Design and Synthesis of Novel Chiral Iodine (III) Reagents for Enantioselective Synthesis

A Thesis Submitted to Cardiff University in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Acknowledgments

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Haifa Alharbi
Abstract

Chiral hypervalent iodine reagents have been used in a broad range of enantioselective oxidative transformations. The high utility of hypervalent iodine reagent in organic synthesis is because of their low toxicity, environmentally friendly nature, unique reactivity, and ease of availability. Although, the design of alternative chiral hypervalent iodine reagents is still highly desirable to reach the highest enantioselectivity for challenging transformations.

In this thesis, chiral iodoarenes possessing a chiral C–N bond have been designed using a simple amide formation strategy. The obtained iodoarenes are synthesised as racemates with $S_{C-N}$ and $R_{C-N}$ configurations, interesting stereochemistry is observed in the generated anilides. However, $N$-alkylated anilides with the $3^\circ$ anilide core are exhibited with acceptable reactivities in various symmetric reactions compared with the corresponding reagents with the $2^\circ$ anilide core.

A new family of hypervalent iodine compounds with axial chiral backbones possessing restricted rotation around the C$_{Ar}$–N axis has been synthesised as diastereoisomers. Different enantioselective transformations are investigated by using axial chiral iodoarenes in either stoichiometric or catalytic applications. Moreover, the stereoselective $\alpha$-oxytosylation of
Ketones are controlled by $\text{C}_{\text{Ar}}$–$\text{N}$ axial chiral iodoarenes to reach high enantioselectivities of up to 80% $\text{ee}$ and good yields of up to 96% under the developed conditions.

Finally, a novel class of chiral iodoarenes possessing a stereogenic sulfoximine is designed using the reported procedures. Introducing chirality through stereogenic sulfoximine instead of sulfoxide is because the chirality of sulfoxide moiety is lost during the facile overoxidation to sulfones under the oxidative conditions to form iodine (III) reagents. The chiral induction of sulfoximines of these designed iodoarenes is investigated in various asymmetric catalytic reactions. However, the oxidation of these chiral iodoarenes is examined, but they seemed to be difficult to oxidise to the corresponding hypervalent iodine reagents.
# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>°C</td>
<td>Degree Celsius</td>
</tr>
<tr>
<td>μL</td>
<td>Microlitre</td>
</tr>
<tr>
<td>Å</td>
<td>Angstrom</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>An</td>
<td>Anisyl</td>
</tr>
<tr>
<td>aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>BINAM</td>
<td>2,2'-Bis(diphenylphosphinoamino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-Bi-2-naphthol</td>
</tr>
<tr>
<td>C</td>
<td>Concentration</td>
</tr>
<tr>
<td>Cat.</td>
<td>Catalytic</td>
</tr>
<tr>
<td>cm</td>
<td>Centimetre</td>
</tr>
<tr>
<td>CPA</td>
<td>Chiral phosphoric acids</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphorsulphonic acid</td>
</tr>
<tr>
<td>CTAB</td>
<td>Cetyltrimethylammonium bromide</td>
</tr>
<tr>
<td>d.r.</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>DABN</td>
<td>[1,1'-Binaphthalene]-2,2'-diamine</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-Dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIC</td>
<td>N,N'-Diisopropylcarbodiimide</td>
</tr>
<tr>
<td>DMDO</td>
<td>Dimethyldioxirane</td>
</tr>
</tbody>
</table>
DMF  
* N, N-Dimethylformamide

DMP  
* Dess-Martin periodinane

DMSO  
* Dimethylsulfoxide

EDC  
1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

* ee  
Enantiomeric excess

* eq.  
Equivalent

Et  
* Ethyl

g  
* Gram

GP  
* General procedure

* h  
Hour

HFIP  
1,1,1,3,3,3-Hexafluoro-2-propanol

HOMO  
* Highest occupied molecular orbital

HPLC  
* High pressure liquid chromatography

HR  
* Hofmann-type rearrangement

HRMS  
* High resolution mass spectroscopy

HTIBs  
Hydroxy(tosyloxy)iodoarenes

Hz  
* Hertz

IBS  
Iodoxybenzenesulphonic acid

IBX  
2-Iodoxybenzoic acid

IOB  
Iodosobenzene

*i-Pr  
Iso-Propyl

IR  
* Infrared

* J  
Coupling constant

L  
* Ligand

LDA  
Lithium diisopropylamide
LUMO

Lowest unoccupied molecular orbital

M

Molarity [mol/l]

m.p.

Melting point

m/z

Mass over charge ratio

\textit{m-CPBA}

\textit{m-Chloroperbenzoic acid}

Me

Methyl

Mes

Mesityl

mL

Millilitre

mmol

Millimole

mol\% 

Mole percentage

NBS

N-Bromosuccinimide

NIS

\(N\)-Iodosuccinimide

nm

Nanometre

NMR

Nuclear magnetic resonance

NOBIN

2-Amino-2'-hydroxy-1,1'-binaphthyl

Ns

Nosyl

Nu

Nucleophile

PIDA

(Diacetoxyiodo)benzene

PIFA

[Bis(trifluoroacetxoy)iodo]benzene

Py

Pyridine

rt

Room temperature

sat.

Saturated

SET

Single-electron transfer

SPINOL

\textit{1,1’-Spirobiindan-7,7’-diol}

t-Bu

Tert-butyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>TEA</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-Tetramethylpiperidine 1-oxyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TFE</td>
<td>2,2,2-Trifluoroethanol</td>
</tr>
<tr>
<td>TfOH</td>
<td>Trifluoromethanesulfonic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMSOTf</td>
<td>Trimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Ts</td>
<td>p-Toluenesulfonyl</td>
</tr>
</tbody>
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Chapter 1

Introduction
1.1 General Considerations about Iodine

Iodine was first discovered by Courtois in 1811 as a violet vapour arising from seaweed ash. The name, iodine, was coined by Gay-Lussac on the basis of its violet colour, from the Greek word Ἰώδης, which means violet. It has the atomic number 53 of the group seven in the periodic table with the electronic configuration [Kr] 4d10 5s2 5p5. It is the heaviest, least electronegative, and most polarisable of the non-radioactive halogens in the periodic table. It is commonly classified as a non-metallic element.

Iodine exhibits in nature as an important component in biological functions. It is present in thyroid hormones such as triiodothyronine T3 and thyroxine T4 (Figure 1.1). In fact, thyroid hormones play a critical role in cellular differentiation and in maintaining the metabolic rate of body cells. Therefore, a deficiency of iodine may have negative effects on the growth and development of bodies as well as lead to many diseases or health problems, such as cretinism, goitre, and myxedema.

![Figure 1.1. Structure of thyroid hormones T3 and T4.](image)

Isotopes of iodine have been recognised and characterised, and most of them have a short half-life. However, some isotopes of iodine have been known to be stable isotopes, and only the stable isotope 127I is naturally found. Although, 123I, 125I, and 131I have been applied extensively in biochemical and pharmaceutical research and nuclear medicine.
It is well known that I\(_2\) molecules are the stable state of the element, similar to the other halogens. In terms of oxidation states, the oxidation state (−1) is recognised as iodide with most elements because of the high electronegativity of iodine. However, iodine can exhibit different oxidation states ranging from +1, +3, +5, and +7. These high oxidation states (+3, +5 and +7) in iodine are observed when the iodonium compound possesses electronegative element such as oxygen and fluorine.\(^2\) They are termed hyper-valency due to bearing more than eight electrons in their valence shells. Iodine reagents with the oxidation states −1 and +1 act as nucleophiles and electrophiles, respectively, while the high oxidation states of the hypervalent reagents make them highly electrophilic.\(^2\)

1.2. Hypervalent Iodine Compounds

The discovery of the first hypervalent iodine reagent, (dichloroiodo)benzene PhICl\(_2\), was reported by Willgerodt in 1886.\(^3\) Since then, considerable efforts have been made by others in the field of hypervalent iodine chemistry in a wide range of applications. Interest in this field is motivated by their low toxicity, environmentally friendly nature, unique reactivity, and ease of availability. Hypervalent iodine reagents are a good alternative oxidant compared to transition metals. In fact, they can have the same or considerably higher efficiency than these metals.\(^4\)

1.3. Structure and Bonding in Hypervalent Iodine Reagents

The term ‘hypervalent molecules’ was defined by Musher in 1969 and refers to molecules of groups V–VIII, exceeding the stable octet number of electrons in the valence shell.\(^5\) In terms of electrons, iodine (III) compounds have 10 electrons at the iodine atom and typically have two electronegative ligands. Iodine (V) compounds have 12 electrons at the iodine atom and typically have four electronegative ligands. Figure 1.2 shows the structural types of iodine (III)
and iodine (V). Accordingly, these compounds were named on the basis of IUPAC recommendations: iodine (III) compounds as $\lambda^3$-iodanes, while iodine (V) compounds as $\lambda^5$-iodanes.

\[ \text{Figure 1.2. Structural types of } \lambda^3 \text{-iodanes and } \lambda^5 \text{-iodanes.} \]

$\lambda^3$-Iodanes ($\text{ArIL}_2$) with a decet structure have a distorted trigonal bipyramidal geometry where the two ligands L are in the apical positions and the carbon substituent (Ar) with the electron pairs are at the equatorial position. The most commonly known reagents which belong to this class are bis(acetoxy)iodobenzene 1 (PIDA), [bis(trifluoroacetoxy)iodo]benzene 2 (PIFA), and Koser’s reagent 3 (Figure 1.3).\textsuperscript{6-8} In contrast, $\lambda^5$-iodanes ($\text{ArIL}_4$) with a dodecet structure have a square bipyramidal geometry where the carbon substituent (Ar) and the electron pairs are at the apical positions and the four ligands L are at the basal positions (Figure 1.2). The most commonly known reagents which belong to this class are iodoxybenzenesulfonic acid 4 (IBS), 2-iodoxybenzoic acid 5 (IBX), and Dess–Martin periodinane 6 (DMP) (Figure 1.3).\textsuperscript{9-11}
The bonding type in these compounds is commonly known as a hypervalent bond and was reported by Rundle and Pimentel in 1951.\textsuperscript{12,13} The 5p orbital at iodine overlaps with the ligand-centred orbitals to generate a linear three-centre–four-electron (3c–4e) bond. To clarify, this bond is highly polarised, longer, and weaker than the usual covalent bond between two atoms. The overlapping between the orbitals generates three molecular orbitals: bonding, non-bonding, and anti-bonding (Figure 1.4). The two lower-energy molecular orbitals, namely bonding and non-bonding, are occupied, and the filled non-bonding molecular orbital has a node at the central iodine. The observed node causes a partial positive charge on the central iodine atom and a partial negative charge on the ligands. As a result, the partial positive charge on iodine forms a highly polarised 3c–4e bond, which describes the high electrophilic reactivity of hypervalent iodine compounds.

