 2

# 2 Chiral Hypervalent Iodine Compounds

## 2.1 Introduction

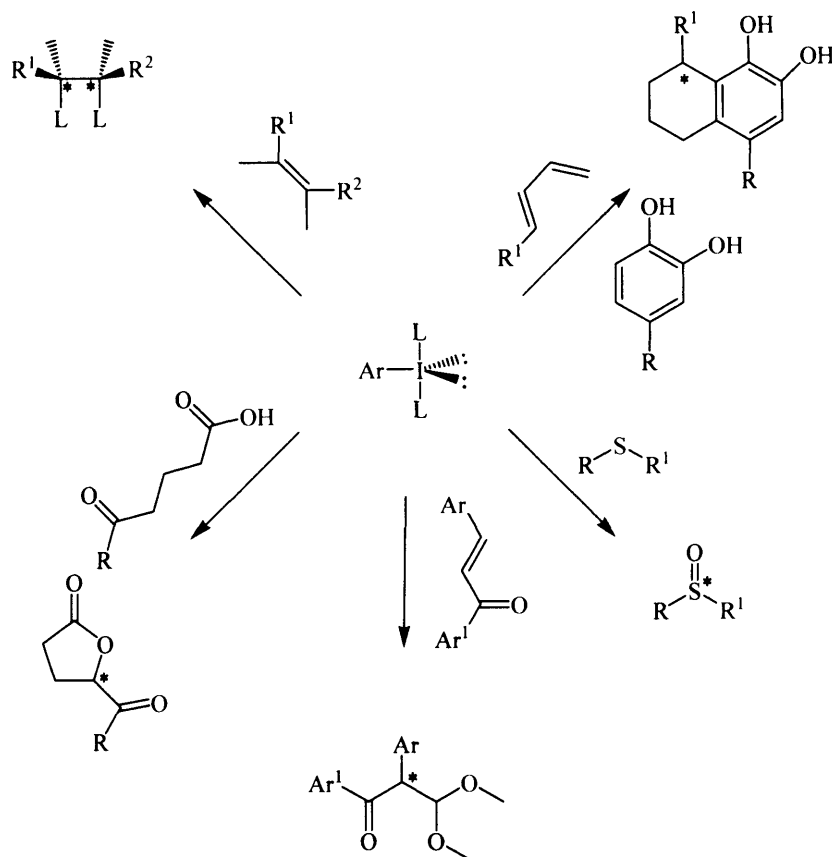
This chapter reviews the previous work that many groups around the world have made towards the synthesis of chiral hypervalent iodine reagents. This has been driven by the requirement for enantiopure products where the synthetic chemist is concerned.

As the interest in hypervalent iodine compounds grew, so did the number of reactions in which they were used. In many of these reactions new stereogenic centres were created (Scheme 2.1).

As racemic reagents were used in these reactions, the products formed were subsequently racemic. As asymmetric synthesis has gained more importance in organic chemistry, methods of synthesising stereogenic centres of known configuration became paramount. Hypervalent iodine compounds are of high synthetic potential by virtue of the fact that they are non-metallic oxidation and oxygenation reagents, thus circumventing the problem of toxicity associated with many of the transition metals commonly used for carrying out such reactions.



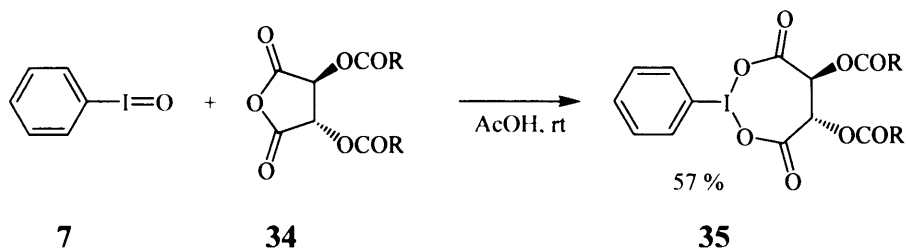
The possible directions, in which the hypervalent Chemist could research, were to integrate centres, axes or planes of chirality.



**Scheme 2.1:** Transformations using hypervalent iodine reagents leading to products containing new stereogenic centres.

## 2.2 Early Chiral Hypervalent Iodine Reagents

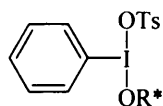
The first chiral hypervalent iodine compound synthesised was in 1986, when Inamoto and Koto reported compounds with  $\text{C}_2$  symmetry (Scheme 2.2).



**Scheme 2.2:** Synthesis of Inamoto and Koto's  $C_2$  symmetric iodine **35**.

These chiral hypervalent reagents were synthesised *in situ* from iodosylbenzene **7** by treatment with derivatives of L-tartaric anhydride **34**.<sup>1</sup> However, it was Koser who first isolated this type of hypervalent iodine compound in 1992.<sup>2</sup>

Following the work of Inamoto and Koto, Ochiai, Koser and Varvoglis reported two independent concepts for chiral hypervalent iodine compounds, derived from homochiral alkoxy ligands.

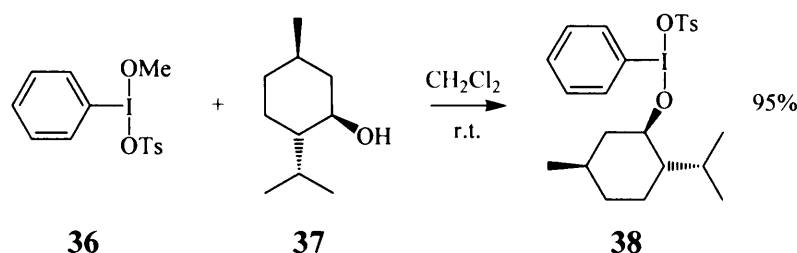


**Figure 2.1:** General structure of chiral hypervalent compounds prepared by Koser and Varvoglis.

To introduce chirality into compounds shown in Figure 2.1 above, Varvoglis<sup>3</sup> used the (+)-10-camphoryl group, whereas Koser<sup>4</sup> utilised the (+) and (-)-menthyloxy groups.

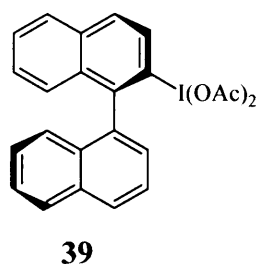
Koser's chiral iodine was prepared via a ligand exchange reaction between [methoxy(tosyloxy)iodo]benzene **36** (MITB) and (2*R*,5*S*)-(-)-menthol **37**. This gave [menthyloxy(tosyloxy)iodo]benzene or MnTIB **38** in good yield. The application of these reagents in stereoselective synthesis yielded mixed results. Many of them were unsuccessful in the oxidation of sulphides to sulfoxides producing racemic products. However, the iodoarene shown in Scheme 2.3

produced the highest enantiomeric excesses of sulfoxides, ranging from 4% to 57% *ee*.<sup>4</sup>



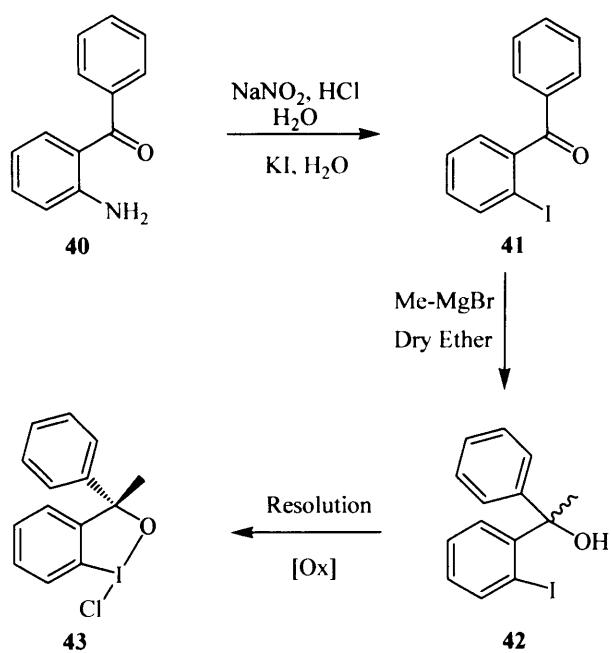
**Scheme 2.3:** Koser's preparation of [(-)-menthyloxy(tosyloxy)iodo]benzene (MnITB) **38**.

Around the same time (ca. 1990), Ochiai<sup>5</sup> reported (*S*)-2-(diacetoxyiodo)-1,1'-binaphthyl **39** (Figure 2.2) where the chirality is derived by the biaryl axis.



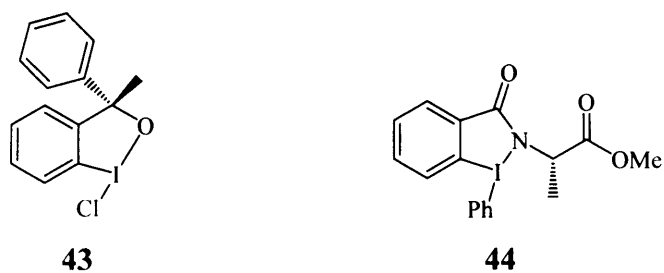
**Figure 2.2:** Ochiai's chiral (*S*)-2-(diacetoxyiodo)-1,1'-binaphthyl compound **39**.

Further work by Koser<sup>6</sup> and later by Zhdankin<sup>7</sup> created a new class of chiral hypervalent iodine compounds, which are structurally close to iodosobenzoic acid or IBA **23**, and are shown in Figure 2.3. They contain the iodine atom in a 5-membered ring. Koser utilised a tetra-substituted carbon in the benzylic position, *ortho* to an iodine, as seen in benziodoxole, to introduce the chirality (Scheme 2.4). Alternatively, Zhdankin introduces chirality through the addition of an amino acid as seen in benziodazoles (Figure 2.3).



**Scheme 2.4:** The synthesis of Koser's chiral benziodoxole **43**.

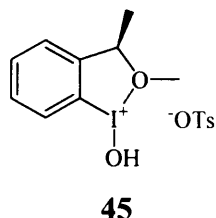
The preparation of Koser's chiral benziodoxole **43** begins with 2-aminobenzophenone **40**. The initial step is the displacement of the amino group by an iodine atom, followed by a Grignard reaction, optical resolution and finally oxidation, to afford the hypervalent product. To prepare the chiral benziodazole type iodo compounds, Zhdankin used peracetic acid to oxidise 2-iodobenzamides, which were derived from alanine or valine (Figure 2.3).



**Figure 2.3:** Koser **43** and Zhdankin **44** chiral iodanes.

## 2.3 Wirth Type Chiral Hypervalent Iodine Compounds

In 1997 Wirth presented another type of chiral iodoarene **45**, loosely modelled on the IBA type compounds of Koser. They based the structure on a pseudo 5-membered ring with the iodine atom in close proximity to the asymmetric centre. The chirality is induced through an asymmetric carbon in the benzylic position, which contains a protected alcohol. These ethers show a large degree of coordination to the hypervalent iodine atom. The hypervalent bond shows the characteristic T-shape observed with Koser's reagent, with an oxygen-iodine-oxygen bond angle of  $167.3^\circ$  (the Koser reagent O-I-O bond angle is  $178.8^\circ$ ).<sup>8</sup>



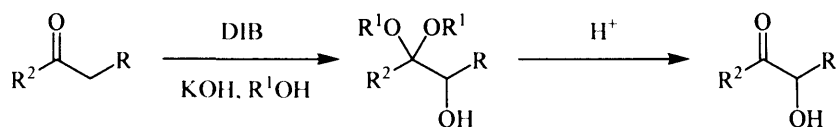
**Figure 2.4:** (*R*)-1-(1-Hydroxy-1-tosyloxy)-iodo-2-(1-methoxyethyl)-benzene **45**.

Interestingly, the oxygen of the methoxy group replaces the oxygen of the tosylate. They observed, through X-ray crystallographic data, a short distance from the oxygen atom of the methoxy-group to the iodine of about 2.47 Å and a longer (tosylate)-oxygen iodine distance of 2.91 Å. The bond length of the (hydroxy)-oxygen atom to iodine is 1.94 Å and of the iodine-carbon bond 2.08 Å and therefore showing strong similarity in both structures.<sup>8</sup>

### 2.3.1 Functionalisation in the $\alpha$ -Position

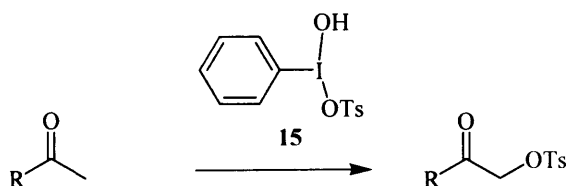
Carbonyl compounds can be functionalised at the  $\alpha$ -position under various conditions. Treatment of ketones with (diacetoxyiodo)benzene **6** under basic conditions provides an efficient route to  $\alpha$ -hydroxylated dialkylacetals.<sup>9,10</sup> This reaction has also been applied to functionalisation in natural product synthesis,<sup>11,12</sup>

because the  $\alpha$ -hydroxylated dialkylacetals can be easily hydrolysed under acidic conditions to  $\alpha$ -hydroxy ketones in good yield (Scheme 2.5).



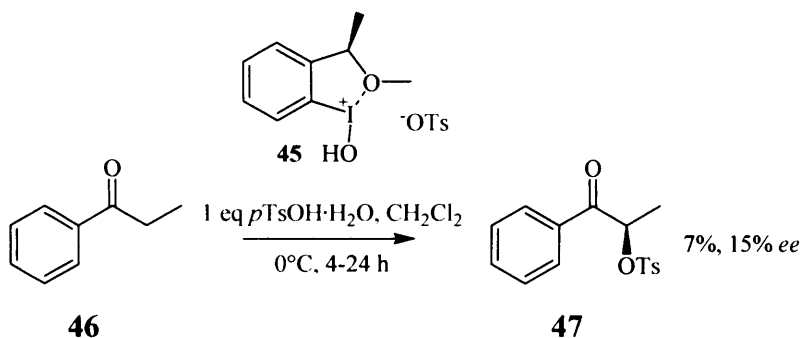
**Scheme 2.5:** Synthesis of  $\alpha$ -hydroxy ketones from ketones.

Using other hypervalent iodine compounds or different reagent combinations, various functional groups can be introduced into the  $\alpha$ -position of a ketone (Scheme 2.6). Oxytosylations of ketones in the  $\alpha$ -position can be performed with [hydroxy(tosyloxy)iodo]benzene **15** (Koser reagent).<sup>13</sup> This reaction can be described mechanistically as an electrophilic attack of the iodine at the double bond of the enol with subsequent  $S_N2$  substitution of the iodine by the tosylate. The major drawback is the low stereoselectivity observed in these reactions when using chiral hypervalent reagents.



**Scheme 2.6:**  $\alpha$ -Oxytosylations of ketones using the Koser reagent **15**.

The Wirth group investigated several chiral hypervalent iodine compounds in this reaction with modest results. The chiral iodane is dissolved in dichloromethane and treated with an excess of propiophenone. The enantiomeric excess of the  $\alpha$ -(tosyloxy)propiophenone product **47** was determined by HPLC after purification on silica gel (40–75% yield). The selectivity observed in the oxytosylated product using chiral derivatives of **45** was up to 40% *ee*.



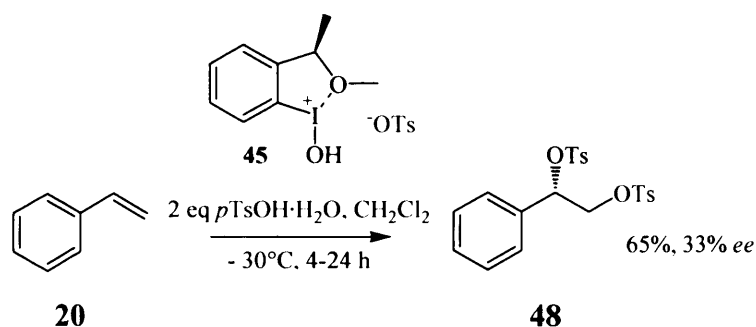
**Scheme 2.7:**  $\alpha$ -Oxytosylation of propiophenone **46** using a Wirth chiral hypervalent reagent **45**.

The products of this reaction are of high interest as they can be used in a variety of subsequent reactions.

### 2.3.2 Functionalisation of Alkenes

Hypervalent iodine compounds can also be used to functionalise alkenes.<sup>14</sup> Koser showed that during the reaction with an alkene, an iodonium intermediate is formed which then reacts twice with tosylates to yield the bis(tosyloxy)alkane. In reactions with non-symmetrically substituted alkenes, new stereogenic centres are formed.

The Wirth group investigated the functionalisation of alkenes using their range of chiral hypervalent compounds with successful results (Scheme 2.8). The chiral iodane and *p*-toluenesulphonic acid monohydrate were dissolved in dichloromethane (DCM) and styrene **20** was added. The solution was stirred at this temperature for 4–24 hours. After filtration through silica gel the solvent was removed and the residue purified by flash chromatography on silica gel to obtain the 1,2-bis(tosyloxy)phenylethane **48** in good yields, ranging from 30–70%. The enantioselectivity observed within these reactions was between 13 and 65% *ee*.<sup>15</sup>



**Scheme 2.8:** Dioxytosylation of styrene **20** using Wirth chiral reagent **45**.

## 2.4 Conclusion

As discussed earlier, chiral iodanes have the potential to be very useful reagents for the synthesis of new chiral centres, of known configuration. The aim of the chiral hypervalent iodine chemist is to develop reagents that will ensure exceptionally high enantiomeric excess in their products. This is the driving force of this project and the initial ideas and further research are based around the Wirth chiral iodanes. The natural progression was to investigate and improve upon the results obtained previously, via greater functionalisation of these iodoarenes to aid the transfer of chiral information from the reagent to the substrate. Chapter Three will outline the synthesis of these next generation chiral hypervalent compounds.



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## Chapter 3

# 3 Synthesis of Chiral Hypervalent Iodine Compounds

## 3.1 Introduction

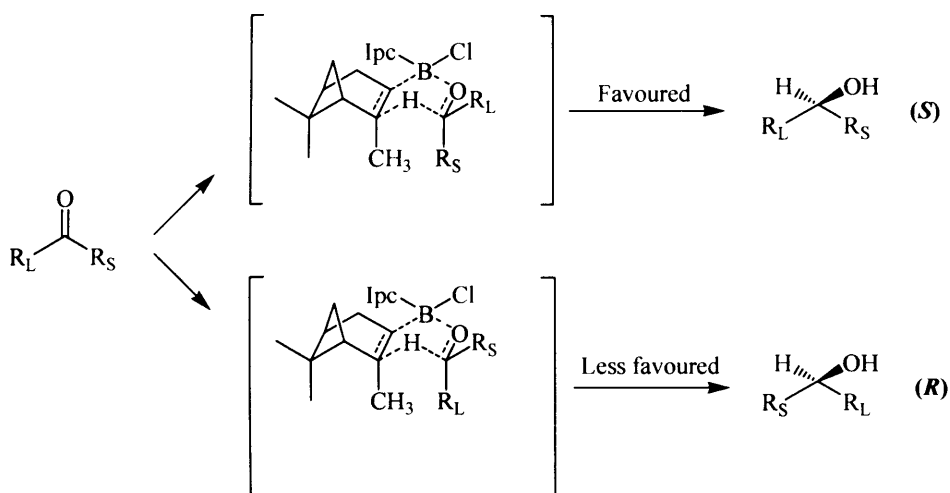
In this chapter, the synthesis of the next generation of chiral hypervalent iodine(III) reagents will be reported. As discussed in Chapter One, there are many known procedures for the synthesis of aryl- $\lambda^3$ -iodanes which were applied to the novel chiral iodine precursors described.

### 3.1.1 Determination of (*R*) and (*S*) Configuration

The (*R*) and (*S*) configuration of all the chiral compounds describe herein have not been determined unequivocally. The proposed configuration is based upon the asymmetric reduction of the corresponding ketone using (-)- $\beta$ -chlorodiisopinocampheylborane ((-)-Ipc<sub>2</sub>BCl). Brown *et al.* proposed a transition state model for this transformation (Scheme 3.0).<sup>1</sup> They proposed a transition state that is similar to the mechanism proposed by Midland for Alpine borane reductions.<sup>2</sup> It forms a six membered, cyclic, 'boat like' transition state, with the boron moiety and  $\beta$ -hydrogen cis, resulting in a syn-elimination. In the preferred transition state, only the smaller alkyl group (*R*<sub>S</sub>) has to face the *syn* axial methyl

interaction, whereas the bulky group ( $R_L$ ) assumes an equatorial orientation. This lends itself toward the predominant formation of the *S* isomer of the alcohol.

Acetophenone derivatives, where the halide is in the *ortho* position on the aromatic ring, give very high enantioselectivities (up to 99% *ee*) but the ketones described in this chapter give varying levels of enantiomeric excess. As the chiral chain length increases, the distance from the phenyl ring to the carbonyl increases. Subsequently, the discrimination between  $R_L$  and  $R_S$  decreases. This results in decreased selectivity in the transition state and decreased asymmetric induction.

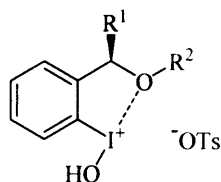


**Scheme 3.0:** The transition state model proposed by Brown *et al* for the asymmetric reduction of ketones.

In addition to this proposal of configuration, each of the racemic alcohols were synthesised using a sodium borohydride reduction, to determine optical purity of the ketones reduced in an asymmetric manner. In each case, the retention time of the proposed *S* enantiomer ( $t_S$ ) was longer than that of the *R* enantiomer ( $t_R$ ). Therefore, the assignment of configuration used throughout this thesis is based upon these two assumptions and is in no way definitive.

## 3.2 Synthesis of Pseudo 6-Membered Chiral Iodine Reagents

The focus here was to develop a range of chiral aryl- $\lambda^3$ -iodanes based on the Wirth chiral compounds (Figure 3.1). An increase in the length of the chiral side chain *ortho* to the iodine atom may help to encompass a greater proportion of the iodine atom into the chiral ring and increase the transfer of chiral information from the chiral reagent to the substrate. Several different iodoarenes were synthesised to investigate this effect.

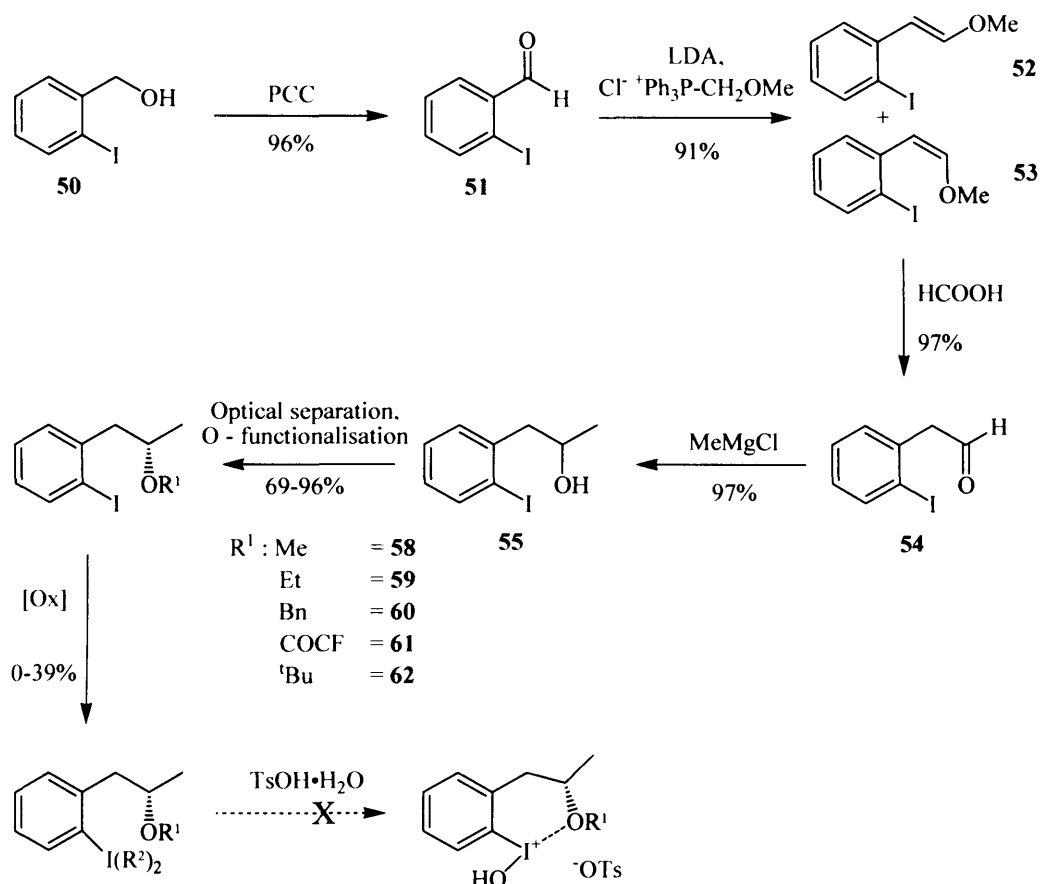


**Figure 3.1:** Wirth pseudo 5-membered ring chiral [hydroxy(tosyloxy)iodo]arene.

### 3.2.1 Attempted Synthesis of (*S*)-3-(2-hydroxy(tosyloxy)-iodophenyl)-2-alkoxypropane

The chiral iodoarenes with one extra carbon atom in the chiral side chain *ortho* to the iodine were planned to be synthesised over 7 steps (Scheme 3.1).

The commercially available 2-iodobenzyl alcohol **50**, was converted into 2-iodobenzaldehyde **51** over 24 hours by oxidation using pyridinium chlorochromate (PCC) in dichloromethane.<sup>3</sup> Following purification over celite<sup>®</sup> and silica gel, the 2-iodobenzaldehyde was isolated in 96% yield.

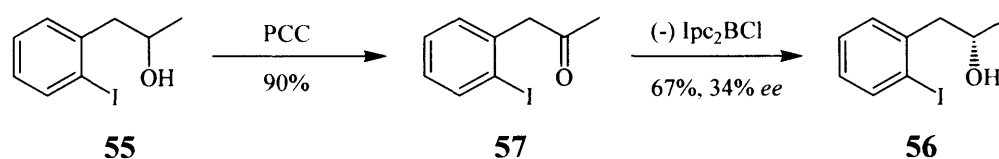


**Scheme 3.1:** The attempted synthesis of (*S*)-3-(2-hydroxy(tosyloxy)-iodophenyl)-2-alkoxypropane.

To introduce an extra carbon atom into the chain, the aldehyde **59** was subjected to a Wittig reaction using (methoxymethyl)triphenylphosphonium chloride to give the (2-iodophenyl)-2-methoxyethenes **52** & **53**. Purification of the vinyl ethers was performed using column chromatography eluting with a diethyl ether/petroleum ether (1:10) mixture to afford both *E* and *Z*-isomers in a 1:1 ratio (91% yield).<sup>4</sup>

The methoxy group of the ether was cleaved through acid hydrolysis. This was achieved by stirring the vinyl ether in the dark with concentrated formic acid, to give the (2-iodophenyl)acetaldehyde **54** in 97% yield.<sup>4</sup> The acetaldehyde was unstable and decomposes if left at room temperature, although it was safe to store at temperatures below 0°C.

To synthesise the racemic alcohol, a simple Grignard reaction was performed, using a methyl magnesium chloride to give Grignard product **55** in 97% yield. To obtain the enantiomerically enriched alcohol, two different routes were investigated. The first was oxidation of the racemic alcohol **55**, using PCC to afford the propanone derivative **57** (90%), followed by an asymmetric reduction of the carbonyl using (-)- $\beta$ -chlorodiisopinocampheylborane ((-)-Ipc<sub>2</sub>BCl) to give the enantiomerically enriched (*S*) alcohol **56** (Scheme 3.2) in 67% yield and 34% *ee*. As this enriched ratio was not sufficiently high enough to proceed with, an alternative approach was examined.



**Scheme 3.2:** Asymmetric reduction of the carbonyl moiety in **57**.

The second method involved separation of the two enantiomers of **55** by preparative chiral HPLC using a Shimadzu LC-10 series HPLC. Several attempts were made using different chiral analytical columns, varying the column temperature, solvent ratios and flow rate. Finally, the conditions for adequate separation were found using an analytical OD-H column and the enantiomers of ( $\pm$ )-1-(2-iodophenyl)propan-2-ol **55** were separated by preparative chiral HPLC. The retention times of the two enantiomers were 128 (*R*) and 144 (*S*) minutes using an OD preparative column. The solvent ratio was hexane/2-propanol (99:1), with 10 °C as the column temperature and a 3 ml/min. flow rate (Figure 3.1). The practical separation of the racemic alcohol required a long time, mainly due to the insolubility of ( $\pm$ )-1-(2-iodophenyl)propan-2-ol **55**. The solubility of the alcohol in the solvent mixture used to separate them was around 50 mg/ml. Additionally, only injections with a maximum of 250  $\mu$ L were possible. Injections with a greater volume produced a severe overlap of the two chromatographic peaks.

**Figure 3.1:** HPLC chromatogram of ( $\pm$ )-1-(2-iodophenyl)propan-2-ol **55**.

In each of the following cases, enantiomer 2 (*S*)-**56**, was carried forward. Alkylation of the alcohol led to the range of chiral hypervalent iodine precursors shown in Table 3.1. Substrates **58–60** were prepared through treatment of the alcohol with sodium hydride followed by addition of an alkyl halide.<sup>5</sup> Ester **61** was prepared by reacting the alcohol with trifluoroacetic anhydride in a solution of triethylamine in dichloromethane.<sup>6</sup> Ether **62** was prepared by the addition of a solution of the alcohol and *t*-butanol in cyclohexane to a vigorously stirred suspension of magnesium sulphate and concentrated sulphuric acid in cyclohexane.<sup>7</sup>

Compound	R <sup>1</sup> group	Yield%
<b>58</b>	Me	96
<b>59</b>	Et	90
<b>60</b>	Bn	72
<b>61</b>	COCF <sub>3</sub>	69
<b>62</b>	<sup>t</sup> Bu	87

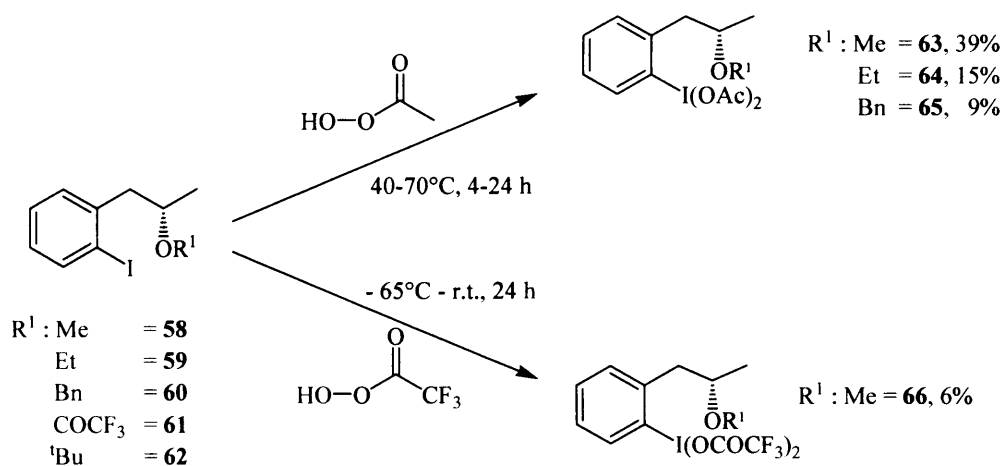
**Table 3.1:** Yield of ethers synthesised from the (*S*) chiral alcohol **56**.

The penultimate step in the synthesis of our proposed chiral reagents was the oxidation of the iodine atom to the iodine(III) state. The oxidation was carried out using the general procedure developed by McKillop,<sup>8</sup> reacting sodium perborate tetrahydrate (NaBO<sub>3</sub>·4H<sub>2</sub>O) in acetic acid at 40°C with the corresponding iodoarene. Oxidation of **58** led to the iodine(III) product **63** that was isolated in 17% yield. The temperature was raised to 50 °C and the reaction

repeated to give an increase in yield of **63** to 26%. Raising the temperature higher than this afforded no further increase in product yield.

An *in situ* generation of peracetic acid from acetic anhydride and 30% hydrogen peroxide,<sup>9</sup> at 40°C gave **63** in 39% yield.

Commercially available peracetic acid was then used as the oxidant at 40°C and this also afforded the (diacetoxy)iodoarene **63** in 39% yield. In each of the above cases, the reaction was performed on a 0.5 mmol scale. Scale up of the reaction proved difficult, as there was a non-linear increase in yield. Other oxidants were employed (Scheme 3.3) to improve on these modest yields.



**Scheme 3.3:** Oxidation of iodoarenes **58–62** with peracetic acid and trifluoroperacetic acid.<sup>1</sup>

Table 3.2 highlights the oxidants applied to the hypervalent precursors **58–62** and the subsequent yields of compounds **63–66**.

The CrO<sub>3</sub>/AcOH/conc.H<sub>2</sub>SO<sub>4</sub> liquid system developed by Skulski,<sup>10</sup> is an alternative reagent used in the synthesis of hypervalent iodine compounds. This also failed, as no oxidation products were observed.

<sup>1</sup> The external examiner of this thesis suggested that the magnitude of the isolated yields of the desired iodine(III) compounds from the oxidation step is simply a solubility issue. Any individual repeating the oxidation step shown here, will need to monitor the work-up procedure and consider the solubility of the iodine(III) compound.



Compound	R <sup>1</sup>	Oxidant	Conditions	Product	Yield%
58	Me	NaBO <sub>3</sub> ·4H <sub>2</sub> O	40–70°C, 24 h	63	26
59	Et			64	15
60	Bn			65	9
61	COCF <sub>3</sub>			-	0
62	<sup>t</sup> Bu			-	trace
58	Me	Peracetic acid or Ac <sub>2</sub> O, 30% H <sub>2</sub> O <sub>2</sub>	40–70°C, 24 h	63	39
59	Et			64	12
60	Bn			65	5
61	COCF <sub>3</sub>			-	0
62				-	trace
58	Me	UHP, CF <sub>3</sub> CO <sub>2</sub> H	–65 °C to rt., 24 h	66	6
59	Et			-	trace
60	Bn			-	trace
61	COCF <sub>3</sub>			-	0
62	<sup>t</sup> Bu			-	trace
58 – 60		<i>m</i> CPBA, AcOH	20–60°C, 24–48 h	-	0
58 – 60		Koser reagent	r.t., 48 h	-	0
58 – 60		CrO <sub>3</sub> /AcOH/H <sub>2</sub> SO <sub>4</sub>	40°C, 2 h	-	0

**Table 3.2:** Oxidative reagents used in the synthesis of the hypervalent iodine(III) reagents.

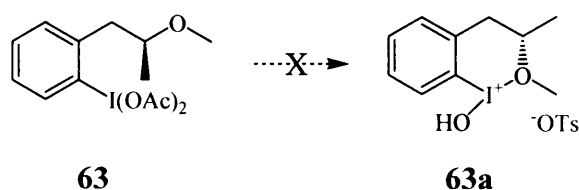
An attempt to oxidize the iodine atom in compounds **58–62** using [hydroxy(tosyloxy)iodo]benzene **15** (Koser reagent), did not result in the expected ligand exchange with formation of the [hydroxy(tosyloxy)iodo]arene derivative.<sup>11</sup> This reaction was monitored for 48 hours, and resulted in the recovery of both starting materials.

The novel urea-hydrogen peroxide/trifluoroacetic anhydride method (as discussed in Chapter Five) was applied to generate the trifluoroacetoxy reagent **66**, with a poor resulting yield of 6%.<sup>12</sup> Once again, the starting iodoarene **58** was easily recoverable.

The final oxidant applied to these iodoarenes, was commercial *m*-chloroperbenzoic acid<sup>13</sup> (*m*CPBA) 70–77% ‘wet’ in acetic acid. Unfortunately, no iodine(III) product was observed during the reaction that was followed for 48 hours and starting material recovered.

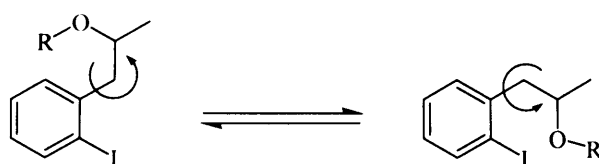
TLC analysis during each of the reactions showed the formation of a new spot consistent with that of a hypervalent iodine product. However, recovery was affected by the stability of the iodoarenes to aqueous work-up and to temperature. In each reaction, the remainder of the reaction mixture was the starting material, which could be recovered easily, through extraction with petroleum ether and evaporation of the solvent under reduced pressure.

The ligand exchange reaction to afford the (*S*)-3-(2-hydroxy(tosyloxy)-iodophenyl)-2-methoxypropane product was performed (Scheme 3.4) using *p*-toluenesulphonic acid monohydrate (*p*TsOH•H<sub>2</sub>O), at room temperature in acetonitrile (CH<sub>3</sub>CN). Unfortunately, no [hydroxy(tosyloxy)iodo]arene product was observed, using either the diacetoxo **63** or trifluoroacetoxy analogues **66** as the starting material. The hypervalent iodine precursors **58–60** were recovered in quantitative yields after this reaction.



**Scheme 3.4:** Failed ligand exchange reaction.

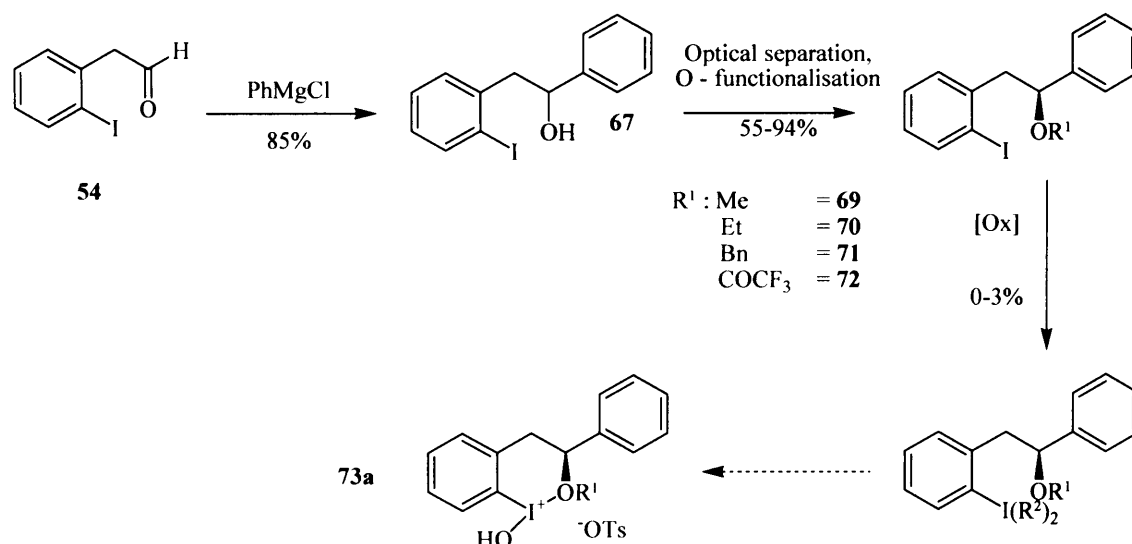
To summarise, the use of the most common methods for oxidising hypervalent iodine compounds proved disappointing. To be synthetically useful, we required stoichiometric quantities of the chiral hypervalent product to react with the alkene and ketone test substrates. The failure of the iodine atom of the hypervalent precursor to oxidise could be related to steric hindrance. The chiral chain now contains an extra carbon that introduces an extra degree of free rotation. This rotation can allow the methoxy group to get closer to the iodine atom to interfere with the oxidation process (Scheme 3.5).



**Scheme 3.5:** Possible conformers of 1-iodo-2-(2-alkoxypropyl)benzene.

### 3.2.2 Attempted Synthesis of (*S*)-3-(2-hydroxy(tosyloxy)-iodophenyl)-1-alkoxyethyl)benzene

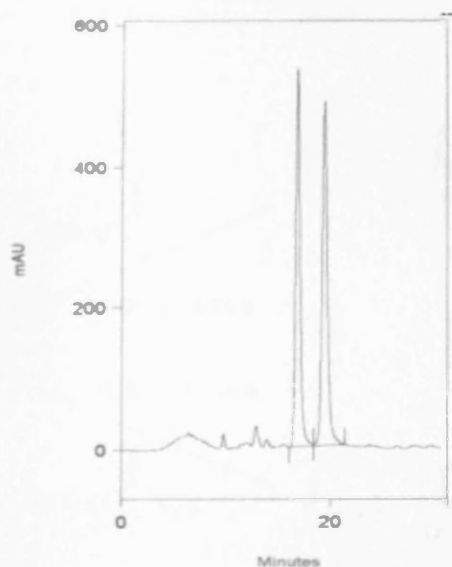
The synthesis of (*S*)-3-(2-hydroxy(tosyloxy)iodophenyl)-1-alkoxyethyl)benzene **73a** is analogous to that of (*S*)-3-(2-hydroxy(tosyloxy)iodophenyl)-2-methoxypropane **63a**. Both can be synthesised over 7 steps, and are identical up to the Grignard addition, where in this case a phenyl Grignard is used, to introduce the phenyl moiety to the end of the chiral side chain.



**Scheme 3.6:** Synthesis toward (*S*)-3-(2-hydroxy(tosyloxy)-iodophenyl)-1-alkoxyethyl)benzene **73a**.

The racemic alcohol **67** was separated by preparative chiral HPLC. The conditions for adequate separation were found using an analytical OD-H column.

The enantiomers of ( $\pm$ )-2-(2-iodophenyl)-1-phenylethanol **67** were resolved by preparative chiral HPLC. The retention times of the two enantiomers were 17 (*R*) and 20 (*S*) minutes using an OD preparative column. The solvent ratio required was hexane/2-propanol (93:7), with 10 °C as the column temperature and a 3 ml/min. flow rate (Figure 3.2).



**Figure 3.2:** HPLC chromatogram of ( $\pm$ )-2-(2-iodophenyl)-1-phenylethanol **67**.

The alkyl ethers that were synthesised from alcohol (*S*)-**68** were prepared under standard reaction conditions in very good yields as shown in Table 3.3.

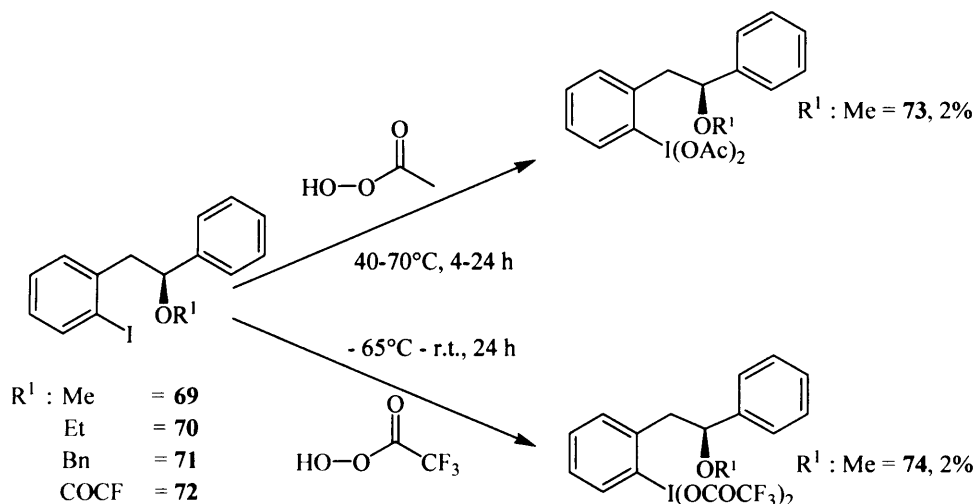
Compound	R <sup>1</sup> group	Yield%
<b>69</b>	Me	95
<b>70</b>	Et	85
<b>71</b>	Bn	74
<b>72</b>	COCF <sub>3</sub>	55

**Table 3.3:** Yield of alkyl ethers synthesised from the (*S*) enantiomer of the chiral alcohol **68**.

As with the attempted synthesis of (*S*)-3-(2-hydroxy(tosyloxy)-iodophenyl)-2-methoxypropane **63a**, the yields to the iodine(III) precursor

compounds **69–72** from the chiral alcohol were very good (55–95%), but the oxidation step again revealed problems.

Several different oxidants were employed to give the hypervalent product but with very limited success. Table 3.4 shows the range of oxidants used along with their respective conditions and yield of product.



**Scheme 3.7:** Oxidation of iodoarenes **69–72** with peracetic acid and trifluoroperacetic acid.

Analogous to (*S*)-3-(2-hydroxy(tosyloxy)iodophenyl)-2-methoxypropane **63a** synthesis, the oxidation did not proceed as planned. When using either Koser reagent or *m*CPBA in acetic acid, no hypervalent product was observed. In addition to this, the stalwart oxidations using sodium perborate in acetic acid, commercial peracetic acid, *in situ* preparation of peracetic acid and the novel method generating trifluoroperacetic acid all generated product, but with very low yield. Scale up of the successful reactions did not produce the expected increase in mass of the hypervalent product.

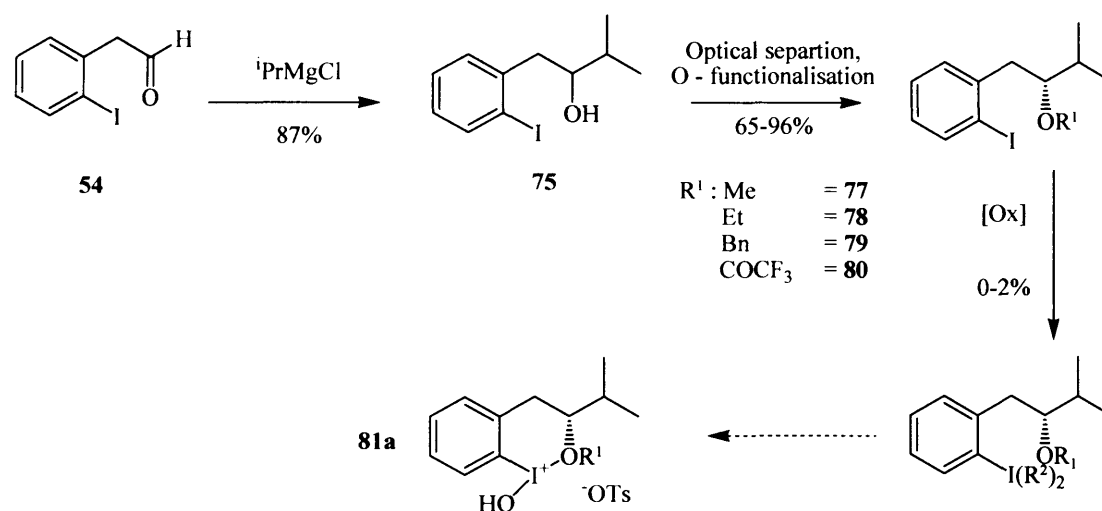
Compound	R <sup>1</sup>	Oxidant	Conditions	Product	Yield%
69	Me	NaBO <sub>3</sub> ·4H <sub>2</sub> O	40–70°C, 24 h	73	2
70	Et			-	Trace
71	Bn			-	Trace
72	COCF <sub>3</sub>			-	0
69	Me	Peracetic acid	40–70°C, 24 h	73	2
70	Et			-	0
71	Bn			-	0
72	COCF <sub>3</sub>			-	0
69	Me	Ac <sub>2</sub> O, 30% H <sub>2</sub> O <sub>2</sub>	40–70°C, 24 h	73	2
70	Et			-	0
71	Bn			-	0
72	COCF <sub>3</sub>			-	0
69	Me	UHP, CF <sub>3</sub> CO <sub>2</sub> H	–65°C to rt., 24 h	74	2
70	Et			-	Trace
71	Bn			-	Trace
72	COCF <sub>3</sub>			-	0
69–72		<i>m</i> CPBA, AcOH	20–60°C, 24–48 h	-	0
69–72		Koser reagent	r.t., 48 h	-	0

**Table 3.4:** Oxidative reagents used in the synthesis of the hypervalent iodine(III) reagents.

From these results it was clear that the [bis(acyloxy)iodo]arenes of this type of compound are lower yielding than those of the 3-(2-diacetoxyiodophenyl)-2-alkoxypropane. Without isolation of sufficient quantities of the [bis(acyloxy)iodo]arenes to perform ligand exchange reactions to give the [hydroxy(tosyloxy)]iodoarenes, this type of hypervalent compound would have very limited synthetic use.

### 3.2.3 Attempted Synthesis of (*R*)-3-(2-hydroxy(tosyloxy)iodophenyl)-2-alkoxy-3-methylbutane

The synthesis of (*R*)-3-(2-hydroxy(tosyloxy)iodophenyl)-2-alkoxy-3-methylbutane **81a** mirrors that of (*S*)-3-(2-hydroxy(tosyloxy)iodophenyl)-2-methoxypropane **63a**. Both were proposed to be synthesised over 7 steps (Scheme 3.8), and are analogous up to the Grignard addition. In this case, an isopropyl halide was used to form the Grignard reagent, to introduce the branched isopropyl side chain in 87% yield.



**Scheme 3.8:** Synthesis toward (*R*)-3-(2-hydroxy(tosyloxy)iodophenyl)-2-methoxy-3-methylbutane **81a**.

The racemic alcohol **75** was resolved by preparative chiral HPLC using a Shimadzu LC-10 series HPLC. The conditions for adequate separation were found using an analytical OD-H column and the enantiomers of ( $\pm$ )-1-(2-iodophenyl)-3-methylbutan-2-ol **75** were resolved and separated by preparative chiral HPLC. The retention times of the two enantiomers were 20 (*R*) and 24 (*S*) minutes using an OD preparative column. The solvent ratio required was hexane/2-propanol (92:8), with 10 °C as the column temperature and a 2 ml/min. flow rate (Figure 3.3).



**Figure 3.3:** HPLC chromatogram of ( $\pm$ )-1-(2-iodophenyl)-3-methylbutan-2-ol **75**.

The subsequent alkylation/acylation step afforded the various ethers or ester in good yields (65–96%).

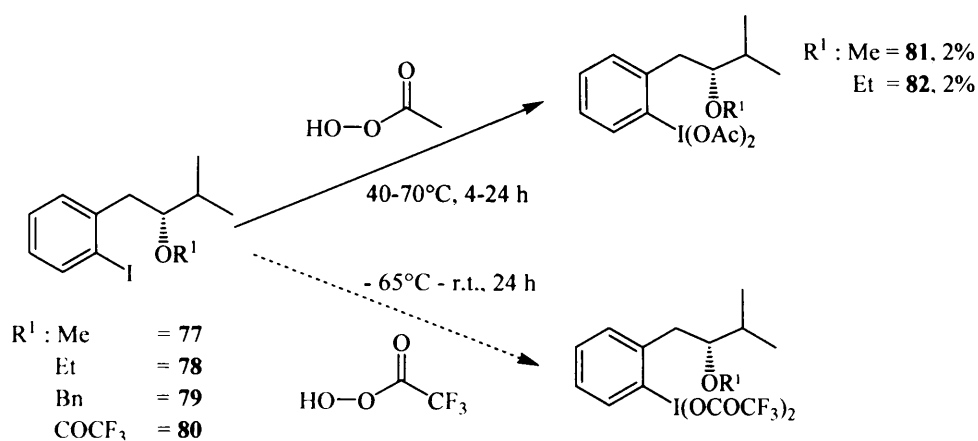
Compound	R <sup>1</sup> group	Yield%
<b>77</b>	Me	96
<b>78</b>	Et	81
<b>79</b>	Bn	72
<b>80</b>	COCF <sub>3</sub>	65

**Table 3.5:** Yield of alkyl ethers synthesised from the (*R*)-enantiopure alcohol **76**.

The yields of the hypervalent iodine precursors **77–80** from (*R*)-**76** were very good, ranging between 65–96%, so there is good atom economy up to this point.

The oxidation of the iodine atom to the iodine(III) compound was performed using a range of oxidants with varying oxidising power (Table 3.6).





**Scheme 3.9:** Oxidation of iodoarenes **77–80** with peracetic acid and trifluoroperacetic acid.

Compound	R <sup>1</sup>	Oxidant	Conditions	Product	Yield%
<b>77</b>	Me	NaBO <sub>3</sub> ·4H <sub>2</sub> O	40–70°C, 24 h	<b>81</b>	2
<b>78</b>	Et			-	2
<b>79</b>	Bn			-	Trace
<b>80</b>	COCF <sub>3</sub>			-	0
<b>77</b>	Me	Peracetic acid or Ac <sub>2</sub> O, 30% H <sub>2</sub> O <sub>2</sub>	40–70°C, 24 h	<b>81</b>	2
<b>78</b>	Et			<b>82</b>	1
<b>79</b>	Bn			-	0
<b>80</b>	COCF <sub>3</sub>			-	0
<b>77–79</b>		UHP, CF <sub>3</sub> CO <sub>2</sub> H	–65°C to rt., 24 h	-	Trace
<b>80</b>	COCF <sub>3</sub>			-	0
<b>77–80</b>		<i>m</i> CPBA, AcOH	20–60°C, 24–48 h	-	0
<b>77–80</b>		Koser reagent	r.t., 48 h	-	0

**Table 3.6:** Oxidative reagents used in the synthesis of the hypervalent iodine(III) reagents.

As a starting point, sodium perborate tetrahydrate was used, generating only a trace of iodine(III) product **81**. The novel urea hydrogen peroxide method also only generated traces of product, whereas *m*CPBA in acetic acid and Koser reagent did not afford any product. The only oxidants that produced any

recoverable iodine(III) product were sodium perborate tetrahydrate and peracetic acid (both commercial and *in situ* preparation) as shown in Table 3.6.