**Figure 1.3.** Common examples of $\lambda^3$-iodanes and $\lambda^5$-iodanes.

The bonding type in these compounds is commonly known as a hypervalent bond and was reported by Rundle and Pimentel in 1951.\textsuperscript{12,13} The 5p orbital at iodine overlaps with the ligand-centred orbitals to generate a linear three-centre–four-electron (3c–4e) bond. To clarify, this bond is highly polarised, longer, and weaker than the usual covalent bond between two atoms. The overlapping between the orbitals generates three molecular orbitals: bonding, non-bonding, and anti-bonding (Figure 1.4). The two lower-energy molecular orbitals, namely bonding and non-bonding, are occupied, and the filled non-bonding molecular orbital has a node at the central iodine. The observed node causes a partial positive charge on the central iodine atom and a partial negative charge on the ligands. As a result, the partial positive charge on iodine forms a highly polarised 3c–4e bond, which describes the high electrophilic reactivity of hypervalent iodine compounds.
1.4. Synthesis of Hypervalent Iodine I(III) Reagents

As discussed in the previous section 1.3, there are two types of hypervalent iodine reagents displaying the iodine atom in +3 or +5 oxidation states. These iodine reagents can be oxidised using different strategies and oxidants such as sodium perborate, meta-chloroperoxybenzoic acid, Selectfluor, and Oxone to establish either two or four ligands. In the case of $\lambda^3$-iodanes, [bis(acyloxy)iodo] arenes, ArI(O$_2$CR)$_2$, are the most common and important reagents in the I(III) family; they can be prepared by oxidising the I(I) reagent, such as PhI, by different oxidants in the presence of acids. Various synthetic methods have been reported to prepare (diacetoxyiodo)arenes 1, ArI(OAc)$_2$, which are the most well-known hypervalent iodine reagents (Figure 1.5). In the initial period of times, the general adopted methodology for oxidizing ArI was using sodium perborate tetrahydrate (NaBO$_3$·4H$_2$O) in the presence of acetic acid at 45 °C within a short period of reaction time.$^{14,15}$ Since then, a more convenient method has been reported using Selectfluor as the oxidant in the presence of acetic acid at room temperature to prepare the corresponding (diacetoxyiodo)arenes.$^{16}$ However, other methods have been reported for the preparation of ArI(OAc)$_2$ by using oxidants other than NaBO$_3$·4H$_2$O.
or Selectfluor. Oxidation with warm peracetic acid requires a long reaction time (12–16 h) and tight control of temperature to prevent overoxidation to pentavalent iodine reagents. The use of oxidants such as sodium periodate (NaIO₄) in Ac₂O/AcOH, sodium hypochlorite pentahydrate (NaOCl·5H₂O) in AcOH, a combination of CrO₃ with H₂SO₄ in Ac₂O/AcOH, mCPBA in AcOH, and potassium peroxydisulfate (K₂S₂O₈) in AcOH have been reported as well to obtain the corresponding (diacetoxyiodo)arenes.¹⁷-²¹ Some of these methods have limitations with respect to electron-rich or electron-deficient iodoarenes and may require the use of certain activators such as strong acids or a specific temperature. There are also some methods to obtain (diacetoxyiodo)arenes by reacting various arenes and I(OAc)₃ without involving an oxidant, but a limitation is that sometimes this needs a Lewis acid activator or high temperatures.²²

Acyloxy ligands derived from trifluoroacetate are also possible, whereby the iodine is bonded to (OCOCF₃) ligands (Figure 1.5).⁷ [Bis(trifluoroacetoxy)iodo]benzene 2, also known as PIFA, has attracted considerable attention and has been prepared using oxidants in the presence of peroxytrifluoroacetic acid. This type of reagent has a similar reactivity to that of (diacetoxyiodo)arenes and is a very useful oxidant in different synthetic applications.²³

![Figure 1.5. Hypervalent iodine (III) compounds.](image-url)
Various types of ligands have also been applied to iodoarenes to synthesise a wide range of I(III) family members, such as hydroxy(tosyloxy)iodoarenes 3, also known as Koser’s reagents (Figure 1.5). Hydroxy(tosyloxy)iodoarenes (HTIBs) are synthesised using a direct and fast strategy to access electron-deficient and electron-rich HTIBs. The synthesis involves the treatment of iodoarenes with $m$-chloroperbenzoic acid (mCPBA) and $p$-toluenesulfonic acid (TsOH) at room temperature. The application of this direct procedure may introduce sulfonic acids other than toluenesulfonic acid into the synthesis of [hydroxy(organosulfonyloxy)]iodoarenes. Additionally, HTIBs can be used in ligand exchange strategies with the (OH) ligand to introduce various ligands such as methoxy when HTIBs are treated with trimethyl orthoformate. Hydroxy(tosyloxy)iodoarenes are very useful and efficient reagents in synthetic applications and are particularly suitable to the $\alpha$-sulfonyloxylation of ketones.

Iodosobenzene (IOB) 7, PhIO, is also a well-known reagent in the family of I(III). It is prepared by the hydrolysis of PIDA with aqueous NaOH. This reagent has a polymeric nature, which prevents recrystallisation from organic solvents. This polymerisation occurs because of the intermolecular network of I···O bonds.

The above-mentioned reagents can be generated using ligand exchange strategies to deliver different structures of useful hypervalent iodine reagents. For example, (diacetoxyiodo)benzene PIDA 1 can undergo ligand exchange with an appropriate carboxylic acid 8 to generate a new type of [bis(acyloxy)iodo]arene 9 (Scheme 1.1).

```
ArI(OAc)$_2$ + 2 RCO$_2$H $\xrightarrow{\text{PhCl, heat}}$ ArI(OCOR)$_2$ + 2 HOAc
1     8                                      9     10
```

Scheme 1.1. Preparation of hypervalent iodine reagents by ligand exchange.
There has been a continuous and regular development of the methodologies to obtain hypervalent iodine reagents in an efficient manner employing a green and sustainable protocol such as electrochemical oxidation. Hypervalent iodine reagents were generated electrochemically under flow conditions using a glassy carbon anode and a platinum cathode in fluorinated alcohols (Scheme 1.2). The anodic oxidation was applied using electricity instead of using hazardous chemical oxidants.

**Scheme 1.2.** Flow electrochemical generator of hypervalent iodine reagents.

### 1.5. General Reactivities of Hypervalent Iodine Reagents

The reactivity of hypervalent iodine reagents is controlled by strongly electrophilic properties and excellent leaving group ability of hypervalent iodine. The highly utilised hypervalent iodine reagent in organic synthesis acts as an oxidant because of the existence of heteroatom ligands, which are coordinated to iodine. In principle, hypervalent iodine (III) reagents with their high oxidation potential have various reactivity pathways, including:

- ligand exchange pathway
- reductive elimination pathway
- radical pathway
- single-electron transfer (SET) pathway
1.5.1. Ligand Exchange Pathway

Because of the strongly electrophilic characteristics of hypervalent iodine reagents, different nucleophiles can replace the heteroatom ligands, which serve as leaving groups. In principle, most reactions of hypervalent iodine reagents apply this pathway containing two mechanistic routes: a dissociative or an associative route (Scheme 1.3).

![Mechanistic routes of $\lambda^3$-iodanes with nucleophiles.](image)

In the case of a dissociative route, the elimination of one of the ligands ($L^-$) occurs before the addition of a nucleophile to generate a hypervalent iodine intermediate (8-I-2) 13b, which is a high-energy iodonium ion [ArIL]+. After the formation of this intermediate, the nucleophile (Nu) can attack to generate the new $\lambda^3$-iodane 14. In the associative route, the nucleophile attacks the positively charged iodine atom to generate a trans-hypervalent iodine intermediate (12-I-4) 13c, which isomerises to cis-intermediate 13d. Then, the elimination of one of the ligands takes place to form the new $\lambda^3$-iodane 14. To conclude these two routes, the exchange of a heteroatom ligand with a nucleophile is more likely to appear via the associative route.
because of the stable intermediate (12-I-4) compared to intermediate (8-I-2), to generate the corresponding hypervalent iodine reagent 14.

### 1.5.2. Reductive Elimination Pathway

A weak hypervalent bond is easily broken in a reductive elimination pathway to form the reduced iodine species, which has a high leaving group ability. Additionally, this pathway is energetically favourable because of the normal valency of the octet structure (Scheme 1.4). After releasing the ArI co-product, the nucleophile reacts with a ligand to generate the Nu-L (15) product. If another nucleophile (Nu`) is present, attack $\lambda^3$-iodane the nucleophile (Nu`) takes place, yielding the product Nu-Nu` (16) along with ArI and L$^-$ as the co-products.

![Scheme 1.4. Reductive elimination pathways for $\lambda^3$-iodanes.](image)

### 1.5.3. Radical Pathway

A radical mechanism is observed for hypervalent iodine reagents, which bear chloro-, oxygen, and nitrogen ligands in a homolytic cleavage pathway (Scheme 1.5). The free radical intermediate can be generated under thermal or photochemical conditions of the weak...
hypervalent bond in these reagents. The common reactions using this pathway are chlorination, azidation, and oxidation of alcohols through radical fragmentation.\textsuperscript{33-37}

1.5.4. Single-Electron Transfer (SET) Pathway

A cation–radical mechanism is observed for hypervalent iodine reagents in the case of a reaction with electron-rich arenes. The cation–radical intermediate can be formed by SET oxidation through a charge-transfer complex between the hypervalent iodine regent and the arene (Scheme 1.6).\textsuperscript{29,37}

1.6. Common Synthetic Applications

Hypervalent iodine reagents are efficient alternative oxidants to highly toxic heavy metals because of their high oxidation potential. Therefore, a large number of applications use hypervalent iodine reagents in either stoichiometric or catalytic quantities in organic synthesis to produce valuable compounds. Consequently, considerable research efforts have been
focused on the design of these reagents to control either asymmetric or symmetric synthesis in the following reactions:

- oxidation
- rearrangement
- dearomatisation
- α-functionalisation
- carbon–carbon bond formation
- carbon–heteroatom bond formation

1.6.1. Oxidation Reaction

Hypervalent iodine reagents have been used for the efficient oxidation of alcohols, amines, and sulfur compounds to obtain the corresponding oxidised products. The conversion of alcohols to their corresponding carbonyl compounds have been reported using numerous $\lambda^3$-iodanes or $\lambda^5$-iodanes. The oxidation of various primary and secondary alcohols to carbonyl compounds was reported by Piancatelli and co-workers in high yields by using PhI(OAc)$_2$ as the stoichiometric oxidant in combination with catalytic amounts of TEMPO. As an example, Scheme 1.7 shows the conversion of secondary alcohol 17 to carbonyl compound 18.$^{38}$

![Scheme 1.7. Oxidation of secondary alcohol to ketone.](image-url)
Amines can also be oxidised by hypervalent iodine reagents to produce either imines, or aldehydes, or ketones. The combination of PhI(OAc)$_2$ with TEMPO was also established as an oxidant to transform amine 19 into the corresponding carbonyl compound 20 (Scheme 1.8).

![Scheme 1.8. Oxidation of amine to aldehyde.](image)

The dehydrogenation of hydroxylamine 21 was investigated to furnish the corresponding oxime 22 by using IBX as the oxidant to achieve this transformation (Scheme 1.9).

![Scheme 1.9. Oxidation of amine to oxime.](image)

Sulfur compounds can be oxidised by hypervalent iodine reagents where thiols are oxidised to disulfides and, likewise, sulfides to sulfoxides. However, the reaction conditions need to be controlled to prevent further oxidation to sulfones. The synthesis of sulfoxides has been widely reported by many researchers with various λ$_3$-iodanes or λ$_5$-iodanes. Among these efforts, Koser’s reagent can selectively oxidise alkyl or aryl sulfides 23 to the corresponding sulfoxide 24 without any further oxidation to sulfones (Scheme 1.10). Similarly, the IBX reagent can selectively oxidised thiols to the corresponding disulfides without any further oxidation.
1.6.2. Rearrangement Reaction

Hypervalent iodine reagents are known for their ability to form cationic intermediates used in different rearrangement reactions, including oxidative ring expansions or ring contractions and aryl or alkyl migrations.\textsuperscript{43-46} Among them, the Hofmann-type rearrangement (HR) has been used effectively for the formation of ureas 27 and carbamates 28 from amides 25 (Scheme 1.11).\textsuperscript{6}

\[
\begin{align*}
\text{PhCH}_2\text{SCH}_2\text{Ph} & \quad \text{PhI(OH)(OTs)} \quad \text{DCM} \quad \text{PhCH}_2\text{SCH}_2\text{Ph} \\
23 & \quad 24
\end{align*}
\]

\textbf{Scheme 1.10.} Oxidation of sulfide to sulfoxide.

\[
\begin{align*}
\text{R}^1\text{NH}_2 & \quad \text{PhIO} \quad \text{R}^1\text{NH}_2 \quad \text{R}^2\text{NH}_2 \\
25 & \quad 26 & \quad 27
\end{align*}
\]

\[
\begin{align*}
\text{R}^3\text{OH} & \quad \text{R}^1\text{NH} \quad \text{R}^3\text{OH} \\
25 & \quad 27 & \quad 28
\end{align*}
\]

\textbf{Scheme 1.11.} Hofmann rearrangement.

Aryl migration has been used through oxidative cyclisation of aryl-substituted carboxylic acid 29 by using [bis(trifluoroacetoxy)iodo] benzene with trimethylsilyl triflate (TMSOTf) to form the rearranged lactone 30 (Scheme 1.12).\textsuperscript{45}

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \quad \text{COOH} \quad \text{Ph} \quad \text{Ph} \\
29 & \quad \text{PhI(OCOCF}_3)_2\text{TMSOTf} \quad \text{MeCN} \quad \text{Ph} \quad \text{Ph} \\
& \quad \text{MeCN} \quad \text{30}
\end{align*}
\]

\textbf{Scheme 1.12.} Cyclisation and rearrangement of acid.
1.6.3. Dearomatisation Reaction

Hypervalent iodine reagents are efficient tools for the oxidative dearomatisation of phenolic compounds. The most known mechanism is the coordination of the phenolic oxygen to the iodine(III) center to form 32a. Then, there are two possible pathways to form dearomatised cyclohexadienone 34 through associative or dissociative routes. Attack of nucleophiles at the \textit{para} positions could take place during reduction of iodine or before through the dissociative route 32c. However, the electrophilic addition of the iodine(III) reagent to the phenolic ring assumes for the oxidative dearomatisation of phenolic compounds (pathway 3). The generated intermediate 32b undergoes the attack of nucleophiles at the \textit{para} positions with reduction of iodine to obtain the dearomatised cyclohexadienone 34 (Scheme 1.13).\cite{47}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme113.png}
\caption{Scheme 1.13. General mechanistic pathways for dearomatisation of phenols.}
\end{figure}
A radical-chain mechanism is also known to promote the dearomatisation of phenols where the mechanism proved by different experimental techniques by Kalek and co-workers in 2020. Phenol is transformed to phenoxy radical 33a which undergoes a single electron oxidation to form the dearomatised cyclohexadienone 34 with an iodanyl(II)radical 33c.

**Scheme 1.14.** Radical-chain mechanism for dearomatisation of phenols.

Various nucleophiles including alcohols, amides, carboxylic acids, water, oximes, alkenes, alkynes, electron-rich aromatic rings, and fluoride ions have been used successfully for the oxidative dearomatisation of phenolic compounds. The oxidative allylation of phenols
was achieved using PIDA by the nucleophilic attack of allylsilane 36 to obtain 2,5-cyclohexadienone 37 (Scheme 1.15).51

\[
\text{35} \rightarrow \text{PIDA} \rightarrow \text{37}
\]

Scheme 1.15. Oxidative allylation of phenols.

1.6.4. \(\alpha\)-Functionalisation of Carbonyl Compounds Reaction

Hypervalent iodine reagents are known for their ability to introduce nucleophiles into the \(\alpha\)-position of carbonyls, through processes such as oxygenation, halogenation, arylation, and alkylation.52 The formation of \(\alpha\)-substituted ketones relies on the diversity of the ligands bound to iodine(III). In particular, the \(\alpha\)-oxytosylation of ketones 38 to 39, which is the most well-known, can be performed by a treatment with [hydroxy(tosyloxy)iodo] benzene (HTIB) to functionalise the ketones through the formation of a carbon heteroatom bond (Scheme 1.16).24

\[
\text{38} \xrightarrow{\text{PhI(OH)(OTs)}} \text{39}
\]

Scheme 1.16. \(\alpha\)-Oxytosylation of ketones using HTIB.
1.7. Chiral Hypervalent Iodine Reagents

The chiral environment around iodine reagent plays a very important role in asymmetric synthesis. Accordingly, the most common strategies used for the preparation of chiral hypervalent iodine reagents are the attachment of chiral ligands to the iodine centres via ligand exchange and the introduction of either chiral substituents or axial chirality through the iodoarene skeleton.

1.7.1. Hypervalent Iodine Reagents with Chiral Ligands

This class of hypervalent iodine reagents can be prepared using ligand exchange strategies with a chiral acid or alcohol as the source of chirality. Diphenyliodonium tartrate is known as the first chiral hypervalent iodine reagent which was reported by Pribam in 1907. Later, Imamoto and co-workers in 1986 reported the generation of iodine (III) tartrates in situ by the reaction of various derivatives of chiral tartaric acid anhydride with iodosylbenzene, but the structure of iodine (III) tartrates was assumed to be a seven-membered cyclic structure without isolation and characterisation (Scheme 1.1).

In 1992, Koser and co-workers demonstrated a similar reagent, but a chiral tartaric acid was reacted with PIDA instead of iodosylbenzene (Scheme 1.18). The structure was
confirmed 10 monomer units by experimental evidence such as element composition and NMR analysis to be polymer 43 instead of the cyclic structure assumed previously.\textsuperscript{55}

\begin{center}
\textbf{Scheme 1.18.} Chiral hypervalent iodine by Koser.
\end{center}

A hypervalent iodine (V) reagent has a reactivity similar to that of the hypervalent iodine (III) reagents towards tartaric acid derivatives. Kita and co-workers, in 1999, reported the reactivity of iodoxybenzene (PhIO\textsubscript{2}) with chiral diacyltartaric acid in the presence of catalytic amounts of cetyltrimethylammonium bromide (CTAB) to generate a new chiral class of hypervalent iodine reagents \textit{in situ}.\textsuperscript{56}

Tartaric acid derivatives are not the only source of chiral acid for the preparation of chiral hypervalent iodine reagents. For example, (+)-camphor sulfonic acids are another source of chirality. Varvoglis and co-workers, in 1990, established the stable chiral hypervalent iodine reagent 45 generated by the ligand exchange of PIDA 1 with (+)-camphor sulfonic acid 44 (Scheme 1.19).\textsuperscript{57}

\begin{center}
\textbf{Scheme 1.19.} (+)-Camphor sulfonic acids based hypervalent iodine reagent.
\end{center}
Various amino acids are another source of chirality and can thus be used instead of tartaric acid derivatives or chiral camphor sulfonic acids to generate chiral hypervalent iodine reagents. Zhdankin and co-workers, in 2004, reported the reaction of PIDA 1 with various chiral amino acids 46 (Scheme 1.20).