In keeping with the iodoarenes discussed in sections 3.2.1 and 3.2.2, the final ligand exchange step failed to produce the target compound in any appreciable quantity. The [bis(acyloxy)iodo]arenes were reduced to their corresponding precursor molecules, which were recovered quantitatively each time.

To summarise, it was clear that a recurring feature of these pseudo 6-membered ring chiral iodine reagents was their instability and difficulty in oxidising to the [bis(acyloxy)iodo]arene. As discussed earlier, for these iodine(III) reagents to be useful in generating new chiral centres in reactions such as dioxytosylation of alkenes and  $\alpha$ -oxytosylation of ketones, we would require them in stoichiometric quantities. Therefore, this type of hypervalent iodine compound in its current application has severe limitations.

### **3.3 Synthesis of Pseudo 7-Membered Ring Chiral Iodine Reagents**

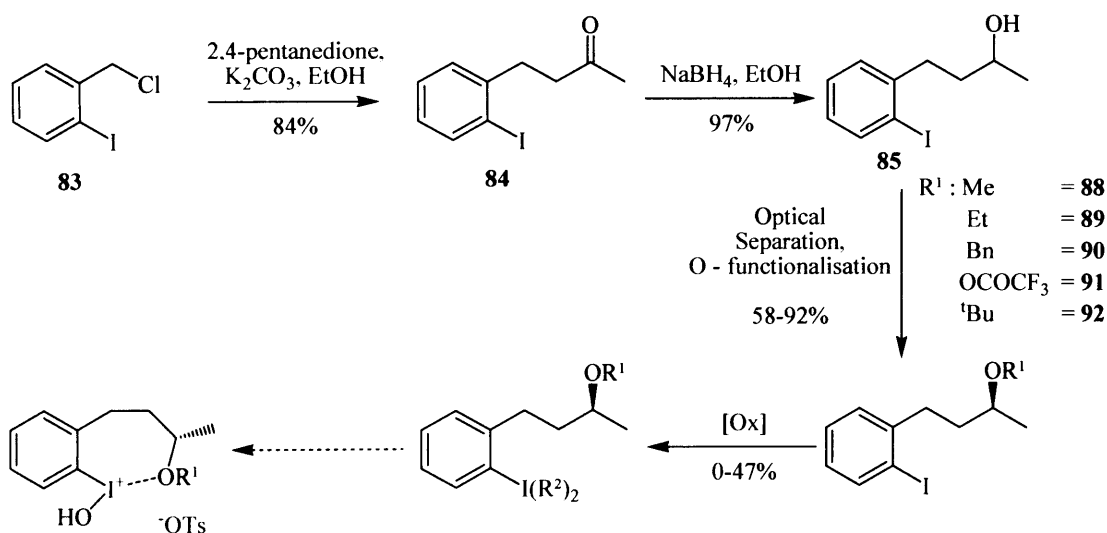
Running parallel to the research into the pseudo 6-membered compounds was the investigation of pseudo 7-membered ring compounds. This was to enable us to observe a wider range of reactivity with alkenes and ketones, from the addition of carbon atoms into the chiral side chain. Analogous to the smaller chain compounds, a range of iodoarenes were synthesised with different substituents attached to the chiral centre and to the hydroxy oxygen.

### 3.3.1 Attempted Synthesis of (*S*)-4-(2-hydroxy(tosyloxy)iodophenyl)-2-methoxy-3-methylpropane

The chiral iodoarenes with two extra carbon atoms in the chiral side chain *ortho* to the iodine were synthesised over 5 steps as outlined in Scheme 3.10.

Commercially available 2-iodobenzyl chloride **83** was refluxed with 2,4-pentanedione and potassium carbonate in ethanol for 24 hours to afford 4-(2-iodophenyl)butan-2-one **84** in excellent yield (84%).<sup>14</sup>

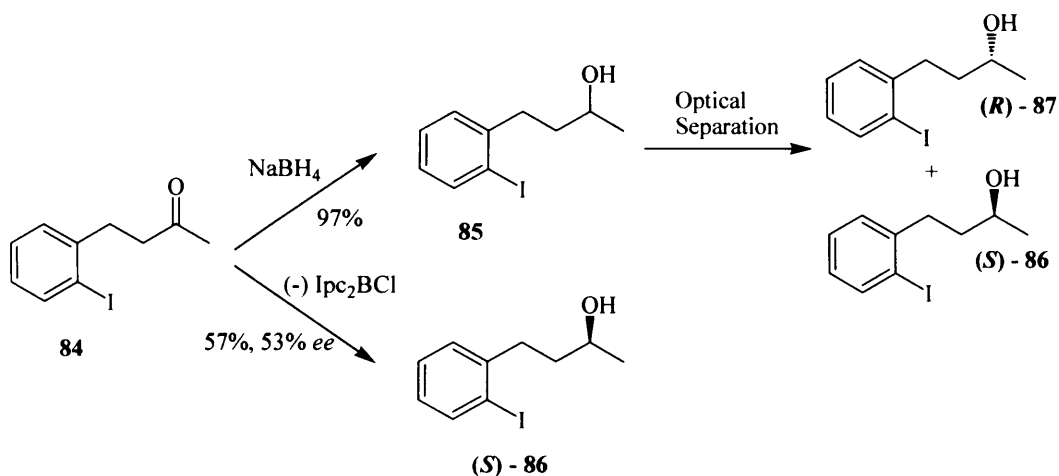
To obtain the enantiomerically pure alcohol, there was a choice of two methods to reduce the carbonyl moiety in **84**. By using (–)- $\beta$ -chlorodiisopinocampheylborane ((–)-Ipc<sub>2</sub>BCl) it would be possible to perform an asymmetric reduction, or alternatively, by synthesising the racemic alcohol **85** by a sodium borohydride reduction followed by HPLC. Both routes were investigated.



**Scheme 3.10:** The synthesis toward (*S*)-4-(2-hydroxy(tosyloxy)iodophenyl)-2-alkoxybutane.

The asymmetric reduction of **84** using (–)-Ipc<sub>2</sub>BCl was performed in dry tetrahydrofuran at –25°C (temperature controlled using a cold finger) for 24

hours. This reaction yielded the (*S*) enantiomerically enriched alcohol **86** (Scheme 3.11) in 57% yield and 53% *ee*.



**Scheme 3.11:** Reduction of 4-(2-iodophenyl)butan-2-one **84** with NaBH<sub>4</sub> and (-)-Ipc<sub>2</sub>BCl.

The failure to obtain the enantiomerically pure alcohol via an asymmetric reduction prompted the search for alternative method. The reduction performed with sodium borohydride in ethanol at reflux for 3 hours, afforded the racemic alcohol **85** in excellent yield (97%).<sup>15</sup> The separation of the enantiomers was performed using preparative HPLC. As discussed in section 3.2.1, a range of analytical columns and conditions were investigated to give separation of the enantiomers.

**Figure 3.4:** HPLC chromatogram of ( $\pm$ )-4-(2-iodophenyl)butan-2-ol **85**.

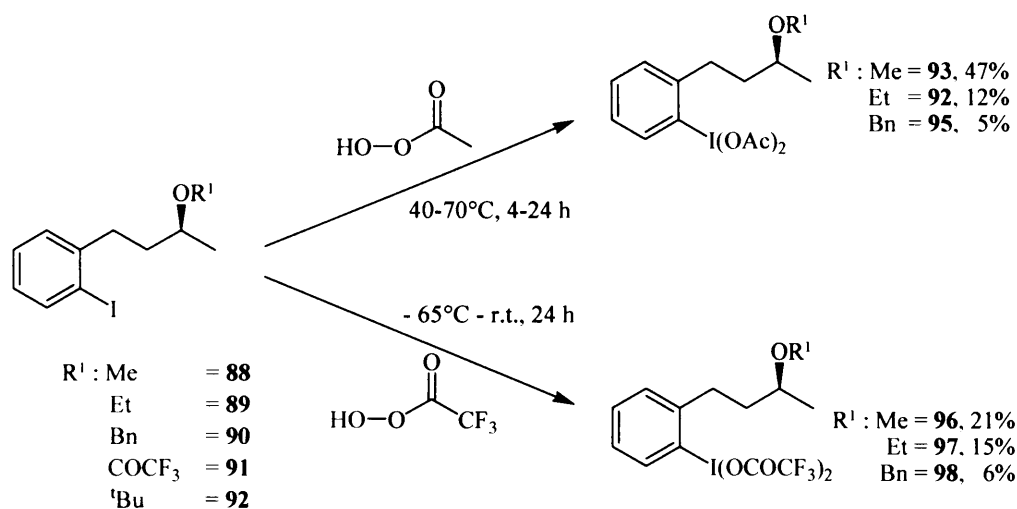
Suitable conditions were found using an OD-H analytical column to allow separation of the enantiomers of ( $\pm$ )-4-(2-iodophenyl)butan-2-ol **85** (figure 3.4). The retention times using an OD preparative column were longer than those with the OD-H column coming in at 25 (*R*) and 32 (*S*) minutes, possibly due to the larger particle size and smaller interaction with the hydroxy moiety. The solvent ratio was hexane/2-propanol (93:7), with 15°C as the column temperature and a 4.5 ml/min flow rate. Solutions of up to 200 mg/ml were possible with injection volumes of up to 400  $\mu$ L.

In each of the following cases, enantiomer 1 (assumed to be the *S*-enantiomer) was carried forward and a simple alkylation of chiral alcohol (*S*)-**86** gave the corresponding alkyl ether/ester in good yields as shown in Table 3.7.

Compound	R <sup>1</sup> group	Yield%
<b>88</b>	Me	96
<b>89</b>	Et	81
<b>90</b>	Bn	72
<b>91</b>	COCF <sub>3</sub>	71
<b>92</b>	<sup>t</sup> Bu	58

**Table 3.7:** Yield of alkyl ethers synthesised from the (*S*) chiral alcohol **86**.

Oxidation of the iodine atom began with the general procedure of using sodium perborate tetrahydrate in acetic acid. The [bis(acyloxy)iodo]arenes were obtained in yields ranging from 5 to 12%. The use of both commercially available peracetic acid and the *in situ* generation using acetic anhydride/hydrogen peroxide provided the iodine(III) product **93** in 47% yield from compound **88**.



**Scheme 3.12:** Oxidation of iodoarenes **88–92** with peracetic acid and trifluoroperacetic acid.

Attempts to oxidize the iodine atom using [hydroxy(tosyloxy)iodo]benzene<sup>16</sup> **15** did not result in the expected ligand exchange. This reaction was monitored for 48 hours, with the recovery of both starting materials.

The novel urea-hydrogen peroxide/trifluoroacetic anhydride method was applied to generate the trifluoroacetoxy analogue, with a low resulting yield of **93** at 21%. Once again, the remaining starting iodoarene **88** was easily recoverable.<sup>12</sup>

The final oxidant applied to these iodoarenes, was *m*-chloroperbenzoic acid<sup>13</sup> (*m*CPBA) in acetic acid. Unfortunately, only a trace of iodine(III) product was observed during the reaction that was followed for 48 hours with the remaining starting material recovered.

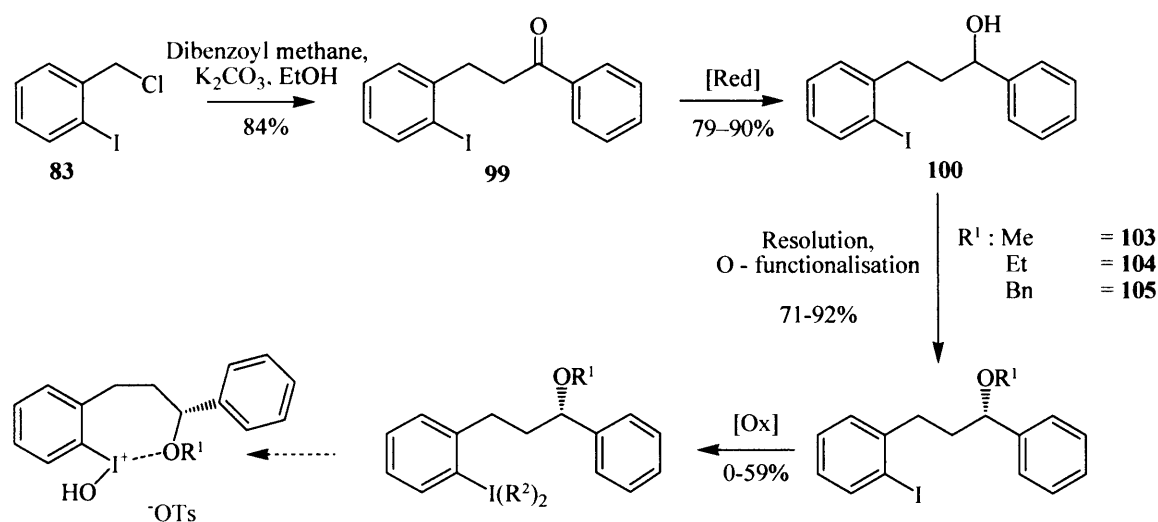
Compound	R <sup>1</sup>	Oxidant	Conditions	Product	Yield%
88	Me	NaBO <sub>3</sub> ·4H <sub>2</sub> O	40–70°C, 24 h	93	12
89	Et			94	6
90	Bn			95	5
91	OCOCF <sub>3</sub>			-	0
92	<sup>t</sup> Bu			-	trace
88	Me	Peracetic acid or Ac <sub>2</sub> O, 30% H <sub>2</sub> O <sub>2</sub>	40–70°C, 24 h	93	47
89	Et			94	12
90	Bn			95	4
91	OCOCF <sub>3</sub>			-	0
92	<sup>t</sup> Bu			-	trace
88	Me	UHP, CF <sub>3</sub> CO <sub>2</sub> H	–65°C to rt., 24 h	96	21
89	Et			97	15
90	Bn			98	6
91	OCOCF <sub>3</sub>			-	0
92	<sup>t</sup> Bu			-	trace
88–92		<i>m</i> CPBA, AcOH	20–60°C, 24–48 h	-	trace
88–92		Koser reagent	r.t., 48 h	-	0

**Table 3.8:** Oxidative reagents used in the synthesis of the hypervalent iodine(III) reagents.

The final step in this procedure was the ligand exchange with toluenesulphonic acid monohydrate to generate the [hydroxy(tosyloxy)iodo]arene. However, analogous to the pseudo 6-membered ring chiral iodine reagents, the ligand exchange step failed to afford the [hydroxy(tosyloxy)iodo]arene. The hypervalent precursors were recovered quantitatively in each case.

### 3.3.2 Attempted Synthesis of (*S*)-1-(2-(Hydroxy(tosyloxy)iodophenyl)-1-methoxypropyl)benzene

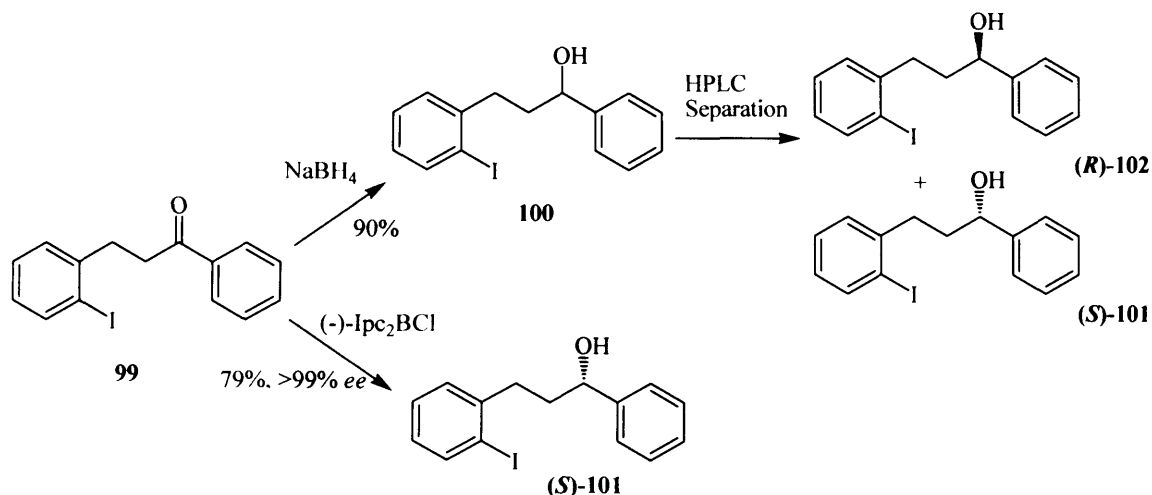
The proposed synthesis of (*S*)-1-(2-(hydroxy(tosyloxy)iodophenyl)-1-methoxypropyl)benzene is analogous to the synthesis described in section 3.3.1 and is outlined in Scheme 3.13.



**Scheme 3.13:** The synthesis toward (*S*)-1-(2-(hydroxy(tosyloxy)iodophenyl)-1-methoxypropyl)benzene.

The 2-iodobenzyl chloride **83** was reacted with dibenzoyl methane to yield the 3-(2-iodophenyl)-1-phenylpropan-1-one **99** in 84% yield as a pale yellow oil. The reduction to the ( $\pm$ )-3-(2-iodophenyl)-1-phenylpropan-1-ol **100** was initially performed using sodium borohydride to give the racemic alcohol **100** in 90% yield. The enantiomers of **100** were easily separated using preparative HPLC, however, this step was time consuming and an alternative approach to yield the enantiomerically pure alcohol was chosen. Through an asymmetric reduction of the carbonyl group using (–)- $Ipc_2BCl$ , it was possible to synthesise the enantiomerically enriched alcohol derivative (*S*)-**101** in 79% yield and 99% *ee*.





**Scheme 3.14:** Reduction of 3-(2-iodophenyl)-1-phenylpropan-1-one **99** with  $\text{NaBH}_4$  and  $(-)\text{-Ipc}_2\text{BCl}$ .

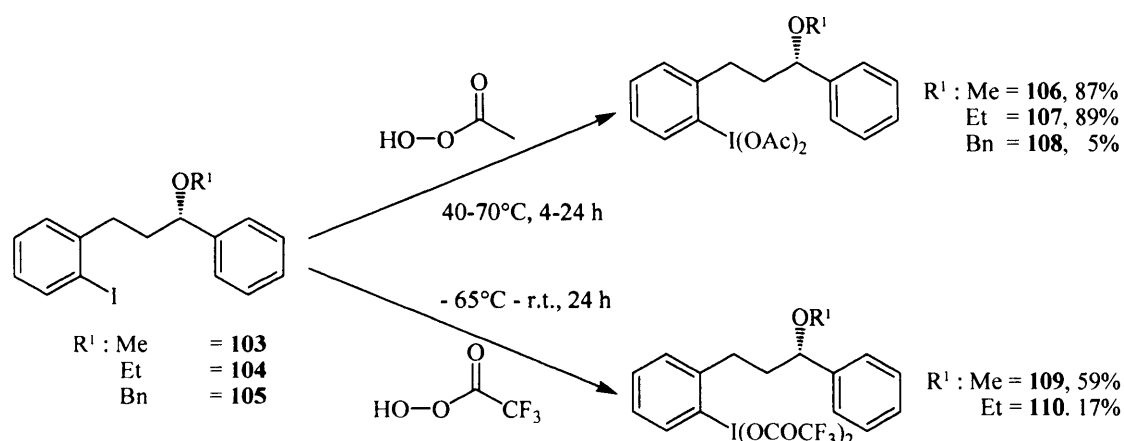
Alkylation of the hydroxy group of **(S)-101** yielded the corresponding chiral ethers in good yields, as shown in Table 3.9.

Compound	R <sup>1</sup> group	Yield%
<b>103</b>	Me	85
<b>104</b>	Et	80
<b>105</b>	Bn	71

**Table 3.9:** Yield of alkyl ethers synthesised from the *(S)* chiral alcohol **101**.

The sodium perborate method of oxidation using reagents **103** and **104** resulted in (diacetoxy)iido arenes in excellent yields up to 87% for **106** and 89% for **104**.

Oxidation efforts using *m*CPBA gave only a trace of product and Koser reagent yielded no [hydroxy(tosyloxy)iido]arene. However, the [bis(trifluoroacetoxy)iido]arene **109** was successfully produced and isolated using the novel urea hydrogen peroxide method with yields up to 59%. Detailed yields are shown in Table 3.10.



**Scheme 3.15:** Oxidation of iodoarenes **103–105** with peracetic acid and trifluoroacetic acid.

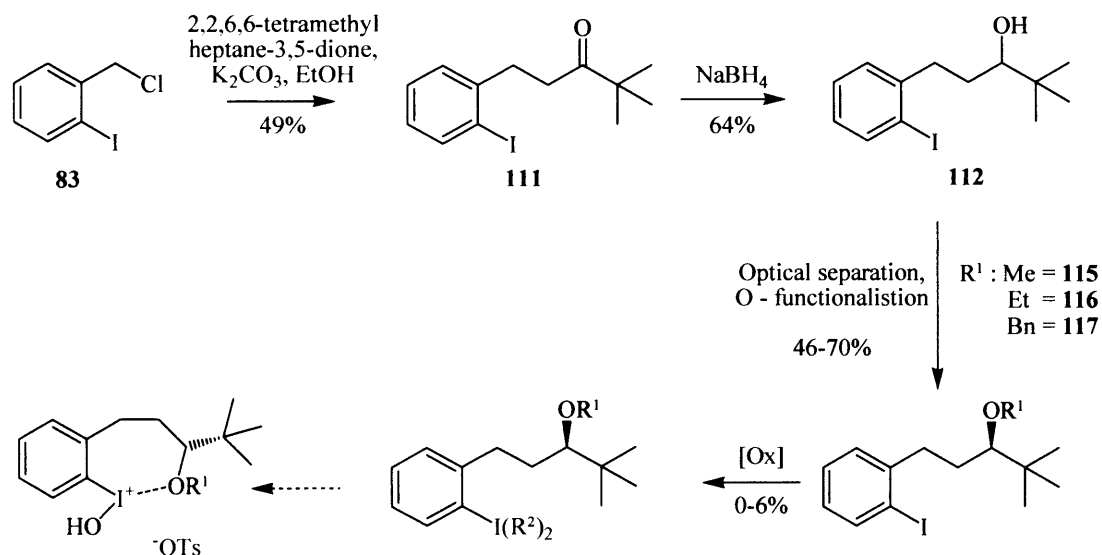
Compound	R <sup>1</sup>	Oxidant	Conditions	Product	Yield%
<b>103</b>	Me	NaBO <sub>3</sub> ·4H <sub>2</sub> O	40–70°C, 24 h	<b>106</b>	87
<b>104</b>	Et			<b>107</b>	89
<b>105</b>	Bn			<b>108</b>	3
<b>103</b>	Me	Peracetic acid	40–70°C, 24 h	<b>106</b>	38
<b>104</b>	Et			<b>107</b>	12
<b>105</b>	Bn			<b>108</b>	4
<b>103</b>	Me	Ac <sub>2</sub> O, 30% H <sub>2</sub> O <sub>2</sub>	40–70°C, 24 h	<b>106</b>	38
<b>104</b>	Et			<b>107</b>	11
<b>105</b>	Bn			<b>108</b>	5
<b>103</b>	Me	UHP, CF <sub>3</sub> CO <sub>2</sub> H	–65°C to rt., 24 h	<b>109</b>	59
<b>104</b>	Et			<b>110</b>	17
<b>105</b>	Bn			-	Trace
<b>103–105</b>		<i>m</i> CPBA, AcOH	20–60°C, 24–48 h	-	Trace
<b>103–105</b>		Koser reagent	r.t., 48 h	-	0

**Table 3.10:** Oxidative reagents used in the synthesis of the hypervalent iodine(III) reagents.

To afford the target [hydroxy(tosyloxy)iodo]arene, the ligand exchange reaction was performed and again no product was observed. The [bis(acyloxy)iodo]arenes appeared to undergo decomposition into the precursor iodine(I) molecule, which in each case were recoverable quantitatively.

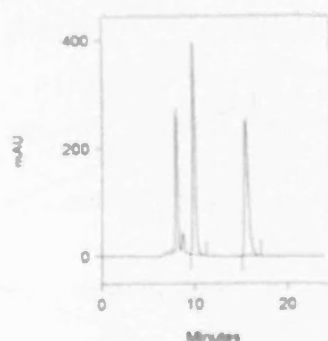
### 3.3.3 Attempted Synthesis of 1-(Hydroxy(tosyloxy)-iodo)2-((*R*)-3-methoxy-4,4-dimethylpentyl)benzene

The final range of compounds in the pseudo 7-membered ring series contained a large sterically demanding tertiary butyl group, attached to the chiral carbon of the side chain (Scheme 3.16). The tertiary butyl group was introduced through the reaction of 2-iodobenzyl chloride **83** with 2,2,6,6-tetramethyl-3,5-heptanedione. The 1-(2-iodophenyl)-4,4-dimethylpentan-3-one **111** was obtained in only 49% yield. Standard reduction using sodium borohydride was performed on **111** to give the racemic ( $\pm$ )-1-(2-iodophenyl)-4,4-dimethylpentan-3-ol **112** as a pale yellow oil in 64% yield.



**Scheme 3.16:** Synthesis towards 1-(hydroxy(tosyloxy)-iodo)2-((*R*)-3-methoxy-4,4-dimethylpentyl)benzene.

Preparative HPLC was successful in separating the enantiomers of **112**. The separation was possible using an OD column and a solvent ratio of 95% hexanes and 5% 2-propanol. The retention times were 10 (*R*) and 16 (*S*) minutes (Figure 3.5).



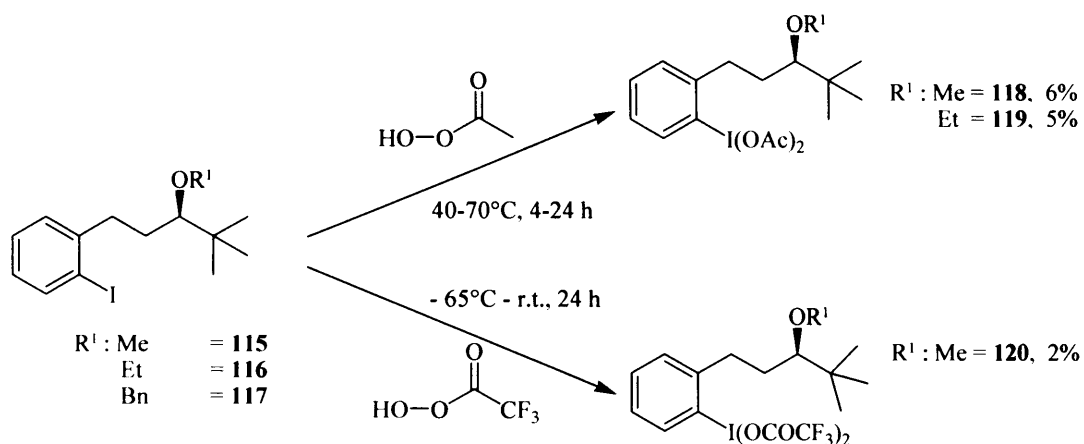
**Figure 3.5:** HPLC chromatogram of (±)-1-(2-iodophenyl)-4,4-dimethylpentan-3-ol **112**.

Simple alkylation of the hydroxy group of (*R*)-1-(2-iodophenyl)-4,4-dimethylpentan-3-ol **113** afforded the corresponding ethers (**115-117**) up to 70% yield as shown in Table 3.11.

Compound	R <sup>1</sup> group	Yield%
<b>115</b>	Me	70
<b>116</b>	Et	69
<b>117</b>	Bn	46

**Table 3.11:** Yield of alkyl ethers synthesised from the chiral alcohol (*R*)-**113**.

The oxidation of the ether precursors followed the pattern of the other pseudo 7-membered ring compounds. *m*CPBA only generated a trace of product and using the Koser reagent no product was observed. The yields obtained using sodium perborate and peracetic acid was again disappointingly low.



**Scheme 3.17:** Oxidation of iodoarenes **115–117** with peracetic acid and trifluoroperacetic acid.

Finally, using the urea hydrogen peroxide method, only the methyl substituted hypervalent iodine compound **120** was isolated, although traces of product were observed with the ethyl and benzyl precursors **116** and **117** (Table 3.12).

Once again we were frustrated by the final step as the ligand exchange reaction failed to produce and of the desired [hydroxy(tosyloxy)iodo]arenes. In each case, the reduced precursor molecules **115** and **116** were recovered quantitatively.

Compound	R <sup>1</sup>	Oxidant	Conditions	Product	Yield%
115	Me	NaBO <sub>3</sub> ·4H <sub>2</sub> O	40–70°C, 24 h	118	6
116	Et			119	5
117	Bn			-	Trace
115	Me	Peracetic acid or Ac <sub>2</sub> O, 30% H <sub>2</sub> O <sub>2</sub>	40–70°C, 24 h	118	5
116	Et			119	5
117	Bn			-	Trace
115	Me	UHP, CF <sub>3</sub> CO <sub>2</sub> H	–65°C to rt., 24 h	120	2
116	Et			-	Trace
117	Bn			-	Trace
115–117		<i>m</i> CPBA, AcOH	20–60°C, 24–48 h	-	Trace
115–117		Koser reagent	r.t., 48 h	-	0

**Table 3.12:** Oxidative reagents used in the synthesis of the hypervalent iodine(III) reagents.

### 3.4 Conclusion

This chapter has covered the attempted synthesis of a wide range of pseudo 6- and 7-membered ring chiral iodine compounds. The most common feature of these iodoarenes was the difficulty in oxidising them to the iodine(III) state. With the myriad of oxidants available, the highest yield of hypervalent product was 89%. This excellent yield was achieved with compound **107**, along with compound **106** returning an 87% yield using sodium perborate as the oxidant.

The novel UHP oxidation method had some success with the difficult chiral iodoarenes particularly compound **109**, which was afforded in 59% yield. However, none of the [bis(acyloxy)iodo]arenes that were isolated were stable enough to undergo the ligand exchange step to yield the [hydroxy(tosyloxy)iodo]arene. In each case, the iodine(I) precursor molecule was recovered. This has implications in the application of this type of chiral hypervalent iodine compound. Currently, to be able to utilize the unique features offered with this type of chiral hypervalent iodane, stoichiometric quantities are required for the functionalisation of alkenes and ketones.

A possible reason for the lack of oxidation may be related to the increased length of the chiral side chain. Compared to the pseudo 5-membered ring compounds previously studied by the Wirth group, the 6- and 7-membered compounds have 1 and 2 extra carbon atoms respectively in the chiral chain. The extra rotation around these carbon carbon bonds could interfere with the formation of the hypervalent species. The chiral hypervalent compounds that were synthesised in very good yield and were stable at room temperature were **106**, **107** and **109**. These reagents contain two phenyl rings, so their stability may be due, in part, to  $\pi$ -stacking of the phenyl rings or quadrupole-quadrupole interactions. Either or both of these could reduce the ability of the carbon-carbon single bond to rotate and affect the oxidation process.

Overall, only five chiral hypervalent compounds were synthesised in sufficient quantities to allow further stoichiometric studies (**63**, **93**, **106**, **107** and **109**). The remaining chiral compounds, at present, could not be studied further. Chapter Four will describe the effectiveness of these chiral hypervalent precursors.



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## Chapter 4

# 4 Reactivity of Chiral Hypervalent Iodine Compounds

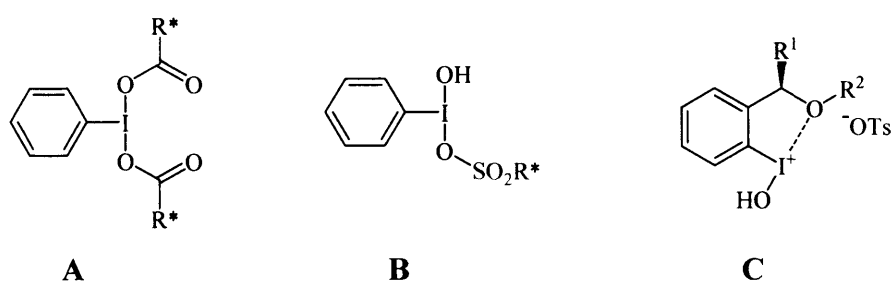
## 4.1 Introduction

In this chapter, the reactivity of the next generation chiral hypervalent iodine(III) reagents will be reported. As discussed earlier, there are several known procedures for the synthesis of asymmetric centres using hypervalent iodine compounds and these methods were applied to the novel chiral iodine compounds as well as their precursors, to investigate their effectiveness as enantioinducing reagents.

## 4.2 Asymmetric Functionalisation of Alkenes and Ketones

The use of hypervalent iodine reagents in asymmetric synthesis can lead to useful synthetic intermediates. Previous work by the Wirth group produced chiral hypervalent reagents that yielded products with new chiral centres in good yield and modest selectivity. They developed optically active reagents to  $\alpha$ -oxytosylate ketones and dioxytosylate alkenes. The research was initially based on chiral selenium electrophiles where they found that selenium cations, which are

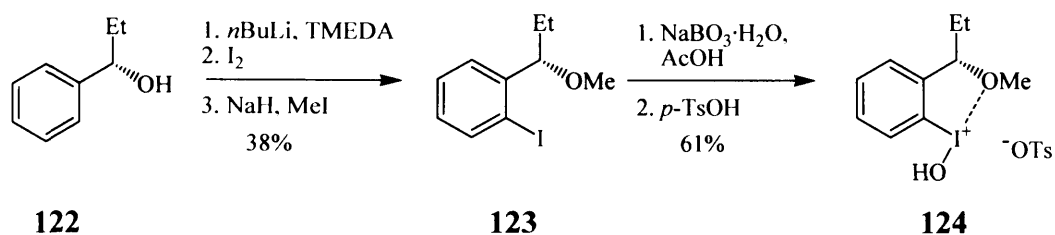
coordinated to the oxygen atom of a chiral alcohol, could perform addition reactions to various alkenes with high diastereoselectivities.<sup>1</sup> The formation of a pseudo 5-membered ring with a close proximity to the chiral centre and the selenium electrophile was found to be advantageous. The earlier chiral hypervalent derivatives were either chiral carboxylate derivative **A** or chiral sulphonic acid adducts **B** (Figure 4.1).<sup>2,3</sup> The stereogenic centres in those chiral hypervalent compounds, were far away from the iodine atom. Therefore Wirth *et al.* planned the synthesis of hypervalent iodine compounds, where the stereogenic centre was much closer to the iodine atom e.g. type **C** (Figure 4.1).<sup>4</sup>



**Figure 4.1:** Early chiral hypervalent iodine compounds **A**, **B** and the Wirth chiral reagent **C**.

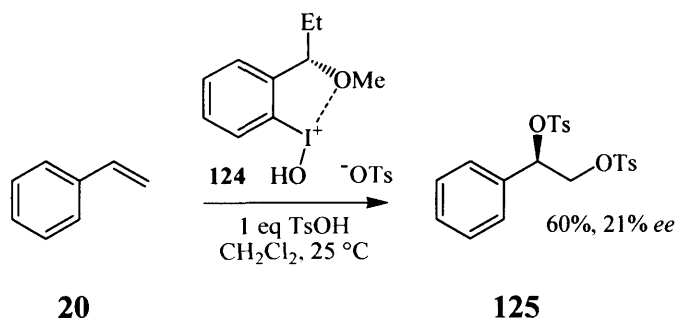
The chiral hypervalent iodine compounds can be used as stoichiometric reagents in oxytosylation reactions of alkenes and ketones. Therefore, they need to be accessible in a short scalable synthetic sequence. The synthesis of compounds of type **C** starts with the chiral alcohol **122**. Compound **122** is commercially available or can be prepared by addition of diethyl zinc to benzaldehyde in the presence of chiral catalysts (>98% *ee*).<sup>5</sup> After *ortho*-lithiation<sup>6</sup> of **122**, iodine can be introduced and the secondary alcohol then converted to the methyl ether **123**. Iodine oxidation can be performed with sodium perborate in glacial acetic acid<sup>7</sup> and leads to the (diacetoxyiodo)benzene derivative. Subsequent treatment with *p*-toluenesulphonic acid monohydrate yields the [hydroxy(tosyloxy)iodo]arene compound **124**. Although the yield from the introduction of iodine in **124** is only 40%, the subsequent formation of the ether and the synthesis of the diacetate are reactions that proceed in very good

yield. The hypervalent iodine compound **124** can be purified by crystallization and is obtained in 68% yield (Scheme 4.1).



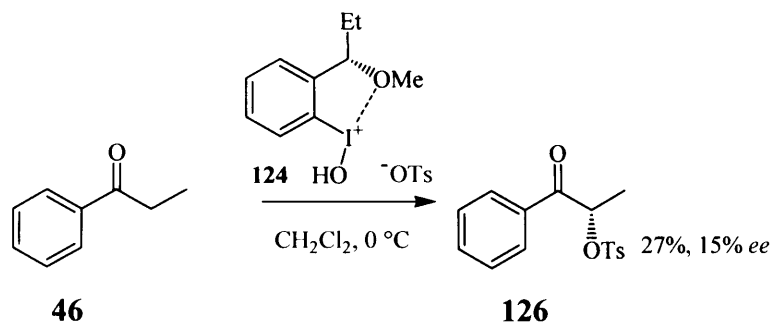
**Scheme 4.1:** Synthesis of Wirth chiral reagent **124**.

Application of this type of reagent in the functionalisation of styrene **20**, resulted good yields of (*R*)-1,2-bis(tosyloxy)phenylethane **125** in up to 75%. The enantioselectivities observed using styrene **20** and reagents of Type C was between 13 and 65% *ee*.<sup>8</sup> Scheme 4.2 shows that chiral reagent **124** yields **125** in 21% *ee*.



**Scheme 4.2:** Stereoselective dioxotenylation of styrene **20** with **124**.

The  $\alpha$ -oxytosylation of propiophenone **46** is less efficient than the dioxotenylation of styrene **20**. Scheme 4.3 shows that reagent **124** produces 15% *ee* of **126** although, up to 40% *ee* can be obtained with this type of reagent and the (*R*)-1-phenyl-oxo-2-tosyloxypropane **126** was isolated in 35% yield. It is known that some ketones show low conversions in the reaction with the Koser reagent.<sup>9</sup>

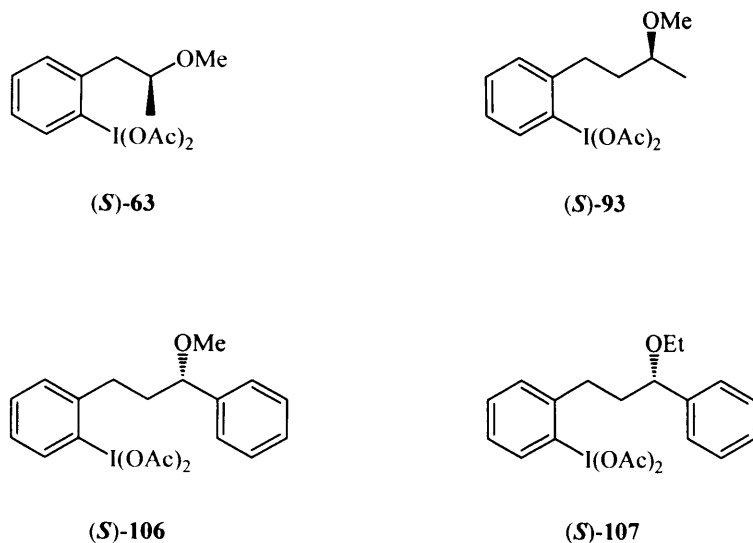


**Scheme 4.3:** Stereoselective  $\alpha$ -oxytosylation of propiophenone **46** with **124**.

During their work using the Koser reagent and its analogues in oxidative functionalisations, the Wirth group observed a dramatic increase of the reaction rate in the dioxytosylation reaction, after the addition of a catalytic quantity of *p*TsOH·H<sub>2</sub>O to the reaction mixture of the hypervalent iodine compound and the alkene. The reactions at room temperature were completed after approximately 4 hours and can be performed even at  $-30^{\circ}\text{C}$ . Only a small amount of the additional *p*TsOH·H<sub>2</sub>O dissolved in the reaction mixture. It was postulated that the Koser reagent (and its analogues) only partially dissociate in the dichloromethane and the additional *p*-toluenesulphonic acid attacks the activated double bond.<sup>10</sup>

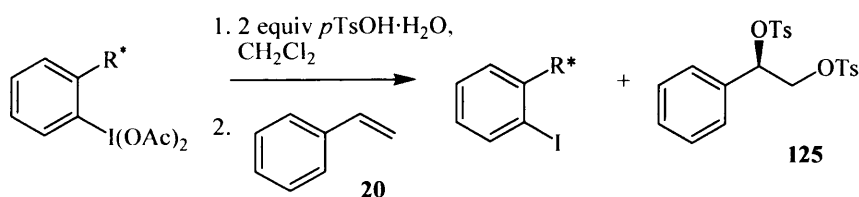
#### 4.2.1 Reactivity of Novel Chiral Hypervalent Iodine Reagents with Styrene

To allow us to investigate the effectiveness of the new range of chiral hypervalent iodine reagents, we needed to generate [hydroxy(tosyloxy)iodo]arenes. As discussed in Chapter Three, it was only possible to isolate five hypervalent compounds in sufficient quantities to allow stoichiometric studies. Reagents **106** and **109** were based on the same iodine(I) precursor, therefore, only **106** was taken forward within these investigations. The four that were studied are shown in Figure 4.2.

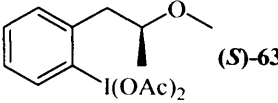
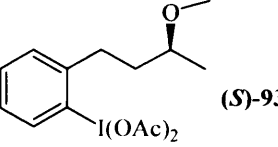
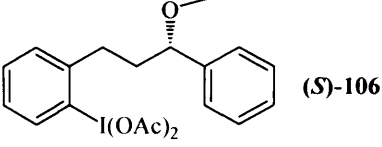
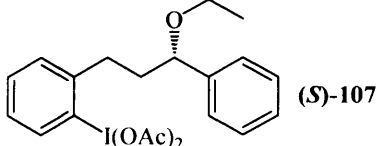


**Figure 4.2:** Chiral iodine(III) reagents used in stoichiometric quantities.

With this in mind an alternative strategy was implemented. The (diacetoxy)iiodoarenes were suspended in dichloromethane and 2 equivalents of *p*-toluenesulphonic acid monohydrate was added portion-wise at room temperature. The resulting mixture was cooled to  $-30^{\circ}\text{C}$  (the initial test reaction was carried out at room temperature) and after 15 minutes freshly distilled styrene **20** was added dropwise (Scheme 4.4). After filtration through silica gel the solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel to yield (*R*)-1,2-bis(tosyloxy)phenylethane **125** (Table 4.1).



**Scheme 4.4:** Synthesis of (*S*)-1,2-bis(tosyloxy)phenylethane **125**.

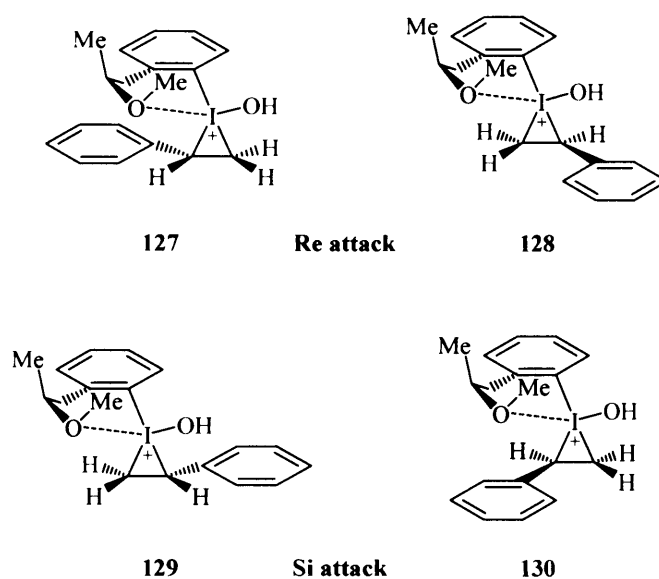
Chiral Reagent	Temperature °C	Yield of 125: %	ee of 125: %
 ( <i>S</i> )-63	25	55	11 ( <i>R</i> )
	-30	51	14 ( <i>R</i> )
 ( <i>S</i> )-93	25	48	9 ( <i>R</i> )
	-30	49	11 ( <i>R</i> )
 ( <i>S</i> )-106	25	67	10 ( <i>R</i> )
	-30	70	16 ( <i>R</i> )
 ( <i>S</i> )-107	25	75	10 ( <i>R</i> )
	-30	59	14 ( <i>R</i> )

**Table 4.1:** Results of dioxytosylation of styrene **20** at room temperature and at  $-30^{\circ}\text{C}$ .

The results show good yields of the dioxytosylated product (48–75%) but low selectivity (9–14% *ee*). As expected, the reaction performed at  $-30^{\circ}\text{C}$  showed higher levels of asymmetric induction than those performed at room temperature, however, these were inferior to those obtained from the iodoarenes with a shorter chiral side chain e.g. **124**.<sup>10</sup>

Although the [hydroxy(tosyloxy)iodo]arene products of **63**, **93**, **106** and **107** have not been isolated, it is proposed that they do form when the (diacetoxy)iodoarene is stirred in the presence of toluenesulphonic acid. The reaction of (*S*)-configured compounds **63**, **93**, **106** and **107** with 2 equivalents of *p*TsOH·H<sub>2</sub>O and styrene **20**, yields the dioxytosylate **125** with (*R*)-configuration. This corresponds to a *Re* facial attack of styrene as seen in the intermediate **127** and **128**. (Figure 4.2). The diastereomeric intermediate **127** (Figure 4.2) can possibly benefit from  $\pi$ -stacking but is assumed to be higher in energy, analogous

to the calculations performed in the Wirth group for the corresponding seleniranium ions.<sup>11</sup>

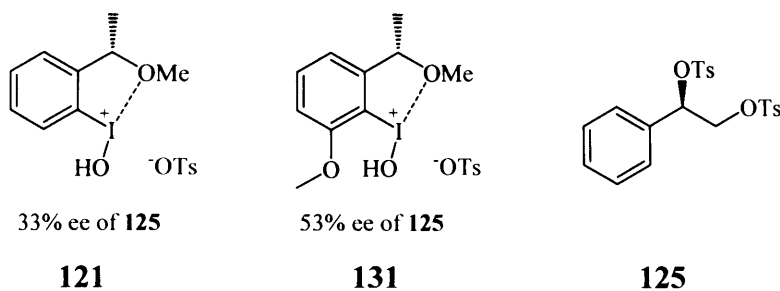


**Figure 4.2:** Possible intermediates **127–130** in the attack of chiral hypervalent reagent **63** on styrene **20**.

A possible way to determine whether **127** is an intermediate would be by altering the electronics of the iodoarene ring. Placing an electron donating substituent (methoxy or amine group) on the iodoarene ring would effectively increase the electron density of the ring and aid the  $\pi$ - $\pi$  interaction. The greater the  $\pi$ -orbital overlap, the more attracted the two aromatic rings will become. The net result of this should be an observed increase in the stereoselectivity of the dioxysylated product. This would increase the likelihood of the tosylate nucleophile attacking from the anti side. Conversely, by introducing an electron withdrawing substituent, one would expect to see a decrease in asymmetric induction.

This effect has been investigated by the Wirth group, and they observed an increase in selectivity when a methoxy group was introduced in the second *ortho* position of the iodoarene ring **131** (Figure 4.3). This evidence leads toward intermediate **127**.

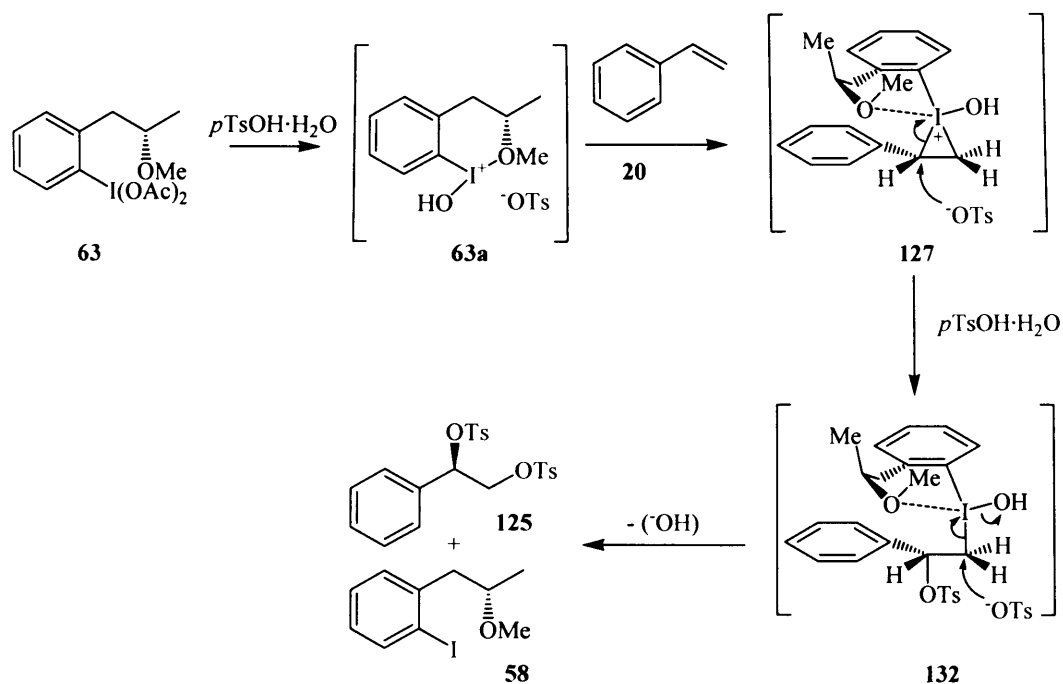




**Figure 4.3:** Comparison of *ee* of (*R*)-**125** when chiral iodanes (*S*)-**121** and (*S*)-**131** are used to dioxytosylate styrene **20**.

To further investigate whether it is in fact **127** or **128** we could increase the steric demand of the styrene moiety. Introducing methyl groups onto both *ortho* positions of the styrene ring would increase the steric requirements of the ring and intermediate **128** may be favoured over **127**.

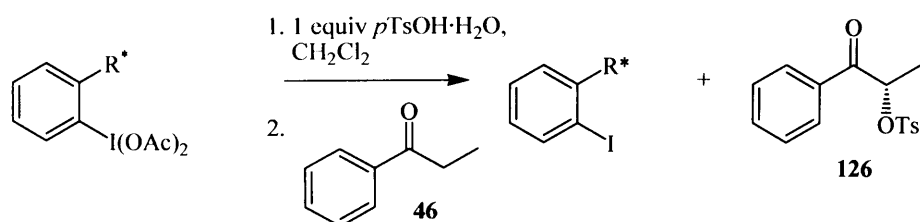
Scheme 4.5 proposes the possible origin of the sense of asymmetric induction observed within these transformations. It is believed that **63** forms the [hydroxy(tosyloxy)iodo]arene intermediate **63a** upon the addition of *p*TsOH·H<sub>2</sub>O. Intermediate **63a** subsequently undergoes electrophilic addition with styrene **20** to form the activated heterocyclic intermediate **127**. The attack of the tosylate anion occurs from the anti-side. The activated heterocyclic intermediate **127**, shields the *syn* face of the intermediate, directing the nucleophile to add from the anti face. The second tosylate anion attacks intermediate **132** from the anti side to give **125**, with the leaving group being the reduced chiral iodine(I) precursor **58**.



**Scheme 4.5:** Proposed mechanism of the dioxytosylation of styrene **20** with **63**.

#### 4.2.2 Reactivity of Novel Chiral Hypervalent Iodine Reagents with Propiophenone

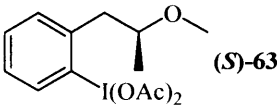
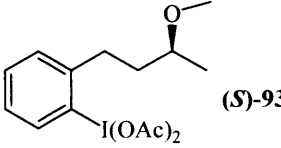
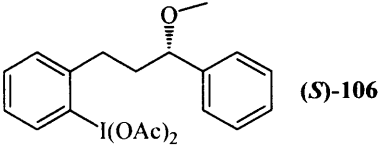
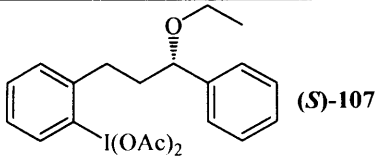
The second model reaction examined was the  $\alpha$ -oxytosylation of propiophenone. Analogous to the stoichiometric reaction with styrene, only chiral reagents that have been oxidised to the hypervalent state can be used to  $\alpha$ -oxytosylate ketones.



**Scheme 4.6:** Synthesis of (*S*)-1-phenyl-oxo-2-tosyloxypropane **126**.

This reaction, like the dioxytosylation of styrene, was only studied with four of the hypervalent compounds that were prepared in Chapter 3

The (diacetoxy)iodoarenes were suspended in dichloromethane and 1 equivalent of *p*-toluenesulphonic acid monohydrate was added portionwise at room temperature. The resulting mixture was cooled to 0°C and after 15 minutes propiophenone was added dropwise (Scheme 4.6). After filtration through silica gel, the solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel to yield (*S*)-1-phenyl-oxo-2-tosyloxypropane **126** (Table 4.2).