Scheme 1.20. Chiral amino acid-based hypervalent iodine reagent.

The introduction of chiral alcohols is an alternative strategy to prepare chiral hypervalent iodine reagents through ligand exchange. In 1990, Koser and co-workers demonstrated this type of hypervalent iodine reagents 50 by using chiral menthol 49 (Scheme 1.21).

Scheme 1.21. Chiral menthol-based hypervalent iodine reagent.
1.7.2. Hypervalent Iodine Reagents with Chiral Substituents

Numerous chiral hypervalent iodine reagents have been synthesised by introducing chiral substituents into the iodoarene skeleton. Wirth and co-workers designed various chiral reagents through esterification between o-iodobenzoyl chloride 51 and chiral alcohols such as (−)-borneol, (−)-menthol, and (−)-fenchol followed by oxidation with dimethyldioxirane (Scheme 1.22).

\[ \text{Scheme 1.22. Synthesis of chiral hypervalent iodine reagents by using chiral alcohols.} \]

Similarly, Birman explored a series of chiral hypervalent iodine reagents starting from o-iodobenzoyl chloride 51 and reacting it with various chiral 2-amino alcohols 54 to obtain chiral oxazolines based reagents 55 (Scheme 1.23).

\[ \text{Scheme 1.23. Synthesis of chiral hypervalent iodine using chiral 2-amino alcohols.} \]
Fujita and co-workers explored lactic acid-derived optically active iodine reagents \(58\) using the Mitsunobu reaction.\(^6\) Correspondingly, a series of chiral iodoarenes were designed by Ishihara and co-workers using Fujita’s synthetic strategy followed by amidation to produce more reactive chiral reagents \(59\) through the intramolecular hydrogen bonding interactions between the acidic hydrogen of amide and the iodine(III) ligand (Scheme 1.24).\(^6\)

![Scheme 1.24. Synthesis of chiral hypervalent iodine using chiral lactates.](image)

To improve the performance of Ishihara’s reagents, an additional stereogenic centre was established by Gong and co-workers using (S)-proline derivatives \(61\) (Scheme 1.25).\(^6\)

![Scheme 1.25. Synthesis of chiral hypervalent iodine using S-proline derivatives.](image)
1.7.3. Hypervalent Iodine Reagents with Axial Chirality

Various axial chiral hypervalent iodine reagents and catalysts have been synthesised using rigid iodobinaphthyl or iodobiphenyl backbones containing C–C chiral axes 63–66 (Figure 1.6). The synthetic strategies of the chiral reagents containing C–C chiral axes have been explored through a kinetic resolution process or by introducing an optically active compound such as a BINOL derivative.

![Axial chiral iodine reagents](image1.png)

**Figure 1.6.** Axial chiral iodine reagents.

Chiral hypervalent iodine reagents containing binaphthyl backbones were prepared by Quideau through a kinetic resolution process (Scheme 1.26). The synthesis is started from 2-naphthol 67 to generate chiral-DABN 68 through the treatment of the obtained rac-DABN with D(+)-10-camphorsulfonic acid. Two subsequent steps were further followed to achieve a binaphthyl based chiral iodine reagent 70.
The chiral pool reaction was also explored by Masson to prepare diastereomers containing a biphenyl backbone. The chiral tert-butylsulfoxide 71 was coupled with iodoarene 72 through the halogen/lithium exchange reaction to generate chiral iodine reagents in the diastereomeric form (Scheme 1.27).
The use of commercially available binaphthyl derivatives to prepare hypervalent iodine reagents was investigated by Wirth and co-workers in one step.\[^{68}\] \((S)-(--)1,1'-\text{Binaphthyl}-2,2'-\text{diamine}\ 74\) was reacted with 2-iodobenzoyl chloride 51 to obtain an axial chiral iodine reagent containing a binaphthyl skeleton 75 (Scheme 1.28).

![Scheme 1.28. Direct synthesis of axial chiral hypervalent iodine reagents.](image)

Einhorn and co-workers designed a family of chiral hypervalent iodine reagents from a readily available BINOL moiety 76 by reacting with 2,6-disubstituted anilines 77 (Scheme 1.29).\[^{69}\] 3,3'-Diiodo-BINOL-fused maleimides 65 were designed with two iodine atoms within the same chiral environment; they contained C–C chiral axes.

![Scheme 1.29. Family of axial chiral hypervalent iodine reagents produced using BINOL derivative.](image)
As described above, a majority of the designed axial chiral iodoarene precursors are focused on a chiral C–C axis, such as biphenyls or binaphthyls. However, a chiral C–N bond is an alternative type of chiral axis, which has rarely been investigated in the field of hypervalent iodine chemistry. Cheng and co-workers reported various reagents containing both the C–N axial chirality and the P-stereogenic chirality by using a kinetic resolution strategy. The synthesis was achieved through an N-allylic alkylation reaction of ortho-iodine substituted phosphamides in the presence of hydroquinidine as the catalyst (Scheme 1.30).

Scheme 1.30. Synthesis of C–N axial chiral hypervalent iodine reagents.
1.8. References


A. Y. Koposov, V. V. Boyarskikh, V. V. Zhdankin, *Org. Lett.* 2004, 6, 3613.


Chapter 2

Synthesis of C–N Axial Chiral Hypervalent Iodine Reagents in Enantiomeric Form
2.1. Introduction of Axial Chirality

Chirality in organic compounds generally refers to different stereogenic units including the centre 81, axis 82, plane 83, and helix 84 (Figure 2.1).\(^1\) Axial chirality is unlike central chirality, which refers to a central atom holding different substituents. Axial chiral compounds have high rotation barriers because of the restricted rotation around C(sp\(^2\))–C(sp\(^2\)) or C(sp\(^2\))–X bonds, where X is a heteroatom N, O, or S, leading to the formation of enantiomeric forms. The restricted rotation of bond was discovered by Christie and Kenner in 1922 by resolving 6,6’-dinitro-2,2’-diphenic acid.\(^2\)

![Figure 2.1. Examples of different forms of chirality.](image)

These types of chirality are found in chiral allenes, spiranes, spiroindanes, biaryls, nonbiaryls, and heterobiaryls, for which a numerous synthetic procedures have been developed along with the investigation of the impact of axial chiral compounds.\(^3\)–\(^5\) Axial chiral compounds have received considerable attention in recent years because many natural products, bioactive molecules, and chiral catalysts possesses the core structure with axial chirality.\(^5\)\(^6\)
2.2. Axial Chiral Biaryl Skeletons

Mostly, common axial chiral compounds have been designed as biaryl skeletons with a phenyl or naphthyl backbone such as BINOL or BINAP, and are well-known chiral ligands containing the 1,1′-biphenyl or 1,1′-binaphthyl core. This class of chirality has a stereogenic C–C axis arising from the hindered rotation of a C–C bond to obtain an enantiopure form. Three or four ortho-substituents are required to ensure sufficiently restricted rotation at room temperature and therefore configurationally stable compounds. Numerous diastere- and enantioselective syntheses have been attempted to design rotationally hindered biaryl compounds, involving kinetic resolution, desymmetrization, cyclization, and direct arylation. Maruoka and co-workers reported the kinetic resolution of chiral BINAM by using chiral phosphoric acids (CPAs) for racemic N-sulfuryl-BINAM to obtain excellent enantiomeric purity (Scheme 2.1).

Scheme 2.1. Kinetic resolution of chiral NOBINs.

2.3. Axial Chiral Nonbiaryl Skeletons

Like biaryl systems, substituted amides, anilides, acyclic imides, carbamates, and ureas can be axial chiral compounds when the rotation barriers are restricted around the C–N bond. Ortho, ortho′-positions, and bulky substituents are required in a nonbiaryl system to achieve a separable and stable atropisomer at room temperature. Ortho-substituted anilides
have been widely synthesised in enantiopure form and are resolvable through chiral HPLC or through the formation of diastereoisomers. Taguchi and co-workers reported the synthesis of enantiomerically pure \(N\)-acryloyl-\(N\)-allyl anilide 91 by using a chiral pool strategy to obtain a separable diastereomeric mixture (Scheme 2.2).\(^{16}\) The \(ortho\)-\(tert\)-butyl anilide derivative 89 is sufficiently hindered to produce these diastereomers owing to the bulky \(tert\)-butyl group to achieve high rotational barriers around the \(C\text{--}N\) bond.

![Scheme 2.2. The synthesis of enantiomerically pure \(N\)-acryloyl-\(N\)-allyl anilide through separable diastereomeric mixture.](image)

**2.4. Axial Chiral Heterobiaryl Skeletons**

Heterobiaryl skeletons have been utilised for designing axial chiral compounds with axial chirality around a \(C(sp^2)\text{--}X\) (heteroatom). Axial chiral imides, pyrroles, indoles, and lactams are examples which feature the axial chirality around a \(C(sp^2)\text{--}N\) bond. Murrastifoline-F (93), which is a heterobiaryllic compound obtained from 92 possess a \(C_{aryl}\text{--}N_{aryl}\) chiral axis bearing a carbazole ring, was reported by Bringmann and co-workers in 2001 (Scheme 2.3).\(^{17}\) The optically pure compounds were obtained by a chromatographic separation (Chiral HPLC) of the diastereomers after treatment with a chiral acid (Mosher’s Acid).
Axial chiral sulfides 94, sulfoxides 95, and sulfones 96 feature the axial chirality around a C(sp²)–S bond. Similarly, C(sp²)–O bond can show axial chirality in diaryl ether compounds 97 (Figure 2.2). However, the axial chirality around a C–O and C–S bond is less common than compounds which exhibit restricted rotation around a C–N bond.\textsuperscript{18}

Highly substituted biaryl ethers are required to achieve high-energy barriers for rotation. However, the bulk of the sulfur atom along with the longer bond length between carbon and sulfur atoms decreases the energy barriers for rotation in the case of axial chiral sulfones, sulfoxides, and sulfides (94–96) compared with similarly substituted diaryl ether 97.\textsuperscript{3}
The first stable axial chiral diaryl ether 100 with a bulky group was resolved in 1998 by Fuji and co-workers by using a chiral HPLC column (Scheme 2.4).\(^\text{19}\)

Scheme 2.4. Synthesis of axial chiral diaryl ether.

The first stable diaryl sulfone 103 was reported by Clayden and co-workers by using a chiral resolution strategy to achieve diastereomeric control with high selectivity (Scheme 2.5).\(^\text{20}\) A chiral sulfanyl substituent 102 on the ortho position allows resolution of the axial chirality where four ortho substituents are required to achieve stable axial chiral C–S compounds.

Scheme 2.5. The synthesis of axial chiral diaryl sulfones.
2.5. Axial Chiral Spirobicyclic Skeletons

1,1’-Spirobiindane is the fundamental structure for systems containing a privileged C2–symmetric core. The two rings in 1,1’-spirobiindane are rigidly linked via a σ bond at a quaternary centre, and these rings occupy perpendicular planes. Spirobicyclic skeletons have been synthesised using chiral resolution strategies where two rings are coupled using a chiral catalyst. For example, Tan and co-workers reported the synthesis of SPINOLS 106 by using 105 catalysed enantiomeric cyclisation reaction (Scheme 2.6).21

![Scheme 2.6. The Synthesis of axial chiral SPINOLS.](image)

2.6. Objectives

The aim is to synthesise a new family of chiral hypervalent iodine compounds displaying axial chirality around a C–N bond. A simple amide formation strategy could provide access to diverse C–N axial chiral compounds by using 2-iodoaniline, which is a suitable backbone for the design. The application of two ortho-substituted anilides has been demonstrated to establish an axial chirality around the C–N bond, where these substituents would be able to restrict the rotation around the C–N bond. Accordingly, substituted anilide derivatives would be generated in enantiomeric forms with $S_{C-N}$ and $R_{C-N}$ configurations, which could be resolved by preparative chiral HPLC columns. Moreover, two types of anilides would be generated, namely the free 2° NH-anilide and the 3°N-alkylated anilide. The stereochemistry of the obtained
anilide derivatives could be studied where they have different rotations around bonds irrespective of the axial chirality and are interesting. Enantiopure iodine reagents with the above-mentioned features, after resolution could be oxidised to the corresponding hypervalent iodine reagents (Figure 2.3). The chiral induction of these reagents would be investigated as a route towards enantioselective transformations as well by studying their reactivities.

![Diagram](image_url)

**Figure 2.3.** Target strategy purposed within this chapter.

### 2.7. Result and Discussion

#### 2.7.1. Synthesis of Axial Chiral Iodine Compounds based on Anilide N–Ar Bond

*Ortho*-substituted anilide derivatives exhibit axial chirality arising from the highly hindered bond rotation around the C–N bond. However, the separation of enantiomers continues to be a challenge because of their identical physical and chemical properties. Although, enantiomeric conformations have been separated, isolated, and characterised using chromatographic separation such as preparative chiral high-performance liquid chromatography (HPLC), which is the most commonly used technique.\(^{22-26}\)
To obtain axial chiral iodine compounds displaying a stereogenic C–N bond, di-ortho-substituted aniline was selected as a backbone-bearing an iodine atom in the ortho position and a bulky group in another ortho position. These di-ortho substituents are needed to provide a significant increase in the N–Ar rotation barriers, and an additional alkyl substituent at the para position could increase the energy barriers further. Therefore, the synthetic strategy towards enantiomeric iodine reagents involved the use of 2-iodo, 4,6-dimethyl aniline, which has a prochiral axis along the C–N bond with an aromatic acid containing pyridine or benzene rings. Initially, 2-iodo, 4,6-dimethyl aniline 108 was synthesised in good yield (88%) by using a simple iodination procedure, where commercially available 2,4-dimethyl aniline 107 was treated with a combination of iodine and sodium bicarbonate (Scheme 2.7).

![Scheme 2.7](image)

**Scheme 2.7.** The synthesis of 2-iodo-4,6-dimethyl aniline skeleton.

Following this, the aromatic acids 109 and 110 were successfully converted to their acyl chloride intermediates without isolation by using thionyl chloride with a catalytic quantity of DMF (Scheme 2.8). Followed by amide formation, benzyol chloride or picolinoyl chloride was treated with substituted aniline 108 in the presence of triethyl amine (TEA) to form 2° N-aryl amides 111 and 112 in good to excellent yields. Next, the axial chiral iodine reagents in their racemic forms (113 and 114) were designed using 111 and 112 via a methylation step.
with methyl iodide in the presence of sodium hydride (NaH) in which the 3° anilide core contained either pyridine or phenyl rings. The iodine reagents were obtained in good yields of 82% and 79%, achieving a sterically hindered rotation around the C–N bond. A variety of aromatic or heteroaromatic acid chloride derivatives were tolerated, affording the desired enantiomers with the stereogenic C–N bond. The purity and retention times of the formed enantiomers were checked by analytical HPLC columns.

Scheme 2.8. The synthesis of enantiomers of axial chiral iodine reagents.
2.7.2. HPLC Resolution of Enantiomers

Chiral high-performance liquid chromatography (HPLC) is undoubtedly the most important technique to resolve and isolate enantiomers. The enantiomeric pairs of 113 and 114 containing either phenyl or pyridine rings are chiral iodine reagents with axial chirality (Sc-N, Rc-N), and both enantiomers were successfully resolved using analytical HPLC columns. To resolve the enantiomers peak of 113, the chiral YMC column was found suitable and resolved successfully to the Sc-N and Rc-N enantiomers at room temperature (Figure 2.4). Alternatively, enantiomers of 114 (Sc-N, Rc-N) were separated by using the analytical (S, S)-Whelk-O column at room temperature (Figure 2.5). The successful resolution of these enantiomers was achieved by the restricted rotation around the C–N axis, and this confirmed that the iodine reagents had a stereogenic axis around the C–N bond. It is worth isolating a racemic mixture into individual enantiomers to obtain enantiopure iodine reagents by using a preparative HPLC column and not an analytical column. By doing so, the chiral induction could be transferred to the products for various enantioselective transformations. However, the isolation process became a daunting challenge because the analytical columns could separate approximately micrograms, which was not sufficient for running an enantioselective reaction. Accordingly, a semipreparative chiralcel OD column was selected for the isolation process, but the resolution was not successful on this column even with optimal conditions. For compounds the 111 and 112, which had NH–anilide cores, different analytical columns were investigated along with various conditions to resolve them. However, these columns unfortunately failed to separate them. Therefore, these reagents might not have highly restricted rotation around the C–N axis to generate two possible enantiomers. There is no evidence to state that these iodine reagents exhibit a stereogenic axis.
HPLC YMC Chiral Amylose-C, \((n\)-Hexane/\(i\)-PrOH = 95/05, flow rate = 0.30 mL/min, 254 nm)

Figure 2.4. HPLC data for axial chiral iodine reagent 113.

HPLC (S, S)-Whelk-O, \((n\)-Hexane/\(i\)-PrOH = 95/05, flow rate = 0.30 mL/min, 254 nm)

Figure 2.5. HPLC data for axial chiral iodine reagents 114.
2.7.3. Stereochemistry of Anilide Compounds

The stereochemistry of anilide compounds is very interesting where different possible conformations are exhibited depending on the bond geometries (Figure 2.6). With respect to the earlier discussion on axial chirality, the restricted rotation about the \( C_{Ar} - N \) bond is well known for many ortho-substituted anilide compounds, allowing the carbonyl side to rotate out of plane. This restricted rotation around the \( C_{Ar} - N \) bond would access to two enantiomers, which could be separated at room temperature by chiral HPLC, as proven in the previous section for the 3° anilides.

![Amide Bond Rotation](image)

Figure 2.6. Rotation around anilide compounds.

The restricted rotation around the \( C_{Ar} - N \) bond was not the only rotation in these compounds, but the rotational feature of the amide \( C(O) - N \) bond is well-known. The amide bond \( C(O) - N \) has a partial double-bond character because the lone pair of electrons on nitrogen is delocalized into the carbonyl group. Hence, a restricted rotation could be expected also around the amide bond due to the double-bond character. The \( cis/trans \) conformations are observed in such anilides where the conformational preference is influenced by different substituents around amide bond.\(^{27-30}\) 2° anilides are preferred \( trans \) conformation than \( cis \) conformation which is preferred by 3° anilides, as shown in Figure 2.7.\(^{27}\) The \( trans \) preference is adopted in 2° anilides to minimize steric hindrance between bulky phenyl rings. However,
the *cis* preference in 3° anilides is observed to prevent electronic repulsion between the carbonyl lone pair electrons and π electrons of phenyl rings.