Chiral Reagent	Temperature °C	Yield of <b>126</b> : %	<i>ee</i> of <b>126</b> : %
 ( <i>S</i> )- <b>63</b>	25	76	3 ( <i>S</i> )
	0	76	5 ( <i>S</i> )
 ( <i>S</i> )- <b>93</b>	25	66	2 ( <i>S</i> )
	0	60	3 ( <i>S</i> )
 ( <i>S</i> )- <b>106</b>	25	70	9 ( <i>S</i> )
	0	74	12 ( <i>S</i> )
 ( <i>S</i> )- <b>107</b>	25	67	7 ( <i>S</i> )
	0	57	9 ( <i>S</i> )

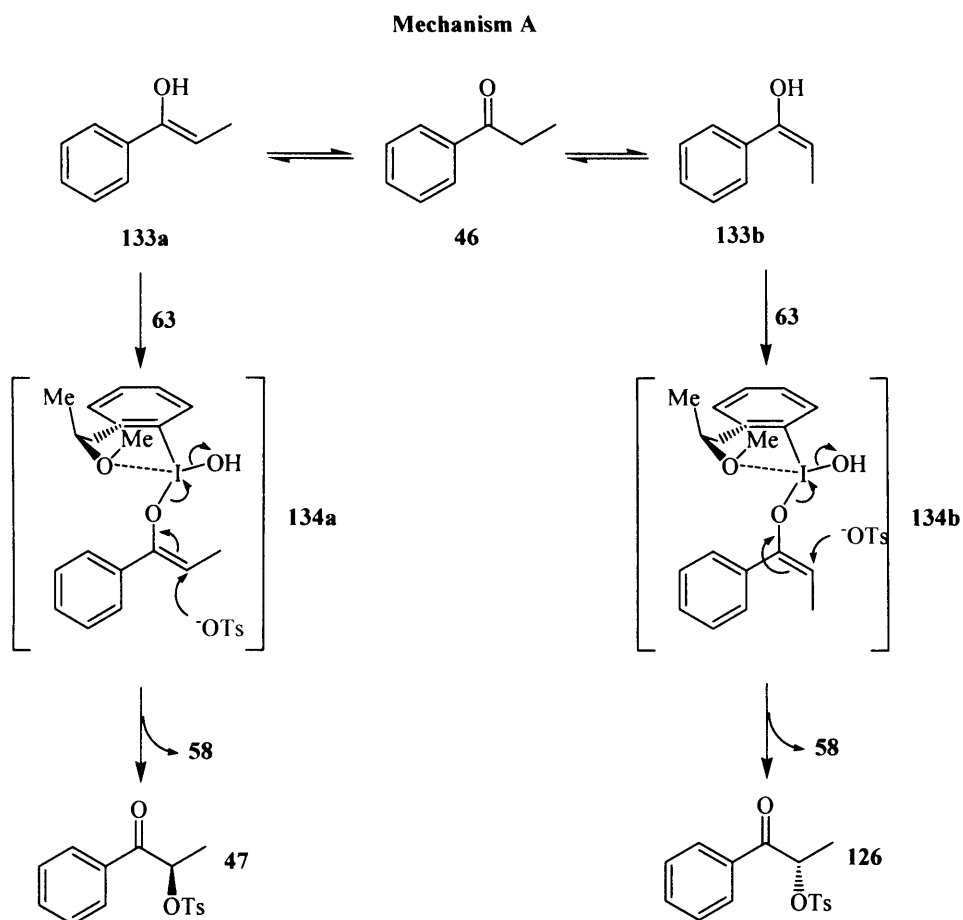
**Table 4.2:**  $\alpha$ -Oxytosylation of propiophenone **46** at room temperature and at -30°C

The results highlight a decrease in selectivity when the chiral chain length increased from a 6- to 7-membered ring. This is observed in the enantioselectivity of product **126** in reactions using reagents **63** (5% *ee*) and **93** (3% *ee*). However, the introduction of a phenyl group at the terminal position of the side chain in

reagent **106** has increased the chiral induction to the substrate providing the oxytosylated product in 12% *ee*.

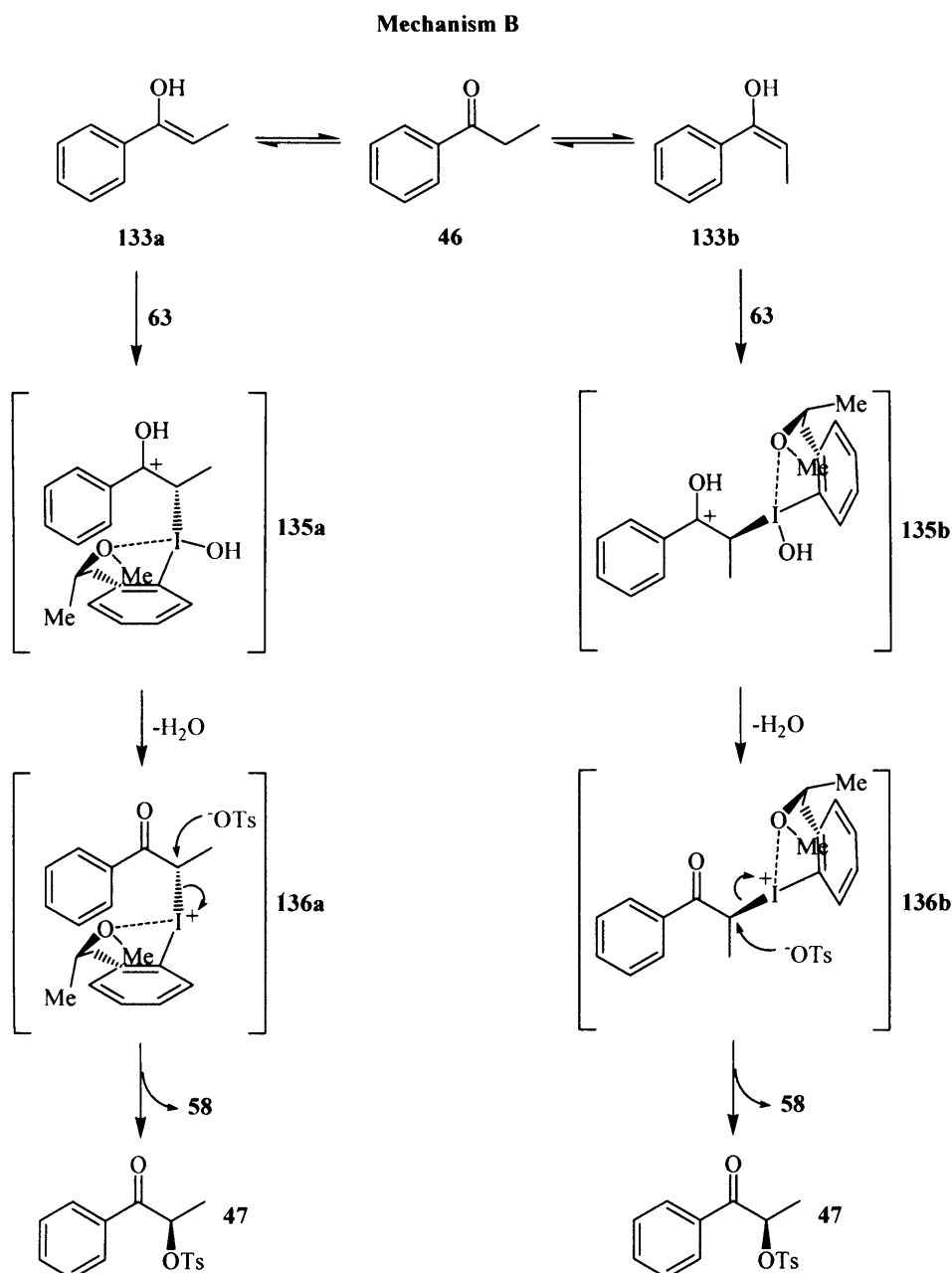
The  $\alpha$ -oxytosylation of propiophenone is a little more complicated than the dioxytosylation of styrene. Both Koser (**A**) and Moriarty (**B**) have proposed mechanisms for this transformation and it is not clear which pathway is favoured. Both mechanisms are plausible and the low enantiomeric excess could be the result of the following:

The enol formed in Mechanism A can be either of *Z* or *E* configuration. If transition state **134a** with the enoxy iodane in the *Z* configuration was present, the dehydration step would be followed (via an S<sub>N</sub>2 type reaction) by a nucleophilic attack of the tosylate ion on the *Si*-face to give the (*R*)-**47**. But if the *E* enoxy iodane formed **134b**, then the tosylate nucleophile would attack from the *Re*-face to generate the (*S*)-**126**. In addition to this, the hypervalent leaving group is attached to the oxygen of the enol, and this single bond can undergo free rotation. Subsequently, the chiral iodine moiety can move and this is not necessarily directing the tosylate nucleophile to one face, resulting in low enantioselectivities (Scheme 4.7).<sup>9,12</sup>



**Scheme 4.7:** Possible transition states during Mechanism A.

A similar problem is occurring during Mechanism B. The electrophilic addition of the iodine(III) reagent to the enol will determine the stereochemistry of the final product. Presently, we have no direct control over which face the addition will occur on. The electrophilic attack of the iodine(III) reagent to the *Z* enol would occur on the *Re*-face and direct the incoming tosylate nucleophile to attack from the *Si*-face leading to (*R*)-**47**. Whereas, attack on the *E* enol will occur on the *Si*-face and lead the tosylate nucleophile to attack from the *Re*-face, to also give the (*R*)-**47** (Scheme 4.8).<sup>13</sup>

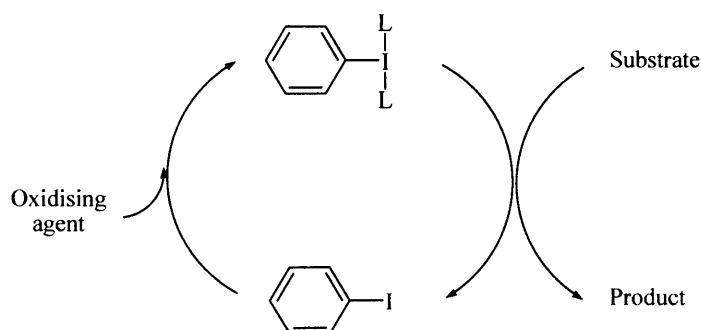


**Scheme 4.8:** Possible transition states during Mechanism B.

If mechanism B takes place then you would expect the final product to have good enantiomeric excess. The configuration of **136a** and **136b** are the same, and would therefore lead to predominantly one enantiomer (*R*)-**47**. This is not observed in the results. It is possible that propiophenone substrate is simply not a good molecule to monitor the effectiveness of these iodine(III) compounds as chiral transfer reagents. Further research will need to be done to identify suitable substrates to demonstrate usefulness of the chiral iodine(III) compounds.

### 4.3 Catalytic Use of Chiral Hypervalent Iodine Compounds

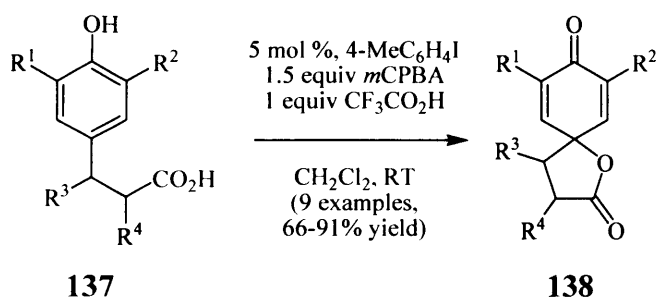
Hypervalent iodine compounds can be used in many synthetic reactions to generate new chiral centres. Until recently, stoichiometric quantities and often an excess of the iodine(III) reagents were required to achieve the desired transformation. The driving force of these reactions was the reduction of the hypervalent iodine to the univalent iodine species, in the reductive elimination step. As previously stated, the stoichiometric quantities required for the oxidation reaction, produce equimolar quantities of aryl iodides as a waste product. Several publications have shown that it is possible to use a catalytic amount of an iodine-containing molecule with a stoichiometric quantity of oxidant and they have recently been reviewed.<sup>14,15</sup> The oxidant generates a hypervalent species *in situ*, and after the key bond forming reaction, the reduced aryl iodide can be re-oxidised. A proposed catalytic cycle is shown in Scheme 4.9.



**Scheme 4.9:** Catalytic cycle with hypervalent iodine compound, where L = OTs, OH, OAc, OR, OCOCF<sub>3</sub>.

Key to the successful catalytic application of hypervalent iodine compounds is the selective oxidation of the aryl iodide in the presence of the substrate. The oxidising agent must be carefully chosen to achieve this selective oxidation. Known oxidants used in the preparation of hypervalent iodine compounds include sodium perborate, peracetic acid and hydrogen peroxide. Recent work reported by Kita *et al.* show the use of *m*CPBA as an oxidant in the synthesis of novel recyclable adamantane-based hypervalent reagents.<sup>16</sup> As a

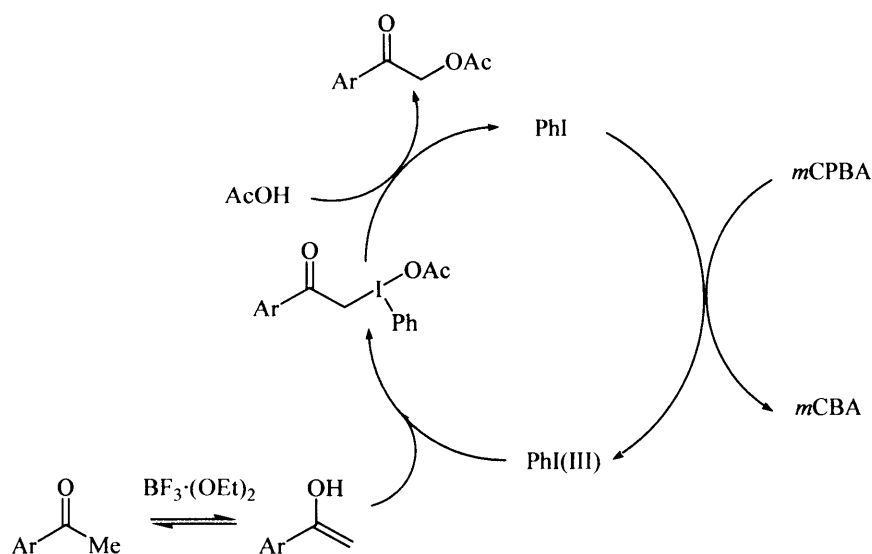
follow up to this, the same research group reported the use of catalytic quantities of iodine(III) reagent in the spirocyclisation of phenol derivatives **137**. Only 5 mol% iodotoluene is used together with 1.5 equivalents of *m*CPBA and 1 equivalent of trifluoroacetic acid to give spirocyclisation to lactones **138** in 66–91% yield (Scheme 4.10).<sup>17</sup>



**Scheme 4.10:** Spirocyclization of phenol derivatives **137** with a catalytic amount of 4-iodotoluene.

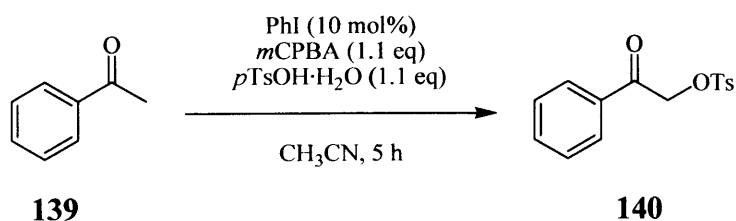
An established reaction involving hypervalent iodine reagents is the  $\alpha$ -oxygenation of carbonyl compounds. Ochiai *et al.* reported the first catalytic  $\alpha$ -acetoxylation of ketones, where (diacetoxyiodo)benzene acts as the catalytic oxidant of ketones with *m*CPBA as the terminal oxidant.<sup>18</sup> To give the  $\alpha$ -acetoxylation of ketones, two additional reagents were required. Firstly, 3 equivalents of boron trifluoride diethyl etherate (BF<sub>3</sub>·OEt<sub>2</sub>) were added to induce enolization of the ketone. No enolization was observed in the absence of the Lewis acid. Secondly, 5 equivalents of water were essential for the reaction to proceed, as without the addition of water, the  $\alpha$ -oxidation was slow with over 95% of the ketone recovered. The reaction was carried out in acetic acid to give the  $\alpha$ -acetoxylation of ketones in moderate yields (43–63%). A proposed catalytic cycle for this reaction is shown in Scheme 4.11. Without the iodoarene, no product was observed. This confirmed that the iodoarene was essential for the  $\alpha$ -oxidation of the ketone. Also, the use of 10 mol% iodoarene was necessary to afford the desired product. Using only 5 mol% significantly slowed down the reaction, allowing the formation of the Baeyer–Villiger product in 38% yield.





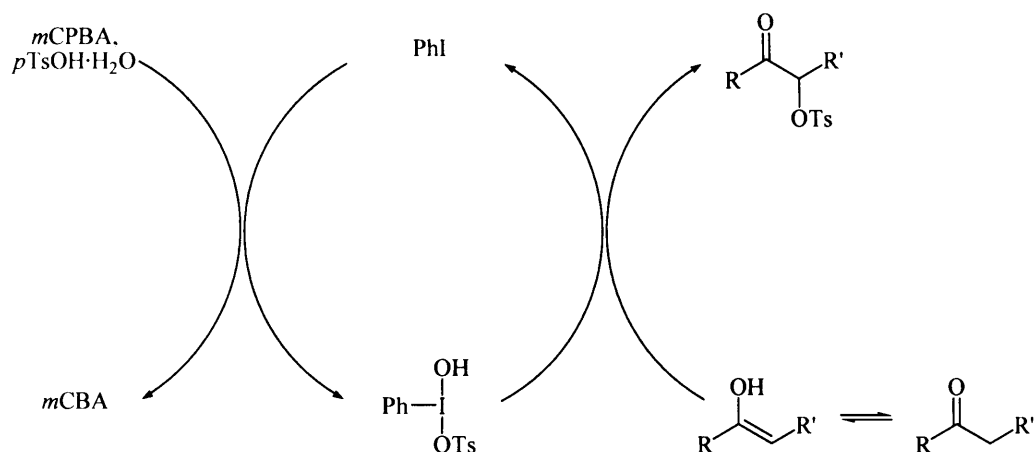
**Scheme 4.11:**  $\alpha$ -Acetoxylation of ketones using catalytic quantities of hypervalent iodine compounds.

As an extension of this reaction, Togo *et al.* used *p*-toluenesulphonic acid in acetonitrile, instead of acetic acid, to synthesise a range of  $\alpha$ -oxytosylated ketones (Scheme 4.12).<sup>19</sup>



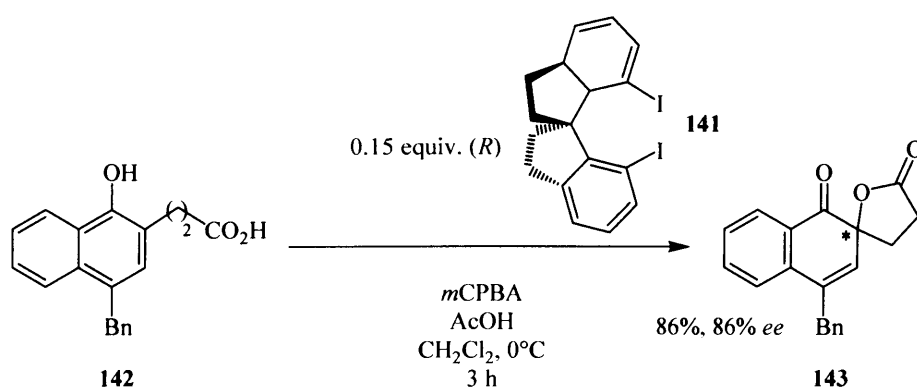
**Scheme 4.12:** ArI-catalysed  $\alpha$ -oxytosylation of acetophenone **139** with *m*CPBA and *p*TsOH·H<sub>2</sub>O.

They found that the use of boron trifluoride diethyl etherate was not necessary to generate the enol exclusively, as the [hydroxy(tosyloxy)iodo]benzene (prepared *in situ*) can react with the small amount of enol tautomer present to provide the  $\alpha$ -oxytosylated ketone **140**. Additionally, water was also not necessary as the reaction proceeds in acetonitrile. The yields obtained in these reactions were very good, ranging from 52–89%. Their proposed catalytic cycle is shown in Scheme 4.13.



**Scheme 4.13:** Proposed reaction pathway for PhI-catalysed  $\alpha$ -oxytosylation of ketones.

After completion of this work, Kita *et al.* published work on a new type of iodoarene catalyst that had a rigid spirobiindane backbone **141**. They have shown that the rigidity maintains the chiral environment around the iodine(III) atom, and it is this that results in high asymmetric induction. They have succeeded in synthesising a range of chiral  $\alpha$ -hydroxy ketones by oxidising alkyl naphthol derivatives using catalytic quantities of the iodoarene **141**, as shown in Scheme 4.14. The  $\alpha$ -hydroxy ketones **143** have been isolated in yields up to 86% and up to 86% *ee*, at 0°C.<sup>20</sup>

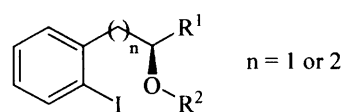


**Scheme 4.14:** Catalytic dearomatisation of phenols using spirobiindane iodoarene **141**.

Subsequently, the use of hypervalent iodine compounds in catalytic reactions represents a very exciting prospect indeed. As discussed in Chapter Three, many of the chiral hypervalent compounds whose synthesis has been attempted, could not be investigated due to the difficulties encountered in the oxidation. Those that were oxidised to the diacetoxy or trifluoroacetoxy arene, failed to yield the corresponding [hydroxy(tosyloxy)iodo]arenes through ligand exchange. This step essentially reduced the hypervalent species to its non-hypervalent precursor. However, the advent of catalytic reactions provided us with the opportunity to circumvent this problem. If the hypervalent species could be prepared *in situ* allowing the electrophilic addition to occur in this one pot reaction, isolation of the hypervalent compound would not be necessary. The following sections report the results found using the enantiopure iodine compounds in catalytic reactions.

### 4.3.1 Catalytic $\alpha$ -Acetoxylation of Ketones with Chiral Iodine Reagents

The synthesis of the hypervalent precursor shown in Figure 4.3, was carried out over 5 steps (where  $n = 1$ ) and 3 steps (where  $n = 2$ ).



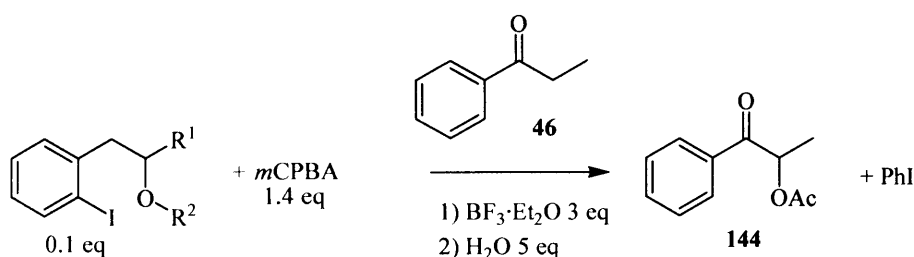
**Figure 4.3:** Novel chiral hypervalent precursor.

All of the precursors were obtained in excellent yields from the corresponding chiral alcohols. The shorter chain iodoarene precursors ( $n = 1$ ) were synthesised in yields ranging between 55–96%, and the longer chain precursors ( $n = 2$ ) were isolated between 58–96% yield.

As the stoichiometric reactions using these compounds were severely limited, the novel catalytic  $\alpha$ -acetoxylation reaction developed by Ochiai<sup>18</sup> offered a possible route to utilize the unique properties of the unisolable hypervalent iodine species. The generation of any  $\alpha$ -acetoxyated product would serve as proof that these compounds were being oxidised to the hypervalent state. With an array of enantiopure hypervalent iodine precursors already prepared, this was an excellent opportunity to investigate their synthetic utility.

#### 4.3.1.1 Reactivity of Pseudo 6-Membered Chiral Iodanes

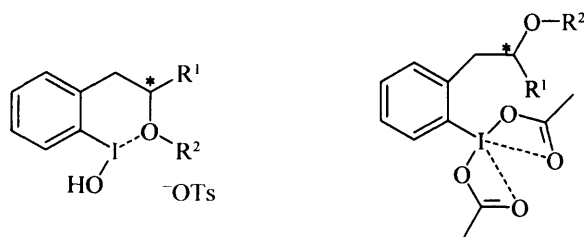
As described in Chapter Three, a wide range of different hypervalent precursors had been prepared. Our primary focus was to determine whether any hypervalent product could be formed within a catalytic cycle. Initial reactions were performed by reacting propiophenone **46** to a catalytic amount (10 mol%) of chiral iodoarene, dry *m*CPBA (1.4 equiv) in acetic acid,  $\text{BF}_3 \cdot \text{OEt}_2$  (3 equiv) and water (5 equiv) at room temperature under argon. Yields of 1-phenyl-oxo-propan-2-acetate **144** synthesised from iodoarene precursors as shown in Scheme 4.15 are shown in Table 4.3.



**Scheme 4.15:** ArI-catalysed  $\alpha$ -acetoxylation of propiophenone **46** with *m*CPBA,  $\text{BF}_3 \cdot \text{OEt}_2$  and water.

The results obtained in the catalytic reaction suggest that these aryl iodides were oxidised to the hypervalent state. If the iodoarene was omitted from the reaction mixture, no  $\alpha$ -acetoxyated product was observed. Even though the yields were only modest, this presented an important result. To determine whether any

transfer of chiral information had occurred, the enantiomeric excess of the acetoxyated product **144** was determined by HPLC. As expected, the traces showed that the racemic product had in been synthesised. This was not surprising, as the selectivity observed with the stoichiometric  $\alpha$ -oxytosylation reactions occur because the oxygen of the chiral side chain coordinates to the iodine atom, effectively replacing the oxygen of the tosylate moiety as shown in Figure 4.4.



**Figure 4.4:** A [hydroxy(tosyloxy)iodo]arene and a (diacetoxy)iodoarene.

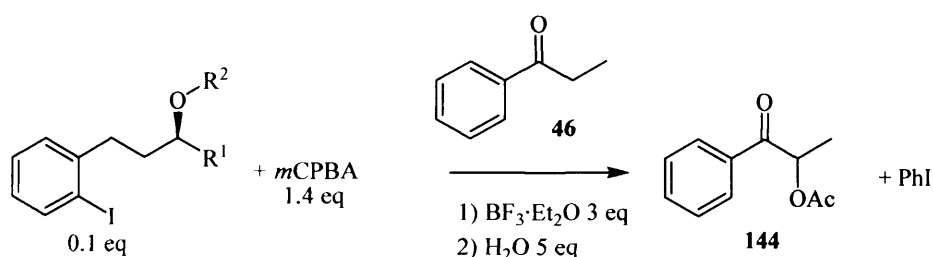
This is not the case with diacetoxy iodoarenes.<sup>10</sup> Here, the iodine is hypervalently bound to two acetoxy ligands where the carbonyl oxygen's coordinate the iodine atom. This decreases the interaction of the oxygen of the chiral side chain from the ensuing reaction, resulting in the racemic product observed.

Reagent	R <sup>1</sup>	R <sup>2</sup>	Yield of 144: %
<b>58</b>	Me	Me	53
<b>59</b>	Me	Et	45
<b>60</b>	Me	Bn	46
<b>61</b>	Me	COCF <sub>3</sub>	0
<b>61</b>	Me	<sup>t</sup> Bu	12
<b>69</b>	Ph	Me	41
<b>70</b>	Ph	Et	37
<b>71</b>	Ph	Bn	29

**Table 4.3:** Catalytic  $\alpha$ -acetoxylation of propiophenone **46**.

4.3.1.2 **Reactivity of Pseudo 7-Membered Chiral Iodanes**

In Chapter Three the preparation of a range of hypervalent iodine precursors based around a pseudo 7-membered chiral ring structure was also discussed. As observed with the pseudo 6-membered range of iodoarenes, this type of hypervalent precursor also encountered problems when attempting to prepare hypervalent derivatives. The results in Table 4.4 show the yield of 1-phenyl-oxo-propan-2-acetate **144** when this type of chiral hypervalent precursor was used within the catalytic  $\alpha$ -acetoxylation reaction (Scheme 4.16).

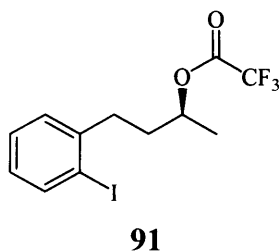


**Scheme 4.16:** ArI-catalysed  $\alpha$ -acetoxylation of propiophenone **46** with *m*CPBA,  $\text{BF}_3 \cdot \text{OEt}_2$  and water.

Reagent	R <sup>1</sup>	R <sup>2</sup>	Yield of <b>144</b> : %
<b>88</b>	Me	Me	55
<b>89</b>	Me	Et	50
<b>90</b>	Me	Bn	39
<b>91</b>	Me	COCF <sub>3</sub>	0
<b>92</b>	Me	<sup>t</sup> Bu	15
<b>103</b>	Ph	Me	57
<b>104</b>	Ph	Et	45
<b>105</b>	Ph	Bn	44
<b>115</b>	<sup>t</sup> Bu	Me	30
<b>116</b>	<sup>t</sup> Bu	Et	32
<b>117</b>	<sup>t</sup> Bu	Bn	27

**Table 4.4:** Catalytic  $\alpha$ -acetoxylation of propiophenone **46**.

Encouragingly, the results indicated that a hypervalent species was being produced in the majority of the examples. The only precursor not to give any 1-phenyl-oxo-propan-2-acetate **144** was chiral reagent **91** which had a trifluoroacetate moiety attached to the oxygen of the chiral carbon (Figure 4.6). In this case the iodine(I) precursor was not recovered and a decomposition product was formed.

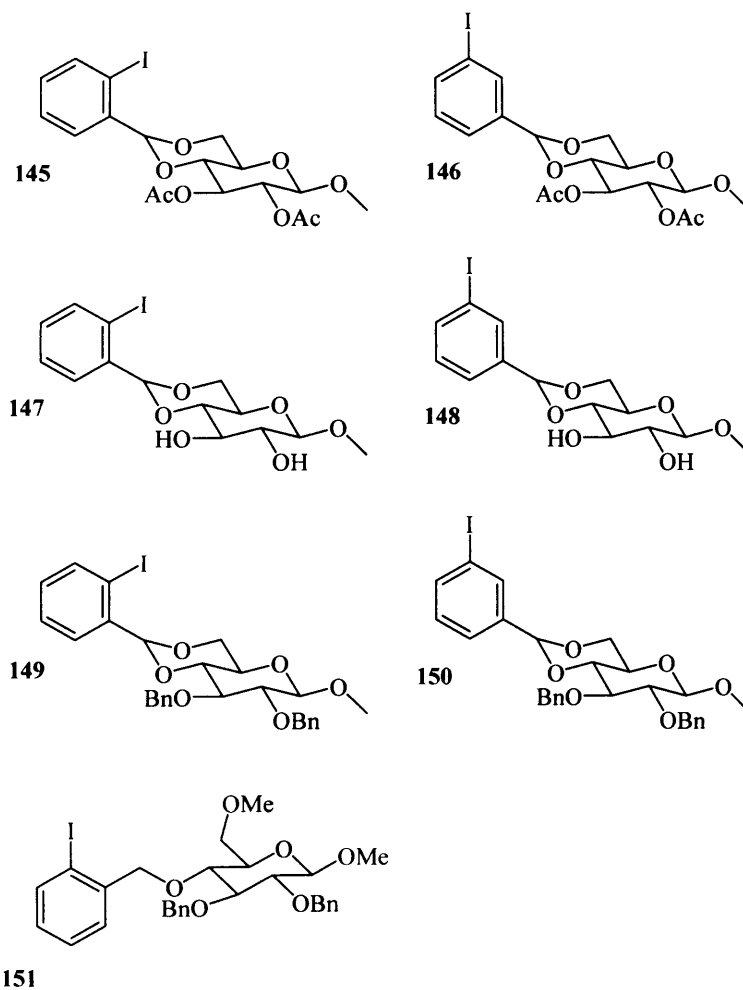


**Figure 4.5:** The unsuccessful trifluoroacetoxo iodoarene **91**.

Again, the important factor is the generation of the  $\alpha$ -acetoxylated product and not the modest yields. The results from this reaction did not yield any enantiomerically enriched ketone, but it served as an indicator to the proposed generation of a hypervalent iodine species.

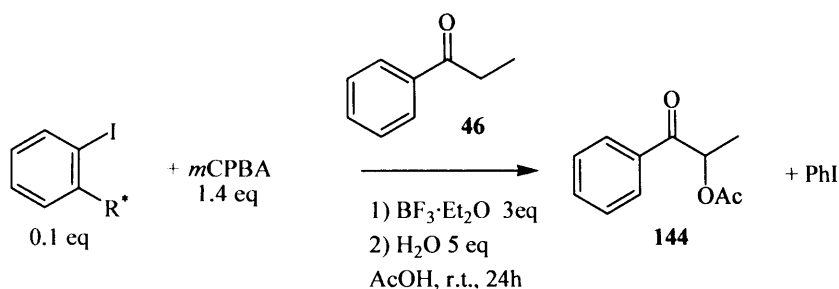
**4.3.1.3 Reactivity of Chiral Sugar Based Iodoarenes**

During 2005, several chiral sugar based hypervalent precursors were prepared by Dr Christian Becker (Figure 4.6).<sup>21</sup> Becker synthesized compounds **145–151** through the introduction of an aryl iodide moiety onto a chiral sugar backbone.



**Figure 4.6:** Chiral sugar derived hypervalent precursors **145–151**.





**Scheme 4.17:** Sugar based iodoarene–catalysed  $\alpha$ -acetoxylation of propiophenone **46** with *m*CPBA,  $\text{BF}_3 \cdot \text{OEt}_2$  and water.

The yields of the iodine(I) precursor compounds were good, but oxidation to the hypervalent state proved elusive. Several oxidative methods were examined with these chiral iodoarenes, but no hypervalent products were observed. Following on from the successful catalytic reactions, it was decided to use these chiral iodoarenes in the  $\alpha$ -acetoxylation of propiophenone (Table 4.5).

Chiral sugar reagent	Yield of <b>144</b> : %
<b>145</b>	5
<b>146</b>	15
<b>147</b>	4
<b>148</b>	5
<b>149</b>	9
<b>150</b>	46
<b>151</b>	0

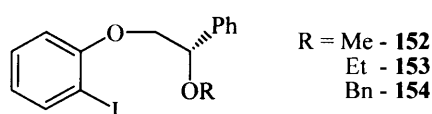
**Table 4.5:** Catalytic  $\alpha$ -acetoxylation of propiophenone **46** using chiral sugar based iodoarenes **145–151**.

The success of these unusual chiral compounds was mixed. The majority of them produced modest yields of the  $\alpha$ -acetoxyated product **144**, with **150** affording 46% of  $\alpha$ -functionalised propiophenone. The only derivative that failed to produce any product was compound **151**. This compound differs slightly in that the iodoaryl group was not attached to an acetal but a single benzylic oxygen

atom. The free rotation available here could possibly be interfering with the oxidation process.

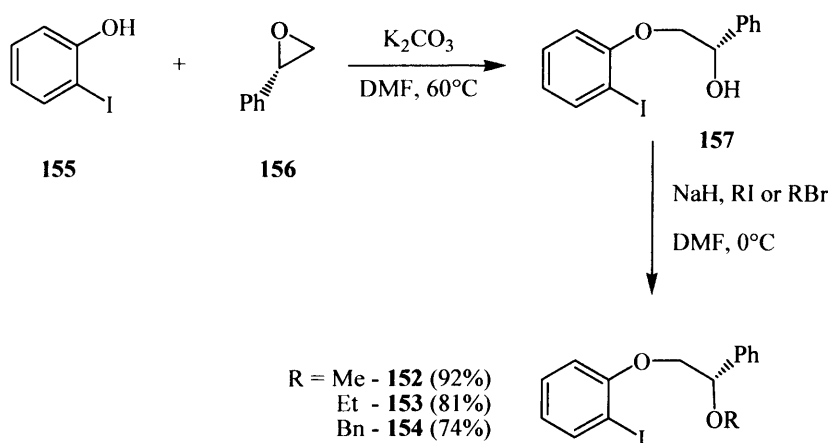
#### 4.3.1.4 Reactivity of Chiral Ether Iodoarenes

Another avenue of chiral hypervalent reagents pursued in the Wirth group is shown below (Figure 4.7).



**Figure 4.7:** Ether based chiral hypervalent iodine compounds **152–154**.

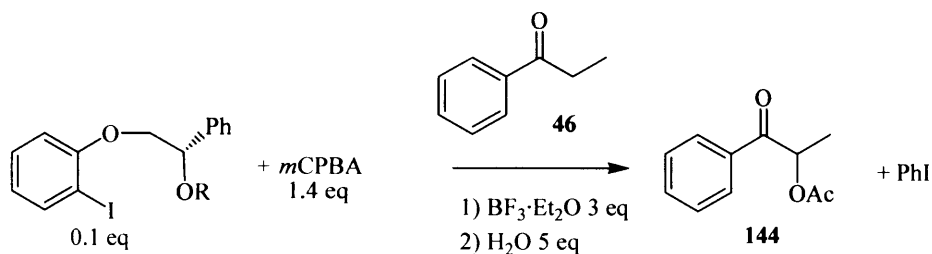
This type of reagent was devised in collaboration between Dr French and Professor Wirth during Dr French's sabbatical year in Cardiff.<sup>22</sup> The synthesis of the chiral hypervalent precursor was realized in only 2 steps.



**Scheme 4.18:** Two-step synthesis of chiral ether iodoarenes **152–154** from 2-iodophenol **155** and (*S*)-phenyloxirane **156**.

The synthesis begins with a chiral epoxide opening using potassium carbonate in dimethyl formamide and the phenol **155**. Subsequent alkylation with

an alkyl iodide or alkyl bromide gave the chiral aryl iodides **152-154** (Scheme 4.18).



**Scheme 4.19:** Chiral ether iodoarene-catalysed  $\alpha$ -acetoxylation of propiophenone **46** with *m*CPBA,  $\text{BF}_3 \cdot \text{OEt}_2$  and water.

With the ongoing problems associated with oxidation of these chiral reagents, these ethers represented ideal candidates to apply within the catalytic reaction (Scheme 4.19). The results obtained are outlined in Table 4.6.

Chiral ether reagent	Yield of <b>144</b> : %
<b>152</b>	55
<b>153</b>	19
<b>154</b>	25

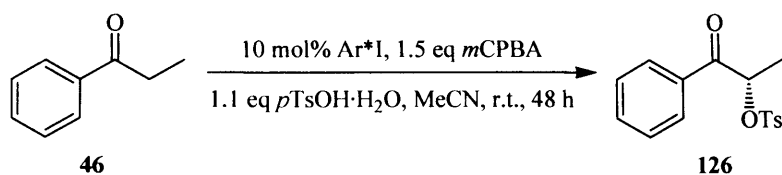
**Table 4.6:** Catalytic  $\alpha$ -acetoxylation of propiophenone **46** using chiral ether iodoarenes **152-154**.

While the yields of the acetoxyated product were only modest (19-55%), it was clear that these ether containing iodoarenes were active catalysts and were being oxidised to the hypervalent state. This was again good news and further research with this type of iodoarene is ongoing.

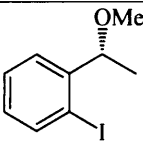
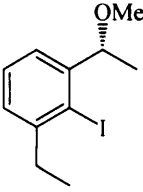
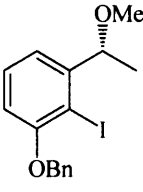
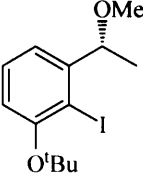
### 4.3.2 Catalytic $\alpha$ -Oxytosylation of Ketones with Chiral Iodine Reagents

The relative success in obtaining the  $\alpha$ -acetoxyated ketones provided good evidence towards the formation of a hypervalent species. A natural progression from this was to find a way of using these reagents. The logical step was to try and prepare the [hydroxy(tosyloxy)iodo]arene in the one-pot catalytic reaction. Further research led onto work by Togo *et al.*<sup>19</sup> As mentioned previously, they used a stoichiometric quantity of *p*TsOH·H<sub>2</sub>O and *m*CPBA with 10 mol% of the hypervalent precursor in acetonitrile to generate the  $\alpha$ -oxytosylated ketone (Scheme 4.12). Most notably in this case was the omission of the additives borontrifluoride diethyl etherate and water. The [hydroxy(tosyloxy)iodo]arene can react sufficiently well with the enol form of the ketone in acetonitrile to provide the  $\alpha$ -oxytosylated ketone.

Initial reactions were performed with several iodoarenes, which were originally synthesised by Hirt, a previous researcher in the Wirth group.<sup>23</sup> These iodoarenes were chosen as they could be oxidised in sufficient quantities to enable studies of the stoichiometric reaction with propiophenone. The only difference between the stoichiometric and catalytic reaction was the temperature. From early studies on the stoichiometric process, it was determined that the optimum temperature for the  $\alpha$ -oxytosylation reaction was 0°C, as this temperature gave the highest enantioselectivity. Catalytic studies at this temperature revealed that the reaction proceeded very slowly and these results were consistent with those of Togo.<sup>19</sup> As the ligand exchange was slow at this temperature, these results suggested that the rate determining step of the catalytic cycle was the oxidation to the hypervalent iodine(III) state. With this in mind we opted to perform the reactions at room temperature, allowing them to run for up to two days to ensure maximum conversion.<sup>24</sup>



**Scheme 4.20:** Catalytic  $\alpha$ -oxytosylation reaction with a range of enantiopure iodoarenes.

Reagent <sup>23</sup>	Reaction type	Temp. °C	Yield of 126:%	ee of 126: %
(S)-158 	Stoichiometric	0	70	15 ( <i>S</i> )
	Catalytic	25	68	12 ( <i>S</i> )
(S)-159 	Stoichiometric	0	65	28 ( <i>S</i> )
	Catalytic	25	59	27 ( <i>S</i> )
(S)-160 	Stoichiometric	0	57	29 ( <i>S</i> )
	Catalytic	25	50	25 ( <i>S</i> )
(S)-161 	Stoichiometric	0	10	11 ( <i>S</i> )
	Catalytic	25	9	3 ( <i>S</i> )

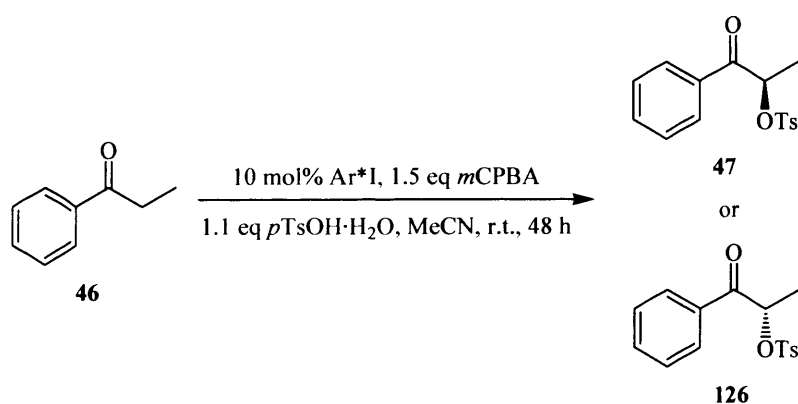
**Table 4.7:** Comparison of results from stoichiometric and catalytic  $\alpha$ -oxytosylation of propiophenone **46** in dichloromethane.

The results obtained at room temperature from the catalytic reaction show the expected relationship to those found at 0°C in the stoichiometric reaction

when performed in dichloromethane (Table 4.7). In most cases both isolated yields and levels of asymmetric induction were similar. This catalytic method therefore represents a significant improvement on previous results with the group.

#### 4.3.2.1 Reactivity of Novel Chiral Hypervalent Precursors

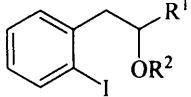
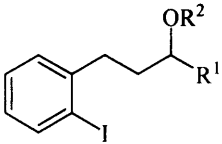
The catalytic  $\alpha$ -oxytosylation reaction allowed us to examine the effectiveness of our novel hypervalent precursors, which up until now had remained redundant. The reactions were performed by treating 0.5 mmol of propiophenone in acetonitrile with 10 mol% iodoarene, 1.5 equivalents of commercial *m*CPBA (dried in a desiccator for 24 hours) as the stoichiometric oxidant and 1.1 equivalents of *p*TsOH·H<sub>2</sub>O as the tosylate nucleophile (Scheme 4.21). The reaction was performed at room temperature to afford either (*R*)-**47** or (*S*)-**126** in yields between 51–76% (Table 4.8).



**Scheme 4.21:** Catalytic  $\alpha$ -oxytosylation reaction with a range of enantiopure iodoarenes.

In all cases the tosylated propiophenone product was observed. The yields of 1-phenyl-oxo-2-tosyloxypropane were good, but the levels of asymmetric induction from these extended chiral iodoarenes was poor. To improve the transfer of chiral information the temperature could be lowered to 0°C. However,

as seen in the stoichiometric reactions the reaction rate reduces, therefore, this opportunity was not examined.

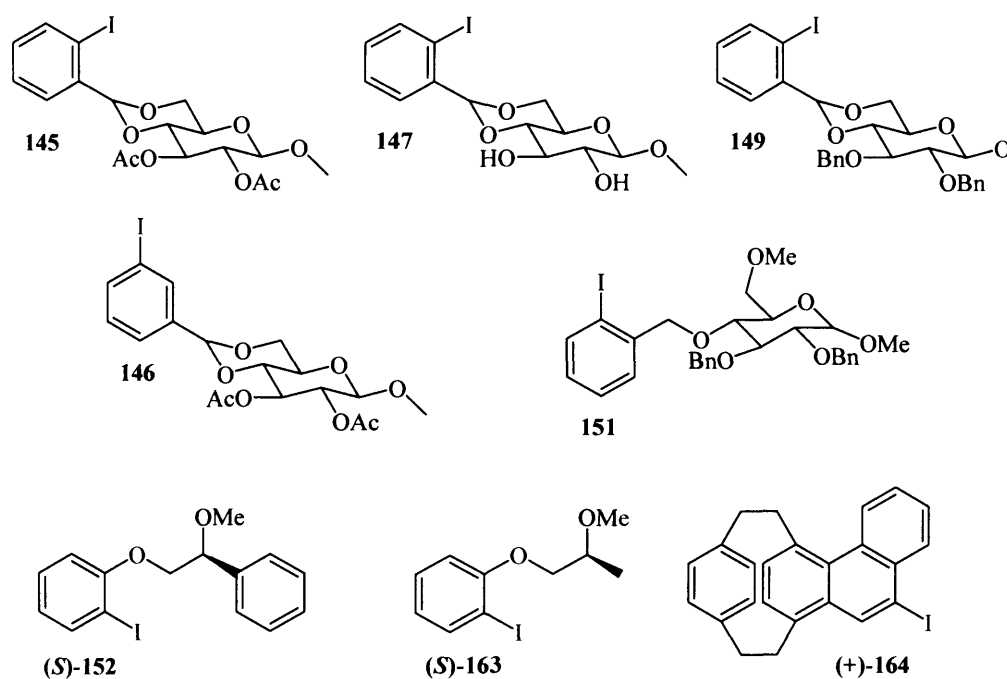
Chiral iodoarene	Number	R <sup>1</sup>	R <sup>2</sup>	Yield of Product : %	ee %
	(S)-58	Me	Me	76	3 (S)-126
	(S)-59	Me	Et	74	2 (S)-126
	(S)-60	Me	Bn	74	2 (S)-126
	(S)-69	Ph	Me	64	5 (S)-126
	(S)-70	Ph	Et	54	3 (S)-126
	(R)-77	<sup>t</sup> Pr	Me	58	3 (R)-47
	(S)-88	Me	Me	66	2 (S)-126
	(S)-89	Me	Et	59	1 (S)-126
	(S)-90	Me	Bn	51	2 (S)-126
	(S)-92	Me	<sup>t</sup> Bu	57	2 (S)-126
	(S)-103	Ph	Me	70	9 (S)-126
	(R)-115	<sup>t</sup> Bu	Me	56	3 (R)-47
(R)-116	<sup>t</sup> Bu	Et	55	1 (R)-47	

**Table 4.8:** Catalytic  $\alpha$ -oxytosylation of propiophenone **46** using novel chiral hypervalent precursors.

The yields observed in the catalytic  $\alpha$ -oxytosylation of propiophenone were very good, but the enantioselectivities were low. Reagents **69** and **103** with a phenyl moiety in the terminal position of the chain R<sup>1</sup> gave the highest selectivities, of 5% and 9% respectively. A methyl group in the R<sup>2</sup> position appears to have a greater influence than either an ethyl or benzyl moiety. The latter pattern shows good correlation with earlier work in the Wirth group.<sup>10</sup>

### 4.3.2.2 Reactivity of Alternate Novel Chiral Hypervalent Precursors

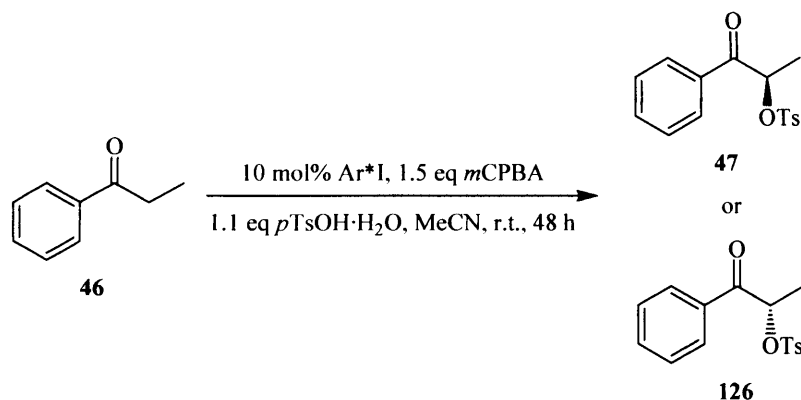
The range of aryl iodides prepared by the Wirth group that also encountered oxidation problems in the preparation of hypervalent iodine reagents were also examined in the catalytic  $\alpha$ -oxytosylation trials (Figure 4.8).



**Figure 4.8:** Alternate chiral hypervalent precursors examined in the catalytic  $\alpha$ -oxytosylation of propiophenone **46**.

The chiral sugar based iodoarenes synthesized by Becker, the chiral ether based iodoarenes derived from styrene epoxide developed by French and several other iodoarenes were tested (Scheme 4.22).<sup>21,22</sup>





**Scheme 4.22:** Catalytic  $\alpha$ -oxytosylation reaction with a range of enantiopure iodoarenes.

Each one of the chiral precursors was subjected to the same reaction conditions as those described section 4.3.2.1 and the results obtained are shown in Table 4.9. The chiral sugar based iodoarenes showed poor product yields even though they were left to react for an extended period (~90 hours) and very little transfer of chiral information resulted, as shown by the low levels of enantioselectivity obtained. This was possibly due to the distance of the iodine atom from the chiral sugar moiety.

Reagent	Yield of Product: %	ee %
145	10	1 ( <i>S</i> )-126
146	17	0
147	11	2 ( <i>S</i> )-126
149	5	1 ( <i>S</i> )-126
151	19	1 ( <i>R</i> )-47
( <i>S</i> )-152	75	25 ( <i>R</i> )-47
( <i>S</i> )-163	91	3 ( <i>R</i> )-47
(+)-164	75	1 ( <i>R</i> )-47

**Table 4.9:** Catalytic  $\alpha$ -oxytosylation of propiophenone using alternative chiral hypervalent reagents.

Surprisingly, the chiral ether iodoarene derived from styrene oxide (*S*)-**152** resulted in excellent conversion and modest enantioselectivity of (*R*)-1-phenyl-oxo-2-tosyloxypropane (*R*)-**47**. The product was isolated in 75% yield and 25% *ee*. This particular result is promising as the hypervalent precursor was synthesized in only two steps. The iodoarene derived from propylene oxide (*S*)-**163** gave a good yield of the tosylated product but resulted poor enantioselectivity within the product. The difference between these results can be attributed to the terminal group on each of the chiral chains. The phenyl group is far larger than the methyl group, which could aid directing the nucleophile, but it is also possible that there was some degree of  $\pi$ -stacking of the phenyl rings. This would lead to increased conformational rigidity and higher enantioinduction. Finally, the iodoparacyclophane derivative (+)-**164** gave very good yields of tosylated product, but with no discernable selectivity.

## 4.4 Conclusion

In this Chapter we have investigated the reactivity of the next generation ‘Wirth chiral reagent’. Their potential use is widespread with environmental benefits over their heavy metal alternatives. As seen in Chapter Three, many of these hypervalent precursors will not oxidise to a stable (diacetoxy) or bis(trifluoroacetoxy)iodoarene. This of course is a very big issue. Until now, stoichiometric quantities of the hypervalent compound had been required to afford new stereogenic centres. The application of chiral reagents **63** and **93** in the dioxytosylation of styrene at  $-30^{\circ}\text{C}$ , afforded 1,2-bis(tosyloxy)phenylethane in 14 and 11% *ee* respectively. These *ee*’s are lower than the result obtained using the smaller chained ‘Wirth’ type iodoarene **124** (15% *ee*). With each carbon that was added to increase the chain length comes a greater degree of free rotation about the carbon-carbon bonds. The interaction of the oxygen atom on the chiral chain with the iodine atom therefore decreases as the chain increases. This results in a decrease in enantioselectivity of the  $\alpha$ -oxytosylated propiophenone product **126**.

Although the results were disappointing, the replacement of the terminal methyl group with a phenyl group increased the selectivity obtained within the product. This is shown in the results obtained from reagents **106** (16% *ee*) and **107** (14% *ee*). Whether this is due to the greater size or because there is an element of  $\pi$ -stacking, involved between the two aromatic rings, will only be determined through further investigation.

With the advent of a catalytic acetoxylation and more importantly the catalytic  $\alpha$ -oxytosylation reactions, we continue to have an avenue to test the ‘Wirth’ type reagents. These reactions have allowed us to observe the potential of these reagents and study their asymmetric induction with in ketone functionalisation. Further work is necessary to develop reagents that reduce the flexibility of the chiral chain, to increase the transfer of chiral information.