![Figure 2.7](image1.png)

*Figure 2.7. Cis/trans conformational preference of 2° and 3° anilides.*

In the case of iodine reagents containing the 3° anilide skeletons 113 and 114, both the reagents had the restricted rotation about the C<sub>Ar</sub>−N bond to generate the resolved enantiomers by chiral HPLC, and they were expected to show the *cis* conformation. The two aromatic rings were in the *cis* relationship to minimise the electronic repulsions between the lone pair of oxygen and the electron density of the aromatic ring. These *cis* conformations were confirmed by the X-ray crystal structure (Figure 2.8).

![Figure 2.8](image2.png)

*Figure 2.8. X-ray structures of 3° iodine reagents 113 and 114.*
In the case of iodine reagents containing the $2^\circ$ anilide skeleton, a *trans* configuration was determined by the X-ray crystal structure, wherein the less sterically repulsive hydrogen atom of the aniline was close to the aromatic ring of the carbonyl side (Figure 2.9).

![Figure 2.9. X-ray structures of $2^\circ$ iodine reagents 111 and 112.](image)

The C(O)–C$_{Ar}$ bond rotation occurs without inducing *cis/trans* conformational exchange.$^{28}$ This type of rotation is consistent with the conformational preference to prevent electronic or steric repulsions. However, the presence of restricted bond rotation around C(O)–C$_{Ar}$ could be observe with sufficiently bulky *ortho* substituents.$^{3}$

The barriers of the bond rotation around C$_{Ar}$–N for iodine reagents containing either $2^\circ$ or $3^\circ$ anilide skeletons were studied by using variable-temperature $^1$H NMR, where the sharp signals were broadened upon heating (Figure 2.10). This could be attributed to the fact that the rotation around C$_{Ar}$–N was not as restricted at a high temperature as it was at room temperature, and the protons of the aromatic rings from the carbonyl carbon side became equivalent.
Figure 2.10. Variable-temperature (VT) $^1$H NMR for iodine reagents containing $2^\circ$ and $3^\circ$ anilide skeletons.
2.7.4. Oxidation of Axial Chiral Iodine Reagents in Racemic Forms

After trials with various oxidants, iodine reagents 112 and 114 displaying pyridine rings were successfully oxidised using \textit{m}-chloroperoxybenzoic acid (\textit{m}-CPBA) as an oxidant in the presence of \textit{p}-toluenesulfonic acid in a mixture of solvents of dichloromethane with 2,2,2-trifluoroethanol (1:1) at room temperature.\textsuperscript{31} Under these conditions, the hypervalent iodine reagents 115 and 116 were isolated in 90\% and 92\% yields, respectively (Scheme 2.9).

Unfortunately, \textit{m}-CPBA was unable to oxidise the iodine reagents 111 and 113 displaying phenyl rings, and it seemed that an efficient oxidant was required to access the hypervalent iodine reagents. The screening of different oxidants revealed that excess amounts of peracetic acid in the presence of acetic acid at 40 °C could oxidise the iodine reagents 111 and 113, to form the hypervalent iodine reagents 117 and 118 in 91\% and 94\% yields, respectively (Scheme 2.10).
2.7.5. Symmetric Transformations

Although axial chiral iodine reagents were not resolved by preparative HPLC, probing their reactivity toward common organic transformations was considered. In the last section, these reagents were successfully oxidised to their corresponding hypervalent iodine reagents containing either acetate or tosyl ligands. The use of these hypervalent iodine reagents in their racemic forms was investigated in different symmetric transformations including oxidation, dimerization, rearrangement, and dearomatisation reactions.

2.7.5.1. Oxidation of Sulfides

Hypervalent iodine reagents are considered effective oxidants, and thus, they were examined for the oxidation of sulfides. They successfully oxidised the sulfides to their corresponding sulfoxides without any further oxidation to sulfones. The typical procedure required 1.2 equivalents of the generated iodine (III) reagents to oxidise thioanisole in acetonitrile at room temperature for 16 h. The reagents (115–118) were used to smoothly oxidise sulfides in good to moderate yields (24%–63%) under mild conditions as summarised in Table 2.1. Iodine (III) reagents containing pyridine rings 115 and 116 with tosyl ligands on iodine
resulted in the desired sulfoxides 120 in good yields (49% and 63%) compared to iodine (III) reagents 117 and 118 displaying acetate ligands (24% and 45%). However, iodine (III) reagents based on 3° anilide skeletons 116 and 118 seemed to be more efficient than their corresponding reagents with 2° anilide skeletons 115 and 117. The best result for the desired sulfoxide was achieved by using reagent 116 in 63% yield. All of these results indicated the ability of iodine (III) reagents in their racemic forms as effective oxidants for sulfide–sulfoxide oxidation. Furthermore, enantiopure sulfoxides could be obtained by resolving these reagents with chiral HPLC before oxidising them to the corresponding hypervalent iodine reagents.

Table 2.1. Synthesis of sulfoxides by various hypervalent iodine reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>I(III)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>115</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>116</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>117</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>118</td>
<td>45</td>
</tr>
</tbody>
</table>

<sup>a</sup> isolated yield.
2.7.5.2. Hofmann Rearrangement

Hypervalent iodine compounds were applied as useful reagents for oxidative rearrangements owing to their properties as electrophiles and a good leaving group.\(^{32}\) Numerous hypervalent iodine reagents can convert amides to ureas or carbamates via the Hofmann rearrangement under mild conditions as an alternative to toxic reagents.\(^{33}\) The investigation of the reactivity of reagents (115–118) towards the Hofmann rearrangement was carried out under known conditions to obtain carbamate. Benzamide 121 was treated in methanol in the presence of 1.2 equivalents of iodine (III) reagents 115, 116, 117, or 118 while refluxing for 6 h. The desired carbamate 122 was obtained in acceptable yields (26%–57%), and the corresponding results are summarised in Table 2.2. Initially, hypervalent iodine reagents oxidised the benzamide to an isocyanate intermediate, and then, the nucleophilic attack of alcohol yielded the desired carbamate. Interestingly, iodine (III) reagents containing 3° anilide skeletons (116 and 118) formed carbamate in 57% and 43% yields, respectively, and they proved to be more efficient reagents than iodine (III) reagents containing 2° anilide skeletons (115 and 117), irrespective of the ligands bound to the iodine atom. However, an examination of the bounded ligands revealed that the iodine (III) reagent 116 with tosyl ligands seemed to pre-form the desired product in a better yield (57%) than the others.
Table 2.2. Synthesis of carbamate by using various hypervalent iodine reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>I(III)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>115</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>116</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>117</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>118</td>
<td>43</td>
</tr>
</tbody>
</table>

<sup>a</sup> isolated yield.

2.7.5.3. Dearomatisation of Phenols

Among the numerous applications of hypervalent iodine reagents, the oxidative dearomatisation strategy is synthetically important, particularly in the total synthesis of many natural products. The oxidative dearomatisation of phenols in the presence of external nucleophiles can lead to the formation of quinone derivatives. The new synthesis of hypervalent iodine reagents (115–118) was carried out to evaluate their reactivity towards phenol dearomatisation using the known mild condition. The dearomatised phenol was obtained using the known method in which 1.2 equivalents of iodine (III) reagents was treated.
with 2,4-dimethylphenol 123 in the presence of an MeCN-H₂O solvent combination for 16 h at room temperature. As shown in Table 2.3, the desired product 124 was formed in only 16% yield when phenol reacted with reagent 117, which contained 2° anilide with phenyl rings. The use of iodine (III) reagents based on 3° anilide with phenyl rings 118 slightly improved the yield to 21% (entry 4). Further improvement was observed upon the use of both reagents 115 and 116, which displayed a pyridine core to form the desired dearomatised phenol in 26% and 42% yields (entries 1 and 2). However, the iodine (III) reagent with 3° anilide and pyridine skeletons 116 achieved the best result among the considered reagents.

Table 2.3. Synthesis of dearomatised phenol by using various hypervalent iodine reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>I(III)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>115</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>116</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>117</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>118</td>
<td>21</td>
</tr>
</tbody>
</table>

<sup>a</sup> isolated yield.
2.7.5.4. Oxidative Dimerization

The most facile and efficient strategy for the synthesis of thiadiazoles is the oxidative dimerization of thioamides by using hypervalent iodine reagents.\textsuperscript{36,37} To evaluate the reactivity of the new hypervalent iodine reagents (115–118), the formation of 3,5-diphenyl-1,2,4-thiadiazole 126 was examined by using the established procedure. Thioamide 125 was treated with various hypervalent iodine reagents (115–118) in acetonitrile at room temperature for 16 h. The desired thiadiazole 126 was obtained in moderate to good yields (34%–77%). The corresponding results are summarised in Table 2.4. It seemed that the iodine (III) reagents containing pyridine rings 115 and 116 yielded better results (61% and 77%) than the reagents containing phenyl rings 117 and 118 (34% and 51%). However, the best result was achieved by using the iodine (III) reagent 116.

Table 2.4. Synthesis of 3,5-diphenyl-1,2,4-thiadiazole by various hypervalent iodine reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArI (III)</th>
<th>Yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>115</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>116</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>117</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>118</td>
<td>51</td>
</tr>
</tbody>
</table>

\textsuperscript{a} isolated yield.
2.8. Conclusion and outlook

The design and synthesis of C–N axial chiral hypervalent iodine reagents in racemic forms was successfully achieved using the simple amide formation strategy. Furthermore, these reagents exhibited unique rotation around a C–N bond with restricted rotation with bulky substituents around the established bond. However, N-alkylated anilides with the 3° anilide core exhibited acceptable reactivities in various symmetric reactions compared with the corresponding reagents with the 2° anilide core. In most cases, the iodine (III) reagents containing pyridine rings with tosyl ligands on iodine were more efficient oxidants than reagents with acetylate ligands on iodine. Therefore, it was worth resolving the enantiomeric forms of axial chiral hypervalent iodine reagents by using a preparative YMC column to obtain enantio-enriched reagents with $S_a$ and $R_a$ configurations. Furthermore, an evaluation of their potential in a number of enantioselective reactions could be valuable because some of the enantioselective transformations remain a challenging task.

The application of an additional chiral source to these reagents could facilitate their separation without the need for preparative HPLC columns. The addition of a new stereogenic centre to these reagents led to a separable mixture of diastereomers (Scheme 2.11), which were slightly easier to separate than enantiomers via crystallisation or column chromatography.
Moreover, an asymmetric reduction of amides would generate a new stereogenic carbon, which would in turn result in a mixture of diastereomers 127.

![Scheme 2.11. Asymmetric reduction of iodine reagents.](image)

The kinetic resolution of racemate compounds is another possible way to obtain enantiopure iodine reagents having the C–N axis. A similar compound was obtained with acceptable enantiopurity by using chiral lithium amide 129, where the desired anilide 130 resulted in an enantiomeric excess of 88% (Scheme 2.12). As a result, this strategy could be applied to achieve the enantiopure C–N axial chiral iodine reagents without the need to resolve the enantiomers by using preparative HPLC.

![Scheme 2.12. The synthesis of enantiopure anilide.](image)
2.9. References


Haifa Alharbi  
Synthesis of C–N Axial Chiral Hypervalent Iodine Reagents in Enantiomeric Form

*J. 2006, 12, 6039.*


Chapter 3

Synthesis of Novel C–N Axial Chiral Hypervalent Iodine Reagents
3.1. Introduction: Synthesis of C–N Axial Chiral Compounds

Axial chiral compounds have received increased attention over the years because of their structural features and wide applications.\textsuperscript{1,2} Axial chiral structures widely are represented in many natural products, bioactive molecules, chiral ligands, and catalysts has been used for various enantioselective transformations.\textsuperscript{1,3} The early efforts introduced the synthesis of axial chiral compounds as a racemate, but the later asymmetric synthesis or kinetic resolution of a racemic mixture has been widely recognised. To date, numerous strategies have been reported for the synthesis of chiral compounds processing a C–C or C–N axial chirality, such as enantio- or diastereoselective preparations and catalytic asymmetric synthesis. Among them, catalytic asymmetric methods are one of the most efficient approaches for the synthesis of axial chiral compounds in an optically enriched form.

3.1.1. Enantioselective Synthesis

Using the kinetic resolution strategy, each of the enantiomers are separated from the racemic mixture employing an appropriate resolving reagent. Simpkins and co-workers reported the enantiopure formation of anilide 130 through the kinetic resolution of racemic anilide 128 with a substoichiometric amount of a chiral lithium amide base 129 (Scheme 3.1).\textsuperscript{4} Enantiopure anilide 130 was obtained with a reasonable enantiomeric excess (88\% $ee$) along with the recovery of the unreacted anilide after methylation.
3.1.2. Diastereoselective Synthesis

The diastereoselective synthesis of C–N axial chiral compounds was realised by reacting optically pure chiral compounds with molecules containing a pre-existing C–N bond, such as aniline or anilide, through a chiral pool approach. With an additional stereogenic unit, the axial chiral molecule would lead to the formation of diastereoisomers, allowing their easy separation. Vallverdú and co-workers reported the more stable and crystalline diastereoisomers 133a and 133b by treating anilide derivatives 131 with (S)–O–acetyl lactoyl chloride 132 to form a mixture of diastereoisomers in a 1:1 ratio (Scheme 3.2). The two diastereomers were easily separated by flash chromatography.

Scheme 3.1. Enantioselective synthesis of C–N axial chiral compounds.

Scheme 3.2. Diastereoselective synthesis of C–N axial chiral compounds.
3.1.3. Catalytic Asymmetric Synthesis

Instead of using stoichiometric amounts of a chiral reagent, enantioselective formation of C–N axial chiral compounds have been synthesised using a chiral catalyst undergoing a catalytic cycle.\(^6\) A successful catalytic enantioselective synthesis of axial chiral anilides have been reported by Taguchi and co-workers by using a chiral Pd catalyst with 4-iodonitrobenzene 135 (Scheme 3.3).\(^7\)\(^-\)\(^9\) Intra- and intermolecular \(N\)-arylation was applied to achiral anilides 134 to obtain the optically active axial chiral anilides 137 with very high stereoselectivities (88\%–96\% ee) due to the formation of a C–N bond near the chiral ligand of the Pd catalyst.\(^9\)

\[ 
\text{R} \quad \text{O} \quad \text{NH} \quad \text{t-Bu} \\
\text{134} 
\]

\[ 
\text{R} \quad \text{O} \quad \text{N} \quad \text{Ar} \quad \text{t-Bu} \\
\text{137 (88-96\% ee)} 
\]

\[ 
\text{5 mol\% (R)-DTBM-SEGPHOS 136} \\
\text{3.3 mol\% Pd(OAc)\textsubscript{2}} \\
\text{1.4 eq t-BuOK} \\
\text{toluene, 80 °C, 2-6 h} \\
\text{R= Me, Et, i-Pr, cyclobexyl, MeCH=CH} \\
\text{Ar= 4-nitrophenyl} 
\]

**Scheme 3.3.** Catalytic enantioselective synthesis of C–N axial chiral compounds.
3.2. Objectives

The aim of this study was to synthesize a new family of hypervalent iodine compounds with axial chiral backbones with a restricted rotation around the C–N axis. Because of the challenges to separate axial chiral compounds in the enantiomeric forms (discussed in the previous chapter), an additional stereogenic centre could solve these challenges by forming pairs of diastereomers, which could be easily separable. Additionally, most of the axial chiral iodine reagents have been designed using biaryl systems, which contain phenyl or naphthyl backbones, and their synthesis routes are typically long. C–N axial chiral iodine compounds have remained unexplored even though they can be made using a simple chiral pool strategy. Thus, diastereoselective synthesis is planned for designing C–N axial chiral iodine reagents by using 2-iodoaniline derivatives and chiral lactate.

The 2-iodo aniline derivatives, which have a pre-existing C–N bond, were selected as the backbone for the design. Then, different bulky substituents could be attached to the aniline moiety to obtain a stable configuration (Figure 3.1). This strategy could be a simple and facile in three steps without involving any expensive metal catalyst or reagents. The use of this strategy would lead to the formation of a pair of diastereoisomers that could possibly be separated easily compared to enantiomers. The isolated axial chiral iodine reagents could be oxidized to the corresponding hypervalent iodine reagents. Following this, the investigation of their potential towards different enantioselective transformations could be explored.
3.3. Results and Discussion

3.3.1. Synthesis of C–N Axial Chiral Iodoarenes

The catalytic asymmetric strategy for designing axial chiral compounds is a relatively efficient strategy, but this strategy requires a complex or expensive catalyst. The chiral resolution strategy is another strategy enabling access to axial chiral compounds by using lactate esters, which avoids the use of complex or expensive catalysts and reagents. The synthesis of axial chiral iodine reagents was accomplished by using a three-step strategy; reacting a simple substituted aniline skeleton with chiral lactate esters. The iodine atom needs to be in the ortho position to the aniline skeleton to ensure a restricted rotation around the axis, which could be done through the electrophilic iodination of anilines.\textsuperscript{10} The iodine was reacted with 2,4-disubstituted anilines 107 and 138 in the presence of sodium bicarbonate to form the corresponding iodoanilines 108 and 139 in 88\% and 40\% yield, respectively (Scheme 3.4). The obtained iodoaniline derivatives were converted to racemic sulfonamides 140a–d in good yields by using sulfonyl chloride derivatives,
namely $p$-tosyl chloride (TsCl), 4-nitobenzenesulfonyl chloride (NsCl), and $p$-anisylsulfonyl chloride (AnCl) in the presence of pyridine. The selection of different protected sulfonyl chlorides could serve as a useful precursor for an easy separation of the resulting diastereomeric compounds in the following step.\(^\text{11}\) After the design of the axial chiral backbone, an additional stereogenic centre was established in the resulting sulfonamides using a Mitsunobu reaction to form chiral iodine reagents with $\text{C}_\text{Ar}–\text{N}$ axial chirality and a stereogenic carbon. In the Mitsunobu reaction, the enantiomerically pure lactates were treated with the sulfonated aniline skeletons 140a–d in the presence of triphenylphosphine ($\text{PPh}_3$) and diisopropyl azodicarboxylate (DIAD) to afford two diastereomers.

\[ \text{Scheme 3.4. Synthesis of novel C–N axial chiral iodoarenes 141a–j. Ts: 4-toluenesulphonyl; Ns: 3-nitrobenzenesulphonyl; An: 4-methoxybenzenesulphonyl.} \]

The obtained diastereoisomers were separated by column chromatography to afford the $S_{\text{C–N}}, R$ diastereomer as the major isomer and the $R_{\text{C–N}}, R$ diastereoisomer as the minor isomer. In all the cases with the $de$ ranging from 10% to 30%. Therefore, novel optically active C–N axial
chiral iodine reagents 141a–j with the restricted rotation around the C–N axis were synthesised in reasonable yields using a simple and fast three-step strategy (Figure 3.2).

![Library of novel C–N axial chiral iodoarenes 141a–j](image)

**Figure 3.2.** Library of novel C–N axial chiral iodoarenes 141a–j.

The synthesis of these chiral iodoarenes was focused mainly on the variation of R\(^1\) substituents attached to the nitrogen atom, which were sulfonayl compounds such as nosyl, tosyl, and anisyl. After oxidation, these iodoarenes acted as a chiral hypervalent iodine (III). Different R\(^1\) or R\(^2\) substituents close to the iodine could influence the selectivity of asymmetric transformations. Moreover, the effect of the substituents R and R\(^2\) towards the change in electron density on the aromatic ring were investigated along with the effects of the different substituents of lactate esters (Figure 3.2).
The absolute configurations of the C<sub>Ar</sub>–N axial chiral iodoarenes were determined by X-ray crystal structure analyses (Figure 3.3). In both compounds 141a and 141b, the two different substituents bearing the nitrogen were perpendicular to the aniline ring, while the iodine in compounds 141a was out of the plane compared with that in 141b. Furthermore, other X-ray structures (141d, 141e, and 141h) were assigned to their corresponding configurations (Figure 3.4).