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<sup>23</sup> Hirt, U. H. *PhD Thesis, University of Basel, 2000.*

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## Chapter 5

# 5 Oxidation to the Hypervalent state

## 5.1 Introduction

In this chapter, the oxidation of iodoarenes will be reported. After a brief overview of the literature of known procedures for the oxidation of iodoarenes to  $\lambda^3$ -iodanes and  $\lambda^5$ -iodanes, the new methodology developed to prepare [bis(trifluoroacetoxy)iodo]arenes will be discussed.

Following Willgerodt's work in the late part of the 19<sup>th</sup> century, the synthetic organic chemist has developed a multitude of hypervalent iodine compounds.<sup>1</sup> By the mid 1950's they numbered 426, as catalogued by Beringer and Gindler.<sup>2</sup> Today, there are too many hypervalent iodine compounds to document in full but the majority of them belong to well-defined families.

Methods for the preparation of hypervalent iodine reagents that have been developed vary considerably but there are several reliable methods that are consistently used. A publication by Varvoglis<sup>3</sup> in 1992 listed an extensive range of preparative methods for individual compounds and another in 1997 gave more selective methods of preparing these compounds.

The general approach for the preparation of the most common hypervalent iodine compounds involves initial oxidation of iodine(I) to iodine(III) or (V). This requires the correct choice of strongly electrophilic reagent as well as conditions which will lead to the formation of either one, for iodine(III), or two, for iodine(V) hypervalent bonds.

It is possible, in principle, to oxidise both aryl iodides and alkyl iodides, although the products from alkyl iodides are considerably more unstable than their aryl counterparts. Of practical importance are hypervalent iodine compounds with halides (chloride, fluoride) and acetoxy or trifluoroacetoxy groups as ligands.

The following sections present the most common synthetic methods for preparation of hypervalent iodine compounds. Sectionalised into the type of ligands attached to the iodine.

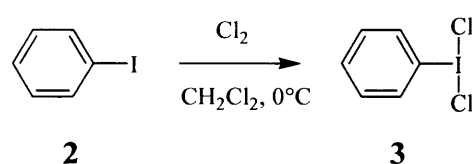
## 5.2 Iodanes with One Iodine-Carbon Covalent Bond

Iodanes with one iodine-carbon covalent bond includes (dichloroiodo)arenes and (difluoroiodo)arenes along with compounds that contain iodine-oxygen bonds, for example, (diacetoxy)iodobenzene **6**, Koser reagent **15**, Dess-Martin periodinane **29**, iodosobenzene **7** and *o*-iodoxybenzoic acid **24**.

The conditions required for the initial oxidation of an iodoarene to the hypervalent state, usually requires a powerful oxidant. However, many hypervalent iodoarenes are prepared through ligand exchange reactions. The conditions in these reactions are particularly mild, since no or little heating is required, protection from daylight is not necessary, and the use of an inert atmosphere is rarely mandatory.

### 5.2.1 Iodanes with Iodine-Chlorine hypervalent bonds

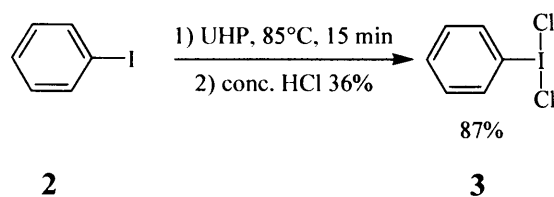
Willgerodt prepared the most useful iodanes with iodine-chlorine hypervalent bonds in 1886.<sup>4</sup> The method, which is still used, relies upon the direct combination of elemental chlorine with the corresponding iodide (Scheme 5.1). The usual procedure is to dissolve the iodoarene **2** in a suitable solvent, preferably chloroform or dichloromethane, and passing chlorine gas through this solution at 0°C:



**Scheme 5.1:** Willgerodt's synthesis of (dichloroiodo)benzene **3**.

This method has been applied to the large-scale preparation of  $\text{PhICl}_2$  where it was obtained in 94% yield starting from 20 kg of iodobenzene.<sup>5</sup> In order to avoid the use of elemental chlorine, its generation *in situ* can be effected by oxidation with hydrochloric acid and sodium perborate tetrahydrate in acetonitrile or tetrachloromethane (possible carcinogen, largely removed from educational and industrial laboratories) at room temperature. Although most aliphatic analogues are unstable, (dichloroiodo)perfluoroalkanes are stable. In order to prepare such compounds only chlorine is necessary without any solvent and the reaction takes place at low or room temperature.<sup>6</sup> A more recent publication describes the oxidation of iodoarenes without the inconvenient use of gaseous chlorine. It was shown that the use of urea-hydrogen peroxide adduct (UHP), which is a stable, inexpensive and safely handled oxidant, and 36% hydrochloric acid resulted in the effective formation of (dichloroiodo)arenes from iodoarenes (Scheme 5.2) with yields ranging from 64–98%.<sup>7</sup>

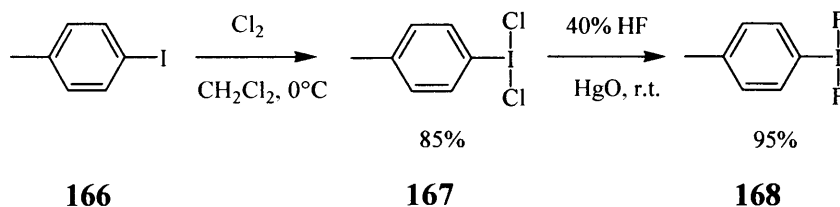




**Scheme 5.2:** Preparation of (dichloriodo)benzene **3** using UHP and HCl.

### 5.2.2 Iodanes with Iodine-Fluorine Hypervalent Bonds

The direct fluorination of iodoarenes and iodoalkanes is possible with either diluted elemental fluorine or xenon difluoride, the latter being rather expensive. The most common method for the preparation of useful  $\text{ArIF}_2$  **168** is through the Carpenter method, which involves two steps.<sup>8</sup> Scheme 5.3 shows the oxidation of an iodide with elemental chlorine followed by ligand exchange of the resulting dichloride **167** with hydrofluoric acid in the presence of mercuric oxide.<sup>9</sup>



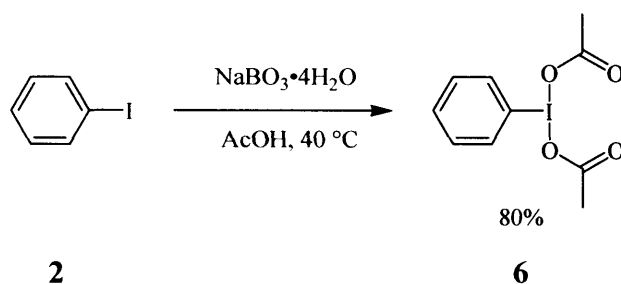
**Scheme 5.3:** Carpenter method for the preparation of (difluoriodo)toluene (DFIT - **168**).

Fluorination of iodobenzene **2**, pentafluoriodobenzene and heptafluoriodopropane with an excess of xenon difluoride or chlorine trifluoride can lead directly to the corresponding tetrafluoriodo compounds.<sup>10</sup>

### 5.2.3 Iodanes with Iodine-Oxygen Bonds

[Bis(acyloxy)iodo]arenes are important compounds that can either be prepared directly from iodoarenes and peroxyacids or by ligand exchange reactions.

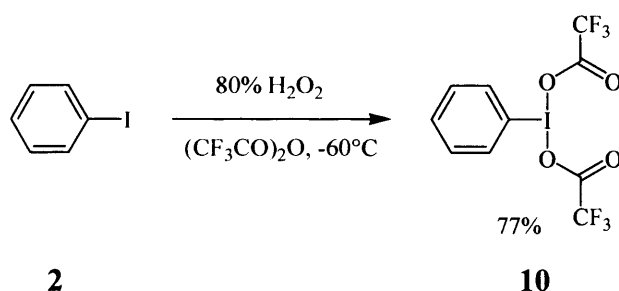
The first method is suitable mainly for diacetoxy-derivatives, which are readily formed, by oxidation of iodoarenes with hydrogen peroxide/acetic acid/acetic anhydride.



**Scheme 5.4:** McKillop and Kemp method for the preparation of (diacetoxy)iodobenzene **6**.

(Diacetoxyiodo)benzene **6** was first synthesised by Willgerodt in 1892 by dissolving iodosylbenzene **7** in acetic acid.<sup>11</sup> Today, there are many direct methods to access this useful reagent. These include methods where alternative oxidising agents are used. McKillop and Kemp reported sodium perborate tetrahydrate in acetic acid<sup>12</sup> (Scheme 5.4) and Skulski reported sodium perborate tetrahydrate in acetic anhydride.<sup>13</sup> The use of sodium periodate/sodium acetate/acetic anhydride and chromium trioxide/acetic acid/acetic anhydride/sulphuric acid, also provides satisfactory results.<sup>14</sup> The standard method for the preparation of **6** is the direct oxidation of the iodide using either 40% peracetic acid or by peracetic acid formed *in situ* from 30% hydrogen peroxide and acetic anhydride at  $40^\circ\text{C}$ .<sup>15</sup> Just 1 equivalent of peracetic acid is necessary for the oxidation of the iodine in the presence of acetic acid. With this method, the temperature must be kept at  $40^\circ\text{C}$  as below this, the oxidation does not occur and at higher temperature and with an excess of peracetic acid, over-oxidation to  $\text{ArIO}_2$  occurs. Another well used method is the use of *m*CPBA in a 1:1 mixture of dichloromethane and acetic acid.<sup>16</sup>

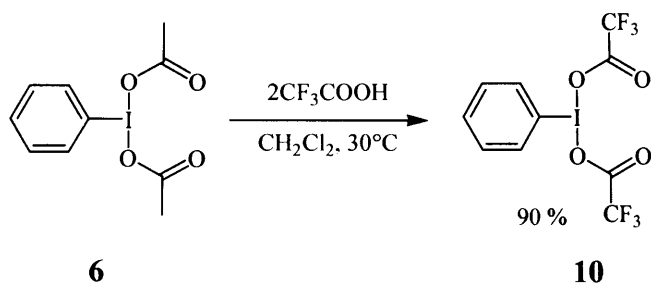
The direct approach can also be applied to some bis(trifluoroacetoxy)iodo analogues such as [bis(trifluoroacetoxy)iodo]pentafluorobenzene **174** and other [bis(acyloxy)iodo]arenes from iodoarenes bearing strong electron withdrawing groups. The reaction rate of electron poor substrates can be very low. In these cases peroxytrifluoroacetic acid can be used (Scheme 5.5). The use of this peracid is limited, as its preparation requires the combination of trifluoroacetic anhydride and 80% hydrogen peroxide, which is dangerous and no longer commercially available.<sup>17</sup>



**Scheme 5.5:** Preparation of [bis(trifluoroacetoxy)iodo]benzene **10** with 80% H<sub>2</sub>O<sub>2</sub> and (CF<sub>3</sub>CO)<sub>2</sub>O.

Very recently, the use of potassium persulfate with trifluoroacetic acid anhydride was reported by Kitamura *et al.* in an efficient synthesis of [bis(trifluoroacetoxy)iodo]arenes.<sup>18</sup>

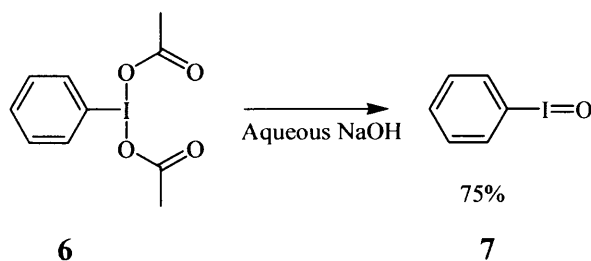
The alternate preparation of [bis(acyloxy)iodo]arenes is an indirect method that involves ligand exchange, usually between (diacetoxyiodo)benzene **6** and a carboxylic acid as shown in Scheme 5.6. The reaction is most effective when performed in mildly heated dichlorobenzene under reduced pressure, followed by azeotropic distillation to remove the acetic acid. This straightforward approach is suitable for the preparation of several [bis(acyloxy)iodo]arenes including dibenzoyloxy derivatives and also 1-adamantylcarboxy derivatives that are formed in high yields.<sup>19,20</sup> In order to prepare [bis(trifluoroacetoxy)iodo]benzene **10** itself, it is enough to simply dissolve (diacetoxyiodo)benzene **6** in trifluoroacetic acid and evaporate to a small volume.<sup>21</sup>



**Scheme 5.6:** Ligand exchange method of preparing [bis(trifluoroacetoxy)iodo]benzene **10**.

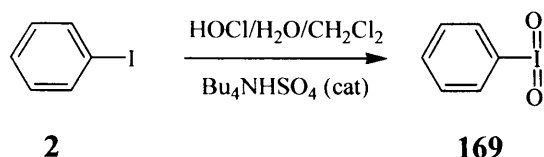
### 5.2.4 Iodosyl Compounds

Although iodosylbenzene **7** is polymeric  $\{-(\text{Ph})\text{I}-\text{O}-\}$ , it is usually written as the monomeric compound  $\text{PhIO}$ . Its standard preparation is shown in Scheme 5.7 which involves the alkaline hydrolysis of either  $\text{PhICl}_2$  **3** or  $\text{PhI}(\text{OAc})_2$  **6**, with the latter the most convenient.



**Scheme 5.7:** Preparation of iodosylbenzene **7** from (diacetoxy)iodobenzene **6**.

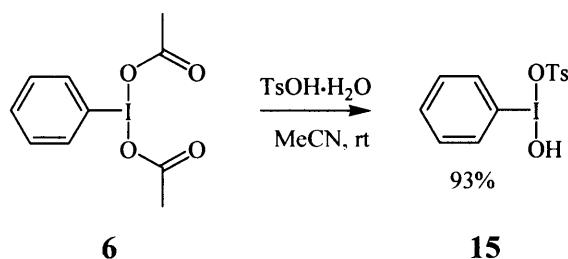
Direct oxidation to the iodyl compound is somewhat more difficult. The use of powerful oxidants to obtain the hypervalent product directly oxidises the iodine (Scheme 5.8) to the aryl- $\lambda^5$ -iodane to give the iodyl compound **169**.<sup>22</sup>



**Scheme 5.8:** Direct preparation of Iodylbenzene **169**.

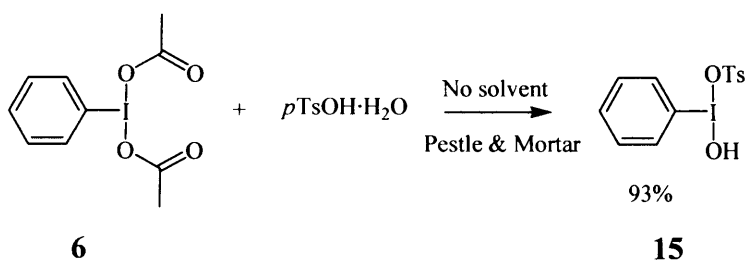
### 5.2.5 Iodanes with Two Different Ligands

Aryl- $\lambda^3$ -iodanes that contain two different ligands in the hypervalent bond, can be formed indirectly by ligand exchange reactions. As previously mentioned in Chapter One, Koser's reagent or [hydroxy(tosyloxy)iodo]benzene **15** is prepared by the addition of *p*-toluenesulphonic acid monohydrate to (diacetoxyiodo)benzene **6** in either acetonitrile or dichloromethane (Scheme 5.9).<sup>23</sup>



**Scheme 5.9:** Preparation of [hydroxy(tosyloxy)iodo]benzene **15**.

Wirth and Yusubov have developed an alternative method (Scheme 5.10) for the preparation of HITB **15**.<sup>24</sup> Because of the continued need for efficient transformations, they developed a solvent-free synthesis.



**Scheme 5.10:** Solvent free synthesis of HTIB **15**.

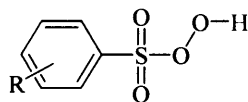
Solvent-free reactions have many advantages, and some important aspects are reduced pollution, lower cost and the simplicity of the processes involved.<sup>25</sup> Because many organic solvents are ecologically harmful, strategies for their minimised usage and developments toward benign chemical technologies are highly sought after.<sup>26</sup> Because many hypervalent iodine reagents have low solubility's in the majority of organic solvents, the development of solvent-free reactions is a big step forward and should lead to an increased use of this chemistry. Only iodine(III) compounds should be considered for these reactions, because some iodine(V) compounds are known to be shock and pressure sensitive.<sup>27</sup>

### 5.3 Direct Oxidation to [Hydroxy(tosyloxy)iodo]benzene

Aryl- $\lambda^3$ -iodanes with two different ligands attached to the iodine atom, are prepared from the iodoarene in 2 steps; initial oxidation to the hypervalent iodine compound, followed by a ligand exchange reaction.

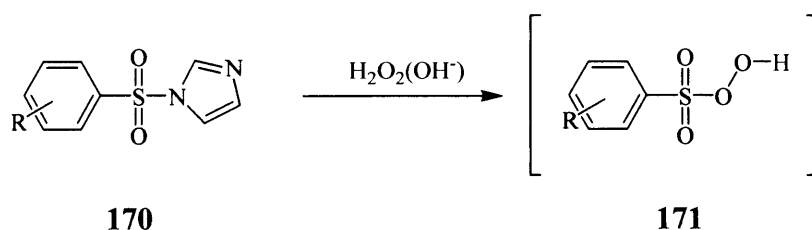
The first step is the oxidation of the iodoarene and requires a peracid, which will nominally generate a (diacetoxyiodo)arene. It is known that it is possible to access aryl sulphonic peracids.<sup>28,29</sup> The direct generation of a [hydroxy(tosyloxy)iodo]arene would prove beneficial to the hypervalent and synthetic chemist alike and it was decided to apply these aryl sulphonic peracids (Figure 5.1) to aryl iodides, to investigate whether they were able to oxidise the

iodoarenes, to directly generate the corresponding aryl- $\lambda^3$ -iodane. Their general structure is reportedly:



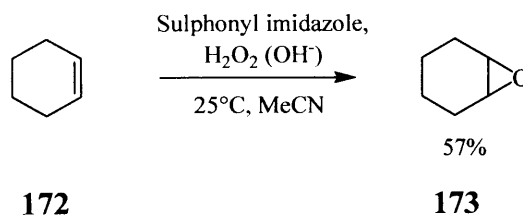
**Figure 5.1:** An aryl sulphonyl peracid.

The primary use of the sulphonyl peracid has been to epoxidise alkenes. They are prepared *in situ* as shown by Schultz *et al.* who prepared the sulphonyl peracid **171** by substitution of aryl sulphonyl imidazoles **170** with 30% hydrogen peroxide (Scheme 5.11).<sup>28</sup>



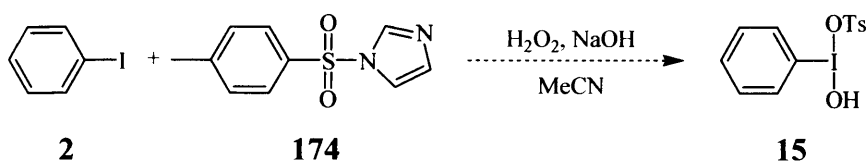
**Scheme 5.11:** Preparation of an Aryl Sulphonyl Peracid **171**.

Although the sulphonyl peracids have not been isolated, it is proposed that they are the intermediates (Scheme 5.12) in the epoxidation of alkenes.<sup>29</sup>



**Scheme 5.12:** Epoxidation of cyclohexene **172** with an *in situ* generated sulphonyl peracid.

Following from Chapter Three, where we encountered significant problems in with the oxidation of chiral iodoarenes. A direct method to access the desired [hydroxy(tosyloxy)iodo]arene from a sulphonic peracid may lead to a 1 step procedure. A series of experiments were conducted, to investigate the oxidative potential of a sulphonic peracid towards the iodoarenes. This method was performed primarily using iodobenzene **2** as a test substrate (Scheme 5.13).

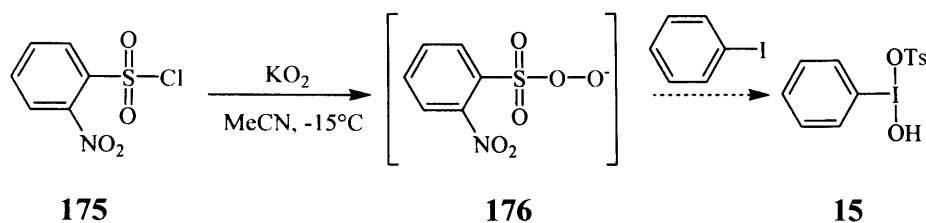


**Scheme 5.13:** Attempted oxidation of iodobenzene **2** with the sulphonic peracid precursor **174**.

Oxidation reactions of iodobenzene **2** were performed to obtain [hydroxy(tosyloxy)iodo]benzene directly. Unfortunately, this method of oxidising iodobenzene proved to be problematic. The reactions ran for up to three days, over a range of temperatures from 0°C to 80°C, but at no point was the desired product **15** observed. It was decided to apply this method to alternate iodoarenes with differing electronic properties; electron donating and withdrawing groups were employed however, in each case no oxidation was observed.

An alternative approach to that of the sulphonic peracid, was the *in situ* generation of a sulphonyl peroxy intermediate (Scheme 5.14). This can be achieved from the reaction between 2-nitrobenzenesulphonyl chloride **175** and potassium superoxide at -15°C (Scheme 5.14).<sup>30</sup> To date, this peroxy intermediate has been used to oxidise selenides to selenoxides in excellent yields.<sup>31</sup>





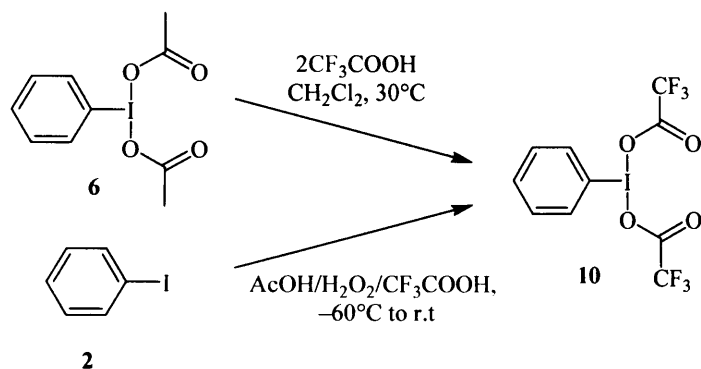
**Scheme 5.14:** Oxidation attempt with  $\text{KO}_2$  generation of 2-nitrobenzenesulfonyl peroxy intermediate 176.

Unfortunately, this method also proved unsuccessful in the production of the [hydroxy(tosyloxy)iodo]benzene. As with the previous method, several different iodoarenes were investigated with the recovery of the starting iodoarene in each case.

## 5.4 A New Direct Synthesis of [Bis(trifluoroacetoxy)iodo]arenes

As discussed above, there are several published methods for the synthesis of [bis(trifluoroacetoxy)iodo]arenes. These reagents can either be prepared by an indirect route, usually by a ligand exchange reaction on an already oxidized iodine(III) compound, or by direct oxidation from aryl iodide precursor molecules (Scheme 5.15).

The most commonly used procedure is a ligand exchange reaction using (diacetoxy)iodobenzene **6** and trifluoroacetic acid.<sup>21</sup> The success of this method is related to the electronic properties of the (diacetoxy)iodoarene; the reaction rate of electron poor substrates can be very low. Other indirect methods include the reaction of (dichloro)iodoarenes with silver trifluoroacetate<sup>32</sup> or the reaction of iodosylarenes with trimethylsilyl trifluoroacetate.<sup>33</sup>



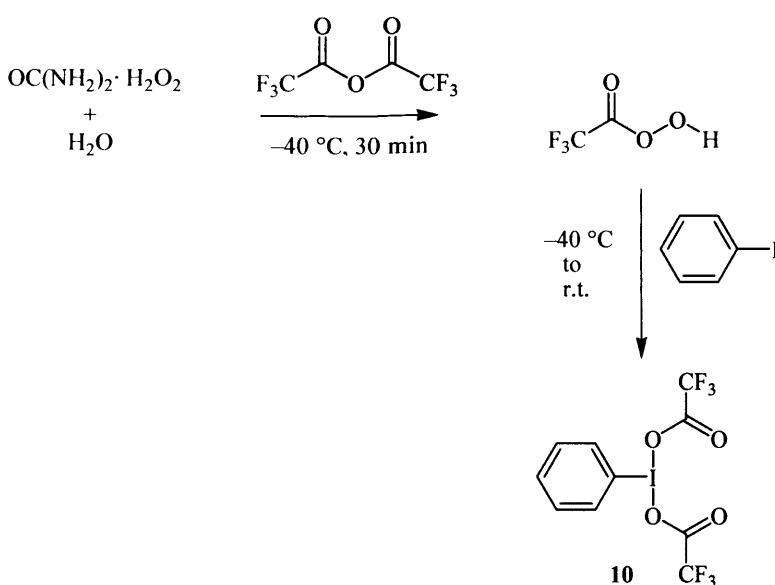
**Scheme 5.15:** Routes to [bis(trifluoroacetoxy)iodo]benzene **10**.

The direct oxidation of iodoarenes is still a more convenient method, although the choice of oxidants has to take into account the structure and the electronic properties of the iodoarene. Deactivated iodoarenes can be oxidised by either fuming nitric acid<sup>34</sup> or sodium percarbonate<sup>35</sup> together with trifluoroacetic anhydride. As shown in Section 5.2.3, the direct synthesis of [bis(trifluoroacetoxy)iodo]arenes is realised through the use of trifluoroacetic anhydride and 80% hydrogen peroxide. However, this method is problematic as 80%  $\text{H}_2\text{O}_2$  is no longer commercially available. Even though 80%  $\text{H}_2\text{O}_2$  can be prepared in the laboratory, a much safer alternative is available to the synthetic chemist. The urea-hydrogen peroxide adduct ( $\text{OC}(\text{NH}_2)_2 \cdot \text{H}_2\text{O}_2$ , UHP) is a cheap, commercially available white crystalline solid, which has good stability at room temperature, a high  $\text{H}_2\text{O}_2$  content (36.2%) and has good solubility in organic solvents.<sup>36</sup> UHP has been known since 1906,<sup>37</sup> and its applications in organic and analytical chemistry, as well as industry, are quickly widening. More recently, Skulski has used it in the solvent-free synthesis of (dichloroiodo)arenes.<sup>7</sup>

To overcome the lack of availability of 80% hydrogen peroxide, we developed two methods to directly afford [bis(trifluoroacetoxy)iodo]arenes.<sup>38</sup> These were based around the *in situ* generation of trifluoroacetic acid, as a variation of the procedure reported by Zhdankin and Stang.<sup>17</sup>

### 5.4.1 Method A

The solubility of hydrogen peroxide is considerably higher in organic solvents than in water.<sup>39</sup> Consequently, urea can be removed from solutions of commercially available urea-hydrogen peroxide adduct in organic solvents by extraction with water. The remaining solution of hydrogen peroxide in an organic solvent can then, after drying, react with trifluoroacetic anhydride to generate trifluoroperacetic acid (Scheme 5.16).



**Scheme 5.16:** Removal of urea before reaction.

If this reaction is performed in the presence of an aryl iodide, the corresponding hypervalent [bis(trifluoroacetoxy)iodo]arenes are obtained in good yields as shown in Table 5.1 and as described in the general procedure **GP14**.

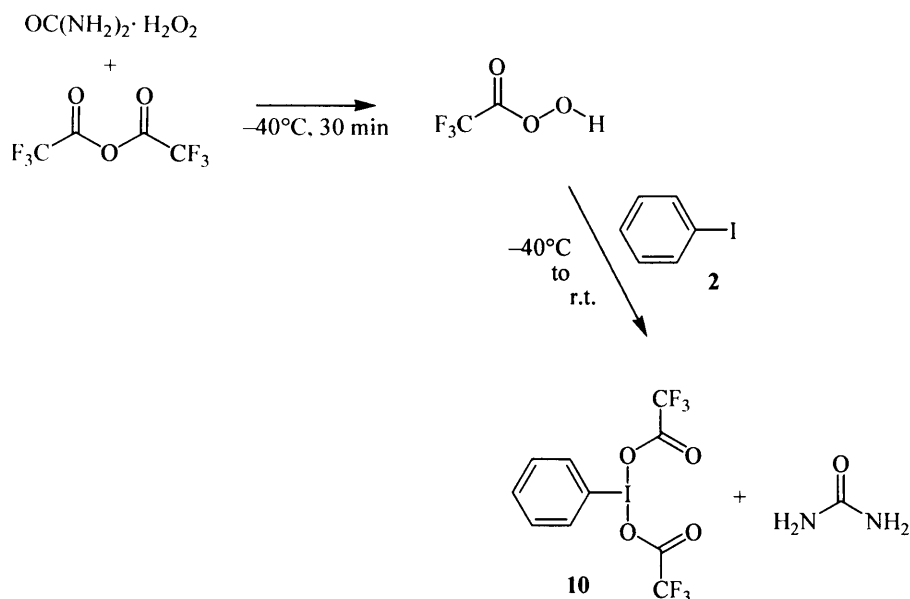
	Product	Method	Yield (%)
177		A	65
178		A	95
179		A	90
180		A	81
181		A	50 <sup>b</sup>

<sup>b</sup> determined by <sup>1</sup>HNMR.

**Table 5.1:** Synthesis of (trifluoroacetoxy) **181** and [bis(trifluoroacetoxy)iodo]arenes **177–180** using Method A.

### 5.4.2 Method B

A mixture of the urea-hydrogen peroxide adduct and trifluoroacetic anhydride can be used directly for the generation of trifluoroperacetic acid. In the presence of an iodoarene, the hypervalent iodine species (Table 5.2) are generated, but the urea has to be removed after the reaction (**GPI5**). This protocol (Scheme 5.17) is therefore only suitable for hypervalent iodine compounds that tolerate aqueous work-up.



Scheme 5.17: Removal of urea after reaction.

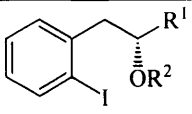
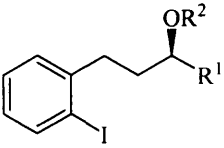
	Product	Method	Yield (%)
10		B	96
182		B	91
183		B	26

Table 5.2: Synthesis of [bis(trifluoroacetoxy)iodo]arenes using Method B.

In both Methods, A and B, the temperature of the reaction was lowered to around  $-40^\circ\text{C}$  in order for the trifluoroperacetic acid to form. At room temperature or even at  $0^\circ\text{C}$ , we observed no peracid formation and subsequently no oxidation. We performed several low-temperature  $^1\text{H}$  NMR studies using a hydrogen peroxide–trifluoroacetic anhydride mixture to determine the temperature at which the trifluoroperacetic acid formed. The initial reaction temperature was  $-60^\circ\text{C}$ , and the reaction repeated at  $10^\circ\text{C}$  intervals. The first signs of oxidation of the iodoarene were observed at  $-30^\circ\text{C}$ . It was at this temperature that we began to

see the appearance of the new aromatic peaks, characteristic of the hypervalent iodine species, downfield of the non-hypervalent iodine species.

As discussed in Chapter 3, many of the new chiral iodoarenes that were based upon the extended chiral side chain, failed to undergo oxidation to the hypervalent species. This novel method was applied to several of these compounds (Table 5.3), to determine whether the [bis(trifluoroacetoxy)iodo]arenes were as unstable as their diacetoxy analogues.

Chiral iodoarene	Reagent	R <sup>1</sup>	R <sup>2</sup>	Product	Yield %
	(S)-58	Me	Me	(S)-66	6
	(S)-69	Ph	Me	(S)-74	2
	(S)-88	Me	Me	(S)-96	21
	(S)-89	Me	Et	(S)-97	15
	(S)-90	Me	Bn	(S)-98	6
	(S)-103	Ph	Me	(S)-109	59
	(S)-104	Ph	Et	(S)-110	17
	(R)-115	<sup>t</sup> Bu	Me	(R)-120	2

**Table 5.3:** Synthesis of chiral [bis(trifluoroacetoxy)iodo]arenes using Method B.

The results shown in Table 5.3, once again highlight the problems associated with the oxidation of the next generation chiral iodides prepared previously. The only reagents that were stable enough to obtain in sufficient quantities to allow further investigation were **96**, **97**, **109** and **110**. As discussed in Chapter Three, the oxidation of **109** and **110** may be attributed to the additional phenyl ring attached to the chiral carbon of the side chain.

## 5.5 Conclusion

In this Chapter a novel alternative oxidative synthetic procedure for the synthesis of [bis(trifluoroacetoxy)iodo]arenes, has been described. Until now, the primary method for the synthesis of these hypervalent iodine compounds was by the use of hazardous 80% hydrogen peroxide. This novel method offers the following advantages:

- It avoids the use of the commercially unavailable and hazardous 80% hydrogen peroxide.
- It is applicable to iodoarenes which contain electron donating or electron withdrawing substituents.
- It represents a high yielding direct synthesis of these useful compounds.
- It allows the synthesis of hypervalent iodine compounds at low temperatures.

For this last point, the oxidation of the iodoarenes at low temperatures allowed us to oxidise iodoarenes that would not oxidise using conventional methods or those which are unstable at higher temperatures. When this method was applied to the chiral iodoarenes that we were unable to oxidise by conventional methods, some success was observed. The chiral iodoarenes that have the longer chiral side chains are the most stable, and as with the majority of these next generation compounds, stability was still an issue. Due to time constraints, the reactivity of these chiral hypervalent iodine reagents were not investigated.

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## Chapter 6

# 6 Conclusion and Future Directions

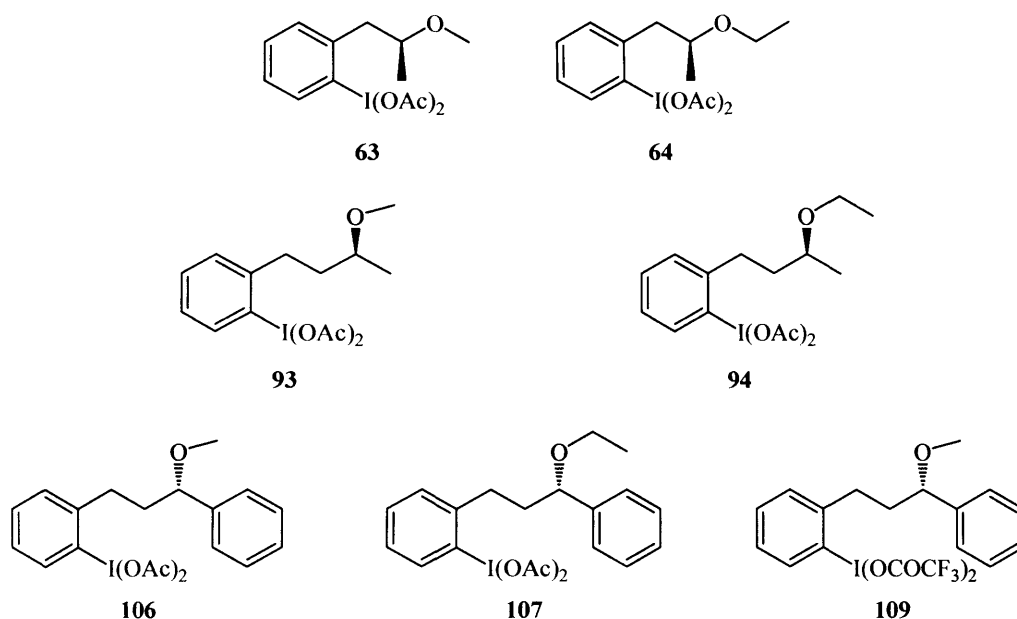
## 6.1 Conclusion

Chiral hypervalent iodine compounds are very extraordinary molecules. They have potential use both in academia and in industry. Their chemistry may allow them to one-day replace toxic heavy metals in synthesis. With environmental alternatives more sought after than ever, these chiral iodine(III) and (V) compounds definitely have a bright future ahead.

The research carried out within this thesis can be summarised as follows:

- Synthesis of chiral iodine(III) compounds
- Oxidation of iodine(I) to iodine(III)
- Reactivity of chiral iodine(III) compounds

The synthesis of chiral iodine(III) compounds revealed many problems associated with oxidation. It became clear that the increasing length of the chiral chain *ortho* to the iodine atom on the benzene ring was affecting the oxidation of the iodine(I) to the iodine(III) state. These results are consistent with the work of Shenjie *et al.*<sup>1</sup> They discovered that an alkyl chain *ortho* to an iodine increased in length, the oxidation of the iodine(I) became more difficult. With these problems arising, only seven iodine(III) compounds were isolated (Figure 6.1).



**Figure 6.1:** Aryl iodides isolated in stoichiometrically useful quantities.

The problems associated with oxidation were apparent using the majority of established oxidation methods. Sodium perborate and peracetic acid predominantly afforded little or no product. The known method to directly access [bis(trifluoroacetoxy)iodo]arenes is oxidation using trifluoroperacetic acid. This method is very difficult and dangerous, as it requires the use of 80% hydrogen peroxide (no longer commercially available).<sup>2</sup> Therefore, an alternative method was devised to resolve this problem. Through the use of urea hydrogen peroxide (34% H<sub>2</sub>O<sub>2</sub>), and trifluoroacetic anhydride in dichloromethane, the corresponding [bis(trifluoroacetoxy)iodo]arenes were generated in very good yields. This method was effective for iodoarenes that contain either electron donating or electron withdrawing substituents.<sup>3</sup>

The chiral hypervalent iodine(III) compounds developed in the Wirth group have been used in the functionalisation of alkenes and ketones. They are required in stoichiometric quantities to perform these transformations and with the oxidation problems associated with these reagents they are limited in their synthetic utility. Recent advances in the area provided an outlet for us to evaluate our range of aryl iodides.<sup>4</sup> With these catalytic cycles available, we were able to

test our chiral iodine(I) compounds and observe use in catalytic oxidation processes.<sup>5</sup>

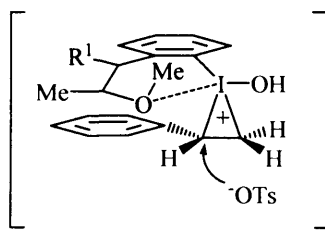
It was found that an increase in chain length resulted in a decrease in the transfer of chiral information to the substrate. By comparing chiral reagents prepared previously within the Wirth group to the ones prepared within this work we observed a downward trend in enantiomeric excesses of the products. The more successful chiral iodine(III) reagents had the chiral centre in a benzylic position and this appears to be the most effective position for asymmetric induction. Further work had begun in synthesising chiral iodine reagents with two chiral centres, one in the benzylic position and a second at the next carbon in the chiral chain.

## 6.2 Future Work

The addition of a second chiral centre in the chain may increase the transfer of chiral information to the substrate. A series of experiments were underway toward the end of the research but unfortunately they currently remain unfinished. This section will outline the ideas and show the current position of the research.

### 6.2.1 6-Membered Chiral Iodoarenes with Two Chiral Centres

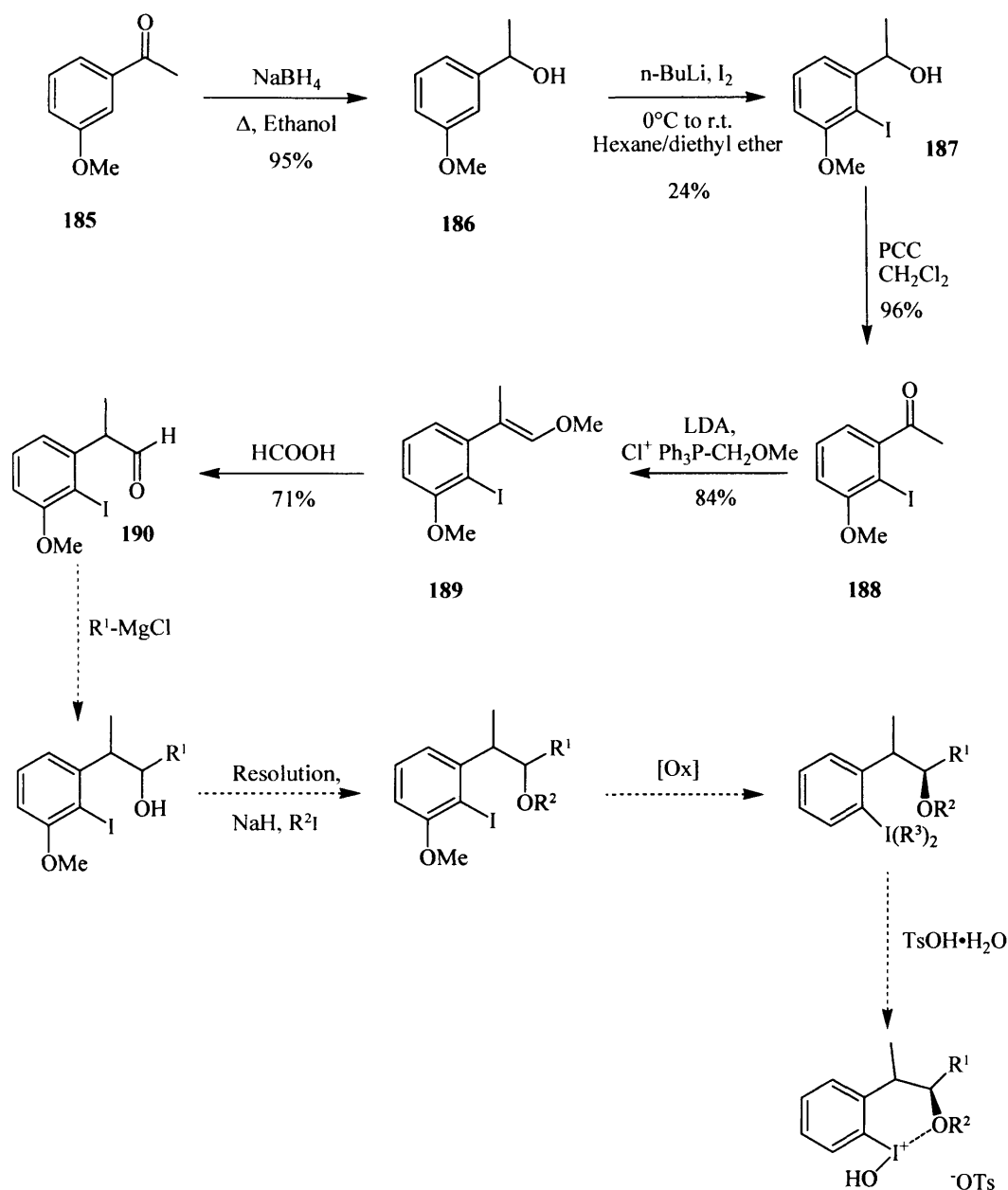
The addition of a second chiral centre in the benzylic position may improve the enantioinducing power of these reagents. Figure 6.1 shows how the introduction of another stereocentre may help to increase the steric shielding of the *syn*-face of the intermediate and direct the tosylate nucleophile toward the *re*-face of the alkene.



184

**Figure 6.1:** Increased steric shielding of *syn*-face in the proposed intermediate **184**.

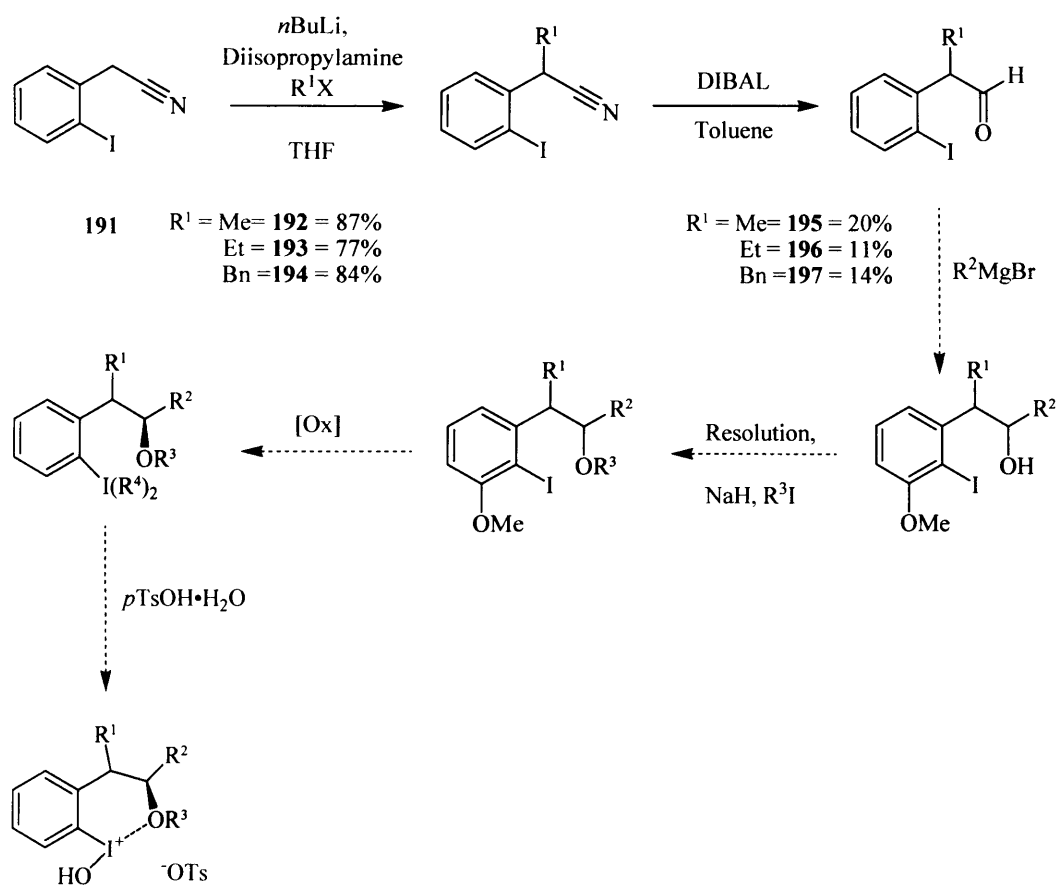
Two routes **A** and **B** to the next generation chiral iodine(III) compounds were explored. The first synthesis is outlined in Scheme 6.1. To include a second chiral centre, this synthesis would involve extra steps. It began with a reduction of 3-methoxyacetophenone **185** to give 1-(3-methoxyphenyl)ethanol **186** in 95% yield. The iodine was then introduced into the ring by *ortho*-lithiation in 24% yield.<sup>6</sup> The alcohol was oxidised back to the carbonyl using PCC (96%) to give **187**, and the side chain homologated using (methoxymethyl)triphenylphosphonium chloride to afford the 2-iodo-1-methoxy-3-(2-methoxyprop-1-en)benzene **188** in 84% yield. The methoxy group of the ether was cleaved through acid hydrolysis (71%). This was achieved by stirring **189** in the dark with concentrated formic acid, to give acetaldehyde **190** in 71% yield.<sup>7</sup> The concurrent steps were never realised due to time constraints, but the groundwork has been laid for a future researcher.



**Scheme 6.1:** Synthesis A – Route to 6-membered chiral iodine(III) compounds with two chiral centres.

The second synthesis is much shorter, although work will have to be done to improve the yields in some steps. The synthesis is outlined in Scheme 6.2. To reduce synthesis time, the chosen starting material was (2-iodophenyl)acetonitrile **191**, which is commercially available. The benzylic position was alkylated through deprotonation using LDA in dry THF to produce the alkylated products yields from 77 to 87%. It could be at this point that separation *via* HPLC could be applied to separate the enantiomers of **192–194**, or alternatively at the

acetaldehyde stage. The subsequent 2-(2-iodophenyl)alkylnitriles can be reduced to the corresponding acetaldehydes through a DIBAL reduction to give **195–197**. The yields for this step are currently poor, ranging between 11 and 20%. The next step would be the Grignard addition and from here on this synthesis mirrors that of Route A.



**Scheme 6.2:** Synthesis **B** – Route to 6-membered chiral iodine(III) compounds with two chiral centres.

The second synthesis contains fewer steps and it allows more flexibility in choosing which alkyl or aryl moiety to attach at the benzylic position. Whether this type of chiral iodoarene will improve on the selectivity previously observed in the functionalisation of alkenes and ketones, remains to be seen.

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## Chapter 7

# 7 Experimental

## 7.1 General Methods

Most reactions were carried out using standard borosilicate glassware of the relevant size. Inert reactions conditions are applied by vacuum dried or oven dried (120°C) apparatus under argon atmosphere. Experiments requiring a precise temperature were performed using either a hot plate with temperature probes in silicon oil or through the use of a cooling machine, Lauda RK 8 LP using methanol as the solvent. Reactions that needed a temperature of -78°C were carried out using a cooling bath with dry ice and acetone.

Solvents were removed using a Büchi R-124 rotary evaporator (final vacuum ~15 mbar). Further drying was achieved through high vacuum at ca. 0.05 mbar. Vacuum distillations were performed using a Büchi GKR-50 Kugelrohr distillation apparatus.

Non-sensitive reactions were performed open to air or in loosely stoppered vessels. All reactions were continually agitated with magnetic stirring unless otherwise stated.

### 7.1.1 Solvent Treatment

THF and diethyl ether were freshly distilled from sodium/benzophenone under inert gas atmosphere of N<sub>2</sub>. Diisopropylamine and dichloromethane were distilled from KOH and CaH<sub>2</sub> respectively, under anhydrous conditions. All other high purity solvents used were bought from Aldrich, Alfa Aeser, Fluka or Acros in septum bottles and handled under argon. Solvents for chromatography and work up were distilled, and all other solvents were used as purchased.

## 7.2 Spectroscopic Analysis

### 7.2.1 <sup>1</sup>H NMR-Spectroscopy

Bruker DPX 500 (500 MHz), Bruker DPX 400 (400 MHz), Bruker DPX 250 (250 MHz). The chemical shifts  $\delta$  are given in ppm relative to an internal standard. Deuterated chloroform solutions containing tetramethylsilane were used to perform the analysis. Additionally, the peak of the deuterated solvent is used as an internal reference: CDCl<sub>3</sub> at  $\delta = 7.26$  ppm, MeOD at  $\delta = 3.30$  ppm, DMSO at  $\delta = 2.50$  ppm. All coupling constant  $J$  are reported in Hertz (Hz). The multiplicity of the signals are abbreviated as follows: 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 labelled 'arom'.

### 7.2.2 <sup>13</sup>C NMR-Spectroscopy

Bruker DPX 500 (125 MHz), Bruker DPX 400 (100.6 MHz) or Bruker DPX 250 (62.5 MHz). The chemical shifts  $\delta$  are given in ppm relative to the solvent signals of deuterated chloroform: CDCl<sub>3</sub> at  $\delta = 77.0$  ppm, MeOD at  $\delta = 49.0$  ppm, DMSO at  $\delta = 39.5$  ppm.

### 7.2.3 Mass Spectrometry

Mass spectrometric analyses were performed either by atmospheric pressure chemical ionisation technique, voltage applied corona discharge pin (APCI) or by voltage on a tip (ES).

- 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 BD-5MS). If not otherwise specified, the following temperatures were used: from 70 to 200 C for 40 minutes. In this case, electron ionisation (EI) was used as an ionisation method.

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

Accurate high-resolution mass spectral data were recorded at either the National Mass Spectrometry Service Centre at the University of Swansea, or at the Mass Spectrometry Laboratory at Cardiff University.

The molecular formulae are given in molecular ion  $[M]^+$ , molecular ion + hydrogen  $[M+H]^+$ , molecular ion – hydrogen  $[M-H]^+$ , molecular ion + ammonium ion  $[M+NH_4]^+$  or molecular ion + sodium ion  $[M+Na]^+$ .

### 7.2.4 Gas Chromatography-Mass Spectroscopy

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

### 7.2.5 IR Spectroscopy

All compounds were analysed on a Perkin-Elmer 1600 FTIR-spectrometer. The wave numbers are reported in  $\text{cm}^{-1}$ . Liquid samples were measured as liquid film. Solid samples were analysed as a film in nujol mull.

### 7.2.6 Melting Points

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

### 7.2.7 Optical Rotation

Optical activity was measured using a LTs. AA-1000 Polarimeter. The samples were measured at 589 nm of wavelength at ambient temperatures. The sample concentration is quoted in g/100 ml.

## 7.3 Chromatographic Methods

### 7.3.1 Thin Layer Chromatography

Thin layer chromatography was performed with Merck Kieselgel 60 F254 pre-coated aluminium backed plates. Visualisation was achieved by UV-fluorescence or after dipping in one of the following solutions:

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

### 7.3.2 Flash Chromatography

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

### 7.3.3 High Performance Liquid Chromatography

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

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

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

## 7.4 General Procedures

### 7.4.1 General Procedure for the Oxidation of 1° and 2°-Alcohols using Pyridinium Chlorochromate (GP1)

The alcohol (21.4 mmol, 1.0 eq) in dichloromethane (15 ml) was added drop wise to a stirred solution of pyridinium chlorochromate (32.1 mmol, 1.5 eq) in dichloromethane (50 ml) at 0°C. The solution was allowed to warm to room temperature and stirred vigorously for 24 hours. Diethyl ether was added (25 ml), and the mixture filtered through a column of Celite<sup>®</sup> over silica gel. Elution of the product with additional ether and evaporation of solvent under reduced pressure yielded the desired product.

### 7.4.2 General Procedure for the Wittig Reaction (GP2)

A solution of *n*BuLi (31.7 mmol, 1.6 eq of a 2.5 M solution in hexanes) and diisopropylamine (31.7 mmol, 1.6 eq) in dry THF (10 ml) was added dropwise over 5 minutes to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (20.8 mmol, 1.1 eq) in dry THF (15 ml) at -10°C under an inert atmosphere of argon. The solution was allowed to warm to room temperature and after 30 minutes, the aldehyde (19.8 mmol, 1.0 eq) in dry THF was added drop wise over 5 minutes. The solution was stirred for 15 hours, quenched with saturated aqueous ammonium chloride solution (2 x 10 ml), the organic layer was decanted and the aqueous layer extracted with diethyl ether (2 x 15 ml). The combined organic fractions were washed with brine (10 ml), dried over magnesium sulphate and the solvent removed under reduced pressure to yield the crude product. Purification was performed using column chromatography to give the desired product.

### 7.4.3 General procedure for acidic hydrolysis of vinyl ethers (GP3)

Formic acid (80.0 mmol, 17.4 eq) was added to a pale yellow solution of (*E*)- and (*Z*)-vinyl ether isomers (4.6 mmol, 1.0 eq). Upon addition the solution immediately deepened to a bright yellow colour. The reaction was stirred at room temperature in a foil-covered vessel. After 64 hours the solution was quenched with water (15 ml) and the layers allowed to separate. The organic layer was decanted and the aqueous layer extracted with dichloromethane (3 x 5 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate (2 x 5 ml), brine (2 x 5 ml), dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The oil produced required no further purification.

### 7.4.4 General procedure for the Grignard reaction (GP4)

A solution of an alkyl magnesium halide (2.24 mmol, 1.0 eq) in dry diethyl ether (5 ml) was added drop wise over 5 minutes, to a solution of an iodoaryl acetaldehyde (2.24 mmol, 1.0 eq) in dry diethyl ether under an argon atmosphere at -10°C. After 1.5 hours, ammonium chloride (1 x 10 ml) was added to the stirred solution. The aqueous phase was extracted with dichloromethane (2 x 5 ml) and the organic layers combined and dried over magnesium sulphate. The solvent was removed under reduced pressure and purification was performed by column chromatography, to yield the desired compound.

### 7.2.5 General procedure for the alkylation of alcohols (GP5)

Sodium hydride (2.22 mmol, 3.0 eq, 55—65% in oil) was washed with pentane (4 x 3 ml) and then suspended in dimethylformamide (12 ml). After cooling to 0°C, a solution of the alcohol (0.74 mmol, 1.0 eq) in

dimethylformamide (2 ml) was added. After stirring for 15 minutes at room temperature, the mixture was cooled to 0°C and the alkyl iodide (0.74 mmol, 1.0 eq) was added. After a further 3 hours at room temperature, water was carefully added. The resulting mixture was extracted with *t*-butyl methyl ether (2 x 5 ml), and the combined organic phases were washed with brine (3 x 5 ml), dried over MgSO<sub>4</sub> and filtered and concentrated under reduced pressure. Purification was performed using column chromatography to give the desired product.

#### **7.4.6 General procedure for the trifluoroacetylation of alcohols (GP6)**

Trifluoroacetic anhydride (1.04 mmol, 1.2 eq) was carefully added to a stirred solution of an alcohol (0.87 mmol, 1.0 eq) and triethylamine (1.04 mmol, 1.2 eq) in dichloromethane (10 ml) at 0°C. After 30 minutes the solvent was removed under reduced pressure and the product was purified by column chromatography.

#### **7.4.7 General procedure for the preparation of *t*-butyl ethers from tertiary butanol (GP7)**

Concentrated sulphuric acid (0.43 mmol, 1.0 eq) was added to a vigorously stirred suspension of anhydrous MgSO<sub>4</sub> (1.72 mmol, 4.0 eq) in cyclohexane (4 ml). The mixture was stirred for 15 minutes and a solution of *t*-butanol (2.15 mmol, 5.0 eq) and the alcohol (0.43 mmol, 1.0 eq) in cyclohexane (2 ml) was then added. The mixture was stoppered and stirred for a further 18 hours at 25°C. The reaction mixture was then quenched with 5% sodium bicarbonate solution (5 ml) and stirred until all the magnesium sulphate had dissolved. The organic phase was separated and washed with brine (2 x 5 ml), The combined organic fractions were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification was performed using column chromatography to give the desired product.



#### **7.4.8 General procedure for the homologation of the carbon side chain (GP8)**

A mixture of 2-iodobenzyl chloride (11.9 mmol, 1.0 eq), the symmetrical 1,3-dione (13.1 mmol, 1.1 eq) and potassium carbonate (12.5 mmol, 1.05 eq) in ethanol (30 ml) was refluxed for 24 hours. The solvent was removed under reduced pressure and the residue partitioned between ether (50 ml) and water (15 ml). The organic layer was dried with magnesium sulphate and concentrated under reduced pressure to yield the crude product. Purification was performed using column chromatography to give the desired product.

#### **7.4.9 General procedure for the asymmetric reduction of ketones (GP9)**

A solution of the propanone or butanone derivative (11.9 mmol, 1.0 eq) in dry THF (5 ml) was added to a solution of (-)- $\beta$ -chlorodiisopinocampheylborane (13.1 mmol, 1.1 eq) in dry THF (25 ml) under an inert argon atmosphere at -25°C. After 15–25 hours, the reaction was warmed up to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (25 ml) and vigorously stirred. To this stirred solution was added diethanolamine (26.2 mmol, 2.2 eq). After stirring at room temperature for a further 2 hours, the suspension was filtered through Celite<sup>®</sup> and washed with diethyl ether (5 x 10 ml). The solvent was removed under reduced pressure, purified by column chromatography to yield the desired product.

#### **7.4.10 General procedure for the reduction of ketones (GP10)**

The propanone or butanone derivative (7.30 mmol, 1.0 eq) was added drop wise over 2 minutes to a stirred suspension of sodium borohydride (NaBH<sub>4</sub>) (4.02

mmol, 0.55 eq) in ethanol (10 ml) under argon at room temperature. The resulting solution was heated to reflux with stirring. After 3 hours, the solution was removed from the oil bath, allowed to cool to room temperature, and quenched with water (10 ml) and acetic acid (3 ml). The resulting mixture was concentrated under reduced pressure, and the residue partitioned between ether (10 ml) and water (10 ml). The aqueous layer was extracted with ether (4 x 10 ml), the organic fractions combined, dried over MgSO<sub>4</sub> and the solvent removed under reduced pressure. Purification was performed using column chromatography to give the desired product.

#### **7.4.11 General procedure for the oxidation of iodoarenes with sodium perborate tetrahydrate<sup>1</sup> (GP11)**

Sodium perborate tetrahydrate (3.10 mmol, 10 eq) was added portion wise to a solution of the iodoarene (0.31 mmol, 1.0 eq) in glacial acetic acid (5 ml), at 40°C. The conversion was monitored by TLC analysis. After completion of the reaction, the solution was concentrated to half its volume by removal of acetic acid by evaporation under reduced pressure. The mixture was diluted with a small volume of water (5 ml) and quickly extracted with chloroform (2 x 10 ml). The combined extracts were washed with brine (2 x 10 ml), dried with MgSO<sub>4</sub> and the solvent was removed under reduced pressure to yield the crude product. The (diacetoxyiodo)arene derivatives could be purified either by recrystallisation from acetic acid/pentane or by flash TLC. Some of the products were found to be unstable and therefore characterized only by NMR spectroscopy.

#### **7.4.12 General procedure for the oxidation of iodoarenes with commercially available peracetic acid<sup>2</sup> (GP12)**

Peracetic acid (0.39 mmol, 0.88 ml of a 30% solution in acetic acid, 1.75 eq) was added drop wise over two minutes to a flask containing the iodoarene (0.22 mmol, 1.0 eq) in acetic acid (5 ml) at 40°C under argon. After stirring for 24

hours, dichloromethane (5 ml) was added to the reaction mixture followed by chloroform (5 ml). Water (3 ml) was added to the solution and the organic phase separated. The aqueous phase was extracted further with chloroform (3 x 5 ml) and the organic phases combined. The organic phase was dried with MgSO<sub>4</sub> and the solvent removed under vacuum, to yield the crude product. The (diacetoxyiodo)arene derivatives could be purified either by recrystallisation from acetic acid/pentane or by flash TLC. Some of the products were found to be unstable and therefore characterized only by NMR spectroscopy.

#### **7.4.13 General procedure for the oxidation of iodoarenes with an *in situ* generation of peracetic acid<sup>2</sup> (GP13)**

Peracetic acid was prepared by stirring a solution of acetic anhydride (6 ml) and hydrogen peroxide (1.6 ml of a 30% solution in water) for 4 hours at exactly 40°C. The iodoarene (1.0 mmol, 1.0 eq) was added to the reaction mixture and stirred for up to 24 hours. Dichloromethane (5 ml) was added to the reaction mixture followed by chloroform (15 ml). Water (5 ml) was added to the solution and the organic phase separated. The aqueous phase was extracted further with chloroform (3 x 10 ml) and the organic phases combined. The organic phase was dried with MgSO<sub>4</sub> and the solvent removed under vacuum, to yield a white solid. The (diacetoxyiodo)arene derivatives could be purified either by recrystallisation from acetic acid/pentane or by flash TLC. Some of the products were found to be unstable and therefore characterized only by NMR spectroscopy.

#### **7.4.14 General procedure for the oxidation of iodoarenes with trifluoroperacetic acid - method A<sup>3</sup> (GP14)**

Urea hydrogen peroxide (2.28 mmol, 2.5 eq) was dissolved in a minimum quantity of deionised water (0.5 ml) and extracted with dichloromethane (3 x 6 ml). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and filtered to give a solution of hydrogen peroxide in dichloromethane. This solution was cooled to –

40°C and trifluoroacetic anhydride (9.10 mmol, 10 eq) was added drop wise. After 30 minutes, the iodoarene (0.91 mmol, 1.0 eq) was added to the solution and the reaction mixture left to stir for a further 7 hours at -40°C. The solution was warmed up to room temperature and stirred for 1 hour. The [bis(trifluoroacetoxy)iodo]arene derivatives could be purified by washing with pentane. The solvent was removed under reduced pressure to yield the corresponding [bis(trifluoroacetoxy)iodo]arene. Some of the products were found to be unstable and therefore characterized only by NMR spectroscopy.

#### **7.4.15 General procedure for the oxidation of iodoarenes with trifluoroperacetic acid – method B<sup>3</sup> (GP15)**

Trifluoroacetic anhydride (25.0 mmol, 10.0 eq) was added drop wise to a stirred solution of urea hydrogen peroxide (6.25 mmol, 2.5 eq) in dichloromethane at -40°C. After 30 minutes, the appropriate iodoarene (2.5 mmol, 1.0 eq) was added, and the resulting solution stirred for 7 hours at -40°C. The solution was warmed to room temperature and stirred for 1 hour. The solution was quickly washed with a small quantity of water, the organic phase separated, dried over MgSO<sub>4</sub> and the solvent removed under reduced pressure to yield crude product. The [bis(trifluoroacetoxy)iodo]arene derivatives could be purified by washing with pentane. Some of the products were found to be unstable and therefore characterized only by NMR spectroscopy.

#### **7.4.16 General procedure for the oxidation of iodoarenes with *m*-CPBA (GP16)**

The iodoarene (1.0 mmol, 1.0 eq) was added to a stirred solution of acetic acid (4 ml), and *m*CPBA (1.05 mmol, 1.05 eq), in dichloromethane (3 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred for up to 24 hours, while the reaction was monitored by TLC. The solution was quenched with a small quantity of water (2 ml), the aqueous phase was washed with chloroform

(2 x 5 ml) the organic phase combined, dried over  $\text{MgSO}_4$  and the solvent removed under reduced pressure to yield a white solid. The (diacetoxyiodo)arene derivatives could be purified by recrystallisation from acetic acid/pentane.

#### **7.4.17 General procedure for the oxidation of iodoarenes with Koser reagent <sup>4</sup> (GP17)**

A solution of the iodoarene (1.0 mmol, 1.0 eq) in dichloromethane (10 ml) was mixed with Koser reagent (1.2 mmol, 1.2 eq) at room temperature for up to 72 hours. The progress was monitored by TLC and  $^1\text{H}$  NMR. The solvent was removed under reduced pressure and the crude solid analysed.

#### **7.4.18 General procedure for the oxidation of iodoarenes with Chromium (VI) oxide <sup>5</sup> (GP18)**

Powdered chromium trioxide (0.30 mmol, 1.0 eq) was slowly added to a stirred solution of glacial acetic acid (0.2 ml) and acetic anhydride (0.1 ml). The temperature was then raised to  $40^\circ\text{C}$  for 1 hour. The deep orange solution was cooled down to  $10^\circ\text{C}$  and the iodoarene (0.45 mmol, 1.5 eq) added drop wise. The temperature was raised to  $40^\circ\text{C}$ . At this temperature, concentrated sulphuric acid (0.06 ml) was added to the reaction mixture and the resulting solution stirred at  $40^\circ\text{C}$ . After 1 hour the reaction was cooled to  $0^\circ\text{C}$  and 20% aqueous ammonium acetate solution (5 ml) was added to the deep-green mixture. The flask was stored at  $4^\circ\text{C}$  for 2 hours the resulting precipitate was filtered with cold acetic acid (2 x 5 ml). The crude product was then purified by recrystallisation from acetic acid/pentane.

#### **7.4.19 General procedure for the preparation of [hydroxy(tosyloxy)iodo]arenes (GP19)**

The (diacetoxyiodo)benzene derivative was dissolved in acetonitrile (~0.9 mol). To this solution exactly 1 equivalent of *p*-toluenesulphonic acid monohydrate in acetonitrile (0.4 mol) was added. After the solution was stirred for 1 hour the solvent was removed under reduced pressure.

#### **7.4.20 General procedure for the dioxytosylation of styrene (GP20)**

The chiral hypervalent iodine compound (0.5 mmol, 1.0 eq) and *p*-toluenesulphonic acid monohydrate (1.2 mmol, 2.4 eq) were dissolved in dichloromethane (3 ml). Styrene (0.5 mmol, 1.0 eq) was added at temperatures between -30°C–25°C. The solution was stirred at this temperature for 4–24 hours. After filtration through silica gel the solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel.

#### **7.4.21 General procedure for the catalytic $\alpha$ -oxytosylation of propiophenone (GP21)**

A solution of propiophenone (1.0 mmol, 1.0 eq) in acetonitrile (1 ml) was added to a solution of iodoarene (0.1 mmol, 0.1 eq), *p*-toluenesulphonic acid monohydrate (1.5 mmol, 1.5 eq) and *m*CPBA (1.5 mmol 77% wet, 1.5 eq) in acetonitrile (2 ml) at room temperature. The resulting solution was stirred for 60 hours, then quenched by addition of saturated aqueous sodium thiosulphate (5 ml) and saturated aqueous sodium carbonate (5 ml). The mixture was extracted with ethyl acetate (3 x 5 ml), the combined organic layers were washed with brine (10 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography to yield the desired product.

#### **7.4.22 General procedure for the catalytic $\alpha$ -acetoxylation of propiophenone (GP22)**

A solution of propiophenone (1.0 mmol, 1.0 eq) in acetic acid (1 ml) was added to a solution of iodoarene (0.10 mmol, 0.1 eq) and *m*-CPBA (1.5 mmol 77% wet, 1.5 eq) in acetic acid (2 ml) at room temperature. Boron trifluoride diethyl etherate (1.5 mmol, 1.5 eq) and water (2.5 mmol, 2.5 eq) was added and the resulting solution stirred for 24 hours, then quenched by addition of saturated aqueous sodium thiosulphate (5 ml) and saturated aqueous sodium carbonate (5 ml). The mixture was extracted with diethyl ether (3 x 5 ml) the combined organic layers were washed with brine (10 ml), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography yield the desired product.

#### **7.4.23 General procedure for iodination via *ortho*-lithiation of aromatic rings (GP23)**

To a stirred solution of the alcohol (10.0 mmol, 1.0 eq) in hexane/diethyl ether (4:1, 100 ml) at 0°C was added *n*BuLi (20 mmol, 2.0 eq of a 2.5 M solution in hexanes) dropwise over 20 minutes. Dry diethyl ether (10 ml) was added, the resulting solution warmed to room temperature and stirred for 4 hours. Iodine (10.0 mmol, 1.0 eq) in diethyl ether (30 ml) was added and the solution stirred for a further 30 minutes. The solution was quenched with aqueous ammonia/ammonium chloride solution (50 ml, pH ~8), and the aqueous phase extracted with diethyl ether (3 x 40 ml). The combined organic fractions were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The product was purified by column chromatography to give the desired product.

#### **7.4.24 General procedure for the alkylation of 2-(iodophenyl)acetonitrile (GP24)**

A solution of 2-(iodophenyl)acetonitrile (10.0 mmol, 1.0 eq) in dry THF (2 ml) was added to a previously prepared solution of *n*BuLi (10.0 mmol, 1.0 eq of a 2.5 M solution in hexanes) and diisopropylamine (10.0 mmol, 1.0 eq) in dry THF (3 ml) at  $-78^{\circ}\text{C}$  under an inert atmosphere of argon. The mixture was stirred for 20 minutes and a solution of the iodoalkane (10.5 mmol, 1.05 eq) in THF (2 ml) was added dropwise and the resulting solution allowed to warm to room temperature. The reaction mixture was quenched with saturated aqueous ammonium chloride (2 x 10 ml), the organic layer was decanted and the aqueous layer extracted with ether (2 x 10 ml). The combined organic fractions were washed with brine (2 x 10 ml), dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The product was purified by column chromatography to give the desired product.

#### **7.2.25 General procedure for the reduction of the 2-(iodophenyl)acetonitrile derivative using DIBAL (GP25)**

DIBAL (41.2 mmol of a 1M solution in toluene, 2.0 eq) was added to a stirred solution of 2-(iodophenyl)acetonitrile derivative (20.6 mmol, 1.0 eq) in dry toluene (10 ml) at  $-78^{\circ}\text{C}$  under an inert atmosphere of argon for 30 minutes. The resulting solution was allowed to warm up to room temperature and stirred for a further hour. The solution was hydrolysed with 5% sulphuric acid (10 ml) and the solution extracted with ethyl acetate (2 x 10 ml). The pH of the aqueous layer was raised to pH 4.5 using sodium hydroxide and further extracted with ethyl acetate (3 x 10 ml). The combined organic fractions were washed with brine (2 x 10 ml), dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The product was purified by column chromatography to give the desired product.

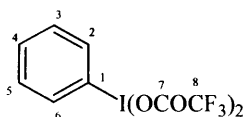


### **7.2.26 General procedure for the $\alpha$ -functionalisation of propiophenone (GP26)**

The chiral hypervalent iodine compound (0.5 mmol, 1.0 eq) and *p*-toluenesulphonic acid monohydrate (0.6 mmol, 1.2 eq) were dissolved in dichloromethane (3 ml). Propiophenone (0.5 mmol, 1.0 eq) was added at temperatures between  $-30^{\circ}\text{C}$ – $25^{\circ}\text{C}$ . The solution was stirred at this temperature for 4–24 hours. After filtration through silica gel, the solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel.

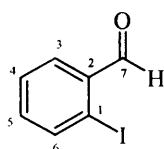
## 7.5 Experimental Data

### [Bis(trifluoroacetoxy)iodo]benzene<sup>6</sup> - 10



Synthesised according to GP15 with iodobenzene **2** (1.5 g, 7.35 mmol) in DCM (5 ml) added to a previously prepared solution of trifluoroacetic anhydride (13.4 g, 63.78 mmol) and urea hydrogen peroxide (1.5 g, 15.95 mmol) in DCM (10 ml). Product was isolated by washing with pentane. Yield 96% (3.034 g, 7.058 mmol) of a white powder. mp = 120–122 °C. Spectroscopic data agrees with literature. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ<sub>H</sub>: 7.62 (2H, d, *J* = 8.0 Hz, *H*-arom), 7.74 (1H, t, *J* = 8.0 Hz, *H*-arom), 8.20 (2H, d, *J* = 8.0 Hz, *H*-arom); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 100 MHz) δ<sub>C</sub>: 112.8 (q, *J*<sub>CF</sub> = 290 Hz, COCF<sub>3</sub>, C-8), 122.8 (C-1), 132.0 (C-3 & 5), 133.7 (C-4), 135.1 (C-2 & 6) 161.1 (q, *J*<sub>CF</sub> = 41 Hz, COCF<sub>3</sub>, C-7).

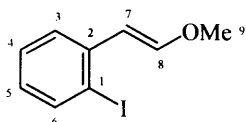
### 2-Iodobenzaldehyde<sup>7</sup> - 51



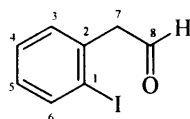
Synthesised according to GP1 with 2-iodobenzyl alcohol **43** (5.0 g, 21.36 mmol) in dichloromethane (15 ml) stirred with pyridinium chlorochromate (9.91 g, 32.01 mmol) in dichloromethane (50 ml) at 0°C. Yield 96% (4.73 g, 21.38 mmol), yellow solid, mp 34–35°C. Spectroscopic data consistent with literature. <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 400 MHz) δ<sub>H</sub>: 7.34 (1H, dd, *J* = 7.4, 1.3 Hz, *H*-arom), 7.51 (1H, dd, *J* = 7.4, 1.1 Hz, *H*-arom), 7.92 (1H, d, *J* = 7.9 Hz, *H*-arom) 8.00 (1H, d, *J* = 7.9 Hz, *H*-arom), 10.13 (1H, s, CHO); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 100.4 MHz) δ<sub>C</sub>: 101.2 (C-1),

129.1 (C-4), 130.7 (C-3), 133.4 (C-2), 135.9 (C-5), 141.0 (C-6), 196.1 (C-7); IR (Nujol):  $\nu_{\max} = \text{C}=\text{O}$  1703  $\text{cm}^{-1}$ .

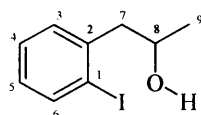
**(E)-and (Z)-1-(2-Iodophenyl)-2-methoxyethene<sup>8</sup> - 51 & 52**



Synthesised according to GP2 with (methoxymethyl)triphenylphosphonium chloride (7.32 g, 21.35 mmol) in dry THF (10 ml), 2-iodobenzaldehyde **51** (4.50 g, 19.40 mmol) stirred in the presence of *n*BuLi (12.42 ml, 31.04 mmol of a 2.5 M solution in hexanes) and diisopropylamine (4.35 ml, 31.04 mmol) in dry THF (5 ml). The resulting solution was columned using petroleum ether / diethyl ether (15:1). Yield 91% (1.50g, 5.77 mmol, (E):(Z) = 1:1), as a pale yellow oil. Spectroscopic data consistent with literature. <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 250 MHz)  $\delta_{\text{H}}$ : 3.77 (3H (E) or (Z), s, CH<sub>3</sub>), 3.81 (3H (E) or (Z), s, CH<sub>3</sub>), 5.50 (1H, d,  $J = 9.4$  Hz, (Z)-CHOCH<sub>3</sub>), 6.02 (1H, d,  $J = 12.8$  Hz, (E)-CHOCH<sub>3</sub>), 6.26 (1H, d,  $J = 7.2$  Hz, (Z)-CH=CHOCH<sub>3</sub>), 6.86-6.90 (2H, m, (E) & (Z) H-5). 6.95 (1H, d  $J = 12.8$  Hz, (E)-CH=CHOCH<sub>3</sub>), 7.27-7.38 (2H, m, (E) & (Z) H-5), 7.85 (2H, ddd,  $J = 7.9, 1.7, 1.5$  Hz, (E) & (Z) H-3), 8.30 (2H, dd,  $J = 7.9, 1.4$  Hz, (E) & (Z) H-6); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 62.5MHz)  $\delta_{\text{C}}$ : 56.6 ((E) OCH<sub>3</sub>), 60.9 ((Z) OCH<sub>3</sub>), 99.5 ((Z) C-1), 99.8 ((E) C-1), 109.1 ((Z) CHOCH<sub>3</sub>), 109.5 ((E) CHOCH<sub>3</sub>), 125.2, 127.4 x 2, 128.0, 128.4, 129.6 ((E) & (Z) C-3,4,5), 138.3 ((Z) C-2) 139.3 ((Z) C-6), 139.5 ((E) C-2), 139.6 ((E) C-6), 149.1 ((Z) CH=CHOCH<sub>3</sub>), 150.6 ((E) CH=CHOCH<sub>3</sub>); MS (EI):  $m/z$  (%) = 260 (65) [M]<sup>+</sup>, 118 (100); HRMS for C<sub>9</sub>H<sub>10</sub>IO: calcd. 259.9693, found 259.9690 [M+H]<sup>+</sup>. IR (Liquid film):  $\nu_{\max} = 1094$  (C-O), 1636 (C=C)  $\text{cm}^{-1}$ .

**(2-iodophenyl) acetaldehyde<sup>8</sup> - 54**

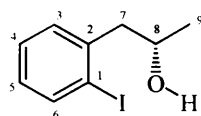
Synthesised according to GP3 with 1-(2-iodophenyl)-2-methoxyethene **51** & **52** (1.20, 4.61 mmol) stirred in formic acid (3.70 ml, 80.38 mmol) in DCM (10 ml). Yield 97% (1.03 g, 4.19 mmol), as a pale yellow oil required no further purification. <sup>1</sup>H-NMR, (CDCl<sub>3</sub>, 400 MHz) δ<sub>H</sub>: 3.80 (2H, s, ArCH<sub>2</sub>), 6.93 (1H, dd, *J* = 7.6, 7.5 Hz, H-arom), 7.14 (1H, d, *J* = 7.5 Hz, H-arom), 7.27 (1H, dd, *J* = 7.5, 7.5 Hz, H-arom), 7.80 (1H, d, *J* = 7.6 Hz, H-arom), 9.70 (1H, s, CHO); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 100.4 MHz) δ<sub>C</sub>: 55.1 (CH<sub>2</sub>), 101.5 (C-1), 129.2 (C-4), 129.7 (C-3), 131.4 (C-2), 136.6 (C-5), 140.1 (C-6), 201.4 (C-8) ; MS (EI) *m/z* (%) = 245 (7) [M]<sup>+</sup>, 217 (62), 119 (100); IR (Neat) : ν<sub>max</sub> = 3058, 2942, 2928, 1724, 1582, 1563, 1467, 1436, 1261, 1156, 1014, 868, 800, 750 cm<sup>-1</sup>.

**(±)-1-(2-Iodophenyl)propan-2-ol – 55**

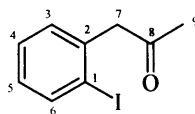
Synthesised according to GP4 with methylmagnesium iodide (372 mg, 2.24 mmol) and (2-iodophenyl) acetaldehyde **54** (550 mg, 2.24 mmol) stirred in dry diethyl ether (5 ml). The product was columned using petroleum ether/diethyl ether (6:1). Yield 97% (568 mg, 2.18 mmol), as a pale yellow oil. HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 98:2, 0.5 ml/min, 10 °C, *t<sub>R</sub>* = 22.9 min (–)-enantiomer, *t<sub>S</sub>* = 24.5 min (+)-enantiomer: <sup>1</sup>H-NMR, (CDCl<sub>3</sub>, 250 MHz) δ<sub>H</sub>: 1.34 (3H, d, *J* = 6.2 Hz, CH<sub>3</sub>), 1.55 (1H, br s, OH), 2.89–2.95 (2H, m, ArCH<sub>2</sub>), 4.10–4.22 (1H, m, CH), 6.96 (1H, ddd, *J* = 7.9, 6.9, 2.2 Hz, H-arom), 7.25–7.36 (2H, m, H-arom), 7.78 (1H, dd, *J* = 7.9, 1.0 Hz, H-arom); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 62.5 MHz) δ<sub>C</sub>: 23.0 (C-9), 49.9 (C-7), 67.7 (C-8), 101.2 (C-1), 128.4 (C-

4), 128.4 (C-3), 130.9 (C-5), 139.8 (C-6), 141.4 (C-2); MS (ES<sup>+</sup>):  $m/z$  (%) = 280 (5) [M+NH<sub>4</sub>]<sup>+</sup>, 262 (4), 218 (45), 105 (5), 91 (100), 45 (47); HRMS for C<sub>9</sub>H<sub>15</sub>I<sub>2</sub>NO: calcd. 280.0193, found 280.0195 [M+NH<sub>4</sub>]<sup>+</sup>; IR (Neat):  $\nu_{\max}$  = 3399, 2930, 1455, 1380, 1151, 1031 cm<sup>-1</sup>.

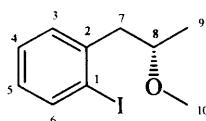
**(S)-1-(2-Iodophenyl)propan-2-ol – 56**



Synthesised according to GP9 with 1-(2-iodophenyl)propan-2-one **57** (550 mg, 2.235 mmol) added to a stirred solution of (-)- $\beta$ -chlorodiisopinocampheylborane (789 mg, 2.459 mmol) in dry THF (5 ml). Diethyl ether (10 ml) was added along with diethanolamine (517 mg, 4.918 mmol). The product was columned using petroleum ether/diethyl ether (6:1). Yield 67%, 34% *ee* (393 mg, 1.498 mmol), pale yellow oil. The enantiomers could be separated by preparative HPLC: Chiracel OD column, hexane/2-propanol, 99:1, 3 ml/min, 10 °C,  $t_R$  = 128.3 min (-)-enantiomer,  $t_S$  = 143.9 min (+)-enantiomer: Enantiomer 2 ( $R_f$  = 143.9 min):  $[\alpha]_D^{25}$  = + 21.28 (c = 0.19, CHCl<sub>3</sub>, >99% *ee*); <sup>1</sup>H-NMR, (CDCl<sub>3</sub>, 250 MHz)  $\delta_H$ : 1.34 (3H, d,  $J$  = 6.2 Hz, CH<sub>3</sub>), 1.55 (1H, br s, OH), 2.89–2.95 (2H, m, ArCH<sub>2</sub>), 4.10–4.22 (1H, m, CH), 6.96 (1H, ddd,  $J$  = 7.9, 6.9, 2.2 Hz, H-arom), 7.25–7.36 (2H, m, H-arom), 7.78 (1H, dd,  $J$  = 7.9, 1.0 Hz, H-arom); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 62.5 MHz)  $\delta_C$ : 23.0 (C-9), 49.9 (C-7), 67.7 (C-8), 101.2 (C-1), 128.4 (C-4), 128.4 (C-3), 130.9 (C-5), 139.8 (C-6), 141.4 (C-2); MS (ES<sup>+</sup>):  $m/z$  (%) = 280 (5) [M+NH<sub>4</sub>]<sup>+</sup>, 262 (4), 218 (45), 105 (5), 91 (100), 45 (47); HRMS for C<sub>9</sub>H<sub>15</sub>I<sub>2</sub>NO: calcd. 280.0193, found 280.0195 [M+NH<sub>4</sub>]<sup>+</sup>; IR (Neat):  $\nu_{\max}$  = 3399, 2930, 1455, 1380, 1151, 1031 cm<sup>-1</sup>.

**1-(2-Iodophenyl)propan-2-one<sup>9</sup> - 57**

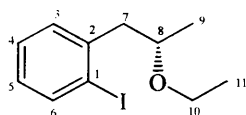
Synthesised according to GP1 with 1-(2-iodophenyl)propan-2-ol **55** (449 mg, 1.71 mmol) in dichloromethane (15 ml) stirred with pyridinium chlorochromate (554 mg, 2.57 mmol) in dichloromethane (10 ml) at 0°C. Yield 90% (401 mg, 1.54 mmol) as a yellow oil. Spectroscopic data agrees with literature. <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 250 MHz) δ<sub>H</sub>: 2.22 (3H, s, CH<sub>3</sub>), 3.89 (2H, s, ArCH<sub>2</sub>), 6.98 (1H, d, *J* = 7.5 Hz, *H*-arom), 7.17 (1H, d, *J* = 7.7 Hz, *H*-arom), 7.31 (1H, d, *J* = 7.7 Hz, *H*-arom), 7.85 (1H, d, *J* = 7.5 Hz, *H*-arom). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 62.5 MHz) δ<sub>C</sub>: 30.4 (C-9), 48.1 (C-7), 99.1 (C-1), 127.4 (C-4), 128.8 (C-5), 130.8 (C-3), 138.1 (C-6), 140.3 (C-2), 208.2 (C-8); HRMS for C<sub>9</sub>H<sub>13</sub>INO: calcd. 278.1750, found 278.1752 [M+NH<sub>4</sub>]<sup>+</sup>; IR (Nujol): ν<sub>max</sub> = 1709 (C=O) cm<sup>-1</sup>

**(S)-1-Iodo-2-(2-methoxypropyl)benzene - 58**

Synthesised according to GP5 with sodium hydride (53 mg, 2.22 mmol) suspended in DMF (2 ml) stirred with (*S*)-1-(2-iodophenyl)propan-2-ol **56** (193 mg, 0.74 mmol) and methyl iodide (105 mg, 0.74 mmol). The product was purified by column chromatography hexane/ethyl acetate (4:1). Yield 96% (195 mg, 0.71 mmol) as a pale yellow oil. [α]<sub>D</sub><sup>25</sup> = +41.22 (c = 0.12, CHCl<sub>3</sub>). <sup>1</sup>H-NMR, (CDCl<sub>3</sub>, 250 MHz) δ<sub>H</sub>: 1.10 (3H, d, *J* = 6.1 Hz, CH<sub>3</sub>), 2.67 (1H, dd, *J* = 13.5, 6.6 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 2.98 (1H, dd, *J* = 13.6, 6.5 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 3.28 (3H, s, OCH<sub>3</sub>), 3.52–3.57 (1H, m, CH), 6.81 (1H, ddd, *J* = 8.0, 6.5, 1.4 Hz, H-arom), 7.12–7.21 (2H, m, H-arom), 7.74 (1H, dd, *J* = 8.0, 1.0 Hz, H-arom); <sup>13</sup>C-NMR, (CDCl<sub>3</sub>, 62.5 MHz) δ<sub>C</sub>: 18.0 (C-9), 28.7 (C-7), 49.1 (C-10), 55.5 (C-8), 100.3 (C-

1), 127.0 (C-4), 127.1 (C-3), 130.1 (C-5), 138.4 (C-6), 140.7 (C-2); MS (ES<sup>+</sup>): *m/z* (%) = 276 (16) [M]<sup>+</sup>, 217 (34), 105 (9), 91 (100), 58 (37); HRMS for C<sub>10</sub>H<sub>14</sub>IO: calcd. 276.112, found 276.1115 [M+H]<sup>+</sup>; IR (Neat):  $\nu_{\max}$  = 2820, 1544, 1469, 1366, 1169, 1122, 1089, 1010, 907, 751, 717 cm<sup>-1</sup>. An authentic sample of racemic **58**, ( $\pm$ )-1-iodo-2-(2-methoxypropyl)benzene, was prepared from **55** as described previously: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 99:1, 0.5 ml/min, 22 °C, *t*<sub>R</sub> = 8.4 min (–)-enantiomer, *t*<sub>S</sub> = 9.9 min (+)-enantiomer. The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

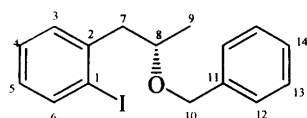
### (S)-1-(2-Ethoxypropyl)-2-iodobenzene - **59**



Synthesised according to GP5 with sodium hydride (55 mg, 2.29 mmol) suspended in DMF (2 ml) stirred with (*S*)-1-(2-iodophenyl)propan-2-ol **56** (200 mg, 0.76 mmol) and ethyl iodide (119 mg, 0.76 mmol). The product was purified by column chromatography hexane/ethyl acetate (4:1). Yield 90% (199 mg, 0.67 mmol) as a pale yellow oil.  $[\alpha]_D^{26} = +39.28$  (*c* = 0.17, CHCl<sub>3</sub>). <sup>1</sup>H-NMR, (CDCl<sub>3</sub>, 250 MHz)  $\delta_{\text{H}}$ : 1.09 (3H, t, *J* = 7.0 Hz, CH<sub>3</sub>CH<sub>2</sub>), 1.15 (3H, d, *J* = 6.0 Hz, CH<sub>3</sub>), 2.65 (1H, dd, *J* = 13.4, 6.5 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 2.96 (1H, dd, *J* = 13.4, 6.5 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 3.47–3.54 (1H, m, CH), 3.55 (2H, d, *J* = 6.9 Hz, CH<sub>3</sub>CH<sub>2</sub>), 6.85 (1H, atd, *J* = 7.9, 1.1 Hz, H-arom), 7.11–7.22 (2H, m, H-arom), 7.73 (1H, dd, *J* = 7.9, 1.0 Hz, H-arom); <sup>13</sup>C-NMR, (CDCl<sub>3</sub>, 62.5 MHz)  $\delta_{\text{C}}$ : 16.9 (C-11), 20.2 (C-9), 37.7 (C-7), 64.0 (C-10), 66.1 (C-8), 99.3 (C-1), 127.0 (C-4), 127.6 (C-5), 130.0 (C-3), 137.7 (C-6), 141.2 (C-2); MS (ES<sup>+</sup>): *m/z* (%) = 290 (11) [M]<sup>+</sup>, 261 (39), 217 (30), 105 (11), 91 (100); HRMS for C<sub>10</sub>H<sub>14</sub>IO: calcd. 290.0201, found 290.0197 [M+H]<sup>+</sup>; IR (Neat):  $\nu_{\max}$  = 2957, 2920, 1559, 1449, 1371, 1110, 1013 cm<sup>-1</sup>. An authentic sample of racemic **59** ( $\pm$ )-1-iodo-2-(2-ethoxypropyl)benzene, was prepared from **55** as described above: HPLC conditions: Chiracel OD-H

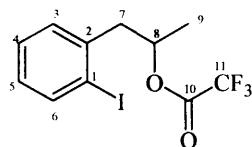
column, hexane/2-propanol, 99:1, 0.5 ml/min, 20 °C,  $t_R$  = 8.9 min (–)-enantiomer,  $t_S$  = 12.1 min (+)-enantiomer. The racemic ether gave baseline separation and 1:1 ratio of integrated areas.

### 1-((*S*)-2-Benzyloxypropyl)-2-iodobenzene- **60**

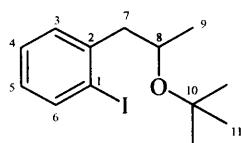


Synthesised according to GP5 with sodium hydride (55 mg, 2.29 mmol) suspended in DMF (2 ml) stirred with (*S*)-1-(2-iodophenyl)propan-2-ol **56** (200 mg, 0.76 mmol) and benzyl chloride (130 mg, 0.76 mmol). The product was purified by column chromatography hexane/ethyl acetate (5:1). Yield 72% (194 mg, 0.55 mmol) as a pale yellow oil.  $[\alpha]_D^{26} = +50.02$  ( $c = 0.22$ ,  $\text{CHCl}_3$ , >99% *ee*). HPLC conditions:  $^1\text{H-NMR}$ , ( $\text{CDCl}_3$ , 250 MHz)  $\delta_{\text{H}}$ : 1.19 (3H, d,  $J = 6.1$  Hz,  $\text{CH}_3$ ), 2.64 (1H, dd,  $J = 12.9, 6.4$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.86 (1H, dd,  $J = 12.9, 6.4$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.45–3.54 (1H, m,  $\text{CH}$ ), 3.60 (2H, d,  $J = 7.0$  Hz,  $\text{OCH}_2$ ), 6.83 (1H, atd,  $J = 7.8, 1.1$  Hz, H-arom), 7.15–7.30 (7H, m, H-arom), 7.65 (1H, dd,  $J = 7.8, 1.0$  Hz, H-arom);  $^{13}\text{C-NMR}$ , ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta_{\text{C}}$ : 20.1 (C-9), 38.7 (C-7), 69.1 (C-8), 69.6 (C-10), 98.3 (C-1), 127.0 (C-4), 127.1 (C-5), 127.5 (C-Ar\*), 127.8 (C-Ar\*), 128.6 (C-Ar\*) 130.1 (C-3), 138.4 (C-6), 138.6 (C-Ar\*), 141.7 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 352 (13)  $[\text{M}]^+$ , 276 (44), 231 (36), 217 (19), 105 (100), 91 (21); HRMS for  $\text{C}_{16}\text{H}_{21}\text{INO}$ : calcd. 370.2348, found 370.2355  $[\text{M}+\text{NH}_4]^+$ ; IR (Neat):  $\nu_{\text{max}} = 2957, 2920, 1559, 1462, 1431, 1372, 1121, 1057, 1009$   $\text{cm}^{-1}$ . An authentic sample of racemic **60**, 1-(±)-2-benzyloxypropyl)-2-iodobenzene, was prepared from **55** as described above: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 98:2, 0.5 ml/min, 21 °C,  $t_R$  = 12.2 min (–)-enantiomer,  $t_S$  = 17.9 min (+)-enantiomer. The racemic ether gave baseline separation and 1:1 ratio of integrated areas.



**(±)-1-(2-Trifluoroacetoxypropyl)-2-iodobenzene<sup>10</sup> - 61**

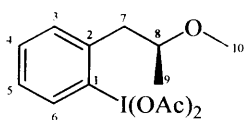
Synthesised according to GP6 with trifluoroacetic anhydride (220 mg, 1.05 mmol) added to a stirred solution of (±)-1-(2-iodophenyl)propan-2-ol **55** (229 mg, 0.87 mmol) and triethylamine (106 mg, 1.05 mmol) in DCM (2 ml). The product was purified by column chromatography petroleum ether/diethyl ether (1:1). Yield 69% (217 mg, 0.61 mmol) as a colourless oil. <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 400 MHz) δ<sub>H</sub>: 1.34 (3H, d, *J* = 6.3 Hz, CH<sub>3</sub>), 2.99–3.04 (2H, m, ArCH<sub>2</sub>), 5.28–5.34 (1H, m, CH), 6.85 (1H, atd, *J* = 7.4, 1.7 Hz, H-arom), 7.11 (1H, dd, *J* = 7.8, 1.7 Hz, H-arom), 7.19 (1H, atd, *J* = 7.8, 1.7 Hz, H-arom), 7.74 (1H, dd, *J* = 7.4, 1.7 Hz, H-arom). <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 100.7 MHz) δ<sub>C</sub>: 19.4 (C-9), 46.1 (C-7), 75.5 (C-8), 100.7 (C-1), 115.0 (q, *J*<sub>CF</sub> = 288 Hz, C-11), 128.4 (C-4), 128.9 (C-5), 130.3 (C-3), 139.7 (C-6), 1403.7 (C-2), 158.7 (q, *J*<sub>CF</sub> = 39.5 Hz, C-10); MS (EI<sup>+</sup>): *m/z* (%) = 358 (100) [M]<sup>+</sup>, 334 (9), 318 (43), 304 (8), 91 (45); IR (Neat): ν<sub>max</sub> = 3102, 1712, 1207, 1180, 1104 cm<sup>-1</sup>.

**(±)-1-(2-Tert-Butoxypropyl)-2-iodobenzene<sup>11</sup> - 62**

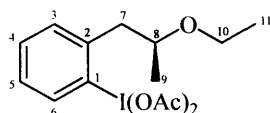
Synthesised according to GP7 with concentrated sulphuric acid (42 mg, 0.43 mmol) added to a stirred suspension of anhydrous MgSO<sub>4</sub> (209 mg, 1.74 mmol) in cyclohexane (3 ml). *t*BuOH (160 mg, 2.2 mmol) and (±)-1-(2-iodophenyl)propan-2-ol **55** (114 mg, 0.43 mmol) was added dropwise to the resulting solution. The product was purified by column chromatography petroleum ether/diethyl ether (5:1). Yield 87% (120 mg, 0.38 mmol) as a pale

yellow oil.  $^1\text{H-NMR}$ , ( $\text{CDCl}_3$ , 250 MHz)  $\delta_{\text{H}}$ : 1.17 (9H, s,  $(\text{CH}_3)_3$ ), 1.20 (3H, d,  $J = 6.4$  Hz,  $\text{CH}_3$ ), 2.78 (1H, dd,  $J = 13.6, 4.7$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.88 (1H, dd,  $J = 13.6, 4.7$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 4.04–4.09 (1H, m,  $\text{CH}$ ), 6.85 (1H, atd,  $J = 7.8, 1.2$  Hz,  $H$ -arom), 7.16–7.21 (2H, m,  $H$ -arom), 7.60 (1H, dd,  $J = 7.8, 1.0$  Hz,  $H$ -arom);  $^{13}\text{C-NMR}$ , ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta_{\text{C}}$ : 22.2 (C-9), 29.6 (C-11), 39.8 (C-7), 66.1 (C-8), 73.0 (C-10), 98.4 (C-1), 127.0 (C-4), 127.4 (C-5), 129.0 (C-3), 137.5 (C-6), 141.5 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 318 (12)  $[\text{M}]^+$ , 261 (37), 217 (100), 105 (17), 91 (45); HRMS for  $\text{C}_{13}\text{H}_{20}\text{IO}$ : calcd. 319.1966, found 319.1970  $[\text{M}+\text{H}]^+$ ; IR (Neat):  $\nu_{\text{max}} = 2967, 2885, 1580, 1480, 1459, 1368, 1110, 1070, 1013 \text{ cm}^{-1}$ .

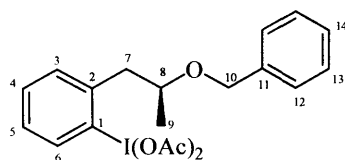
### (*S*)-1-(Diacetoxyiodo)-2-(-2-methoxypropyl)benzene - 63



Synthesised according to GP12 with peracetic acid (0.88 ml of a 30% solution in acetic acid) added to a stirred solution of (*S*)-1-iodo-2-(-2-methoxypropyl)benzene **58** (63 mg, 0.22 mmol) in acetic acid (5 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 39% (35 mg, 0.09 mmol) as a white powder. mp = 107–110°C.  $[\alpha]_{\text{D}}^{24} = +89.41$  (c = 0.34,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$ , ( $\text{CDCl}_3$ , 250 MHz)  $\delta_{\text{H}}$ : 1.16 (3H, d,  $J = 6.1$  Hz,  $\text{CH}_3$ ), 1.87 (6H, s,  $(\text{OCOCH}_3)_2$ ), 2.94–3.01 (2H, m,  $\text{ArCH}_2$ ), 3.44 (3H, s,  $\text{OCH}_3$ ), 3.59–3.64 (1H, m,  $\text{CH}_2\text{CH}$ ), 7.19 (1H, d,  $J = 7.7$  Hz,  $H$ -arom), 7.40–7.47 (2H, m,  $H$ -arom), 8.10 (1H, d,  $J = 7.8$  Hz,  $H$ -arom);  $^{13}\text{C-NMR}$ , ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta_{\text{C}}$ : 20.3 ( $(\text{OCOCH}_3)_2$ , C-12), 21.3 (C-9), 33.9 (C-7), 49.1 (C-10), 58.9 (C-8), 118.3 (C-1), 127.9 (C-Ar), 127.1 (C-Ar), 130.1 (C-Ar), 139.0 (C-6), 141.7 (C-2), 175.6 (C=O, C-11), 175.7 (C=O, C-11); IR (Nujol):  $\nu_{\text{max}} = 2906, 1720, 1615, 1560, 1455, 1380, 1149, 1012 \text{ cm}^{-1}$ .

**(S)-1-(Diacetoxyiodo)-2-(-2-ethoxypropyl)benzene - 64**

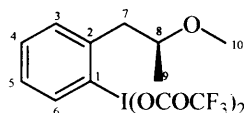
Synthesised according to GP11 with sodium perborate tetrahydrate (477 mg, 3.10 mmol) added portion wise to a solution of (*S*)-1-(-2-ethoxypropyl)-2-iodobenzene **59** (89 mg, 0.31 mmol) in glacial acetic acid (5 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 15% (19 mg, 0.047 mmol) as a white powder. mp = 99–103 °C.  $[\alpha]_D^{21} = +61.1$  (c = 0.12, CHCl<sub>3</sub>). <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 250 MHz)  $\delta_H$ : 1.16 (3H, t,  $J = 7.0$  Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.21 (3H, d,  $J = 6.0$  Hz, CH<sub>3</sub>), 1.90 (6H, s, (OCOCH<sub>3</sub>)<sub>2</sub>), 2.96–3.00 (2H, m, ArCH<sub>2</sub>), 3.75 (2H, q,  $J = 7.0$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.56–3.60 (1H, m, CH), 7.14 (1H, d,  $J = 7.8$  Hz, *H*-arom), 7.39–7.44 (2H, m, *H*-arom), 8.11 (1H, d,  $J = 8.0$  Hz, *H*-arom); <sup>13</sup>C-NMR, (CDCl<sub>3</sub>, 62.5 MHz)  $\delta_C$ : 20.0 (C-11), 20.6, ((OCOCH<sub>3</sub>)<sub>2</sub>, C-13), 21.3 (C-9), 33.5 (C-7), 49.6 (C-10), 59.0 (C-8), 118.0 (C-1), 127.8 (C-Ar), 128.3 (C-Ar), 130.1 (C-Ar), 139.1 (C-6), 142.5 (C-2), 175.9 (C=O, C-12), 176.1 (C=O, C-12); IR (Nujol):  $\nu_{\max} = 2944, 2910, 1710, 1559, 1455, 1375, 1122, 1013$  cm<sup>-1</sup>.

**(S)-1-(Diacetoxyiodo)-2-(-2-benzyloxypropyl)benzene - 65**

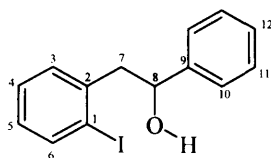
Synthesised according to GP11 with sodium perborate tetrahydrate (354 mg, 2.30 mmol) added portion wise to a solution of (*S*)-1-(-2-benzyloxypropyl)-2-iodobenzene **60** (100 mg, 0.23 mmol) in glacial acetic acid (5 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 9% (12 mg, 0.026 mmol) as a white powder. mp = 110–113°C.  $[\alpha]_D^{21} = +77.2$  (c = 0.12, CHCl<sub>3</sub>). <sup>1</sup>H-NMR, (CDCl<sub>3</sub>, 250 MHz)  $\delta_H$ : 1.19 (3H, d,  $J = 6.1$  Hz, CH<sub>3</sub>), 2.01 (6H, s,

(OCOCH<sub>3</sub>)<sub>2</sub>), 2.77 (1H, dd, *J* = 13.2, 6.7 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 2.96 (1H, dd, *J* = 13.1, 7.2 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 3.38–3.42 (1H, m, CH), 3.99 (2H, d, *J* = 7.0 Hz, OCH<sub>2</sub>), 7.02 (1H, atd, *J* = 8.2, 1.1 Hz, *H*-arom), 7.15–7.46 (7H, m, *H*-arom), 8.02 (1H, dd, *J* = 8.2, 1.2 Hz, *H*-arom); <sup>13</sup>C-NMR, (CDCl<sub>3</sub>, 62.5 MHz) δ<sub>C</sub>: 20.1 (C-9), 20.5 ((OCOCH<sub>3</sub>)<sub>2</sub>, C-16), 38.7 (C-7), 69.1 (C-8), 69.6 (C-10), 127.5 (C-Ar), 127.8 (C-Ar), 128.6 (C-Ar), 129.8 (C-Ar), 130.2 (C-Ar), 130.9 (C-3), 132.2 (C-1), 138.6 (C-Ar), 139.4 (C-6), 143.0 (C-2), 176.9 (C=O, C-15), 177.0 (C=O, C-15); No IR obtained.

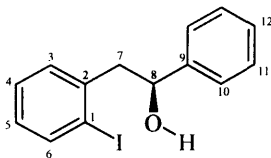
**(*S*)-1-[Bis(trifluoroacetoxy)iodo]-2-(-2-methoxypropyl)benzene – 66**



Synthesised according to GP15 with (*S*)-1-iodo-2-(-2-methoxypropyl)benzene **58** (100 mg, 0.36 mmol) in DCM (2 ml) was added to a previously prepared trifluoroacetic anhydride (190 mg, 0.905 mmol) and urea hydrogen peroxide (341 mg, 3.62 mmol) in DCM (5 ml). Yield 6% (11 mg, 0.022 mmol) of a white powder. <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 400 MHz) δ<sub>H</sub>: 1.29 (3H, d, *J* = 6.1 Hz, CH<sub>3</sub>), 2.84–2.90 (2H, m, ArCH<sub>2</sub>), 3.47 (3H, s, OCH<sub>3</sub>), 4.00–4.05 (1H, m, CH), 7.09–7.25 (2H, m, *H*-arom), 7.60 (1H, d, *J* = 7.7 Hz, *H*-arom), 8.16 (1H, d, *J* = 8.0 Hz, *H*-arom); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.7 MHz): δ = 24.0 (C-9), 39.0 (C-7), 57.5 (C-10), 83.4 (C-8), 113.0 (q, *J*<sub>CF</sub> = 290 Hz, CF<sub>3</sub>, C-12), 126.9 (C-Ar), 128.6 (C-Ar), 131.4 (C-Ar), 133.4 (C-1), 141.4 (C-6), 144.3 (C-2), 161.5 (q, *J*<sub>CF</sub> = 40 Hz, C=O, C-11); No IR obtained.

**(±)-2-(2-Iodophenyl)-1-phenylethanol<sup>12</sup> – 67**

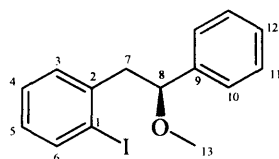
Synthesised according to GP4 with phenylmagnesium bromide (1.275 g, 7.03 mmol) and (2-iodophenyl) acetaldehyde **54** (1.730 g, 7.03 mmol) stirred in dry diethyl ether (10 ml). The product was columned using petroleum ether/diethyl ether (7:1). Yield 85% (1.94 g, 5.98 mmol), pale yellow oil. The enantiomers could be separated by preparative HPLC: Chiracel OD column, hexane/2-propanol, 93:7, 3 ml/min, 10 °C,  $t_R$  = 17.2 min (+)-enantiomer,  $t_S$  = 19.9 min (-)-enantiomer: <sup>1</sup>H-NMR, (CDCl<sub>3</sub>, 500 MHz)  $\delta_H$ : 1.82 (1H, br s, OH), 3.02 (1H, dd,  $J$  = 13.8, 9.0 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 3.09 (1H, dd,  $J$  = 13.8, 4.3 Hz, ArCH<sub>A</sub>CH<sub>B</sub>) 4.93 (1H, dd,  $J$  = 9.0, 4.3 Hz, CHOH), 6.86 (1H, atd,  $J$  = 7.6, 1.7 Hz, *H*-arom), 7.12 (1H, dd,  $J$  = 7.7, 1.1 Hz, *H*-arom), 7.18 (1H, dd,  $J$  = 7.7, 7.2 Hz, *H*-arom), 7.22 (1H, atd,  $J$  = 7.3, 1.5 Hz, *H*-arom), 7.29 (2H, d,  $J$  = 7.5 Hz, *H*-arom), 7.37 (2H, d,  $J$  = 7.5 Hz, *H*-arom), 7.79 (1H, dd,  $J$  = 7.6, 1.1 Hz, *H*-arom); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 125 MHz)  $\delta_C$ : 50.5 (C-7), 73.5 (C-8), 101.1 (C-2), 126.7 (C-5), 127.2 (C-Ar), 127.6 (C-Ar), 128.3 (C-4), 129.0 (C-Ar), 131.4 (C-3), 139.7 (C-6), 140.3, (C-9), 143.8 (C-1); MS (EI<sup>+</sup>):  $m/z$  (%) = 324 (1) [M]<sup>+</sup>, 307 (1), 218 (93), 107 (100), 90 (17); HRMS for C<sub>14</sub>H<sub>14</sub>IO: calcd. 324.0011, found 324.0029 [M+H]<sup>+</sup>; IR (Neat):  $\nu_{max}$  = 3153, 2966, 2921, 2358, 2320, 1795, 1722, 1676, 1563, 1098 cm<sup>-1</sup>.

**(S)-2-(2-Iodophenyl)-1-phenylethanol<sup>12</sup> – 68**

Synthesised according to GP4 with phenylmagnesium bromide (1.275 g, 7.03 mmol) and (2-iodophenyl) acetaldehyde **54** (1.730 g, 7.03 mmol) stirred in dry

diethyl ether (10 ml). The product was columned using petroleum ether/diethyl ether (7:1). Yield 85% (1.94 g, 5.98 mmol), of a pale yellow oil. HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 93:7, 0.5 ml/min, 10 °C,  $t_R = 10.2$  min (+)-enantiomer,  $t_S = 14.7$  min (–)-enantiomeaqr.  $[\alpha]_D^{23} = -48.72$  ( $c = 0.26$ ,  $\text{CHCl}_3$ , >99% *ee*);  $^1\text{H-NMR}$ , ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.82 (1H, br s, *OH*), 3.02 (1H, dd,  $J = 13.8, 9.0$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.09 (1H, dd,  $J = 13.8, 4.3$  Hz,  $\text{ArCH}_A\text{CH}_B$ ) 4.93 (1H, dd,  $J = 9.0, 4.3$  Hz, *CHOH*), 6.86 (1H, atd,  $J = 7.6, 1.7$  Hz, *H-arom*), 7.12 (1H, dd,  $J = 7.7, 1.1$  Hz, *H-arom*), 7.18 (1H, dd,  $J = 7.7, 7.2$  Hz, *H-arom*), 7.22 (1H, atd,  $J = 7.3, 1.5$  Hz, *H-arom*), 7.29 (2H, d,  $J = 7.5$  Hz, *H-arom*), 7.37 (2H, d,  $J = 7.5$  Hz, *H-arom*), 7.79 (1H, dd,  $J = 7.6, 1.1$  Hz, *H-arom*);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125 MHz)  $\delta_{\text{C}}$ : 50.5 (C-7), 73.5 (C-8), 101.1 (C-2), 126.7 (C-5), 127.2 (C-Ar), 127.6 (C-Ar), 128.3 (C-4), 129.0 (C-Ar), 131.4 (C-3), 139.7 (C-6), 140.3, (C-9), 143.8 (C-1); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 324 (1)  $[\text{M}]^+$ , 307 (1), 218 (93), 107 (100), 90 (17); HRMS for  $\text{C}_{14}\text{H}_{14}\text{IO}$ : calcd. 324.0011, found 324.0029  $[\text{M}+\text{H}]^+$ ; IR (Neat):  $\nu_{\text{max}} = 3153, 2966, 2921, 2358, 2320, 1795, 1722, 1676, 1563, 1098$   $\text{cm}^{-1}$ .

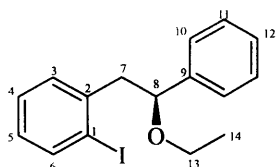
**(S)-1-(–(2-Iodophenyl)-1-methoxyethyl)benzene - 69**



Synthesised according to GP5 with sodium hydride (14 mg, 0.593 mmol) suspended in DMF (2 ml) stirred with (*S*)-2-(2-iodophenyl)-1-phenylethanol **68** (64 mg, 0.197 mmol) and methyl iodide (28 mg, 0.197 mmol). The product was purified by column chromatography petroleum ether/diethyl ether (20:1). Yield 95% (63 mg, 0.188 mmol) as a pale yellow oil.  $[\alpha]_D^{23} = -57.80$  ( $c = 0.20$ ,  $\text{CHCl}_3$ ):  $^1\text{H-NMR}$ , ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 2.92 (1H, dd,  $J = 13.8, 9.0$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.11 (1H, dd,  $J = 13.8, 8.2$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 4.35 (1H, dd,  $J = 8.2, 5.3$  Hz, *CH*), 5.20 (3H, s,  $\text{OCH}_3$ ) 6.81 (1H, atd,  $J = 7.7, 1.7$  Hz, *H-arom*), 6.99

(1H, dd,  $J = 7.6, 1.7$  Hz,  $H$ -arom), 7.12 (1H, dd,  $J = 7.5, 1.7$  Hz,  $H$ -arom), 7.15–7.28 (5H, m,  $H$ -arom), 7.75 (1H, dd,  $J = 7.7, 1.2$  Hz,  $H$ -arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 49.3 (C-7), 57.0 (C-13), 83.0 (C-8), 101.0 (C-1), 126.7 (C-Ar), 127.6 (C-4), 128.3 (C-5), 128.4 (C-Ar), 129.0 (C-Ar), 131.5 (C-3), 139.3 (C-6), 141.2, (C-9), 141.5 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 338 (36)  $[\text{M}]^+$ , 323 (100), 307 (12), 231 (40); HRMS for  $\text{C}_{15}\text{H}_{16}\text{IO}$ : calcd. 338.1282, found 338.1282  $[\text{M}+\text{H}]^+$ ; IR (Neat):  $\nu_{\text{max}} = 3079, 3054, 2901, 1610, 1586, 1190, 1159, 1037, 1002$   $\text{cm}^{-1}$ . An authentic sample of racemic **69**, ( $\pm$ )-1-(-2-(2-iodophenyl)-1-methoxyethyl)benzene, was prepared from **67** as described above: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 98:2, 0.5 ml/min, 24 °C,  $t_{\text{R}} = 14.3$  min (+)-enantiomer,  $t_{\text{S}} = 17.7$  min (–)-enantiomer. The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

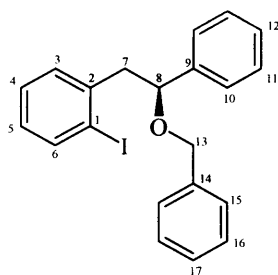
#### (*S*)-1-(-1-Ethoxy-2-(2-iodophenyl)ethyl)benzene - **70**



Synthesised according to GP5 with sodium hydride (18 mg, 0.759 mmol) suspended in DMF (2 ml) stirred with (*S*)-2-(2-iodophenyl)-1-phenylethanol **68** (82 mg, 0.253 mmol) and ethyl iodide (39 mg, 0.253 mmol). The product was purified by column chromatography petroleum ether/diethyl ether (20:1). Yield 85% (76 mg, 0.215 mmol) as a pale yellow oil.  $[\alpha]_{\text{D}}^{20} = -57.76$  ( $c = 0.11$ ,  $\text{CHCl}_3$ ):  $^1\text{H}$ -NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.01 (1H, t,  $J = 7.0$  Hz,  $\text{CH}_3$ ), 2.92 (1H, dd,  $J = 13.8, 4.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.10 (1H, dd,  $J = 13.8, 8.6$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.40 (2H, q,  $J = 7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 4.43 (1H, dd,  $J = 8.6, 4.9$  Hz,  $\text{CH}$ ), 6.79 (1H, atd,  $J = 8.0, 1.7$  Hz,  $H$ -arom), 6.99 (1H, dd,  $J = 7.6, 1.6$  Hz,  $H$ -arom), 7.10 (1H, atd,  $J = 7.5, 1.0$  Hz,  $H$ -arom), 7.18–7.26 (4H, m,  $H$ -arom), 7.37 (1H, d,  $J = 7.4$  Hz,  $H$ -arom), 7.73 (1H, dd,  $J = 8.0, 0.9$  Hz,  $H$ -arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 15.2 (C-14), 49.4 (C-7), 46.5 (C-13), 81.0 (C-8), 101.1 (C-1), 126.6 (C-

Ar), 127.5 (C-4), 127.7 (C-5), 128.0 (C-Ar), 128.3 (C-Ar), 131.6 (C-3), 139.2 (C-6), 141.4, (C-9), 142.3 (C-2); MS ( $\text{Cl}^-$ ):  $m/z$  (%) = 370 (43)  $[\text{M}+\text{NH}_4]^+$ , 324 (100), 307 (6), 244 (45), 198 (81); HRMS for  $\text{C}_{16}\text{H}_{21}\text{INO}$ : calcd. 370.0662, found 370.0662  $[\text{M}+\text{NH}_4]^+$ ; IR (Neat):  $\nu_{\text{max}}$  = 3055, 2898, 2875, 1609, 1570, 1455, 1165, 1042, 999  $\text{cm}^{-1}$ . An authentic sample of racemic **70**, ( $\pm$ )-1-(-1-ethoxy-2-(2-iodophenyl)ethyl)benzene, was prepared from **67** as described above: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 98:2, 0.5 ml/min, 24 °C,  $t_{\text{R}}$  = 12.0 min (+)-enantiomer,  $t_{\text{S}}$  = 16.3 min (–)-enantiomer. The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

### (*S*)-1-(-1-(Benzyloxy)-2-(2-iodophenyl)ethyl)benzene - **71**

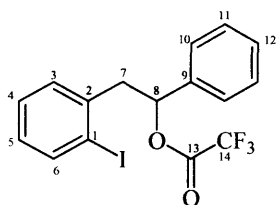


Synthesised according to GP5 with sodium hydride (17 mg, 0.723 mmol) suspended in DMF (2 ml) stirred with (*S*)-2-(2-iodophenyl)-1-phenylethanol **68** (78 mg, 0.241 mmol) and benzyl chloride (41 mg, 0.241 mmol). The product was purified by column chromatography petroleum ether/diethyl ether (20:1). Yield 74% (74 mg, 0.179 mmol) as a pale yellow oil.  $[\alpha]_D^{21} = -35.56$  ( $c = 0.50$ ,  $\text{CHCl}_3$ ):  $^1\text{H-NMR}$ , ( $\text{CDCl}_3$ , 400 MHz)  $\delta_{\text{H}}$ : 2.96 (1H, dd,  $J = 13.8, 4.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.15 (1H, dd,  $J = 13.8, 8.6$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 4.47 (2H, s,  $\text{OCH}_2$ ), 4.55 (1H, dd,  $J = 8.6, 4.9$  Hz,  $\text{CH}$ ), 6.72 (2H, dd,  $J = 7.6, 1.7$  Hz,  $H\text{-arom}$ ), 6.77 (2H, dd,  $J = 7.7, 7.5$  Hz,  $H\text{-arom}$ ), 6.81 (1H, atd,  $J = 7.9, 1.6$  Hz,  $H\text{-arom}$ ), 7.02 (1H, dd,  $J = 7.3, 2.0$  Hz,  $H\text{-arom}$ ), 7.05 (1H, dd,  $J = 7.5, 1.8$  Hz,  $H\text{-arom}$ ), 7.12 (1H, dd,  $J = 7.5, 0.9$  Hz,  $H\text{-arom}$ ), 7.15–7.30 (5H, m,  $H\text{-arom}$ ), 7.72 (1H, dd,  $J = 7.9, 1.0$  Hz,  $H\text{-arom}$ );  $^{13}\text{C NMR}$ , ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 49.5 (C-7), 70.6 (C-13), 80.4 (C-8), 101.1 (C-1), 126.8 (C-5), 127.4 (C-Ar), 127.5 (C-4), 127.7 (C-Ar), 127.8 (C-Ar), 127.7 (C-Ar), 128.1 (C-Ar), 128.2 (C-Ar), 128.3 (C-Ar), 131.8 (C-3), 138.4 (C-

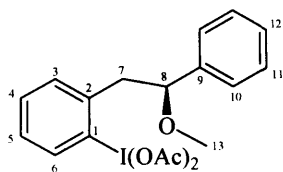


14), 139.3 (C-6), 141.2, (C-9), 141.6 (C-2); MS (CI<sup>+</sup>):  $m/z$  (%) = 432 (83) [M+NH<sub>4</sub>]<sup>+</sup>, 324 (74), 306, (76), 198 (100); HRMS for C<sub>21</sub>H<sub>23</sub>INO: calcd. 432.0819, found 432.0821 [M+NH<sub>4</sub>]<sup>+</sup>; IR (Neat):  $\nu_{\max}$  = 3056, 2980, 2930, 2822, 1449, 1399, 1356, 1209, 1110, 1003 cm<sup>-1</sup>. An authentic sample of racemic **71**, ( $\pm$ )-1-(-1-ethoxy-2-(2-iodophenyl)ethyl)benzene, was prepared from **67** as described above: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 99:1, 0.5 ml/min, 23 °C,  $t_R$  = 18.3 min (+)-enantiomer,  $t_S$  = 22.1 min (-)-enantiomer. The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

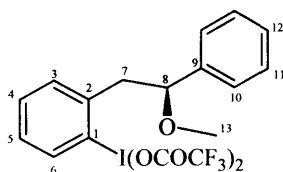
**( $\pm$ )-2-(2-Iodophenyl)-1-phenylethyl 2,2,2-trifluoroacetate<sup>10</sup> - 72**



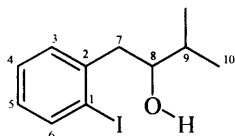
Synthesised according to GP6 with trifluoroacetic anhydride (108 mg, 0.514 mmol) added to a stirred solution of ( $\pm$ )-1-(2-iodophenyl)propan-2-ol **57** (139 mg, 0.428 mmol) and triethylamine (52 mg, 0.514 mmol) in DCM (2 ml). The product was purified by column chromatography petroleum ether/diethyl ether (1:1). Yield 55% (99 mg, 0.236 mmol) as a colourless oil. <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 250 MHz)  $\delta_H$ : 2.98 (1H, dd,  $J$  = 13.0, 3.1 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 3.20 (1H, dd,  $J$  = 13.0, 7.9 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 5.49 (1H, dd,  $J$  = 7.9, 3.1 Hz, CH), 6.84 (1H, d,  $J$  = 7.3 Hz, *H*-arom), 6.96 (1H, d,  $J$  = 7.6 Hz, *H*-arom), 7.15–7.28 (6H, m, *H*-arom), 7.60 (1H, d,  $J$  = 7.9 Hz, *H*-arom); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 125.7 MHz)  $\delta_C$ : 45.2 (C-7), 77.5 (C-8), 100.6 (C-1), 114.4 (q,  $J_{CF}$  = 290 Hz, C-14), 127.0 (C-Ar), 127.7 (C-Ar), 128.0 (C-4), 128.6 (C-5), 129.1 (C-Ar), 130.9 (C-3), 139.7 (C-6), 140.5 (C-9), 142.7 (C-2), 158.1 (q,  $J_{CF}$  = 39.5 Hz, C-13); No IR obtained, product is unstable at room temperature.

**(S)-1-(-2-(2-(Diacetoxy)iodophenyl)-1-methoxyethyl)benzene - 73**

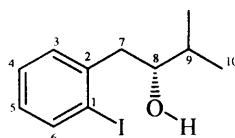
Synthesised according to GP11 with sodium perborate tetrahydrate (505 mg, 3.28 mmol) added portion wise to a solution of (*S*)-1-(-2-(2-iodophenyl)-1-methoxyethyl)benzene **69** (150 mg, 0.328 mmol) in glacial acetic acid (5 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 2% (3 mg, 0.07 mmol) as a white powder.  $^1\text{H-NMR}$ , ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 2.01 (6H, s,  $(\text{OCOCH}_3)_2$ ), 2.98–3.02 (2H, m,  $\text{ArCH}_2$ ), 3.19 (3H, s,  $\text{OCH}_3$ ), 4.42–4.48 (1H, m,  $\text{CH}$ ), 7.01 (1H, d,  $J = 7.7$  Hz,  $H\text{-arom}$ ), 7.14 (1H, d,  $J = 7.6$  Hz,  $H\text{-arom}$ ), 7.20 (2H, d,  $J = 7.5$  Hz,  $H\text{-arom}$ ), 7.30–7.55 (4H, m,  $H\text{-arom}$ ), 8.03 (1H, d,  $J = 7.8$  Hz,  $H\text{-arom}$ ); No  $^{13}\text{C}$  obtained, insufficient quantity synthesised.

**(S)-1-(-2-(2-[Bis(trifluoroacetoxy)iodo]phenyl)-1-methoxyethyl)benzene – 74**

Synthesised according to GP15 with (*S*)-1-iodo-2-(2-methoxypropyl)benzene **69** (110 mg, 0.325 mmol) in DCM (2 ml) added to a solution of trifluoroacetic anhydride (171 mg, 0.813 mmol) and urea hydrogen peroxide (306 mg, 3.25 mmol) in DCM (5 ml). Yield 2% (4 mg, 0.006 mmol) of a white powder.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 400 MHz)  $\delta_{\text{H}}$ : 1.30 (3H, d,  $J = 6.1$  Hz,  $\text{CH}_3$ ), 2.96–3.00 (2H, m,  $\text{ArCH}_2$ ), 3.15 (3H, s,  $\text{OCH}_3$ ), 4.18–4.23 (1H, m,  $\text{CH}$ ), 6.90 (1H, d,  $J = 6.9$  Hz,  $H\text{-arom}$ ), 7.05 (2H, d,  $J = 7.7$  Hz,  $H\text{-arom}$ ), 7.15 (1H, d,  $J = 7.8$  Hz,  $H\text{-arom}$ ), 7.27 (1H, d,  $J = 7.7$  Hz,  $H\text{-arom}$ ), 7.39–7.60 (3H, m,  $H\text{-arom}$ ), 8.18 (1H, d,  $J = 7.8$  Hz,  $H\text{-arom}$ ); No  $^{13}\text{C}$  obtained, insufficient quantity synthesised.

**(±)-1-(2-Iodophenyl)-3-methylbutan-2-ol – 75**

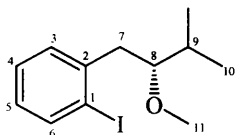
Synthesised according to GP4 with isopropylmagnesium chloride (723 mg, 7.03 mmol) and (2-iodophenyl) acetaldehyde **54** (1.73 g, 7.03 mmol) stirred in dry diethyl ether (5 ml). The product was columned using petroleum ether/diethyl ether (6:1). Yield 87% (1.775 g, 6.12 mmol), pale yellow oil. HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 90:10, 0.5 ml/min, 10 °C,  $t_R$  = 16.8 min (–)-enantiomer,  $t_S$  = 19.4 min (+)-enantiomer:  $^1\text{H-NMR}$ , ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 0.93 (3H, d,  $J$  = 6.8 Hz,  $\text{CH}_3$ ), 0.98 (3H, d,  $J$  = 6.8 Hz,  $\text{CH}_3$ ), 1.60 (1H, br s, OH), 1.72–1.81 (1H, m,  $\text{CH}(\text{CH}_3)_2$ ), 2.64 (1H, dd,  $J$  = 13.7, 9.9 Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.95 (1H, dd,  $J$  = 13.7, 2.9 Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.62 (1H, ddd,  $J$  = 9.9, 5.1, 2.9 Hz, CH), 6.86 (1H, atd,  $J$  = 7.5, 2.0 Hz,  $H$ -arom), 7.19–7.24 (2H, m,  $H$ -arom), 7.77 (1H, d,  $J$  = 7.5 Hz,  $H$ -arom);  $^{13}\text{C NMR}$ , ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 17.5 (C-10), 33.7 (C-9), 45.1 (C-7), 75.7 (C-8), 101.1 (C-1), 128.3 (C-4), 128.4 (C-5), 131.0 (C-3), 139.7 (C-6), 142.0 (C-2); MS ( $\text{Cl}^+$ ):  $m/z$  (%) = 308 (37)  $[\text{M}+\text{NH}_4]^+$ , 291 (40), 249 (17), 221 (100); HRMS for  $\text{C}_{11}\text{H}_{19}\text{INO}$ : calcd. 308.0255, found 308.0250  $[\text{M}+\text{NH}_4]^+$ ; IR (Neat):  $\nu_{\text{max}}$  = 3385, 2969, 2928, 1583, 1560, 1465, 1433, 1374, 1088, 1008  $\text{cm}^{-1}$ .

**(R)-1-(2-Iodophenyl)-3-methylbutan-2-ol – 76**

Synthesised according to GP4 with isopropylmagnesium chloride (723 mg, 7.03 mmol) and (2-iodophenyl) acetaldehyde **54** (1.73 g, 7.03 mmol) stirred in dry diethyl ether (5 ml). The product was columned using petroleum ether/diethyl

ether (6:1). Yield 87% (1.775 g, 6.12 mmol), pale yellow oil. The enantiomers could be separated by preparative HPLC: Chiracel OD column, hexane/2-propanol, 92:8, 2 ml/min, 10 °C,  $t_R = 19.8$  min (–)-enantiomer,  $t_S = 23.7$  min (+)-enantiomer: Enantiomer 1 ( $R_f = 19.8$  min):  $[\alpha]_D^{27} = -66.02$  ( $c = 0.26$ ,  $\text{CHCl}_3$ , >99% *ee*);  $^1\text{H-NMR}$ , ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 0.93 (3H, d,  $J = 6.8$  Hz,  $\text{CH}_3$ ), 0.98 (3H, d,  $J = 6.8$  Hz,  $\text{CH}_3$ ), 1.60 (1H, br s, OH), 1.72–1.81 (1H, m,  $\text{CH}(\text{CH}_3)_2$ ), 2.64 (1H, dd,  $J = 13.7, 9.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.95 (1H, dd,  $J = 13.7, 2.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.62 (1H, ddd,  $J = 9.9, 5.1, 2.9$  Hz, CH), 6.86 (1H, atd,  $J = 7.5, 2.0$  Hz, *H*-arom), 7.19–7.24 (2H, m, *H*-arom), 7.77 (1H, d,  $J = 7.5$  Hz, *H*-arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 17.5 (C-10), 33.7 (C-9), 45.1 (C-7), 75.7 (C-8), 101.1 (C-1), 128.3 (C-4), 128.4 (C-5), 131.0 (C-3), 139.7 (C-6), 142.0 (C-2); MS ( $\text{CI}^+$ ):  $m/z$  (%) = 308 (37)  $[\text{M}+\text{NH}_4]^+$ , 291 (40), 249 (17), 221 (100); HRMS for  $\text{C}_{11}\text{H}_{19}\text{INO}$ : calcd. 308.0255, found 308.0250  $[\text{M}+\text{NH}_4]^+$ ; IR (Neat):  $\nu_{\text{max}} = 3385, 2969, 2928, 1583, 1560, 1465, 1433, 1374, 1088, 1008$   $\text{cm}^{-1}$ .

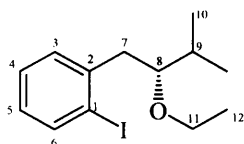
**(*R*)-1-Iodo-2-(2-methoxy-3-methylbutyl)benzene - 77**



Synthesised according to GP5 with sodium hydride (18 mg, 0.754 mmol) suspended in DMF (2 ml) stirred with (*R*)-1-(2-iodophenyl)-3-methylbutan-2-ol **76** (73 mg, 0.252 mmol) and methyl iodide (36 mg, 0.252 mmol). The product was purified by column chromatography petroleum ether/diethyl ether (14:1). Yield 96% (74 mg, 0.243 mmol) as a pale yellow oil.  $[\alpha]_D^{25} = -72.54$  ( $c = 0.78$ ,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$ , ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 0.94 (3H, d,  $J = 6.8$  Hz,  $\text{CH}_3$ ), 0.98 (3H, d,  $J = 6.8$  Hz,  $\text{CH}_3$ ), 1.71–1.80 (1H, m,  $\text{CH}(\text{CH}_3)_2$ ), 2.71 (1H, dd,  $J = 13.8, 8.9$  Hz,  $\text{ArCH}_2$ ), 2.82 (1H, dd,  $J = 13.3, 3.6$  Hz,  $\text{ArCH}_2$ ), 3.08 (3H, s,  $\text{OCH}_3$ ), 3.16 (1H, td  $J = 8.9, 3.6$  Hz CH), 6.82 (1H, ddd,  $J = 8.0, 7.6, 1.9$  Hz, *H*-arom), 7.18 – 7.23 (2H, m, *H*-arom), 7.74 (1H, dd,  $J = 8.0, 1.1$  Hz, *H*-arom);  $^{13}\text{C-NMR}$ , ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 18.5 (C-11), 29.7 (C-9), 42.4 (C-7), 58.8 (C-11), 85.7 (C-

8), 100.8 (C-1), 127.9 (C-4), 129.4, (C-5), 131.4 (C-3), 139.4 (C-6), 142.4 (C-2); MS (EI<sup>+</sup>):  $m/z$  (%) = 304 (28) [M]<sup>+</sup>, 273 (100), 231 (42), 217 (29); HRMS for C<sub>12</sub>H<sub>18</sub>IO: calcd. 304.0299, found 304.300 [M+H]<sup>+</sup>; IR (Neat):  $\nu_{\max}$  = 3055, 2970, 2929, 2821, 1575, 1456, 1411, 1331, 1204, 1111, 1071, 1000 cm<sup>-1</sup>. An authentic sample of racemic **77**, ( $\pm$ )-1-iodo-2-(-2-methoxy-3-methylbutyl)benzene, was prepared from **75** as described previously: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 98:2, 0.5 ml/min, 20 °C,  $t_R$  = 16.9 min (–)-enantiomer,  $t_S$  = 22.0 min (+)-enantiomer. Enantiomer 1 ( $R_f$  = 16.9 min): The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

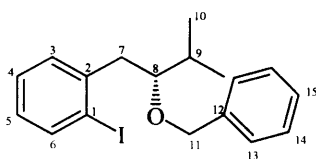
### (*R*)-1-(2-Ethoxy-3-methylbutyl)-2-iodobenzene - **78**



Synthesised according to GP5 with sodium hydride (17 mg, 682 mmol) suspended in DMF (2 ml) stirred with (*R*)-1-(2-Iodophenyl)-3-methylbutan-2-ol **76** (66 mg, 0.227 mmol) and ethyl iodide (53 mg, 0.227 mmol). The product was purified by column chromatography petroleum ether/diethyl ether (14:1). Yield 81% (57 mg, 0.184 mmol) as a pale yellow oil.  $[\alpha]_D^{25} = -82.69$  ( $c = 0.39$ , CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 0.89 (3H, t,  $J = 7.0$  Hz, CH<sub>2</sub>CH<sub>3</sub>), 0.93 (3H, d,  $J = 6.8$  Hz, (CH<sub>3</sub>)), 0.96 (3H, d,  $J = 6.8$  Hz, (CH<sub>3</sub>)), 1.76 (1H, m, CH(CH<sub>3</sub>)<sub>2</sub>), 2.68 (1H, dd,  $J = 13.6, 9.3$  Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 2.86 (1H, dd,  $J = 13.6, 3.8$  Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 3.28 (1H, ddd,  $J = 9.3, 4.9, 3.8$  Hz, CH), 3.40 (2H, q,  $J = 7.0$ , Hz, CH<sub>2</sub>CH<sub>3</sub>), 6.81 (1H, ddd,  $J = 7.9, 7.4, 1.6$  Hz, *H*-arom), 7.19 (1H, d,  $J = 7.6$  Hz, *H*-arom), 7.23 (1H, dd, 7.6, 7.4 Hz, *H*-arom), 7.73 (1H, dd,  $J = 7.9, 1.1$  Hz, *H*-arom); <sup>13</sup>C-NMR, (CDCl<sub>3</sub>, 125.7 MHz)  $\delta_C$ : 15.4 (C-10), 18.8 (C-12), 32.2 (C-9), 43.4 (C-7), 65.5 (C-11), 83.9 (C-8), 100.8 (C-1), 127.8 (C-4), 128.0, (C-5), 131.6 (C-3), 139.3 (C-6), 142.6 (C-2); MS (EI<sup>+</sup>):  $m/z$  (%) = 318 (25) [M]<sup>+</sup>, 303 (31), 261 (39), 217 (30), 105 (11), 91 (100); HRMS for C<sub>13</sub>H<sub>20</sub>IO: calcd. 318.1833, found 318.1830 [M+H]<sup>+</sup>; IR (Neat):  $\nu_{\max}$  = 3057, 2964, 2927, 2820, 1574, 1455, 1411, 1366, 1203, 1112, 1059,

1006  $\text{cm}^{-1}$ . An authentic sample of racemic **78**, ( $\pm$ )-1-(2-ethoxy-3-methylbutyl)-2-iodobenzene, was prepared from **75** as described previously: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 98:2, 0.5 ml/min, 19 °C,  $t_R$  = 15.7 min (–)-enantiomer,  $t_S$  = 19.9 min (+)-enantiomer. Enantiomer 1 ( $R_f$  = 15.7 min): The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

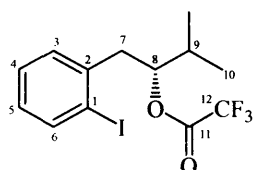
**(R)-1-(1-(2-Iodophenyl)-3-methylbutan-2-yloxy)benzene – 79**



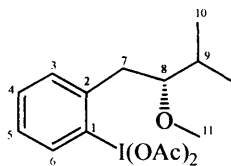
Synthesised according to GP5 with sodium hydride (18 mg, 0.765 mmol) suspended in DMF (2 ml) stirred with (*R*)-1-(2-iodophenyl)-3-methylbutan-2-ol **76** (74 mg, 0.255 mmol) and benzyl bromide (44 mg, 0.255 mmol). The product was purified by column chromatography petroleum ether/diethyl ether (14:1). Yield 72% (70 mg, 0.184 mmol) as a pale yellow oil.  $[\alpha]_D^{25} = -81.11$  ( $c = 0.50$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 0.96 (3H, d,  $J = 6.8$  Hz,  $\text{CH}_3$ ), 1.00 (3H, d,  $J = 6.9$  Hz,  $\text{CH}_3$ ), 1.83–1.90 (1H, m,  $\text{CH}(\text{CH}_3)_2$ ), 2.78 (1H, dd,  $J = 13.7, 6.3$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.89 (1H, dd,  $J = 13.7, 3.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.44 (1H, ddd,  $J = 6.3, 4.7, 3.9$  Hz,  $\text{CH}$ ), 4.04 (2H, s,  $\text{OCH}_2$ ), 6.84 (1H, ddd,  $J = 7.7, 7.5, 1.3$  Hz,  $H$ -arom), 7.05, (2H, d,  $J = 7.2$  Hz,  $H$ -arom), 7.13–7.21 (3H, m,  $H$ -arom), 7.23 (2H, dd,  $J = 7.6, 1.7$  Hz,  $H$ -arom), 7.74 (1H, dd,  $J = 7.9, 1.1$  Hz,  $H$ -arom);  $^{13}\text{C-NMR}$ , ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_C$ : 18.5 (C-10), 31.7 (C-9), 42.6 (C-7), 72.2 (C-11), 83.5 (C-8), 100.9 (C-1), 127.7 (C-4), 127.8 (C-13), 128.0 (C-15), 128.2 (C-5), 128.4 (C-14), 131.8 (C-3), 138.4 (C-11), 139.4 (C-6), 142.4 (C-2); MS ( $\text{CI}^+$ ):  $m/z$  (%) = 398 (100)  $[\text{M}+\text{NH}_4]^+$ , 22 (51), 182 (47), 106 (74) 91 (15); HRMS for  $\text{C}_{18}\text{H}_{25}\text{INO}$ : calcd. 398.3012, found 398.3002  $[\text{M}+\text{NH}_4]^+$ ; IR (Neat):  $\nu_{\text{max}} = 3056, 2972, 2927, 2820, 1451, 1399, 1366, 1228, 1109, 1003$   $\text{cm}^{-1}$ . An authentic sample of racemic **79**, ( $\pm$ )-1-(1-(2-Iodophenyl)-3-methylbutan-2-yloxy)benzene, was prepared from **75** as described previously: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 98:2, 0.5 ml/min, 23 °C,  $t_R$  = 21.3 min (–)-enantiomer,  $t_S$  = 26.8 min

(+)-enantiomer: Enantiomer 1 ( $R_f = 21.3$  min): The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

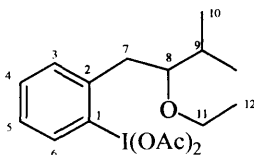
**(*R*)-1-Iodo-2-(-2-trifluoroacetoxy-3-methylbutyl)benzene<sup>10</sup> - 80**



Synthesised according to GP6 with trifluoroacetic anhydride (64 mg, 0.306 mmol) added to a stirred solution of (*R*)-1-(2-iodophenyl)-3-methylbutan-2-ol **76** (74 mg, 0.255 mmol) and triethylamine (312 mg, 0.306 mmol) in DCM (2 ml). The product was purified by column chromatography petroleum ether/diethyl ether (1:1). Yield 65% (64 mg, 0.165 mmol) as a colourless oil.  $[\alpha]_D^{25} = -106.77$  ( $c = 0.89$ ,  $\text{CHCl}_3$ ).  $^1\text{H-NMR}$ , ( $\text{CDCl}_3$ , 250 MHz)  $\delta_{\text{H}}$ : 0.99 (3H, d,  $J = 7.0$  Hz,  $\text{CH}_3$ ), 1.04 (3H, d,  $J = 7.0$  Hz,  $\text{CH}_3$ ), 1.87 (1H, m,  $\text{CH}(\text{CH}_3)_2$ ), 2.93 (1H, dd,  $J = 14.6$ , 8.8 Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.04 (1H, dd,  $J = 14.5$ , 3.7 Hz,  $\text{ArCH}_A\text{CH}_B$ ), 5.40 (1H, m,  $\text{CH}$ ), 6.84 (1H, atd,  $J = 7.8$ , 1.0 Hz,  $H$ -arom), 7.17–7.25 (2H, m,  $H$ -arom), 7.74 (1H, dd,  $J = 7.8$ , 1.2 Hz,  $H$ -arom);  $^{13}\text{C-NMR}$ , ( $\text{CDCl}_3$ , 62.3 MHz)  $\delta_{\text{C}}$ : 20.5 (C-10), 29.9 (C-9), 44.3 (C-7), 85.0 (C-8), 101.8 (C-1), 115.6 (q,  $J_{\text{CF}} = 291$  Hz, C-12), 128.5 (C-4), 129.0 (C-5), 130.4 (C-3), 139.4 (C-6), 141.3 (C-2), 157.6 (q,  $J_{\text{CF}} = 40$  Hz, C-11). No IR obtained, product is unstable at room temperature.

**(*R*)-1-Iodo-2-(-2-methoxy-3-methylbutyl)benzene - 81**

Synthesised according to GP11 with sodium perborate tetrahydrate (371 mg, 2.41 mmol) added portion wise to a solution of (*R*)-1-iodo-2-(-2-methoxy-3-methylbutyl)benzene **77** (70 mg, 0.241 mmol) in glacial acetic acid (5 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 2% (2 mg, 0.005 mmol) as a white powder.  $^1\text{H-NMR}$ , ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.01 (3H, d,  $J = 6.9$  Hz,  $\text{CH}_3$ ), 1.05 (3H, d,  $J = 6.9$  Hz,  $\text{CH}_3$ ), 1.79 (1H, m,  $\text{CH}(\text{CH}_3)_2$ ), 2.04 (6H, s,  $(\text{OCOCH}_3)_2$ ), 2.90 (1H, dd,  $J = 13.6, 8.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.00 (1H, dd,  $J = 13.6, 3.6$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.32 (3H, s,  $\text{OCH}_3$ ), 3.49 (1H, ddd  $J = 8.9, 8.8, 3.6$  Hz  $\text{CH}$ ), 7.01 (1H, d,  $J = 7.9$  Hz,  $H$ -arom), 7.30–7.43 (2H, m,  $H$ -arom), 8.08 (1H, d,  $J = 7.9$  Hz,  $H$ -arom); No  $^{13}\text{C}$  obtained, insufficient quantity synthesised.

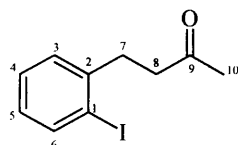
**(*R*)-1-(2-Ethoxy-3-methylbutyl)-2-(diacetoxyiodo)benzene – 82**

Synthesised according to GP11 with sodium perborate tetrahydrate (265 mg, 1.72 mmol) added portion wise to a solution of (*R*)-1-(2-ethoxy-3-methylbutyl)-2-iodobenzene **78** (50 mg, 0.172 mmol) in glacial acetic acid (5 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 2% (2 mg, 0.003 mmol) as a white powder.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz)  $\delta$ : 1.01 (3H, d,  $J = 7.0$  Hz,  $\text{CH}_3$ ), 1.05 (3H, d,  $J = 7.0$  Hz,  $\text{CH}_3$ ), 1.18 (3H, t,  $J = 7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.94 (1H, m,  $\text{CH}(\text{CH}_3)_2$ ), 2.06 (6H, s,  $(\text{OCOCH}_3)_2$ ), 2.80 (1H, dd,  $J = 14.0, 9.1$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.92 (1H, dd,  $J = 14.0, 4.3$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.43 (2H, q,  $J = 7.0$ , Hz,  $\text{CH}_2\text{CH}_3$ ), 3.57 (1H, ddd,  $J = 9.1, 7.9, 4.3$  Hz,  $\text{CH}$ ), 7.09 (1H, d,  $J = 7.6$  Hz,



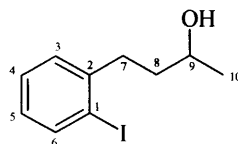
*H*-arom), 7.34–7.52 (2H, m, *H*-arom ), 8.10 (1H, d,  $J = 7.6$  Hz, *H*-arom); No  $^{13}\text{C}$  obtained, insufficient quantity synthesised.

### 1-(2-Iodophenyl)butan-3-one<sup>13</sup> – 84



Synthesised according to GP8 with 2-iodobenzyl chloride **83** (3.0g, 11.88 mmol), 2,4-pentanedione (1.35 ml, 13.08 mmol) and potassium carbonate (1.65 g, 12 mmol) in ethanol (30 ml). The product was purified by column chromatography hexane / ethyl acetate (4:1). Yield 84% (2.74 g, 10.0 mmol) as a colourless oil. Spectroscopic data agrees with literature.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 250 MHz)  $\delta_{\text{H}}$ : 2.20 (3H, s,  $\text{CH}_3$ ), 2.78 (2H, t,  $J = 7.7$  Hz,  $\text{ArCH}_2\text{CH}_2$ ), 3.03 (2H, t,  $J = 7.7$  Hz,  $\text{ArCH}_2$ ), 6.93 (1H, atd,  $J = 7.7, 1.9$  Hz, *H*-arom), 7.24–7.31 (2H, m, *H*-arom), 7.84 (1H, d,  $J = 7.7$  Hz, *H*-arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta_{\text{C}}$ : 30.1 (C-10), 34.8 (C-8), 43.7 (C-7), 100.3 (C-1), 128.1 (C-4), 128.6 (C-5), 129.7 (C-5), 139.6 (C-6), 143.6 (C-2), 207.5 (C-9); IR (Neat) :  $\nu_{\text{max}} = 2941, 2909, 1716, 1500, 1440, 1326, 1186, 1153, 1017 \text{ cm}^{-1}$ .

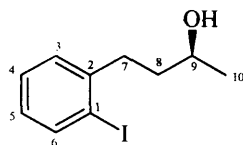
### (±)-4-(2-Iodophenyl)butan-2-ol – 85



Synthesised according to GP10 with 1-(2-iodophenyl)butan-3-one **84** (2.0 g, 7.3 mmol) added to a stirred solution of sodium borohydride (152 mg, 4.02 mmol) in ethanol (10 ml). The product was purified by column chromatography petroleum ether/diethyl ether (4:1). Yield 97% (1.95 g, 7.08 mmol) as a colourless oil. HPLC

conditions: Chiracel OD-H preparative column, hexane/2-propanol, 93:7, 0.5 ml/min, 15 °C,  $t_R = 18.6$  min (–)-enantiomer,  $t_S = 23.7$  min (+)-enantiomer:  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 250 MHz)  $\delta_{\text{H}}$ : 1.20 (3H, d,  $J = 6.2$ ,  $\text{CH}_3$ ), 1.43 (1H, br s, OH), 1.64–1.70 (2H, m,  $\text{ArCH}_2\text{CH}_2$ ), 2.70 (1H, ddd,  $J = 13.7, 9.6, 6.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.80 (1H, ddd,  $J = 13.7, 9.5, 6.4$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.81 (1H, dqd,  $J = 8.4, 6.2, 4.1$ , Hz, CH), 6.81 (1H, ddd,  $J = 7.9, 7.5, 2.0$  Hz,  $H$ -arom), 7.15–7.22 (2H, m,  $H$ -arom), 7.74 (1H, dd,  $J = 7.9, 1.1$  Hz  $H$ -arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta_{\text{C}}$ : 23.6 (C-10), 37.1 (C-8), 39.6 (C-7), 67.5 (C-9), 100.6 (C-1), 127.8 (C-4), 128.5 (C-5), 129.5 (C-3), 139.5 (C-6), 144.6 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 276 (16)  $[\text{M}]^+$ , 258 (54), 217 (68), 107 (80), 91 (100); HRMS for  $\text{C}_{10}\text{H}_{17}\text{INO}$ : calcd. 294.0349, found 294.0353  $[\text{M}+\text{NH}_4]^+$ ; IR (Neat):  $\nu_{\text{max}} = 3371, 2922, 1463, 1376, 1155, 1010$   $\text{cm}^{-1}$ .

#### (S)-4-(2-Iodophenyl)butan-2-ol – 86

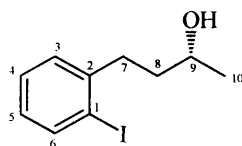


Synthesised according to GP9 with 1-(2-iodophenyl)butan-3-one **84** (2.70 g, 9.85 mmol) added to a stirred solution of (–)-*B*-chlorodiisopinocampheylborane (3.48 g, 10.84 mmol) in dry THF (15 ml). Diethyl ether (20 ml) was added along with diethanolamine (2.28 g, 21.67 mmol). The product was purified by column chromatography petroleum ether/diethyl ether (4:1). Yield 57%, 53% *ee* (1.55 g, 5.62 mmol) as a colourless oil. The enantiomers could be separated by preparative HPLC: Chiracel OD preparative column, hexane/2-propanol, 93:7, 4.5 ml/min, 15 °C,  $t_R = 23.2$  min (–)-enantiomer,  $t_S = 32.5$  min (+)-enantiomer. Enantiomer 2 ( $R_f = 32.5$  min):  $[\alpha]_D^{26} = +9.25$  ( $c = 1.14$ ,  $\text{CHCl}_3$ , >99% *ee*);  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 250 MHz)  $\delta_{\text{H}}$ : 1.20 (3H, d,  $J = 6.2$ ,  $\text{CH}_3$ ), 1.43 (1H, br s, OH), 1.64–1.70 (2H, m,  $\text{ArCH}_2\text{CH}_2$ ), 2.70 (1H, ddd,  $J = 13.7, 9.6, 6.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.80 (1H, ddd,  $J = 13.7, 9.5, 6.4$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.81 (1H, dqd,  $J = 8.4, 6.2, 4.1$ , Hz, CH), 6.81 (1H, ddd,  $J = 7.9, 7.5, 2.0$  Hz,  $H$ -arom), 7.15–7.22 (2H, m,  $H$ -arom), 7.74 (1H, dd,

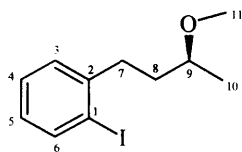
$J = 7.9, 1.1$  Hz  $H$ -arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta_{\text{C}}$ : 23.6 (C-10), 37.1 (C-8), 39.6 (C-7), 67.5 (C-9), 100.6 (C-1), 127.8 (C-4), 128.5 (C-5), 129.5 (C-3), 139.5 (C-6), 144.6 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 276 (16)  $[\text{M}]^+$ , 258 (54), 217 (68), 107 (80), 91 (100); HRMS for  $\text{C}_{10}\text{H}_{17}\text{INO}$ : calcd. 294.0349, found 294.0353  $[\text{M}+\text{NH}_4]^+$ ; IR (Neat):  $\nu_{\text{max}} = 3371, 2922, 1463, 1376, 1155, 1010$   $\text{cm}^{-1}$ .

HPLC conditions:

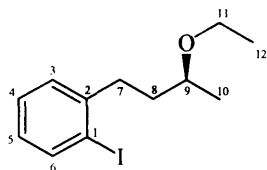
### (*R*)-4-(2-Iodophenyl)butan-2-ol – 87



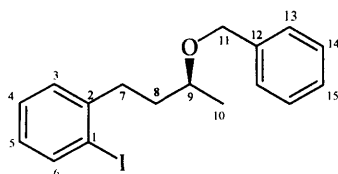
Synthesised according to GP10 with 1-(2-iodophenyl)butan-3-one **84** (2.0 g, 7.3 mmol) added to a stirred solution of sodium borohydride (152 mg, 4.02 mmol) in ethanol (10 ml). The product was purified by column chromatography petroleum ether/diethyl ether (4:1). Yield 97% (1.95 g, 7.08 mmol) as a colourless oil. The enantiomers could be separated by preparative HPLC: Chiracel OD preparative column, hexane/2-propanol, 93:7, 4.5 ml/min, 15 °C,  $t_{\text{R}} = 23.2$  min (–)-enantiomer,  $t_{\text{S}} = 32.5$  min (+)-enantiomer. Enantiomer 1 ( $R_{\text{f}} = 23.2$  min):  $[\alpha]_{\text{D}}^{26} = -10.54$  ( $c = 0.93$ ,  $\text{CHCl}_3$ , >99%  $ee$ ):  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 250 MHz)  $\delta_{\text{H}}$ : 1.20 (3H, d,  $J = 6.2$ ,  $\text{CH}_3$ ), 1.43 (1H, br s, OH), 1.64–1.70 (2H, m,  $\text{ArCH}_2\text{CH}_2$ ), 2.70 (1H, ddd,  $J = 13.7, 9.6, 6.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.80 (1H, ddd,  $J = 13.7, 9.5, 6.4$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.81 (1H, dqd,  $J = 8.4, 6.2, 4.1$ , Hz, CH), 6.81 (1H, ddd,  $J = 7.9, 7.5, 2.0$  Hz,  $H$ -arom), 7.15–7.22 (2H, m,  $H$ -arom), 7.74 (1H, dd,  $J = 7.9, 1.1$  Hz  $H$ -arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta_{\text{C}}$ : 23.6 (C-10), 37.1 (C-8), 39.6 (C-7), 67.5 (C-9), 100.6 (C-1), 127.8 (C-4), 128.5 (C-5), 129.5 (C-3), 139.5 (C-6), 144.6 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 276 (16)  $[\text{M}]^+$ , 258 (54), 217 (68), 107 (80), 91 (100); HRMS for  $\text{C}_{10}\text{H}_{17}\text{INO}$ : calcd. 294.0349, found 294.0353  $[\text{M}+\text{NH}_4]^+$ ; IR (Neat):  $\nu_{\text{max}} = 3371, 2922, 1463, 1376, 1155, 1010$   $\text{cm}^{-1}$ .

**(S)-1-Iodo-2-(3-methoxybutyl)benzene - 88**

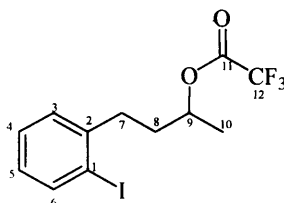
Synthesised according to GP5 with sodium hydride (261 mg, 10.87 mmol) suspended in DMF (15 ml) stirred with (*S*)-4-(2-iodophenyl)butan-2-ol **86** (1.0 g, 3.62 mmol) and methyl iodide (515 mg, 3.62 mmol). The product was purified by column chromatography hexane/ethyl acetate (4:1). Yield 96% (1.01 g, 3.47 mmol) as a pale yellow oil.  $[\alpha]_D^{27} = +53.02$  ( $c = 0.91$ ,  $\text{CHCl}_3$ );  $^1\text{H NMR}$ , ( $\text{CDCl}_3$ , 400 MHz)  $\delta_{\text{H}}$ : 1.14 (3H, d,  $J = 6.2$  Hz,  $\text{CH}_3$ ), 1.68 (2H, m,  $\text{ArCH}_2\text{CH}_2$ ), 2.69 (1H, ddd,  $J = 13.4, 10.2, 5.6$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.73 (1H, ddd,  $J = 13.4, 10.0, 6.4$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.19 (1H, m,  $\text{CH}$ ), 3.38 (3H, s,  $\text{OCH}_3$ ), 6.80 (1H, atd,  $J = 7.9, 1.3$   $H$ -arom), 7.15 (1H, d,  $J = 7.7$  Hz,  $H$ -arom), 7.20 (1H, atd,  $J = 7.7, 7.6$  Hz,  $H$ -arom), 7.74 (1H, dd,  $J = 7.9, 1.2$  Hz,  $H$ -arom);  $^{13}\text{C NMR}$ , ( $\text{CDCl}_3$ , 100.4MHz)  $\delta_{\text{C}}$ : 19.4 (C-10), 37.0 (C-8), 37.5 (C-7), 56.4 (C-9), 76.4 (C-11), 100.9 (C-1), 128.1 (C-4), 128.7 (C-5), 129.9 (C-3), 139.9 (C-6), 145.3 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 290 (22)  $[\text{M}]^+$ , 276 (27), 259 (13), 217 (68), 107 (100), 91 (50); HRMS for  $\text{C}_{11}\text{H}_{16}\text{IO}$ : calcd. 291.0240, found 291.0239  $[\text{M}+\text{H}]^+$ ; IR (Neat):  $\nu_{\text{max}} = 3059, 2824, 2819, 1465, 1434, 1372, 1169, 1136, 1093, 1010$   $\text{cm}^{-1}$ . An authentic sample of racemic **88**, ( $\pm$ )-1-iodo-2-(3-methoxybutyl)benzene, was prepared from **85** as described previously: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 95:5, 0.5 ml/min, 20 °C,  $t_{\text{R}} = 8.9$  min (–)-enantiomer,  $t_{\text{S}} = 12.4$  min (+)-enantiomer. Enantiomer 2 ( $R_{\text{f}} = 12.4$  min). The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

**(S)-1-Iodo-2-(3-ethoxybutyl)benzene– 89**

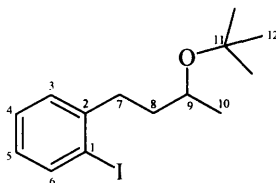
Synthesised according to GP5 with sodium hydride (131 mg, 5.47 mmol) suspended in DMF (5 ml) stirred with (*S*)-4-(2-iodophenyl)butan-2-ol **86** (500 mg, 1.82 mmol) and ethyl iodide (285 mg, 1.82 mmol). The product was purified by column chromatography hexane/ethyl acetate (5:1). Yield 81% (449 mg, 1.48 mmol) as a pale yellow oil.  $[\alpha]_D^{27} = +36.77$  ( $c = 1.05$ ,  $\text{CHCl}_3$ ):  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.02, (3H, t,  $J = 6.7$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.14 (3H, d,  $J = 6.1$  Hz,  $\text{CH}_3$ ), 1.62 (1H, dddd,  $J = 13.4, 7.4, 7.1, 6.9$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 1.77 (1H, dddd,  $J = 13.4, 9.9, 8.0, 5.3$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.44 (1H, ddd,  $J = 13.3, 8.0, 7.1$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.59 (1H, ddd,  $J = 13.3, 9.9, 6.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.09 (1H, m,  $\text{CH}$ ), 3.33 (2H, q,  $J = 6.7$  Hz,  $\text{CH}_2\text{CH}_3$ ), 6.83 (1H, atd,  $J = 7.9, 1.6$ ,  $H\text{-arom}$ ), 7.17 (1H, dd,  $J = 7.8, 1.6$  Hz,  $H\text{-arom}$ ), 7.24 (1H, atd,  $J = 7.8, 1.2$  Hz,  $H\text{-arom}$ ), 7.70 (1H, dd,  $J = 7.9, 1.2$  Hz,  $H\text{-arom}$ );  $^{13}\text{C NMR}$ , ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 16.9 (C-12), 18.8 (C-10), 29.0 (C-7), 36.6 (C-7), 39.8 (C-8), 60.2 (C-11), 88.0 (C-9), 100.0 (C-1), 127.4 (C-4), 128.0 (C-5), 128.9 (C-3), 138.1 (C-6), 142.4 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 305 (44)  $[\text{M}]^+$ , 276 (100), 217 (33), 107 (39), 91 (16); HRMS for  $\text{C}_{12}\text{H}_{18}\text{IO}$ : calcd. 305.1653, found 305.1650  $[\text{M}+\text{H}]^+$ ; IR (Neat):  $\nu_{\text{max}} = 2844, 2815, 1470, 1437, 1370, 1170, 1133, 1089, 1004$   $\text{cm}^{-1}$ . An authentic sample of racemic **89**, ( $\pm$ )-1-iodo-2-(3-ethoxybutyl)benzene, was prepared from **85** as described previously: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 96:4, 0.5 ml/min, 22 °C,  $t_{\text{R}} = 13.2$  min (–)-enantiomer,  $t_{\text{S}} = 16.6$  min (+)-enantiomer. Enantiomer 2 ( $R_{\text{f}} = 16.6$  min). The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

**(S)-1-(4-(2-Iodophenyl)butan-2-methyl)benzene - 90**

Synthesised according to GP5 with sodium hydride (26 mg, 1.095 mmol) suspended in DMF (4 ml) stirred with (*S*)-4-(2-iodophenyl)butan-2-ol **86** (100 mg, 0.365 mmol) and benzyl chloride (46 mg, 0.365 mmol). The product was purified by column chromatography hexane/ethyl acetate (5:1). Yield 72% (96 mg, 0.263 mmol) as a pale yellow oil.  $[\alpha]_D^{20} = +48.00$  ( $c = 0.70$ ,  $\text{CHCl}_3$ ):  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.17 (3H, d,  $J = 6.2$  Hz,  $\text{CH}_3$ ), 1.79 (1H, dddd,  $J = 13.4, 9.4, 7.3, 5.4$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 1.90 (1H, dddd,  $J = 13.4, 9.9, 8.0, 6.3$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.81 (1H, ddd,  $J = 13.7, 9.4, 6.3$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.99 (1H, ddd,  $J = 13.7, 9.9, 7.3$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.67 (1H, dqd,  $J = 8.0, 6.2, 5.4$  Hz,  $\text{CH}$ ), 4.39 (2H, s,  $\text{OCH}_2$ ), 6.85 (1H, atd,  $J = 7.9, 1.3$  Hz,  $H$ -arom), 7.03–7.31 (7H, m,  $H$ -arom), 7.72 (1H, dd,  $J = 7.9, 1.0$  Hz,  $H$ -arom);  $^{13}\text{C NMR}$ , ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 20.9 (C-10), 29.1 (C-7), 35.7 (C-8), 72.2 (C-11), 80.3 (C-9), 101.1 (C-1), 125.5 (C-Ar), 125.6 (C-Ar), 126.8 (C-5), 127.5 (C-4), 127.7 (C-Ar), 131.8 (C-3), 138.4 (C-12), 139.3 (C-6), 141.6 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 366 (17)  $[\text{M}]^+$ , 305 (26) 276 (51), 217 (100), 107 (42), 91 (39); HRMS for  $\text{C}_{17}\text{H}_{19}\text{IO}$ : calcd. 366.2404, found 366.2406  $[\text{M}]^+$ ; IR (Neat):  $\nu_{\text{max}} = 2860, 2819, 1471, 1430, 1363, 1164, 1129, 1070, 1007$   $\text{cm}^{-1}$ . An authentic sample of racemic **90**, ( $\pm$ )-1-(4-(2-iodophenyl)butan-2-methyl)benzene, was prepared from **85** as described previously: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 98:2, 0.5 ml/min, 25 °C,  $t_{\text{R}} = 11.9$  min (–)-enantiomer,  $t_{\text{S}} = 17.7$  min (+)-enantiomer. Enantiomer 2 ( $R_{\text{f}} = 17.7$  min). The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

**(±)-4-(2-Iodophenyl)butan-3-trifluoroacetate<sup>10</sup> – 91**

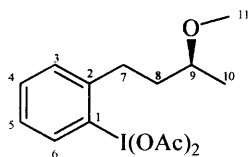
Synthesised according to GP6 with trifluoroacetic anhydride (202 mg, 0.96 mmol) added to a stirred solution of (±)-4-(2-iodophenyl)butan-2-ol **85** (221 mg, 0.80 mmol) and triethylamine (97 mg, 0.96 mmol) in DCM (2 ml). The product was purified by column chromatography petroleum ether/diethyl ether (1:1). Yield 71% (212 mg, 0.570 mmol) as a colourless oil. <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 400 MHz) δ<sub>H</sub>: 1.35 (3H, d, *J* = 6.3 Hz, CH<sub>3</sub>), 1.89 (2H, m, ArCH<sub>2</sub>CH<sub>2</sub>) 2.70 (2H, m, ArCH<sub>2</sub>), 5.08 (1H, m, CH), 6.85 (1H, atd, *J* = 8.1, 1.2 Hz, *H*-arom), 7.13 (1H, dd, *J* = 7.7, 1.2 Hz, *H*-arom), 7.20 (1H, atd, *J* = 7.7, 1.0 Hz, *H*-arom), 7.75 (1H, dd, *J* = 8.2, 1.0 Hz *H*-arom); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 125.7 MHz) δ<sub>C</sub>: 19.5 (C-10), 36.4 (C-7), 46.2 (C-8), 75.8 (C-9), 100.8 (C-2), 114.5 (q, *J* = 286 Hz, C-12), 128.2 (C-4), 129.4 (C-5), 130.9 (C-6), 139.7 (C-3), 143.2 (C-1), 157.2 (q, *J* = 42 Hz, C-11). No IR obtained, product decomposes at room temperature.

**(±)-1-(3-tert-Butoxybutyl)-3-iodobenzene - 92**

Synthesised according to GP7 with concentrated sulphuric acid (46 mg, 0.47 mmol) added to a stirred suspension of anhydrous MgSO<sub>4</sub> (226 mg, 1.88 mmol) in cyclohexane (4 ml). <sup>t</sup>BuOH (174 mg, 2.35 mmol) and (±)-4-(2-iodophenyl)butan-2-ol **85** (130 mg, 0.47 mmol) was added dropwise to the resulting solution. The product was purified by column chromatography petroleum ether/diethyl ether

(8:1). Yield 58% (91 mg, 0.274 mmol) as a pale yellow oil.  $^1\text{H-NMR}$ , ( $\text{CDCl}_3$ , 250 MHz)  $\delta_{\text{H}}$ : 1.16 (9H, s,  $(\text{CH}_3)_3$ ), 1.21 (3H, d,  $J = 6.5$  Hz,  $\text{CH}_3$ ), 1.70 (1H, dddd,  $J = 13.6, 8.9, 6.4, 5.2$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 1.88 (1H, dddd,  $J = 13.6, 9.1, 8.1, 6.5$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.56 (1H, ddd,  $J = 13.4, 9.1, 6.4$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.87 (1H, ddd,  $J = 13.4, 8.9, 6.5$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.98 (1H, dqd,  $J = 8.1, 6.5, 5.2$  Hz,  $\text{CH}$ ), 6.85 (1H, atd,  $J = 7.8, 1.6$  Hz,  $H\text{-arom}$ ), 7.19–7.26 (2H, m,  $H\text{-arom}$ ), 7.60 (1H, dd,  $J = 7.6, 1.0$  Hz,  $H\text{-arom}$ );  $^{13}\text{C-NMR}$ , ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta_{\text{C}}$ : 21.2 (C-10), 27.7 (C-7), 30.3 (C-12), 38.6 (C-8), 69.1 (C-9), 70.1 (C-11), 100.4 (C-1), 127.4 (C-5), 127.7 (C-4), 129.2 (C-3), 137.7 (C-6), 141.5 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 332 (57)  $[\text{M}]^+$ , 275 (100), 242 (29), 217 (38), 117 (17); HRMS for  $\text{C}_{14}\text{H}_{22}\text{IO}$ : calcd. 333.2190, found 333.2188  $[\text{M}+\text{H}]^+$ . No IR obtained.

### (*S*)-1-(2-Diacetoxyiodophenyl)-3-methoxybutane - 93

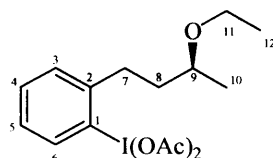


Synthesised according to GP12 with peracetic acid (0.88 ml of a 30% solution in acetic acid) added to a stirred solution of (*S*)-1-iodo-2-(3-methoxybutyl)benzene **88** (88 mg, 0.22 mmol) in acetic acid (5 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 47% (58 mg, 0.143 mmol) as a white powder. mp = 114–117 °C.  $[\alpha]_D^{24} = +105.41$  ( $c = 1.01$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$ , ( $\text{CDCl}_3$ , 400 MHz)  $\delta_{\text{H}}$ : 1.90 (1H, d,  $J = 6.7$  Hz,  $\text{CH}_3$ ), 1.96 (1H, dddd,  $J = 14.0, 10.1, 6.1, 4.9$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.02 (6H, s,  $(\text{OCOCH}_3)_2$ ), 2.09 (1H, dddd,  $J = 14.0, 8.6, 8.1, 5.4$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.90 (1H, ddd,  $J = 14.3, 8.6, 6.1$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.06 (1H, ddd,  $J = 14.3, 10.1, 5.4$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.18 (3H, s,  $\text{OCH}_3$ ), 4.10 (1H, dqd,  $J = 8.1, 6.7, 4.9$  Hz,  $\text{CH}$ ), 7.22 (1H, atd,  $J = 7.7, 1.8$  Hz,  $H\text{-arom}$ ), 7.42 (1H, dd,  $J = 7.6, 1.8$  Hz,  $H\text{-arom}$ ), 7.47 (1H, atd,  $J = 7.6, 1.2$  Hz,  $H\text{-arom}$ ), 8.11 (1H, dd,  $J = 7.7, 1.2$  Hz,  $H\text{-arom}$ );  $^{13}\text{C NMR}$ , ( $\text{CDCl}_3$ , 100.5 MHz)  $\delta_{\text{C}}$ : 20.3 (C-10), 20.4 ( $(\text{OCOCH}_3)_2$ , C-13), 35.7 (C-7), 39.3 (C-8), 56.7 (C-11), 82.4 (C-9), 127.8 (C-Ar), 128.7 (C-Ar), 130.2 (C-3), 132.2 (C-1), 141.7 (C-6), 144.0



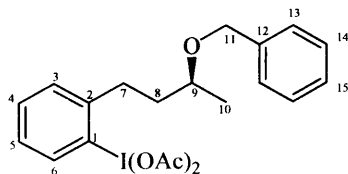
(C-2), 176.4 (C=O, C-12), 176.6 (C=O, C-12). IR (Nujol):  $\nu_{\max}$  = 2965, 2906, 2855, 1660, 1623, 1563, 1462, 1377, 1201, 1170, 1001  $\text{cm}^{-1}$ .

**(S)-1-(2-Diacetoxyiodophenyl)-3-ethoxybutane - 94**



Synthesised according to GP12 with peracetic acid (1.73 ml of a 30% solution in acetic acid) added to a stirred solution of (*S*)-1-iodo-2-(3-ethoxybutyl)benzene **89** (132 mg, 0.433 mmol) in acetic acid (10 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 12% (22 mg, 0.052 mmol) as a white powder. mp = 110–114°C.  $[\alpha]_D^{25} = +99.41$  (c = 0.82,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 400 MHz)  $\delta_{\text{H}}$ : 1.14, (3H, t,  $J = 7.0$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.19 (1H, d,  $J = 7.4$  Hz,  $\text{CH}_3$ ), 2.00 (6H, s,  $(\text{OCOCH}_3)_2$ ), 2.08 (2H, m,  $\text{ArCH}_2\text{CH}_2$ ), 2.91 (1H, ddd,  $J = 14.3, 9.5, 6.2$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.08 (1H, ddd,  $J = 14.3, 9.7, 5.4$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.55 (2H, q,  $J = 7.0$  Hz,  $\text{OCH}_2$ ), 4.20 (1H, dqd,  $J = 8.2, 7.4, 4.8$  Hz,  $\text{CH}$ ), 7.21–7.26 (2H, m, *H*-arom), 7.47 (1H, d,  $J = 7.4$  Hz, *H*-arom), 8.08 (1H, d,  $J = 7.9$  Hz, *H*-arom); No  $^{13}\text{C}$  obtained, insufficient quantity synthesised.

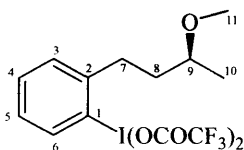
**(S)-1-(2-Diacetoxyiodophenyl)-3-benzyloxybutane - 95**



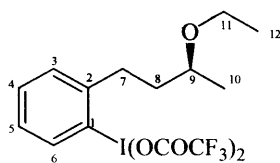
Synthesised according to GP11 with sodium perborate tetrahydrate (321 mg, 2.065 mmol) added portion wise to a solution of (*S*)-1-(4-(2-iodophenyl)butan-2-methyl)benzene **90** (76 mg, 0.206 mmol) in glacial acetic acid (5 ml). Product was

isolated by recrystallisation from acetic acid/pentane. Yield 5% (5 mg, 0.010 mmol) as a white powder. mp = 109–112°C.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 400 MHz)  $\delta_{\text{H}}$ : 1.80 (1H, d,  $J = 6.7$  Hz,  $\text{CH}_3$ ), 1.89 (1H, dddd,  $J = 13.8, 10.7, 7.9, 6.1$  Hz,  $\text{ArCH}_2\text{CH}_\text{A}\text{CH}_\text{B}$ ), 2.00 (1H, dddd,  $J = 13.8, 9.4, 6.4, 5.0$  Hz,  $\text{ArCH}_2\text{CH}_\text{A}\text{CH}_\text{B}$ ), 2.06 (6H, s,  $(\text{OCOCH}_3)_2$ ), 2.85 (1H, ddd,  $J = 14.3, 9.4, 6.1$  Hz,  $\text{ArCH}_\text{A}\text{CH}_\text{B}$ ), 3.01 (1H, ddd,  $J = 14.3, 10.7, 6.4$  Hz,  $\text{ArCH}_\text{A}\text{CH}_\text{B}$ ), 3.80 (1H, dqd,  $J = 7.9, 6.7, 5.0$  Hz,  $\text{CH}$ ), 4.19 (2H, s,  $\text{OCH}_2$ ), 7.19 (1H, dd,  $J = 7.9, 1.6$  Hz,  $H$ -arom), 7.24 (2H, atd,  $J = 7.7, 1.4$  Hz,  $H$ -arom), 7.28 (2H, dd,  $J = 7.7, 1.6$  Hz,  $H$ -arom), 7.37 (1H, dd,  $J = 7.9, 7.4$  Hz,  $H$ -arom), 7.49 (1H, dd,  $J = 7.6, 1.3$  Hz,  $H$ -arom), 7.57 (1H, d,  $J = 7.4$  Hz,  $H$ -arom), 8.14 (1H, d,  $J = 7.9$  Hz,  $H$ -arom); No  $^{13}\text{C}$  obtained.

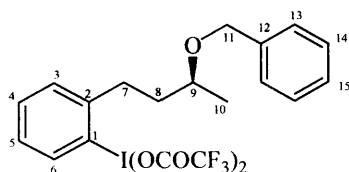
**(*S*)-1-(2-[Bis(trifluoroacetoxy)iodo]phenyl)-3-methoxybutane - 96**



Synthesised according to GP15 with (*S*)-1-iodo-2-(3-methoxybutyl)benzene **88** (53 mg, 0.184 mmol) in DCM (2 ml) added to a previously prepared solution of trifluoroacetic anhydride (193 mg, 0.920 mmol) and urea hydrogen peroxide (211 mg, 0.307 mmol) in DCM (5 ml). Yield 21% (20 mg, 0.039 mmol) of a white powder.  $[\alpha]_{\text{D}}^{22} = +92.9$  ( $c = 0.77$ ,  $\text{CHCl}_3$ ):  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 400 MHz)  $\delta_{\text{H}}$ : 2.00 (3H, d,  $J = 6.7$  Hz,  $\text{CH}_3$ ), 2.88 (1H, dddd,  $J = 14.2, 9.0, 7.5, 6.7$  Hz,  $\text{ArCH}_2\text{CH}_\text{A}\text{CH}_\text{B}$ ), 3.02 (1H, dddd,  $J = 14.2, 8.8, 5.5, 5.2$  Hz,  $\text{ArCH}_2\text{CH}_\text{A}\text{CH}_\text{B}$ ), 3.10 (1H, ddd,  $J = 14.3, 9.0, 5.5$  Hz,  $\text{ArCH}_\text{A}\text{CH}_\text{B}$ ), 3.06 (1H, ddd,  $J = 14.3, 8.8, 6.7$  Hz,  $\text{ArCH}_\text{A}\text{CH}_\text{B}$ ), 3.18 (3H, s,  $\text{OCH}_3$ ), 4.08–4.15 (1H, dqd,  $J = 7.5, 6.7, 5.2$  Hz,  $\text{CH}$ ), 7.25 (1H, d,  $J = 7.7$  Hz,  $H$ -arom), 7.40 (1H, d,  $J = 6.9$  Hz,  $H$ -arom), 7.55 (1H, d,  $J = 6.9$  Hz,  $H$ -arom), 8.15 (1H, d,  $J = 7.7$  Hz,  $H$ -arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 100.7 MHz)  $\delta_{\text{C}}$ : 36.0 (C-10), 38.1 (C-7), 40.3 (C-8), 60.7 (C-11), 85.4 (C-9), 111.8 (q,  $J_{\text{CF}} = 290$  Hz,  $\text{CF}_3$ ), 127.4 (C-Ar), 128.5 (C-Ar), 129.9 (C-3), 133.4 (C-1), 141.0 (C-6), 144.3 (C-2), 164.7 (q,  $J_{\text{CF}} = 40$  Hz,  $\text{C}=\text{O}$ ). IR (Nujol):  $\nu_{\text{max}} = 2939, 2870, 1731, 1711, 1465, 1379, 1240, 1195, 1150, 996$   $\text{cm}^{-1}$ .

**(S)-1-(2-[Bis(trifluoroacetoxy)iodo]phenyl)-3-ethoxybutane - 97**

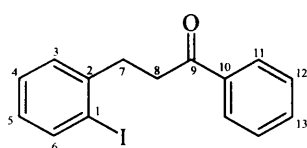
Synthesised according to GP15 with (*S*)-1-iodo-2-(3-ethoxybutyl)benzene **89** (55 mg, 0.184 mmol) in DCM (2 ml) added to a previously prepared solution of trifluoroacetic anhydride (193 mg, 0.920 mmol) and urea hydrogen peroxide (211 mg, 0.307 mmol) in DCM (5 ml). Yield 15% (15 mg, 0.028 mmol) of a white powder.  $[\alpha]_D^{23} = +100.6$  ( $c = 0.95$ ,  $\text{CHCl}_3$ ):  $^1\text{H NMR}$ , ( $\text{CDCl}_3$ , 250 MHz)  $\delta_{\text{H}}$ : 1.35, (3H, d,  $J = 6.7$  Hz,  $\text{CH}_2\text{CH}_3$ ) 1.41 (3H, d,  $J = 6.7$  Hz,  $\text{CH}_3$ ), 2.41–2.49 (1H, m,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.58–2.65 (1H, m,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 3.00 (1H, ddd,  $J = 14.3, 9.2, 7.3$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.03 (2H, q,  $J = 6.7$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 3.02–3.08 (1H, m,  $\text{ArCH}_A\text{CH}_B$ ), 4.20–4.5 (1H, m,  $\text{CH}$ ), 7.28–7.35 (2H, m, *H*-arom), 7.58 (1H, d,  $J = 6.9$  Hz, *H*-arom), 8.15 (1H, d,  $J = 7.7$  Hz, *H*-arom);  $^{13}\text{C NMR}$ , ( $\text{CDCl}_3$ , 67.5 MHz)  $\delta_{\text{C}}$ : 33.4 (C-12), 36.6 (C-10), 37.7 (C-7), 42.1 (C-8), 62.6 (C-11), 84.5 (C-9), 114.6 (q,  $J = 285$  Hz,  $\text{CF}_3$ ), 127.7 (C-Ar), 127.8 (C-Ar), 130.2 (C-3), 134.1 (C-1), 141.6 (C-6), 144.6 (C-2), 166.3 (q,  $J = 39$  Hz, C=O). No IR obtained.

**(S)-1-(2-[Bis(trifluoroacetoxy)iodo]phenyl)-3-benzyloxybutane - 98**

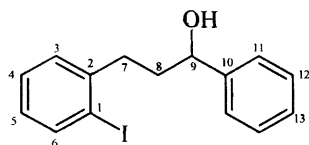
Synthesised according to GP15 with (*S*)-1-(4-(2-iodophenyl)butan-2-methyl)benzene **90** (60 mg, 0.164 mmol) in DCM (2 ml) added to a previously prepared solution of trifluoroacetic anhydride (172 mg, 0.819 mmol) and urea hydrogen peroxide (172 mg, 0.247 mmol) in DCM (2 ml). Yield 6% (6 mg, 0.010 mmol) of a white powder.  $^1\text{H NMR}$ , ( $\text{CDCl}_3$ , 400 MHz)  $\delta_{\text{H}}$ : 2.05 (3H, d,  $J = 7.0$

Hz,  $CH_3$ ), 2.83–2.95 (2H, m,  $ArCH_2CH_2$ ), 2.94 (1H, ddd,  $J = 13.0, 10.1, 6.9$  Hz,  $ArCH_ACH_B$ ), 3.11 (1H, ddd,  $J = 13.1, 10.1, 5.4$  Hz,  $ArCH_ACH_B$ ), 3.80 (1H, dqd,  $J = 7.9, 7.0, 5.0$  Hz,  $CH$ ), 4.63 (2H, s,  $OCH_2$ ), 7.30 (1H, d,  $J = 6.3$  Hz,  $H$ -arom), 7.49–7.57 (2H, m,  $H$ -arom), 8.17 (1H, d,  $J = 7.9$  Hz,  $H$ -arom); No  $^{13}C$  obtained, insufficient quantity synthesised.

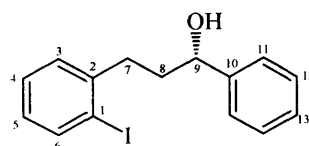
### 3-(2-Iodophenyl)-1-phenylpropan-1-one<sup>9,13</sup> - 99



Synthesised according to GP8 with 2-iodobenzyl chloride **83** (5.0g, 19.67 mmol), dibenzoyl methane (4.64 g, 20.65 mmol) and potassium carbonate (2.99 g, 21.64 mmol) in ethanol (50 ml). The product was purified by column chromatography hexane/ethyl acetate (9:1). Yield 84% (5.55 g, 16.52 mmol) as colourless crystals. mp 49–50 °C;. Spectroscopic data agrees with literature.  $^1H$  NMR, ( $CDCl_3$ , 250 MHz)  $\delta_H$ : 3.10 (2H, t,  $J = 8.1$  Hz,  $ArCH_2$ ), 3.22 (2H, t,  $J = 8.1$  Hz,  $ArCH_2CH_2$ ), 6.84 (1H, ddd,  $J = 7.6, 7.5, 2.0$  Hz,  $H$ -arom), 7.16–7.54 (4H, m,  $H$ -arom), 7.75 (1H, d,  $J = 8.0$  Hz,  $H$ -arom), 7.90 (2H, dd,  $J = 8.4, 7.9$  Hz,  $H$ -arom), 7.98 (1H, dd,  $J = 8.2, 1.0$  Hz,  $H$ -arom);  $^{13}C$  NMR, ( $CDCl_3$ , 62.5 MHz)  $\delta_C$ : 35.2 (C-8), 38.9 (C-7), 100.3 (C-1), 128.1 (C-12), 128.3 (C-5), 128.5 (C-4), 128.6 (C-11), 129.5 (C-3), 129.9 (C-13), 133.1 (C-6), 133.9 (C-10), 139.6 (C-2), 198.8 (C-9); MS ( $EI^+$ ):  $m/z$  (%) = 336 (21)  $[M]^+$ , 274 (42), 217 (100), 119 (34), 105 (39), 91 (16); HRMS for  $C_{15}H_{14}IO$ : calcd. 336.1712, found 336.1709  $[M+H]^+$ ; IR (Neat):  $\nu_{max} = 1706, 1688$   $cm^{-1}$ ;

**(±)-3-(2-Iodophenyl)-1-phenylpropan-1-ol – 100**

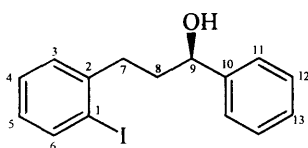
Synthesised according to GP10 with 1-(2-iodophenyl)butan-3-one **99** (1.0 g, 2.975 mmol) added to a stirred solution of sodium borohydride (62 mg, 1.636 mmol) in ethanol (10 ml). The product was columned using petroleum ether/diethyl ether (15:1). Yield 90% (0.91 g, 2.677 mmol), pale yellow oil. HPLC conditions: Chiracel OD-H column, hexane/ 2-propanol, 90:10, 0.5 ml/min, 15 °C,  $t_R$  = 19.8 min (–)-enantiomer,  $t_S$  = 22.2 min (+)-enantiomer.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 250 MHz)  $\delta_{\text{H}}$ : 1.60 (1H, br s, OH), 1.91–2.04 (2H, m,  $\text{ArCH}_2\text{CH}_2$ ), 2.65 (1H, ddd,  $J$  = 13.9, 10.3, 5.1 Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.78 (1H, ddd,  $J$  = 13.9, 9.6, 6.6 Hz,  $\text{ArCH}_A\text{CH}_B$ ), 4.69 (1H, dd,  $J$  = 8.0, 5.2 Hz, CH), 6.79 (1H, ddd,  $J$  = 7.6, 7.5, 1.9 Hz,  $H$ -arom), 7.12 (2H, ddd,  $J$  = 7.9, 7.6, 1.4 Hz,  $H$ -arom), 7.18–7.24 (1H, m,  $H$ -arom), 7.27–7.35 (4H, m,  $H$ -arom), 7.72 (1H, dd,  $J$  = 7.6, 1.0 Hz,  $H$ -arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta_{\text{C}}$ : 23.6 (C-7), 37.1 (C-8), 74.5 (C-9), 100.0 (C-1), 126.2 (C-13), 127.8 (C-5), 128.0 (C-4), 129.3 (C-11), 129.5 (C-12), 129.8 (C-3), 137.9 (C-10), 139.2 (C-6), 140.7 (C-2); MS ( $\text{Cl}^+$ ):  $m/z$  (%) = 356 (34)  $[\text{M}+\text{NH}_4]^+$ , 338 (59), 228 (100), 212 (13), 52 (36); HRMS for  $\text{C}_{15}\text{H}_{19}\text{INO}$ : calcd. 356.0506, found 356.0505  $[\text{M}+\text{NH}_4]^+$ ; IR (Neat):  $\nu_{\text{max}}$  = 3345, 2952, 2923, 1795, 1576, 1563, 1244, 1168, 1098, 1017  $\text{cm}^{-1}$ .

**(S)-3-(2-Iodophenyl)-1-phenylpropan-1-ol – 101**

Synthesised according to GP9 with 3-(2-iodophenyl)-1-phenylpropan-1-one **99** (4.0 g, 11.90 mmol) added to a stirred solution of (–)-*B*

chlorodiisopinocampheylborane (4.20 g, 13.89 mmol) in dry THF (20 ml). Diethyl ether (25 ml) was added along with diethanolamine (2.75 g, 26.18 mmol). The product was columned using petroleum ether/diethyl ether (15:1). Yield 79%, >99% *ee* (3.18 g, 9.40 mmol), pale yellow oil.  $[\alpha]_D^{25} = +46.10$  ( $c = 1.03$ ,  $\text{CHCl}_3$ ). HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 90:10, 0.5 ml/min, 15 °C,  $t_R = 19.8$  min (–)-enantiomer,  $t_S = 22.2$  min (+)-enantiomer. Enantiomer 2 ( $R_f = 22.2$  min);  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 250 MHz)  $\delta_H$ : 1.60 (1H, br s, OH), 1.91–2.04 (2H, m,  $\text{ArCH}_2\text{CH}_2$ ), 2.65 (1H, ddd,  $J = 13.9, 10.3, 5.1$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.78 (1H, ddd,  $J = 13.9, 9.6, 6.6$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 4.69 (1H, dd,  $J = 8.0, 5.2$  Hz, CH), 6.79 (1H, ddd,  $J = 7.6, 7.5, 1.9$  Hz, *H*-arom), 7.12 (2H, ddd,  $J = 7.9, 7.6, 1.4$  Hz, *H*-arom), 7.18–7.24 (1H, m, *H*-arom), 7.27–7.35 (4H, m, *H*-arom), 7.72 (1H, dd,  $J = 7.6, 1.0$  Hz, *H*-arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta_C$ : 23.6 (C-7), 37.1 (C-8), 74.5 (C-9), 100.0 (C-1), 126.2 (C-13), 127.8 (C-5), 128.0 (C-4), 129.3 (C-11), 129.5 (C-12), 129.8 (C-3), 137.9 (C-10), 139.2 (C-6), 140.7 (C-2); MS ( $\text{CI}^+$ ):  $m/z$  (%) = 356 (34)  $[\text{M}+\text{NH}_4]^+$ , 338 (59), 228 (100), 212 (13), 52 (36); HRMS for  $\text{C}_{15}\text{H}_{19}\text{INO}$ : calcd. 356.0506, found 356.0505  $[\text{M}+\text{NH}_4]^+$ ; IR (Neat):  $\nu_{\text{max}} = 3345, 2952, 2923, 1795, 1576, 1563, 1244, 1168, 1098, 1017$   $\text{cm}^{-1}$ .

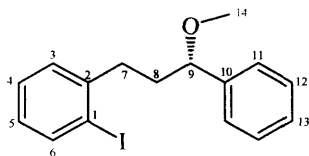
### (*R*)-3-(2-Iodophenyl)-1-phenylpropan-1-ol – 102



Synthesised according to GP10 with 1-(2-iodophenyl)butan-3-one **99** (1.0 g, 2.975 mmol) added to a stirred solution of sodium borohydride (62 mg, 1.636 mmol) in ethanol (10 ml). The product was columned using petroleum ether/diethyl ether (15:1). Yield 90% (0.91 g, 2.677 mmol), pale yellow oil. The enantiomers could be separated by preparative HPLC: Chiracel OD column, hexane/2-propanol, 90:10, 2.5 ml/min, 15 °C,  $t_R = 17.0$  min (–)-enantiomer,  $t_S = 25.1$  min (+)-enantiomer. Enantiomer 1 ( $R_f = 17.0$  min):  $[\alpha]_D^{25} = -45.61$  ( $c = 0.12$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 250 MHz)  $\delta_H$ : 1.60 (1H, br s, OH), 1.91–2.04 (2H, m,

ArCH<sub>2</sub>CH<sub>2</sub>), 2.65 (1H, ddd,  $J = 13.9, 10.3, 5.1$  Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 2.78 (1H, ddd,  $J = 13.9, 9.6, 6.6$  Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 4.69 (1H, dd,  $J = 8.0, 5.2$  Hz, CH), 6.79 (1H, ddd,  $J = 7.6, 7.5, 1.9$  Hz, *H*-arom), 7.12 (2H, ddd,  $J = 7.9, 7.6, 1.4$  Hz, *H*-arom), 7.18–7.24 (1H, m, *H*-arom), 7.27–7.35 (4H, m, *H*-arom), 7.72 (1H, dd,  $J = 7.6, 1.0$  Hz, *H*-arom); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 62.5 MHz) δ<sub>C</sub>: 23.6 (C-7), 37.1 (C-8), 74.5 (C-9), 100.0 (C-1), 126.2 (C-13), 127.8 (C-5), 128.0 (C-4), 129.3 (C-11), 129.5 (C-12), 129.8 (C-3), 137.9 (C-10), 139.2 (C-6), 140.7 (C-2); MS (CI<sup>+</sup>):  $m/z$  (%) = 356 (34) [M+NH<sub>4</sub>]<sup>+</sup>, 338 (59), 228 (100), 212 (13), 52 (36); HRMS for C<sub>15</sub>H<sub>19</sub>INO: calcd. 356.0506, found 356.0505 [M+NH<sub>4</sub>]<sup>+</sup>; IR (Neat): ν<sub>max</sub> = 3345, 2952, 2923, 1795, 1576, 1563, 1244, 1168, 1098, 1017 cm<sup>-1</sup>.

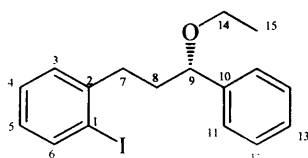
**(S)-1-(3-(2-Iodophenyl)-1-methoxypropyl)benzene - 103**



Synthesised according to GP5 with sodium hydride (213 mg, 8.89 mmol) suspended in DMF (10 ml) stirred with (*S*)-3-(2-iodophenyl)-1-phenylpropan-1-ol **101** (1.0 g, 2.96 mmol) and methyl iodide (420 mg, 2.96 mmol). The product was purified by column chromatography petroleum ether/diethyl ether (10:1). Yield 85% (0.88 g, 2.499 mmol) as a pale yellow oil.  $[\alpha]_D^{22} = +38.92$  ( $c = 1.12$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ<sub>H</sub>: 1.87 (1H, dddd,  $J = 13.7, 10.5, 6.6, 6.2$  Hz, ArCH<sub>2</sub>CH<sub>A</sub>CH<sub>B</sub>), 1.97 (1H, dddd,  $J = 13.7, 10.1, 8.1, 5.9$  Hz, ArCH<sub>2</sub>CH<sub>A</sub>CH<sub>B</sub>), 2.65 (1H, ddd,  $J = 13.9, 10.5, 5.9$  Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 2.78 (1H, ddd,  $J = 13.9, 10.1, 6.6$  Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 3.18 (3H, s, OCH<sub>3</sub>), 4.06 (1H, dd,  $J = 8.1, 6.2$  Hz, CH), 6.79 (1H, ddd,  $J = 7.6, 7.6, 1.3$  Hz, *H*-arom), 7.12 (1H, dd,  $J = 7.6, 1.7$  Hz, *H*-arom), 7.17 (1H, dd,  $J = 7.3, 1.0$  Hz, *H*-arom), 7.18–7.31 (5H, m, *H*-arom), 7.72 (1H, dd,  $J = 7.9, 1.0$  Hz, *H*-arom); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 125.7 MHz) δ<sub>C</sub>: 36.1 (C7), 37.3 (C-8), 55.6 (C-14), 82.0 (C-9), 99.5 (C-1), 125.6 (C-11), 126.5 (C-13), 126.6 (C-5), 127.2 (C-4), 127.2 (C-12), 128.4 (C-3), 138.4 (C-6), 140.9 (C-10), 143.5 (C-2); MS (EI<sup>+</sup>):  $m/z$  (%) = 352 (36) [M]<sup>+</sup>, 337 (56), 321 (100), 274 (29), 107 (61), 91

(19); HRMS for  $C_{10}H_{21}INO$ : calcd. 370.0662, found 370.0662  $[M+NH_4]^+$ ; IR (Neat):  $\nu_{max} = 3045, 2952, 2843, 2815, 1526, 1463, 1435, 1359, 1227, 1099, 1025$   $cm^{-1}$ . An authentic sample of racemic **103**, ( $\pm$ )-1-(3-(2-iodophenyl)-1-methoxypropyl)benzene, was prepared from **100** as described previously: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 98:2, 0.5 ml/min, 24 °C,  $t_R = 13.5$  min (–)-enantiomer,  $t_S = 17.4$  min (+)-enantiomer. Enantiomer 2 ( $R_f = 17.4$  min): The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

### (S)-1-(1-Ethoxy-3-(2-iodophenyl)propyl)benzene - 104

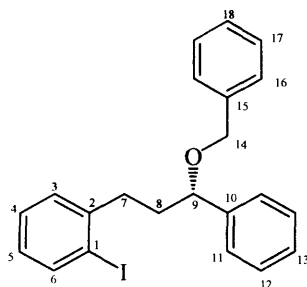


Synthesised according to GP5 with sodium hydride (213 mg, 8.89 mmol) suspended in DMF (10 ml) stirred with (*S*)-3-(2-iodophenyl)-1-phenylpropan-1-ol **101** (1.0 g, 2.96 mmol) and ethyl iodide (462 mg, 2.96 mmol). The product was purified by column chromatography petroleum ether/diethyl ether (10:1). Yield 80% (0.86 g, 2.359 mmol) as a pale yellow oil.  $[\alpha]_D^{19} = +35.19$  ( $c = 0.87$ ,  $CHCl_3$ );  $^1H$  NMR, ( $CDCl_3$ , 500 MHz)  $\delta_H$ : 1.14 (3H, t,  $J = 7.0$  Hz,  $CH_2CH_3$ ), 1.87 (1H, dddd,  $J = 13.6, 9.4, 6.5, 5.1$  Hz,  $ArCH_2CH_ACH_B$ ), 1.97 (1H, dddd,  $J = 13.6, 9.9, 8.2, 5.2$  Hz,  $ArCH_2CH_ACH_B$ ), 2.67 (1H, ddd,  $J = 13.8, 9.9, 6.5$  Hz,  $ArCH_ACH_B$ ), 2.78 (1H, ddd,  $J = 13.8, 9.4, 5.2$  Hz,  $ArCH_ACH_B$ ), 3.41 (2H, q,  $J = 7.0$  Hz,  $ArCH_2CH_2$ ), 4.16 (1H, dd,  $J = 8.2, 5.1$  Hz,  $CH$ ), 6.79 (1H, ddd,  $J = 7.6, 7.5, 1.7$  Hz,  $H$ -arom), 7.13 (1H, dd,  $J = 7.7, 1.7$  Hz,  $H$ -arom), 7.17 (1H, dd,  $J = 7.3, 0.9$  Hz,  $H$ -arom), 7.18–7.30 (5H, m,  $H$ -arom), 7.72 (1H, dd,  $J = 7.9, 0.8$  Hz,  $H$ -arom);  $^{13}C$  NMR, ( $CDCl_3$ , 125.7 MHz)  $\delta_C$ : 15.3 (C-15), 37.2 (C-8), 38.4 (C-7), 64.2 (C-14), 81.2 (C-9), 100.7 (C-1), 126.6 (C-13), 127.5 (C-5), 127.6 (C-4), 128.3 (C-12), 128.4 (C-11), 129.5 (C-3), 139.5 (C-6), 142.8 (C-10), 144.6 (C-2); MS ( $CI^+$ ):  $m/z$  (%) = 383 (55)  $[M+NH_4]^+$ , 321 (34), 217 (45), 107 (100), 91 (30); HRMS for  $C_{17}H_{23}INO$ : calcd. 384.0819, found 384.0817  $[M+NH_4]^+$ ; IR (Neat):  $\nu_{max} = 3044,$



2950, 2929, 2851, 2822, 1541, 1459, 1435, 1366, 1219, 1112, 1014  $\text{cm}^{-1}$ . An authentic sample of racemic **104**, ( $\pm$ )-1-(3-(2-iodophenyl)-1-ethoxypropyl)benzene, was prepared from **100** as described previously: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 99:1, 0.5 ml/min, 24 °C,  $t_R = 17.0$  min (-)-enantiomer,  $t_S = 24.6$  min (+)-enantiomer. Enantiomer 2 ( $R_f = 24.6$  min): The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

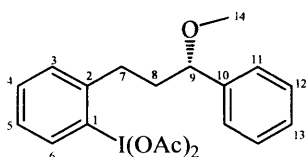
**(S)-1-(1-(Benzyloxy)-3-(2-iodophenyl)propyl)benzene - 105**



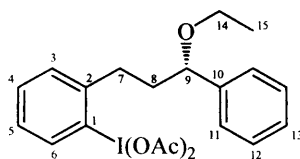
Synthesised according to GP5 with sodium hydride (213 mg, 8.89 mmol) suspended in DMF (10 ml) stirred with (*S*)-3-(2-iodophenyl)-1-phenylpropan-1-ol **101** (1.0 g, 2.96 mmol) and benzyl bromide (506 mg, 2.96 mmol). The product was purified by column chromatography petroleum ether/diethyl ether (10:1). Yield 71% (0.90g, 2.100 mmol) as a pale yellow oil.  $[\alpha]_D^{23} = +40.06$  ( $c = 1.19$ ,  $\text{CHCl}_3$ ):  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.92 (1H, dddd,  $J = 13.5, 10.3, 6.3, 5.2$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.01 (1H, dddd,  $J = 13.5, 10.1, 8.0, 5.1$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.70 (1H, ddd,  $J = 13.4, 10.1, 6.3$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.81 (1H, ddd,  $J = 13.4, 10.3, 5.1$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 4.15 (1H, dd,  $J = 8.0, 5.2$  Hz,  $\text{CH}$ ), 4.49 (2H, s,  $\text{OCH}_2$ ), 6.81 (1H, ddd,  $J = 7.8, 6.7, 1.4$  Hz,  $H$ -arom), 7.12–7.16 (5H, m,  $H$ -arom), 7.18–7.35 (7H, m,  $H$ -arom), 7.75 (1H, dd,  $J = 8.0, 1.2$  Hz,  $H$ -arom);  $^{13}\text{C NMR}$ , ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 28.1 (C7), 36.9 (C-8), 74.9 (C-14), 85.3 (C-9), 100.6 (C-1), 125.5 (C-Ar), 125.6 (C-Ar), 126.5 (C-Ar), 126.6 (C-5), 127.2 (C-4), 127.2 (C-Ar), 128.4 (C-3), 128.9 (C-Ar), 129.5 (C-Ar), 138.4 (C-6), 139.9 (C-Ar), 140.3 (C-Ar), 143.5 (C-2); MS ( $\text{Cl}^+$ ):  $m/z$  (%) = 428 (27)  $[\text{M}+\text{H}]^+$ , 337 (12), 321

(46), 217 (100), 107 (41), 91 (19); HRMS for  $C_{22}H_{22}IO$ : calcd. 428.0901, found 428.0899  $[M+H]^+$ ; No IR obtained. An authentic sample of racemic **105**, ( $\pm$ )-1-(1-(benzyloxy)-3-(2-iodophenyl)propyl)benzene, was prepared from **100** as described previously: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 99:1, 0.5 ml/min, 24 °C,  $t_R$  = 15.9 min (–)-enantiomer,  $t_S$  = 26.5 min (+)-enantiomer. Enantiomer 2 ( $R_f$  = 26.5 min): The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

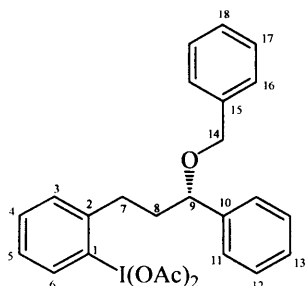
**(S)-1-(1-Methoxy-3-(2-(diacetoxy)iodophenyl)propyl)benzene - 106**



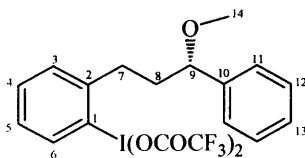
Synthesised according to GP11 with sodium perborate tetrahydrate (734 mg, 4.77 mmol) added portion wise to a solution of (*S*)-1-(3-(2-iodophenyl)-1-methoxypropyl)benzene **103** (168 mg, 0.477 mmol) in glacial acetic acid (5 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 87% (195 mg, 0.415 mmol) as a white powder. mp = 120–122°C.  $[\alpha]_D^{26} = +75.1$  ( $c = 0.97$ ,  $CHCl_3$ ).  $^1H$  NMR, ( $CDCl_3$ , 400 MHz)  $\delta_H$ : 1.93–2.04 (2H, m,  $ArCH_2CH_2$ ), 2.05 (6H, s,  $(OCOCH_3)_2$ ), 2.91 (1H, ddd,  $J = 14.0, 10.6, 6.0$  Hz,  $ArCH_ACH_B$ ), 3.12 (1H, ddd,  $J = 14.0, 10.8, 5.4$  Hz,  $ArCH_ACH_B$ ), 3.46 (3H, s,  $OCH_3$ ), 4.06 (1H, dd,  $J = 8.1, 4.9$  Hz,  $CH$ ), 7.10 (1H, dd,  $J = 8.0, 1.9$  Hz,  $H$ -arom) 7.18 (1H, dd,  $J = 7.6, 1.5$  Hz,  $H$ -arom), 7.21–7.40 (5H, m,  $H$ -arom), 7.48 (1H, dd,  $J = 8.0, 1.8$  Hz,  $H$ -arom), 8.11 (1H, d,  $J = 7.9$  Hz,  $H$ -arom);  $^{13}C$  NMR ( $CDCl_3$ , 100.6 MHz):  $\delta = 20.3$  ( $(OCOCH_3)_2$ ), 35.7 (C-8), 39.3 (C-7), 56.7 (C-14), 82.8 (C-9), 124.9 (C-1), 126.5 (C-11), 127.8 (C-13), 128.5 (C-12), 128.7 (C-5), 130.2 (C-4), 132.7 (C-3), 137.9 (C-10), 141.7 (C-6), 144.0 (C-2), 176.4 ( $(OCOCH_3)_2$ ); IR (Nujol):  $\nu_{max} = 2950, 2910, 2889, 1659, 1620, 1560, 1477, 1462, 1380, 1304, 1147, 1009$   $cm^{-1}$ .

**(S)-1-(1-Ethoxy-3-(2-(diacetoxy)iodophenyl)propyl)benzene - 107**

Synthesised according to GP11 with sodium perborate tetrahydrate (574 mg, 3.73 mmol) added portion wise to a solution of (*S*)-1-(3-(2-iodophenyl)-1-ethoxypropyl)benzene **104** (137 mg, 0.373 mmol) in glacial acetic acid (5 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 89% (161 mg, 0.333 mmol) as a white powder. mp = 120–123°C.  $[\alpha]_D^{25} = +70.7$  (c = 1.09, CHCl<sub>3</sub>). <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 500 MHz)  $\delta_H$ : 1.14 (3H, t,  $J = 7.1$  Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.02 (6H, s, (CH<sub>3</sub>COO)<sub>2</sub>), 2.07 (1H, dddd,  $J = 14.0, 10.7, 5.5, 5.1$  Hz, ArCH<sub>2</sub>CH<sub>2</sub>), 2.19 (1H, dddd,  $J = 14.0, 9.8, 8.2, 6.5$  Hz, ArCH<sub>2</sub>CH<sub>2</sub>), 2.93 (1H, ddd,  $J = 13.9, 10.7, 6.5$  Hz, ArCH<sub>2</sub>), 3.05 (1H, ddd,  $J = 13.9, 9.8, 5.5$  Hz, ArCH<sub>2</sub>), 3.95 (2H, q,  $J = 7.1$  Hz, CH<sub>2</sub>CH<sub>3</sub>), 4.20 (1H, dd,  $J = 8.2, 5.1$  Hz, CH), 7.09 (1H, d,  $J = 7.2$  Hz, *H*-arom), 7.20 (1H, dd,  $J = 7.6, 1.7$  Hz, *H*-arom), 7.25–7.49 (5H, m, *H*-arom), 7.79 (1H, d,  $J = 6.9$  Hz, *H*-arom), 8.15 (1H, dd,  $J = 7.8, 1.0$  Hz, *H*-arom); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 125.7 MHz)  $\delta_C$ : 20.0 (C-15), 20.6 ((OCOCH<sub>3</sub>)<sub>2</sub>), 39.9 (C-8), 41.2 (C-7), 66.2 (C-14), 85.3 (C-9), 126.6 (C-13), 127.5 (C-Ar), 127.6 (C-11), 128.3 (C-12), 128.4 (C-Ar), 131.0 (C-3), 133.5 (C-1), 140.4 (C-6), 143 (C-10), 145.7 (C-2), 175.5 ((OCOCH<sub>3</sub>)<sub>2</sub>). IR (Nujol):  $\nu_{\max} = 2979, 2915, 2872, 1690, 1560, 1477, 1462, 1380, 1304, 1147, 1000$  cm<sup>-1</sup>.

**(S)-1-(1-(Benzyloxy)-3-(2-(diacetoxy)iodophenyl)propyl)benzene - 108**

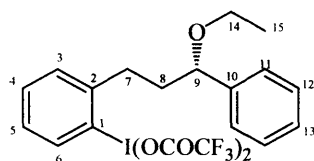
Synthesised according to GP13 with (S)-1-(1-(benzyloxy)-3-(2-iodophenyl)propyl)benzene **105** (63 mg, 0.146 mmol) added to a stirred solution of acetic anhydride (8.76 ml, 92.7 mmol) and hydrogen peroxide (2.34 ml of a 30% solution in acetic acid) in glacial acetic acid (5 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 5% (4 mg, 0.007 mmol) as a white powder. mp = 120–123°C. <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 400 MHz) δ<sub>H</sub>: 2.02 (6H, s, (OCOCH<sub>3</sub>)<sub>2</sub>), 2.04–2.10 (H, m, ArCH<sub>2</sub>CH<sub>A</sub>CH<sub>B</sub>), 2.20 (1H, ddd, *J* = 14.2, 9.7, 6.1, 5.0 Hz, ArCH<sub>2</sub>CH<sub>A</sub>CH<sub>B</sub>), 2.99 (1H, ddd, *J* = 14.3, 9.9, 6.1 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 3.17 (1H, ddd, *J* = 14.3, 9.7, 5.7 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 3.89 (1H, dd, *J* = 8.0, 5.0 Hz, CH), 4.19 (2H, s, OCH<sub>2</sub>), 6.90 (2H, atd, *J* = 7.9, 1.6 Hz, *H*-arom), 7.12 (1H, dd, *J* = 7.6, 1.6 Hz, *H*-arom), 7.15–7.48 (9H, d, *J* = 6.3 Hz, *H*-arom), 7.57 (1H, t, *J* = 7.4 Hz, *H*-arom), 8.14 (1H, d, *J* = 7.9 Hz, *H*-arom); No <sup>13</sup>C obtained, insufficient quantity synthesised.

**(S)-1-(3-(2-[Bis(trifluoroacetoxy)iodo]phenyl)-1-methoxypropyl)benzene - 109**

Synthesised according to GP15 with (S)-1-(3-(2-iodophenyl)-1-methoxypropyl)benzene **103** (52 mg, 0.147 mmol) in DCM (2 ml) added to a previously prepared solution of trifluoroacetic anhydride (154 mg, 0.733 mmol) and urea hydrogen peroxide (23 mg, 0.249 mmol) in DCM (2 ml). Product was

isolated by recrystallisation from acetic acid/pentane. Yield 59% (50 mg, 0.086 mmol) of a white powder. mp = 99–102°C.  $[\alpha]_D^{24} = + 82.0$  (c = 0.56, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta_H$ : = 2.00–2.13 (2H, m, ArCH<sub>2</sub>CH<sub>2</sub>), 2.90–2.99 (1H, m, ArCH<sub>A</sub>CH<sub>B</sub>), 3.08 (1H, m, ArCH<sub>A</sub>CH<sub>B</sub>), 3.19 (3H, s, OCH<sub>3</sub>), 4.15 (1H, dd, *J* = 8.0, 2.8 Hz, CH), 7.10–7.31 (6H, m, *H*-arom), 7.5 (1H, d, *J* = 8.2 Hz, *H*-arom), 7.58 (1H, atd, *J* = 7.6, 2.0 Hz, *H*-arom), 8.21 (1H, d, *J* = 8.1 Hz, *H*-arom); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.7 MHz):  $\delta$  = 35.5 (C-8), 39.3 (C-7), 56.6 (C-14), 83.4 (C-9), 112.9 (q, *J*<sub>CF</sub> = 288 Hz, CF<sub>3</sub>), 126.5 (C-Ar), 126.8 (C-Ar), 128.5 (C-5), 128.7 (C-Ar), 129.5 (C-4), 131.1 (C-3), 134.6 (C-1), 138.3 (C-10), 141.0 (C-6), 144.5 (C-2), 161.0 (q, *J*<sub>CF</sub> = 40 Hz, COCF<sub>3</sub>); IR (Nujol):  $\nu_{\max}$  = 2930, 2861, 1739, 1709, 1469, 1390, 1362, 1234, 1189, 1147, 990 cm<sup>-1</sup>.

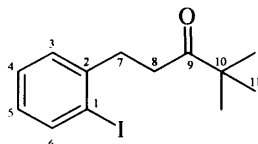
**(S)-1-(1-Ethoxy-3-(2-(diacetoxy)iodophenyl)propyl)benzene - 110**



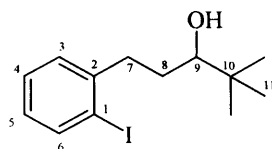
Synthesised according to GP15 with (S)-1-(3-(2-iodophenyl)-1-ethoxypropyl)benzene **104** (33 mg, 0.090 mmol) in DCM (2 ml) added to a previously prepared solution of trifluoroacetic anhydride (94 mg, 0.450 mmol) and urea hydrogen peroxide (14 mg, 0.153 mmol) in DCM (2 ml). Product was isolated by washing with pentane. Yield 17% (9 mg, 0.015 mmol) of a white powder. mp = 100–104°C.  $[\alpha]_D^{23} = + 76.9$  (c = 0.22, CHCl<sub>3</sub>). <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 500 MHz)  $\delta_H$ : 1.29 (3H, t, *J* = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.27 (1H, dddd, *J* = 13.7, 10.6, 7.9, 5.4 Hz, ArCH<sub>2</sub>CH<sub>A</sub>CH<sub>B</sub>), 2.45 (1H, dddd, *J* = 13.7, 9.9, 6.5, 5.1 Hz, ArCH<sub>2</sub>CH<sub>A</sub>CH<sub>B</sub>), 3.10 (1H, ddd, *J* = 14.0, 10.6, 6.5 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 3.33 (1H, ddd, *J* = 14.0, 9.9, 5.4 Hz, ArCH<sub>A</sub>CH<sub>B</sub>), 3.60 (2H, q, *J* = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.61 (1H, dd, *J* = 7.9, 5.1 Hz, CH), 6.99 (1H, d, *J* = 6.8 Hz, *H*-arom), 7.10 (1H, atd, *J* = 6.9, 1.8 Hz, *H*-arom), 7.16–7.49 (5H, m, *H*-arom), 7.60 (1H, d, *J* = 7.2 Hz, *H*-

arom), 8.22 (1H, dd,  $J = 8.1, 1.0$  Hz,  $H$ -arom); No  $^{13}\text{C}$  obtained, insufficient sample synthesised.

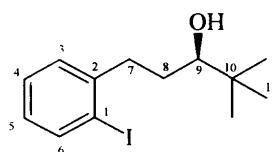
### 1-(2-Iodophenyl)-4,4-dimethylpentan-3-one – 111



Synthesised according to GP8 with 2-iodobenzyl chloride **83** (3.00 g, 12.24 mmol), 2,2,6,6-tetramethyl-3,5-heptandione (2.481 g, 13.46 mmol) and potassium carbonate (1774 g, 12.85 mmol) in ethanol (50 ml). The product was purified by column chromatography hexane/ethyl acetate (20:1). Yield 49% (1.83 g, 5.78 mmol) as a colourless oil.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.05 (9H, s,  $(\text{CH}_3)_3$ ), 2.72 (2H, t,  $J = 7.7$  Hz,  $\text{ArCH}_2\text{CH}_2$ ), 2.90 (2H, t,  $J = 7.7$ ,  $\text{ArCH}_2\text{CH}_2$ ), 6.82 (1H, atd,  $J = 7.5, 2.1$ ,  $H$ -arom), 7.12–7.24 (2H, m,  $H$ -arom), 7.73 (1H, dd,  $J = 7.9, 0.9$  Hz,  $H$ -arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 26.3 (C-11), 35.2 (C-7), 36.8 (C-8), 44.2 (C-10), 100.2 (C-1), 127.9 (C-5), 128.4 (C-4), 129.8 (C-3), 139.6 (C-6), 144.1 (C-2), 214.6 (C-9); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 316 (10)  $[\text{M}]^+$ , 259 (9), 217 (19), 105 (13), 85 (32), 57 (100); HRMS for  $\text{C}_{13}\text{H}_{16}\text{IO}$ : calcd. 315.0255, found 315.0246  $[\text{M} - \text{H}]^+$ ; IR (Neat):  $\nu_{\text{max}} = 2979, 2891, 1719, 1485, 1369, 1344, 1277, 1138, 1012 \text{ cm}^{-1}$ .

**(±)-1-(2-Iodophenyl)-4,4-dimethylpentan-3-ol – 112**

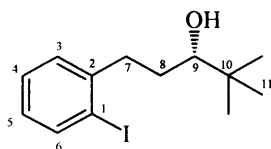
Synthesised according to GP10 with 1-(2-iodophenyl)-4,4-dimethylpentan-3-one **111** (3.00 g, 9.488 mmol) added to a stirred solution of sodium borohydride (251 mg, 6.642 mmol) in ethanol (20 ml). The product was columned using petroleum ether/diethyl ether (8:1). Yield 64% (1.933 g, 6.074 mmol), pale yellow oil. HPLC conditions: Chiracel OD column, hexane/ 2-propanol, 95:5, 2.5 ml/min, 10 °C,  $t_R$  = 9.9 min (–)-enantiomer,  $t_S$  = 15.5 min (+)-enantiomer.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_H$ : 0.83 (9H, s,  $(\text{CH}_3)_3$ ), 1.44 (1H, dddd,  $J = 13.9, 10.6, 10.4, 4.9$ , Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 1.52 (1H, s, OH), 1.80 (1H, dddd,  $J = 13.9, 10.8, 6.1, 1.7$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.66 (1H, ddd,  $J = 13.6, 10.4, 6.1$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.95 (1H, ddd,  $J = 13.6, 10.8, 4.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.20 (1H, dd,  $J = 10.6, 1.7$  Hz, CH), 6.81 (1H, ddd,  $J = 8.1, 6.6, 1.3$  Hz,  $H$ -arom), 7.17–7.23 (2H, m,  $H$ -arom), 7.74 (1H, d,  $J = 8.2$  Hz,  $H$ -arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_C$ : 25.7 (C-11), 32.2 (C-7), 35.1 (C-8), 38.4 (C-10), 79.6 (C-9), 100.6 (C-1), 127.7 (C-5), 128.4 (C-4), 129.6 (C-3), 129.5 (C-6), 145.0 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 318 (100)  $[\text{M}]^+$ , 300 (82), 285 (90); HRMS for  $\text{C}_{13}\text{H}_{19}\text{IO}$ : calcd. 318.0475, found 318.0473  $[\text{M}]^+$ ; IR (Neat): 3395, 2975, 2878, 1480, 1456, 1383, 1200, 1195, 1017  $\text{cm}^{-1}$ .

**(R)-1-(2-Iodophenyl)-4,4-dimethylpentan-3-ol – 113**

Synthesised according to GP10 with 1-(2-iodophenyl)-4,4-dimethylpentan-3-one **111** (3.00 g, 9.488 mmol) added to a stirred solution of sodium borohydride (251 mg, 6.642 mmol) in ethanol (20 ml). The product was columned using petroleum

ether / diethyl ether (8:1). Yield 64% (1.933 g, 6.074 mmol), pale yellow oil. The enantiomers could be separated by preparative HPLC: Chiracel OD column, hexane/ 2-propanol, 95:5, 2.5 ml/min, 10 °C,  $t_R = 9.9$  min (–)-enantiomer,  $t_S = 15.5$  min (+)-enantiomer. Enantiomer 1 (9.9 mins).  $[\alpha]_D^{25} = -81.06$  ( $c = 1.03$ ,  $\text{CHCl}_3$ , >99% *ee*).  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 0.83 (9H, s,  $(\text{CH}_3)_3$ ), 1.44 (1H, dddd,  $J = 13.9, 10.6, 10.4, 4.9$ , Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 1.52 (1H, s, OH), 1.80 (1H, dddd,  $J = 13.9, 10.8, 6.1, 1.7$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.66 (1H, ddd,  $J = 13.6, 10.4, 6.1$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.95 (1H, ddd,  $J = 13.6, 10.8, 4.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.20 (1H, dd,  $J = 10.6, 1.7$  Hz, CH), 6.81 (1H, ddd,  $J = 8.1, 6.6, 1.3$  Hz, *H*-arom), 7.17–7.23 (2H, m, *H*-arom), 7.74 (1H, d,  $J = 8.2$  Hz, *H*-arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 25.7 (C-11), 32.2 (C-7), 35.1 (C-8), 38.4 (C-10), 79.6 (C-9), 100.6 (C-1), 127.7 C-5), 128.4 (C-4), 129.6 (C-3), 129.5 (C-6), 145.0 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 318 (100)  $[\text{M}]^+$ , 300 (82), 285 (90); HRMS for  $\text{C}_{13}\text{H}_{19}\text{IO}$ : calcd. 318.0475, found 318.0473  $[\text{M}]^+$ ; IR (Neat): 3395, 2975, 2878, 1480, 1456, 1383, 1200, 1195, 1017  $\text{cm}^{-1}$ .

**(S)-1-(2-Iodophenyl)-4,4-dimethylpentan-3-ol – 114**

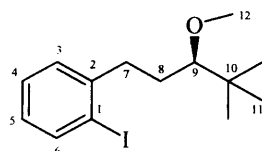


Synthesised according to GP10 with 1-(2-iodophenyl)-4,4-dimethylpentan-3-one **111** (3.00 g, 9.488 mmol) added to a stirred solution of sodium borohydride (251 mg, 6.642 mmol) in ethanol (20 ml). The product was columned using petroleum ether / diethyl ether (8:1). Yield 64% (1.933 g, 6.074 mmol), pale yellow oil. The enantiomers could be separated by preparative HPLC: Chiracel OD column, hexane/ 2-propanol, 95:5, 2.5 ml/min, 10 °C,  $t_R = 9.9$  min (–)-enantiomer,  $t_S = 15.5$  min (+)-enantiomer. Enantiomer 2 (15.5 mins).  $[\alpha]_D^{25} = +80.35$  ( $c = 1.02$ ,  $\text{CHCl}_3$ , >99% *ee*).  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 0.83 (9H, s,  $(\text{CH}_3)_3$ ), 1.44 (1H, dddd,  $J = 13.9, 10.6, 10.4, 4.9$ , Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 1.52 (1H, s, OH), 1.80 (1H, dddd,  $J = 13.9, 10.8, 6.1, 1.7$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.66 (1H, ddd,  $J = 13.6,$



10.4, 6.1 Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.95 (1H, ddd,  $J = 13.6, 10.8, 4.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.20 (1H, dd,  $J = 10.6, 1.7$  Hz,  $\text{CH}$ ), 6.81 (1H, ddd,  $J = 8.1, 6.6, 1.3$  Hz,  $H\text{-arom}$ ), 7.17–7.23 (2H, m,  $H\text{-arom}$ ), 7.74 (1H, d,  $J = 8.2$  Hz,  $H\text{-arom}$ );  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 25.7 (C-11), 32.2 (C-7), 35.1 (C-8), 38.4 (C-10), 79.6 (C-9), 100.6 (C-1), 127.7 (C-5), 128.4 (C-4), 129.6 (C-3), 129.5 (C-6), 145.0 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 318 (100)  $[\text{M}]^+$ , 300 (82), 285 (90); HRMS for  $\text{C}_{13}\text{H}_{19}\text{IO}$ : calcd. 318.0475, found 318.0473  $[\text{M}]^+$ ; IR (Neat): 3395, 2975, 2878, 1480, 1456, 1383, 1200, 1195, 1017  $\text{cm}^{-1}$ .

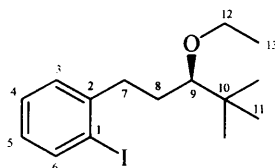
**(*R*)-1-Iodo-2-(3-methoxy-4,4-dimethylpentyl)benzene – 115**



Synthesised according to GP5 with sodium hydride (42 mg, 1.754 mmol) suspended in DMF (5 ml) stirred with (*R*)-1-(2-iodophenyl)-4,4-dimethylpentan-3-ol **113** (186 mg, 0.585 mmol) and methyl iodide (83 mg, 0.585 mmol). The product was purified by column chromatography hexane/ethyl acetate (4:1). Yield 70% (136 mg, 0.409 mmol) as a pale yellow oil.  $[\alpha]_D^{24} = -67.82$  ( $c = 0.55$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 0.84 (9H, s,  $(\text{CH}_3)_3$ ), 1.52 (1H, dddd,  $J = 14.0, 11.9, 9.4, 4.8$ ,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 1.75 (1H, dddd,  $J = 14.1, 11.0, 4.0, 2.4$ ,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.64 (1H, ddd,  $J = 13.4, 11.9, 4.9$ ,  $\text{ArCH}_A\text{CH}_B$ ), 2.75 (1H, dd,  $J = 9.4, 2.4$ ,  $\text{CH}$ ), 2.90 (1H, ddd,  $J = 13.4, 11.0, 4.8$ ,  $\text{ArCH}_A\text{CH}_B$ ), 3.46 (3H, s,  $\text{OCH}_3$ ), 6.80 (1H, atd,  $J = 7.5, 2.1$  Hz,  $H\text{-arom}$ ), 7.19 (2H, m,  $H\text{-arom}$ ), 7.73 (1H, d,  $J = 7.8$  Hz,  $H\text{-arom}$ );  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 26.3 (C-11), 32.1 (C-7), 36.1 (C-8), 38.9 (C-10), 61.5 (C-12), 90.4 (C-9), 100.7 (C-1), 127.7 (C-5), 128.4 (C-4), 129.3 (C-3), 139.5 (C-6), 145.3 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 332 (9)  $[\text{M}]^+$ , 300 (10), 274 (53), 243 (34), 217 (100); HRMS for  $\text{C}_{14}\text{H}_{21}\text{IO}$ : calcd. 332.0637, found 332.0622  $[\text{M}]^+$ ; IR (Neat): 2996, 2888, 1469, 1436, 1373, 1170, 1139, 1008  $\text{cm}^{-1}$ . An authentic sample of racemic **115**, ( $\pm$ )-1-iodo-2-(3-methoxy-4,4-dimethylpentyl)benzene, was prepared from **112** as described previously:

HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 95:5, 0.5 ml/min, 20 °C,  $t_R = 7.8$  min (–)-enantiomer,  $t_S = 9.5$  min (+)-enantiomer. Enantiomer 1 ( $R_f = 7.8$  min). The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

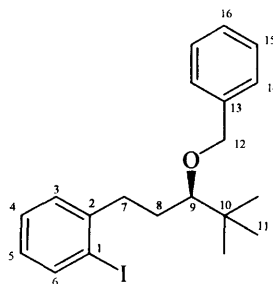
**(R)-1-(3-Ethoxy-4,4-dimethylpentyl)-2-iodobenzene – 116**



Synthesised according to GP5 with sodium hydride (45 mg, 1.895 mmol) suspended in DMF (5 ml) stirred with (*R*)-1-(2-iodophenyl)-4,4-dimethylpentan-3-ol **113** (201 mg, 0.632 mmol) and ethyl iodide (99 mg, 0.632 mmol). The product was purified by column chromatography hexane/ethyl acetate (4:1). Yield 69% (151 mg, 0.436 mmol) as a pale yellow oil.  $[\alpha]_D^{27} = -71.02$  ( $c = 1.09$ ,  $\text{CHCl}_3$ ):  $^1\text{H NMR}$ , ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.14 (9H, s,  $(\text{CH}_3)_3$ ), 1.18 (3H, t,  $J = 6.9$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.42 (1H, dddd,  $J = 13.9, 10.6, 10.4, 4.9$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 1.78 (1H, dddd,  $J = 13.9, 10.8, 6.0, 1.7$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.65 (1H, ddd,  $J = 13.6, 10.4, 6.0$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.94 (1H, ddd,  $J = 13.6, 10.8, 4.9$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.20 (1H, dd,  $J = 10.6, 1.7$  Hz,  $\text{CH}$ ), 3.54 (2H, q,  $J = 6.9$  Hz,  $\text{CH}_2\text{CH}_3$ ), 6.89 (1H, ddd,  $J = 8.2, 6.5, 2.6$  Hz,  $H\text{-arom}$ ), 7.17–7.23 (2H, m,  $H\text{-arom}$ ), 7.72 (1H, d,  $J = 8.2$  Hz,  $H\text{-arom}$ );  $^{13}\text{C NMR}$ , ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 25.7 (C-13), 26.4 (C-11), 32.1 (C-7), 35.1 (C-8), 38.4 (C-10), 66.3, (C-12), 79.5 (C-9), 100.6 (C-1), 127.7 (C-5), 128.4 (C-4), 129.6 (C-3), 129.5 (C-6), 145.1 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 346 (17)  $[\text{M}]^+$ , 332 (12), 300 (20), 274 (76), 243 (21), 217 (100); HRMS for  $\text{C}_{14}\text{H}_{21}\text{IO}$ : calcd. 346.0794, found 346.0790  $[\text{M}]^+$ ; IR (Neat): 3002, 2850, 2819, 1475, 1426, 1366, 1170, 1140, 1001  $\text{cm}^{-1}$ . An authentic sample of racemic **116**, ( $\pm$ )-1-iodo-2-(3-ethoxy-4,4-dimethylpentyl)benzene, was prepared from **112** as described previously: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 95:5, 0.5 ml/min, 20 °C,  $t_R = 13.6$  min (–)-enantiomer,  $t_S =$

26.6 min (+)-enantiomer. Enantiomer 1 ( $R_f = 13.6$  min). The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

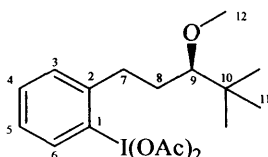
**(*R*)-1-((1-(2-Iodophenyl)-4-methylpentan-3-yloxy)methyl)benzene - 117**



Synthesised according to GP5 with sodium hydride (50 mg, 2.065 mmol) suspended in DMF (5 ml) stirred with (*R*)-1-(2-iodophenyl)-4,4-dimethylpentan-3-ol **114** (219 mg, 0.688 mmol) and benzyl bromide (118 mg, 0.688 mmol). The product was purified by column chromatography hexane/ethyl acetate (4:1). Yield 69% (129 mg, 0.317 mmol) as a pale yellow oil.  $[\alpha]_D^{26} = -73.99$  ( $c = 1.00$ ,  $\text{CHCl}_3$ ):  $^1\text{H NMR}$ , ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 0.90 (9H, s,  $(\text{CH}_3)_3$ ), 1.62 (1H, dddd,  $J = 14.1, 11.7, 9.0, 5.2$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 1.80 (1H, dddd,  $J = 14.1, 11.9, 4.8, 2.7$  Hz,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 2.63 (1H, ddd,  $J = 13.4, 11.7, 4.8$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 2.90 (1H, ddd,  $J = 13.4, 11.9, 5.2$  Hz,  $\text{ArCH}_A\text{CH}_B$ ), 3.05 (1H, dd,  $J = 9.0, 2.7$  Hz, CH), 4.39 (2H, s,  $\text{OCH}_2$ ), 6.78 (1H, ddd,  $J = 7.6, 7.5, 1.7$  Hz,  $H\text{-arom}$ ), 7.11 (2H, dd,  $J = 7.7, 1.6$  Hz,  $H\text{-arom}$ ), 7.16–7.20 (2H, m,  $H\text{-arom}$ ), 7.27–7.34 (2H, m,  $H\text{-arom}$ ), 7.72 (1H, dd,  $J = 7.9, 0.8$  Hz,  $H\text{-arom}$ );  $^{13}\text{C NMR}$ , ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 26.6(C-11), 32.2 (C-7), 36.4 (C-8), 39.0 (C-10), 75.1 (C-12), 88.3 (C-9), 100.7 (C-2), 127.4 (C-5), 127.6 (C-Ar), 128.3 (C-Ar), 128.4 C-3), 129.3 (C-3), 139.3 (C-Ar), 139.5 (C-6), 145.3 (C-1); MS ( $\text{ES}^+$ ):  $m/z$  (%) = 426 (43)  $[\text{M}+\text{NH}_4]^+$ , 300 (34), 208 (100), 106 (48), 91, (13); HRMS for  $\text{C}_{10}\text{H}_{17}\text{INO}$ : calcd. 426.1288, found 426.1288  $[\text{M}+\text{NH}_4]^+$ . An authentic sample of racemic **117**, ( $\pm$ )-1-((1-(2-Iodophenyl)-4-methylpentan-3-yloxy)methyl)benzene, was prepared from **112** as described previously: HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 95:5, 0.5 ml/min, 20 °C,  $t_{\text{R}} = 15.9$  min (–)-enantiomer,  $t_{\text{S}} = 23.1$  min

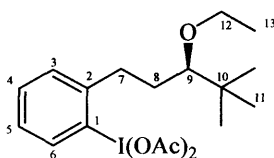
(+)-enantiomer. Enantiomer 1 ( $R_f = 15.9$  min). The racemic ether gave baseline separation and a 1:1 ratio of integrated areas.

**(R)-1-(Diacetoxy)iodo-2-(3-methoxy-4,4-dimethylpentyl)benzene – 118**



Synthesised according to GP11 with sodium perborate tetrahydrate (484 mg, 3.103 mmol) added portion wise to a solution of (*R*)-1-iodo-2-(3-methoxy-4,4-dimethylpentyl)benzene **115** (100 mg, 0.310 mmol) in glacial acetic acid (5 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 6% (8 mg, 0.018 mmol) as a white powder.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.20 (9H, s,  $(\text{CH}_3)_3$ ), 1.88–2.00 (2H, m,  $\text{ArCH}_2\text{CH}_2$ ), 2.07 (6H, s,  $(\text{OCOCH}_3)_2$ ), 2.77–2.84 (1H, m,  $\text{ArCH}_A\text{CH}_B$ ), 2.95–3.02 (1H, m,  $\text{ArCH}_A\text{CH}_B$ ), 3.46 (3H, s,  $\text{OCH}_3$ ), 3.66 (1H, dd,  $J = 8.6, 2.8$ ,  $\text{CH}$ ), 7.33 (1H, d,  $J = 7.4$  Hz,  $H\text{-arom}$ ), 7.42 (1H, d  $J = 7.4$ ,  $H\text{-arom}$ ), 7.63 (1H, d,  $J = 7.8$  Hz,  $H\text{-arom}$ ), 8.03 (1H, d,  $J = 7.8$  Hz,  $H\text{-arom}$ ). No  $^{13}\text{C}$  obtained, insufficient quantity synthesised.

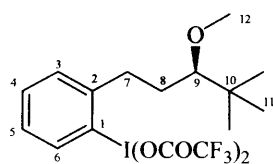
**(R)-1-(3-Ethoxy-4,4-dimethylpentyl)-2-(diacetoxyiodo)benzene – 119**



Synthesised according to GP12 with peracetic acid (1.12 ml of a 30% solution in acetic acid) added to a stirred solution of (*R*)-1-(3-ethoxy-4,4-dimethylpentyl)-2-iodobenzene **116** (97 mg, 0.280 mmol) in acetic acid (10 ml). Product was isolated by recrystallisation from acetic acid/pentane. Yield 5% (7 mg, 0.014 mmol) as a white powder.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.20 (3H, t,  $J = 6.9$

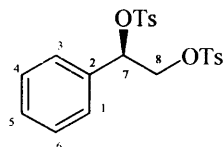
Hz,  $\text{CH}_2\text{CH}_3$ ), 1.24 (9H, s,  $(\text{CH}_3)_3$ ), 1.51–1.61 (2H, m,  $\text{ArCH}_2\text{CH}_2$ ), 2.02 (6H, s,  $(\text{OCOCH}_3)_2$ ), 2.77–2.84 (1H, m,  $\text{ArCH}_2$ ), 2.98–3.05 (1H, m,  $\text{ArCH}_2$ ), 3.58 (2H, q,  $J = 6.9$  Hz,  $\text{CH}_2\text{CH}_3$ ), 3.74 (1H, d,  $J = 10.6$  Hz,  $\text{CH}$ ), 7.35 (1H, d,  $J = 7.5$  Hz,  $H$ -arom), 7.62 (2H, m,  $H$ -arom), 8.07 (1H, d,  $J = 7.8$  Hz,  $H$ -arom). No  $^{13}\text{C}$  obtained, insufficient quantity synthesised.

**(*R*)-1-[Bis(trifluoroacetoxy)iodo]-2-(3-methoxy-4,4-dimethylpentyl)benzene - 120**



Synthesised according to GP15 with (*R*)-1-iodo-2-(3-methoxy-4,4-dimethylpentyl)benzene **115** (110 mg, 0.341 mmol) in DCM (2 ml) added to a previously prepared solution of trifluoroacetic anhydride (358 mg, 1.705 mmol) and urea hydrogen peroxide (55 mg, 0.580 mmol) in DCM (5 ml). Yield 2% (4 mg, 0.014 mmol) of a white powder.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 400 MHz)  $\delta_{\text{H}}$ : 1.70 (9H, s,  $(\text{CH}_3)_3$ ), 2.87–2.95 (1H, m,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 3.02–3.09 (1H, m,  $\text{ArCH}_2\text{CH}_A\text{CH}_B$ ), 3.11–3.21 (2H, m,  $\text{ArCH}_2$ ), 3.18 (3H, s,  $\text{OCH}_3$ ), 4.10–4.13 (1H, m,  $\text{CH}$ ), 7.24 (1H, d,  $J = 7.7$  Hz,  $H$ -arom), 7.44 (1H, d,  $J = 6.9$  Hz,  $H$ -arom), 7.57 (1H, d,  $J = 6.9$  Hz,  $H$ -arom) 8.22 (1H, d,  $J = 7.7$  Hz,  $H$ -arom); No  $^{13}\text{C}$  obtained, insufficient quantity synthesised.

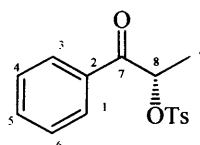
**(*R*)-1,2-Bis(tosyloxy)phenylethane<sup>14</sup> - 125**



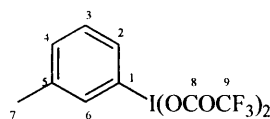
Synthesised according to GP20 with styrene added to a stirred mixture of the (*S*)-1-(1-ethoxy-3-(2-(diacetoxyiodo)phenyl)propyl)benzene **107** (165 mg, 0.34

mmol) and *p*TsOH•H<sub>2</sub>O (129 mg, 0.68 mmol) in DCM (5 ml) at 25°C. The product was purified by column chromatography using hexane/ethyl acetate (1:1). Yield 75%, 10% *ee* (116 mg, 0.259 mmol) as a white powder. Spectroscopic data agrees with literature. HPLC conditions: Chiracel OD-H column, hexane/2-propanol, 90:10, 0.5 ml/min, 254 nm, 20 °C, *t*<sub>R</sub> = 14.2 min (*R*), *t*<sub>S</sub> = 17.0 min (*S*). <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 500 MHz) δ<sub>H</sub>: 2.42 (3H, s, CH<sub>3</sub>), 2.48 (3H, s, CH<sub>3</sub>), 4.05 (1H, dd, *J* = 11.2, 4.2 Hz, CH<sub>A</sub>CH<sub>B</sub>), 4.13 (1H, dd, *J* = 11.2, 7.8 Hz, CH<sub>A</sub>CH<sub>B</sub>), 5.49 (1H, dd, *J* = 7.8, 4.2 Hz, CH), 7.15–7.26 (7H, m, *H*-arom), 7.62–7.67 (4H, m, *H*-arom).

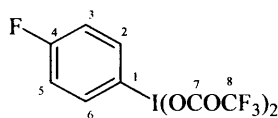
### (*S*)-1-Phenyl-oxo-2-tosyloxypropane<sup>15</sup> - 126



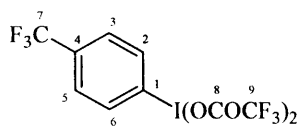
Synthesised according to GP21 with propiophenone (67 mg, 0.5 mmol) added to a stirred mixture of (*S*)-1-iodo-2-(2-methoxypropyl)benzene **58** (14 mg, 0.05 mmol), *p*TsOH•H<sub>2</sub>O (285 mg, 1.5 mmol), *m*CPBA (366 mg, 1.5 mmol) in acetonitrile (3 ml). The product was purified by column chromatography using hexane/ethyl acetate (4:1). Yield 76%, 3% *ee* (116 mg, 0.379 mmol) as a white powder. Spectroscopic data agrees with literature. HPLC conditions: Chiracel OB-H column, hexane/2-propanol, 40:60, 0.5 ml/min, 40 °C, *t*<sub>R</sub> = 18.1 min, *t*<sub>S</sub> = 21.6 min. <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 400 MHz) δ<sub>H</sub>: 1.51 (3H, d, *J* = 7.0 Hz, CH<sub>3</sub>), 2.31 (3H, s, arom-CH<sub>3</sub>), 5.72 (1H, q, *J* = 7.0 Hz, CH), 7.04 (2H, dd, *J* = 7.8, 1.8 Hz, *H*-arom), 7.19 (2H, d, *J* = 7.7 Hz, *H*-arom), 7.48 (1H, atd, *J* = 7.4, 1.8 Hz, *H*-arom), 7.68 (2H, d, *J* = 7.7 Hz, *H*-arom), 7.81 (2H, dd, *J* = 7.8, 7.4, Hz, *H*-arom).

**1-[Bis(trifluoroacetoxy)iodo]-3-methylbenzene**<sup>16</sup> - 177

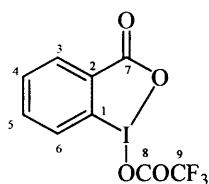
Synthesised according to GP14 with 3-iodotoluene **166** (200 mg, 0.917 mmol) in DCM (2 ml) added to a previously prepared solution of trifluoroperacetic acid (918 mg, 9.17 mmol) in DCM (5 ml). Product was isolated by washing with pentane. Yield 65% (265 mg, 0.596 mmol) of a white powder. mp = 96–97°C. Spectroscopic data agrees with literature. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ<sub>H</sub>: 2.39 (3H, s, CH<sub>3</sub>), 7.41 (1H, t, *J* = 7.8 Hz, *H*-arom), 7.47 (1H, d, *J* = 7.8 Hz, *H*-arom), 7.62 (1H, d, *J* = 7.6 Hz, *H*-arom), 7.94 (1H, s, *H*-arom).

**1-[Bis(trifluoroacetoxy)iodo]-4-(fluoro)benzene**<sup>6</sup> - 179

Synthesised according to GP14 with 4-fluoro-1-iodobenzene (201 mg, 0.917 mmol), added to a previously prepared solution of trifluoroperacetic acid (918 mg, 9.17 mmol) in DCM (5 ml). Product was isolated by washing with pentane. Yield 90% (368 mg, 0.822 mmol) of colourless crystals. mp = 94–96°C. Spectroscopic data agrees with literature. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ<sub>H</sub>: 7.23 (2H, dd, *J* = 8.9, 5.1 Hz, *H*-arom), 8.16 (2H, dd, *J* = 8.9, 5.1 Hz, *H*-arom); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.7 MHz) δ<sub>C</sub>: 112.8 (q, *J*<sub>CF</sub> = 286 Hz, COCF<sub>3</sub>), 116.4 (C-1), 119.8 (d, *J*<sub>CF</sub> = 23 Hz, C-3 & 5), 138.3 (d, *J*<sub>CF</sub> = 9 Hz, C-2 & 6), 161.2 (q, *J*<sub>CF</sub> = 41 Hz, COCF<sub>3</sub>), 165.3 (q, *J*<sub>CF</sub> = 259 Hz, COCF<sub>3</sub>).

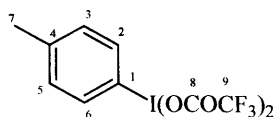
**1-[Bis(trifluoroacetoxy)iodo]-4-(trifluoromethyl)benzene<sup>17</sup> – 180**

Synthesised according to GP14 with 4-trifluoromethyl-1-iodobenzene (249 mg, 0.917 mmol), added to a previously prepared solution of trifluoroacetic acid (918 mg, 9.17 mmol) in DCM (5 ml). Product was isolated by washing with pentane. Yield 81% (369 mg, 0.714 mmol) of colourless crystals. mp = 62°C. Spectroscopic data agrees with literature. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ<sub>H</sub>: 7.74 (2H, d, *J* = 8.3 Hz, *H*-arom), 8.26 (2H, d, *J* = 8.3 Hz, *H*-arom).

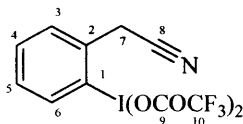
**1-Trifluoroacetoxy-1,2-benziodoxol-3(1H)-one<sup>18</sup> - 181**

Synthesised according to GP15 with 2-iodobenzoic acid (223 mg, 0.917 mmol) in DCM (2 ml) added to a previously prepared solution of trifluoroacetic anhydride (1.926 g, 9.17 mmol) and urea hydrogen peroxide (216 mg, 2.29 mmol) in DCM (5 ml). Product was isolated by washing with pentane. Yield 26% (112 mg, 0.239 mmol) of a white powder. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ<sub>H</sub>: 7.74 (1H, atd, *J* = 7.4, 1.5 Hz, *H*-arom), 7.90 (1H, d, *J* = 8.3 Hz, *H*-arom), 7.90–8.10 (1H, m, *H*-arom), 8.23 (1H, dd, *J* = 7.9, 1.5 Hz, *H*-arom).

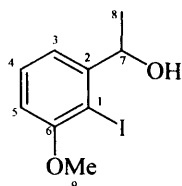


**1-[Bis(trifluoroacetoxy)iodo]-4-(methyl)benzene<sup>16</sup> - 182**

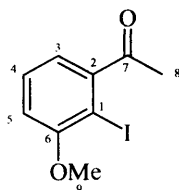
Synthesised according to GP15 with 4-iodotoluene **166** (140 mg, 0.642 mmol) in DCM (2 ml) added to a previously prepared solution of trifluoroacetic anhydride (672 mg, 3.195 mmol) and urea hydrogen peroxide (100 mg, 1.067 mmol) in DCM (2 ml). Product was isolated by washing with pentane. Yield 91% (259 mg, 0.584 mmol) of a white powder. mp = 114–115°C. Spectroscopic data agrees with literature. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ<sub>H</sub>: 2.43 (3H, s, CH<sub>3</sub>), 7.32 (2H, d, *J* = 8.5 Hz, *H*-arom), 8.01 (2H, d, *J* = 8.5 Hz, *H*-arom);

**2-[Bis(trifluoroacetoxy)iodo]acetonitrile – 183**

Synthesised according to GP15 with 2-iodoacetonitrile **191** (223 mg, 0.917 mmol) in DCM (2 ml) added to a previously prepared solution of trifluoroacetic anhydride (1.926 g, 9.17 mmol) and urea hydrogen peroxide (216 mg, 2.29 mmol) in DCM (5 ml). Product was isolated by washing with pentane. Yield 26% (112 mg, 0.239 mmol) of a white powder. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ<sub>H</sub>: 4.30 (2H, s, CH<sub>2</sub>), 7.57 (1H, dd, *J* = 7.8, 1.3 Hz, *H*-arom), 7.87 (1H, atd, *J* = 7.7, 1.1 Hz, *H*-arom), 7.99 (1H, dd, *J* = 7.7, 1.3 Hz, *H*-arom), 8.40 (1H, d, *J* = 7.8, 1.1 Hz, *H*-arom); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125.7 MHz) δ<sub>C</sub>: 27.5 (C-7), 112.6 (q, *J*<sub>CF</sub> = 289 Hz, CF<sub>3</sub>), 115.2 (C-8), 126.2 (C-1), 130.7 (C-5), 131.9 (C-4), 134.0 (C-3), 135.4 (C-6), 138.2 (C-2), 161.3 (q, *J*<sub>CF</sub> = 41 Hz, COCF<sub>3</sub>). No IR obtained.

**(±)-1-(2-iodo-3-methoxyphenyl)ethanol<sup>19</sup> - 187**

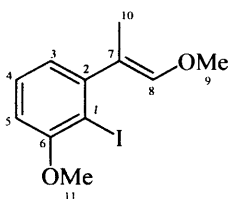
Synthesised according to GP23 with 1-(3-methoxyphenyl)ethanol (9.034 g, 59.36 mmol), stirred in hexane/diethyl ether (3:1, 200 ml), *n*BuLi (7.60 g, 118.72 mmol of a 2.5 M solution in hexanes) and iodine (7.71 g, 59.36 mmol) in diethyl ether (50 ml). The product was columned using pentane/ethyl acetate (10:1). Yield 24% (3.96 g, 14.25 mmol) as a crystalline solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ<sub>H</sub>: 1.46 (3H, d, *J* = 6.4 Hz, CH(OH)CH<sub>3</sub>), 2.00 (1H, br s, OH), 3.89 (3H, s, OCH<sub>3</sub>), 5.19 (1H, qd, *J* = 6.2, 2.2 Hz, CH), 6.77 (1H, dd, *J* = 8.0, 1.4 Hz, *H*-arom), 7.19 (1H, dd, *J* = 7.8, 1.4 Hz, *H*-arom), 7.32 (1H, dd, *J* = 8.0, 7.8 Hz, *H*-arom); <sup>13</sup>C NMR, (CDCl<sub>3</sub>, 125.7 MHz) δ<sub>C</sub>: 23.5 (C-8), 56.5 (C-9), 73.7 (C-7), 89.6 (C-1), 109.7 (C-5), 118.6 (C-4), 129.4 (C-3), 149.6 (C-2), 157.8 (C-6); MS (EI<sup>+</sup>): *m/z* (%) = 278 (100) [M]<sup>+</sup>, 263 (93), 218 (5), 135 (37), 107 (12), 92 (19); HRMS for C<sub>9</sub>H<sub>11</sub>IO: calcd. 277.9814, found 277.9804 [M]<sup>+</sup>; IR (Neat): ν<sub>max</sub> = 3604, 2867, 1567, 1466, 1427, 1059 cm<sup>-1</sup>.

**2-Iodo-3-methoxy acetophenone – 188<sup>20</sup>**

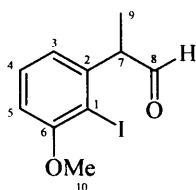
Synthesised according to GP1 with (±)-1-(2-iodo-3-methoxyphenyl)ethanol **187** (5.72 g, 20.58 mmol) in dichloromethane (20 ml) stirred with pyridinium chlorochromate (6.65 g, 30.87 mmol) in dichloromethane (50 ml) at 0 °C. The product was columned using hexane/diethyl ether (10:1). Yield 96% (5.45 g, 19.75 mmol), as a pale yellow solid. Spectroscopic data consistent with literature

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 2.53 (3H, s,  $\text{COCH}_3$ ), 3.84 (3H, s,  $\text{OCH}_3$ ), 6.80 (1H, d,  $J = 8.2$  Hz,  $H$ -arom), 6.84 (1H, d,  $J = 7.5$  Hz,  $H$ -arom), 7.28 (1H, atd,  $J = 8.2, 7.5$  Hz,  $H$ -arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 30.3 (C-8), 56.7 (C-9), 83.0 (C-1), 112.0 (C-5), 119.4 (C-4), 129.7 (C-3), 147.9 (C-2), 158.3 (C-6), 203.5 (C-7).

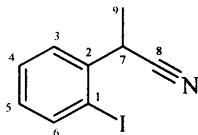
### 1-(2-Iodophenyl)-1-methyl-2-methoxyethene – 189



Synthesised according to GP2 with (methoxymethyl)triphenylphosphonium chloride (7.141 g, 20.83 mmol) in dry THF (10 ml), 2-iodo-3-methoxyacetophenone **188** (5.476 g, 19.85 mmol) stirred in the presence of  $n\text{BuLi}$  (13.3 ml, 33.33 mmol of a 2.5 M solution in hexanes) and diisopropylamine (3.373 ml, 33.33 mmol) in dry THF (5 ml). The product was purified by column chromatography using petroleum ether/diethyl ether (15:1) to yield the desired product. Yield 84% (5.067 g, 16.66 mmol) as a pale yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.71 (3H, s,  $\text{ArCCH}_3$ ), 3.51 (3H, s,  $\text{OCH}_3$ ), 3.66 (3H, s,  $\text{ArOCH}_3$ ), 6.21 (1H, s,  $\text{CHOMe}$ ), 6.89 (1H, d,  $J = 7.0$  Hz,  $H$ -arom), 7.05 (1H, d,  $J = 6.6$  Hz,  $H$ -arom), 7.13 (1H, dd,  $J = 7.0, 6.6$  Hz,  $H$ -arom). No  $^{13}\text{C}$  obtained.

**(±)-2-(2-iodo-3-methoxyphenyl)propanal – 190**

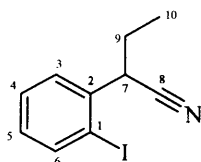
Synthesised according to GP3 with 1-(2-iodophenyl)-1-methyl-2-methoxyethene **189** (5.30 g, 17.73 mmol) stirred in formic acid (16 ml, 348.6 mmol) in DCM (50 ml). Yield 71% (3.59 g, 12.37 mmol), as a pale yellow oil. The product was purified by column chromatography using petroleum ether/diethyl ether (15:1) to yield the desired product.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.41 (3H, d,  $J = 7.3$  Hz,  $\text{CH}_3$ ), 3.66 (1H, q,  $J = 7.3$  Hz,  $\text{CHCH}_3$ ), 3.62 (1H, s,  $\text{OCH}_3$ ), 6.89 (1H, atd,  $J = 7.0, 1.8$  Hz,  $H\text{-arom}$ ), 7.25 (1H, atd,  $J = 7.4, 1.8$  Hz,  $H\text{-arom}$ ), 7.59 (1H, dd,  $J = 7.4, 7.0$  Hz,  $H\text{-arom}$ ), 9.89 (1H, s,  $\text{CHO}$ );  $^{13}\text{C NMR}$ , ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 12.7 (C-9), 48.9 (C-7), 56.0 (C-10), 95.1 (C-1), 118.4 (C-5), 125.8 (C-3), 129.2 (C-4), 143.8 (C-2), 165.3 (C-6), 199.9 (C-8). MS ( $\text{EI}^+$ ):  $m/z$  (%) = 291 (65)  $[\text{M}]^+$ , 260 (30), 230 (21), 217 (100), 104 (33); HRMS for  $\text{C}_{10}\text{H}_{11}\text{IO}_2$ : calcd. 289.9804, found 289.9802  $[\text{M}]^+$ ; IR (Neat):  $\nu_{\text{max}} = 3045, 2939, 2867, 1727, 1577, 1464, 1430, 1011$   $\text{cm}^{-1}$ .

**(±)-2-(2-iodophenyl)propanenitrile – 192**

Synthesised according to GP24 with a solution of (2-iodophenyl) acetonitrile **191** (1.5 g, 6.17 mmol) in dry THF (2 ml) was added to a previously prepared solution of  $n\text{BuLi}$  (2.47 ml, 6.17 mmol of a 2.5 M solution in hexanes) and diisopropylamine (0.87 ml, 6.17 mmol) in dry THF (3 ml). Methyl iodide (920 mg, 6.48 mmol) was added to yield the crude product. The product was purified by column chromatography using hexanes/ethyl acetate (9:1). Yield 87% (1.38 g,

5.37 mmol) as a colourless oil.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.49 (3H, d,  $J = 7.2$  Hz,  $\text{CH}_3$ ), 4.13 (1H, q,  $J = 7.1$  Hz, ArCH), 6.92 (1H, atd,  $J = 7.7, 1.0$  Hz,  $H$ -arom), 7.35 (1H, atd,  $J = 8.0, 1.3$  Hz,  $H$ -arom), 7.50 (1H, d,  $J = 7.7$  Hz,  $H$ -arom), 7.74 (1H, d,  $J = 8.0$  Hz,  $H$ -arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 20.6 (C-9), 36.3 (C-7), 98.4 (C-1), 121.2 (C-8), 127.4 (C-4), 127.7 (C-5), 129.9 (C-3), 139.9 (C-6), 140.1 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 257 (100)  $[\text{M}]^+$ , 242 (43), 229 (5), 130 (39), 84 (35); HRMS for  $\text{C}_9\text{H}_8\text{IN}$ : calcd. 256.9702, found 256.9706  $[\text{M}]^+$ ; IR (Neat):  $\nu_{\text{max}} = 3075, 3025, 2991, 2939, 2867, 2242, 1590, 1473, 1399, 1072, 1025, 990 \text{ cm}^{-1}$ .

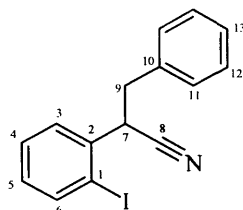
### (±)-2-(2-iodophenyl)butanenitrile – 193



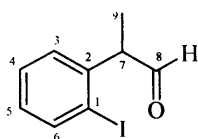
Synthesised according to GP24 with a solution of (2-iodophenyl) acetonitrile **191** (1.5 g, 6.17 mmol) in dry THF (2 ml) was added to a previously prepared solution of  $n\text{BuLi}$  (2.47 ml of a 2.5 M solution in hexanes, 6.17 mmol,) and diisopropylamine (0.87 ml, 6.17 mmol) in dry THF (3 ml). Ethyl iodide (0.518 ml, 6.48 mmol) was added to yield the crude product. The product was purified by column chromatography using hexanes/ethyl acetate (8:1). Yield 87% (1.29 g, 4.75 mmol) of a colourless oil.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.04 (3H, dt,  $J = 7.4, 7.2$  Hz,  $\text{CH}_3$ ), 1.71 (1H, ddq,  $J = 14.8, 8.8, 7.2$  Hz,  $\text{CH}_\text{A}\text{CH}_\text{B}\text{CH}_3$ ), 1.83 (1H, dqd,  $J = 14.8, 7.4, 5.2$  Hz,  $\text{CH}_\text{A}\text{CH}_\text{B}\text{CH}_3$ ), 4.04 (1H, dd,  $J = 8.8, 5.2$ , ArCH), 6.95 (1H, atd,  $J = 7.7, 1.5$  Hz,  $H$ -arom), 7.33 (1H, atd,  $J = 7.6, 1.1$  Hz,  $H$ -arom), 7.49 (1H, dd,  $J = 8.0, 1.5$  Hz,  $H$ -arom) 7.78 (1H, d,  $J = 8.0, 1.1$  Hz,  $H$ -arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 11.7 (C-10), 28.2 (C-9), 43.4 (C-7), 99.2 (C-1), 121.5 (C-8), 128.4 (C-4), 129.5 (C-5), 130.5 (C-3), 139.8 (C-6), 140.3 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 271 (100)  $[\text{M}]^+$ , 242 (58), 217 (17), 144 (4), 117 (21), 115 (50), 89 (26); HRMS for  $\text{C}_{10}\text{H}_{10}\text{IN}$ : calcd. 270.9858, found 270.9860  $[\text{M}]^+$ ; IR (Neat):

$\nu_{\max} = 3071, 3030, 2987, 2920, 2870, 2237, 1599, 1480, 1410, 1090, 1022, 994$   
 $\text{cm}^{-1}$ .

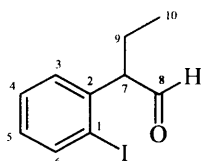
**(±)-2-(2-iodophenyl)-3-phenylpropanenitrile –194**



Synthesised according to GP24 with a solution of (2-iodophenyl) acetonitrile **191** (1.5 g, 6.17 mmol) in dry THF (2 ml) was added to a previously prepared solution of *n*BuLi (2.47 ml, 6.17 mmol of a 2.5 M solution in hexanes) and diisopropylamine (0.87 ml, 6.17 mmol) in dry THF (3 ml). Benzyl chloride (0.746 ml, 6.48 mmol) was added to yield the crude product. The product was purified by column chromatography using hexanes/ethyl acetate (10:1). Yield 84% (1.73 g, 5.18 mmol) as a colourless oil.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 2.89 (1H, dd,  $J = 13.6, 9.9$  Hz,  $\text{CH}_A\text{CH}_B\text{Ar}$ ), 3.13 (1H, dd,  $J = 13.6, 4.6$  Hz,  $\text{CH}_A\text{CH}_B\text{Ar}$ ), 4.43 (1H, dd,  $J = 9.9, 4.6$  Hz, ArCH), 6.87 (1H, atd,  $J = 7.7, 1.5$  Hz, *H*-arom), 7.14–7.16 (6H, m, *H*-arom), 7.37 (1H, dd,  $J = 8.0, 1.5$  Hz, *H*-arom), 7.72 (1H, dd,  $J = 8.0, 1.0$  Hz, *H*-arom);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 40.8 (C-7), 44.7 (C-9), 99.1 (C-1), 120.1 (C-8), 127.7 (C-13), 128.7 (C-4), 128.8 (12), 129.2 (C-5), 129.4 (C-11), 130.2 (C-3), 136.1 (C-10), 138.0 (C-6), 140.2 (C-2); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 333 (27)  $[\text{M}]^+$ , 270 (38), 256 (44), 242 (100), 217 (55), 117 (9); HRMS for  $\text{C}_{15}\text{H}_{12}\text{IN}$ : calcd. 333.1669, found 333.1670  $[\text{M}]^+$ ; IR (Neat):  $\nu_{\max} = 3046, 3029, 2977, 2894, 2865, 2244, 1584, 1481, 1418, 1077, 1019, 990$   $\text{cm}^{-1}$ .

**(±)-2-(2-iodophenyl)propanal – 195**

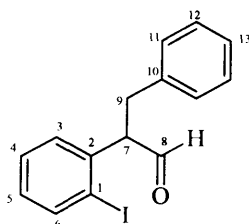
Synthesised according to GP25 with DIBAL (1.29 ml, 7.78 mmol of a 1M solution in toluene) was added to a stirred solution of 2-(2-iodophenyl)propanenitrile **192** (1.00 g, 3.89 mmol) in dry toluene (10 ml). The product was purified by column chromatography using petroleum ether/diethyl ether (12:1). Yield 20% (202 mg, 0.777 mmol) as a colourless oil.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 1.33 (3H, d,  $J = 7.0$  Hz,  $\text{CH}_3$ ), 4.02 (1H, q,  $J = 7.0$  Hz, ArCH), 6.92 (1H, atd,  $J = 7.7$ , 1.6 Hz,  $H$ -arom), 6.94 (1H, dd,  $J = 7.9$ , 1.6 Hz,  $H$ -arom), 7.30 (1H, dd,  $J = 7.7$ , 1.2 Hz,  $H$ -arom), 7.85 (1H, d,  $J = 7.9$ , 1.2  $H$ -arom), 9.66 (1H, s, CHO);  $^{13}\text{C}$  NMR, ( $\text{CDCl}_3$ , 125.7 MHz)  $\delta_{\text{C}}$ : 14.5 (C-9), 29.9 (C-7), 99.4 (C-1), 127.7 (C-4) 129.4 (C-5), 129.8 (C-3), 139.9 (C-6), 140.1 (C-2), 200.3 C-8); MS ( $\text{EI}^+$ ):  $m/z$  (%) = 260 (8)  $[\text{M}]^+$ , 257 (45), 231 (100), 217 (7), 133 (5), 104 (32); HRMS for  $\text{C}_9\text{H}_9\text{IO}$ : calcd. 259.9698, found 259.9702  $[\text{M}]^+$ ; IR (Neat):  $\nu_{\text{max}} = 3061, 2990, 2953, 2836, 1725, 1580, 1469, 1422, 1149, 1061, 1009 \text{ cm}^{-1}$ .

**(±)-2-(2-iodophenyl)butanal – 196**

Synthesised according to GP25 with DIBAL (1.22 ml, 7.36 mmol of a 1M solution in toluene) was added to a stirred solution of 2-(2-iodophenyl)butanenitrile **192** (1.00 g, 3.68 mmol) in dry toluene (10 ml). The product was purified by column chromatography using petroleum ether/diethyl ether (12:1). Yield 11% (111 mg, 0.406 mmol) as a colourless oil.  $^1\text{H}$  NMR, ( $\text{CDCl}_3$ , 500 MHz)  $\delta_{\text{H}}$ : 0.89 (3H, t,  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.70 (1H, ddq,  $J = 14.5, 8.6,$

7.3 Hz,  $CH_ACH_BCH_3$ ), 1.98 (1H, dqd,  $J = 14.5, 7.3, 5.3$  Hz,  $CH_ACH_BCH_3$ ), 3.92 (1H, dd,  $J = 8.6, 5.3$  Hz, ArCH), 6.92 (1H, atd,  $J = 7.9, 1.0$  Hz,  $H$ -arom), 6.98 (1H, dd,  $J = 7.8, 1.6$  Hz,  $H$ -arom) 7.29 (1H, atd,  $J = 7.8, 1.0$  Hz,  $H$ -arom), 7.85 (1H, dd,  $J = 7.9, 1.6$  Hz,  $H$ -arom), 9.62 (1H, s, CHO);  $^{13}C$  NMR, (CDCl<sub>3</sub>, 125MHz)  $\delta_C$ : 11.4 (C-10), 29.9 (C-9), 56.7 (C-7), 99.2 (C-1), 128.3 (C-5), 129.0 (C-4), 129.8 (C-3), 138.6 (C-6), 140.1 (C-2), 200.1 (C-8); MS (EI<sup>+</sup>):  $m/z$  (%) = 274 (49) [M]<sup>+</sup>, 257 (13), 231 (57), 217 (100), 133 (15); HRMS for C<sub>10</sub>H<sub>11</sub>IO: calcd. 274.0982, found 274.0979 [M]<sup>+</sup>; IR (Neat):  $\nu_{max} = 3055, 2999, 2970, 2848, 1724, 1567, 1480, 1428, 1152, 1070, 1002$  cm<sup>-1</sup>.

### (±)-2-(2-iodophenyl)-3-phenylpropanal – 197



Synthesised according to GP25 with DIBAL (0.994 ml, 6.00 mmol of a 1M solution in toluene) was added to a stirred solution of 2-(2-iodophenyl)-3-phenylpropanenitrile **194** (1.00 g, 3.00 mmol) in dry toluene (10 ml). The product was purified by column chromatography using petroleum ether/diethyl ether (12:1). Yield 14% (141 mg, 0.419 mmol) as a colourless oil.  $^1H$  NMR, (CDCl<sub>3</sub>, 500 MHz)  $\delta_H$ : 2.89 (1H, dd,  $J = 13.6, 9.9$  Hz,  $CH_ACH_BAr$ ), 3.13 (1H, dd,  $J = 13.6, 4.6$  Hz,  $CH_ACH_BAr$ ), 4.05 (1H, dd,  $J = 9.9, 4.6$  Hz, ArCH), 6.97 (1H, atd,  $J = 7.9, 1.6$  Hz,  $H$ -arom), 7.15–7.28 (5H, m,  $H$ -arom), 7.32 (1H, atd,  $J = 7.7, 1.2$  Hz,  $H$ -arom), 7.44 (1H, dd,  $J = 7.7, 1.6$  Hz,  $H$ -arom), 7.81 (1H, dd,  $J = 7.9, 1.2$  Hz,  $H$ -arom), 9.65 (1H, s, CHO);  $^{13}C$  NMR, (CDCl<sub>3</sub>, 125MHz)  $\delta_C$ : 40.8 (C-9), 44.5 (C-7), 98.9(C-2), 126.4 C-Ar), 127.6 (C-5), 128.0 (C-Ar), 128.7 (C-Ar), 129.5 (C-4), 130.5 (C-3), 138.0 (C-6), 139.8 (C-10), 140.1 (C-2), 199.1 (C-8); No MS obtained.



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