**Figure 3.3.** X-ray structures of C–N axial chiral iodoarenes 141a and 141b.
3.3.2. Synthesis of C–N Axial Chiral Hypervalent Iodoarenes

In order to access the C–N axial chiral hypervalent iodoarenes, the typical method was applied to the iodine reagent 141a using sodium perborate NaBO$_3$·4H$_2$O in the presence of acetic acid at 45°C. However, the complete conversion of iodoarene 141a into the corresponding hypervalent iodoarene 142a was not reached even if more amount of oxidant or more time was used under the same conditions. Then, the oxidation was carried out by the treatment with Selectfluor® in acetic acid and acetonitrile for 16 h. The formation of the hypervalent iodine reagent 142a was achieved in a reasonable yield of 87%. The same oxidation reaction conditions were applied for 141b, that resulted in the corresponding hypervalent iodoarene 142b in good yield, 87%. The reaction conditions were investigated for various iodoarenes to produce the
corresponding hypervalent iodoarene 142a–j in good to excellent yields (86%–94%), as shown in Table 3.1. Iodoarenes bearing tosylated substituents 141c and 141d, which have either the S_{C–N} or the R_{C–N} configuration, were reacted with Selectfluor® for 16 h to achieve the formation of hypervalent iodoarenes 142c and 142d in good yields. Similarly, the hypervalent iodoarenes 142e and 142f were obtained in good yields of 93% and 90%, respectively. The yields of the hypervalent iodoarenes 142g and 142h increased slightly to 94% and 93%, respectively, where chlorine was in the para position of the anilide backbone. Finally, the formation of the hypervalent iodoarenes 142i and 142j decreased slightly to 86% and 87%, respectively. The formation was confirmed by $^1$H NMR spectroscopy where the proton close to iodine was shifted downfield. Additionally, the $^1$H NMR observation of these C–N axial chiral hypervalent iodoarenes showed a single peak for the acetoxy group, which established that the iodine could coordinate with the nearby heteroatom along with the acetoxy group. The presence of the I–O bond was detected by the IR analysis at 810 cm$^{-1}$. However, attempts to grow X-ray-quality crystals of the hypervalent iodoarenes were unsuccessful; thus, the coordination between the iodine centre and the nearby heteroatom could not be determined at this point.
Table 3.1. Oxidation of C–N axial chiral iodine reagents

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<thead>
<tr>
<th>Entry</th>
<th>Ar’I</th>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>142 Yield (%)</th>
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<tr>
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<td>Me</td>
<td>NO₂</td>
<td>Me</td>
<td>87</td>
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<tr>
<td>2</td>
<td>141b</td>
<td>Me</td>
<td>NO₂</td>
<td>Me</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>141c</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>91</td>
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<tr>
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<td>86</td>
</tr>
<tr>
<td>10</td>
<td>141j</td>
<td>Me</td>
<td>NO₂</td>
<td>Bn</td>
<td>87</td>
</tr>
</tbody>
</table>
3.3.3. Enantioselective Transformation Reaction using C–N Axial Chiral Hypervalent Iodine Reagents

Hypervalent iodine reagents have been widely used as stoichiometric or catalytic oxidants for numerous enantioselective transformations.\textsuperscript{12-14} To date, numerous hypervalent iodine reagents with different chiral sources have achieved highly enantiocontrolled outcomes towards asymmetric transformations because of their ability to provide a suitable chiral environment around iodine.\textsuperscript{13} However, it is to note that limited applications were investigated using axial chiral hypervalent iodine reagents even though they obtained reasonable success in asymmetric applications.\textsuperscript{15-17} Thus far, axial chiral hypervalent iodine reagents have successfully resulted in high enantioselectivities for the oxidative spirolactonization of phenol derivatives, known as the Kita reaction.\textsuperscript{18-20} Additionally, chiral hypervalent iodine reagents processing axial chirality achieved moderate enantioselectivity (67\% \textit{ee}) for the asymmetric $\alpha$-oxytosylation of ketones even though the improved enantioselectivity is still desirable.\textsuperscript{15} Thus, it is highly attractive to investigate the potential of C–N axial chiral hypervalent iodine reagents in a stoichiometric or catalytic manner for wide asymmetric applications, including the functionalisation of an alkene or ketone, rearrangement, and oxidative dearomatization.
3.3.4. Enantioselective Transformations in A Stoichiometric Manner

3.3.4.1. Enantioselective Oxidative Rearrangement of Alkenes

Hypervalent iodine reagents can promote oxidative rearrangement through the migration of one of the substituents on the double-bond system in a single step to generate α-arylated ketones. Thus, the reactivity and the enantioselectivity of the new C–N axial chiral hypervalent iodine reagents 142a–j were investigated through the oxidative rearrangement of alkenes, where these reagents were studied as stoichiometric oxidants. The reaction of 1,1-diphenylpentene 143 with C–N axial chiral iodine (III) reagents 142a–j (1.2 equivalents) was investigated in the presence of p-TsOH·H₂O and methanol at −78 °C.²¹ The desired α-arylated ketones 144 were generated in acceptable yields (20%–58%), and only with reagents 142a and 142i (entries 1 and 9). The enantiomeric excess of the desired α-arylated ketones 144 was reasonable (39%–84% ee) except for reagents 142i (33% ee, entry 9) and 142j (35% ee, entry 10). The best results were achieved using reagent 142h (entry 8) where (R)-144 was generated in moderate yield (58%) and with good enantioselectivity (84% ee). In contrast, reagent 142c (entry 3) provided the best results for the opposite enantiomer (S)-144. The absolute configuration of the desired products was determined by the comparison of the optical rotation of the reported product. Interestingly, the obtained enantiomers were affected by the configuration of the C–N axial chirality, where the Rₐ configuration always formed 144 with the (R)-configuration. This implied that enantioinduction was mostly dominated by axial chirality and not by the stereogenic carbon in the lactate moiety.
Table 3.2. Enantioselective oxidative rearrangement of alkenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar*I(III)</th>
<th>Yield [%]a</th>
<th>ee [%]b</th>
<th>Configurationc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>142a</td>
<td>16</td>
<td>44</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>142b</td>
<td>38</td>
<td>42</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>142c</td>
<td>47</td>
<td>81</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>142d</td>
<td>52</td>
<td>83</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>142e</td>
<td>48</td>
<td>39</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>142f</td>
<td>32</td>
<td>42</td>
<td>R</td>
</tr>
<tr>
<td>7</td>
<td>142g</td>
<td>41</td>
<td>71</td>
<td>S</td>
</tr>
<tr>
<td>8</td>
<td>142h</td>
<td>58</td>
<td>84</td>
<td>R</td>
</tr>
<tr>
<td>9</td>
<td>142i</td>
<td>13</td>
<td>33</td>
<td>S</td>
</tr>
<tr>
<td>10</td>
<td>142j</td>
<td>20</td>
<td>35</td>
<td>R</td>
</tr>
</tbody>
</table>

a isolated yields.  b determined by chiral-phase HPLC analysis.  c determined by comparison with literatures.21
3.3.5. **Enantioselective Transformations in A Catalytic Manner**

The ability to use hypervalent iodine reagents catalytically, has been an active area for the development of numerous stereoselective applications. In the catalytic methods, iodine reagents are used as catalysts with a co-oxidant, which is added in stoichiometric amounts to generate the corresponding hypervalent iodine reagents *in situ* (Figure 3.5). To date, many co-oxidants have been used to promote asymmetric transformations, such as *m*CPBA, Oxone®, Selectfluor®, hydrogen peroxide, and peracetic acid. The iodine reagents do not have to be isolated since purification can be difficult. Besides the advantage of avoiding the considerable wastage produced in stoichiometric methods, the reduced iodine compounds can be re-oxidised and reused after the oxidative transformation in catalytic methods. Accordingly, various catalytic reactions can be applied using C–N axial chiral iodine reagents to investigate both their ability to be a catalyst and their reactivity and enantioselectivity. The catalytic enantioselective version of the α-oxytosylation of ketones, lactonization of acids, and dearomatization of phenols was examined using the C–N axial chiral iodine reagents.

![Diagram](image)

**Figure 3.5.** The catalytic method.
3.3.5.1. Enantioselective α-Oxytosylation of Ketones

The introduction of nucleophiles to the α-position of ketones was investigated by using the C–N axial chiral iodoarenes (141a–j) and applying the reported standard reaction. Propiophenone 145 was treated with 3 equivalents of mCPBA and 3 equivalents of pTsOH·H2O in the presence of 0.1 equivalents of the C–N chiral iodine catalysts 141a–j in MeCN at room temperature for 72 h. The desired α-oxytosylated ketones 146 were formed in good to excellent yields for most of the catalysts, and only with catalyst 141j (entry 10) a low yield was obtained. Enantiomeric excess of the desired α-oxytosylated ketones 146 was observed in moderate to good (31%–67 % ee) except for catalysts 141h and 141j, which just achieved 21% ee and 9% ee, respectively (entries 7 and 9). The results are summarised in Table 3.3. The best results were achieved using reagent 141d (entry 4) where (S)-146 was generated in excellent reactivity (96%) and with good enantioselectivity (67% ee). In contrast, catalyst 141c (entry 3) provided the highest yield for the opposite enantiomer (R)-146.
Table 3.3. Catalytic enantioselective α-oxytosylation of ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar*I</th>
<th>Yield [%]a</th>
<th>ee [%]b</th>
<th>Configurationc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>141a</td>
<td>40</td>
<td>47</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>141b</td>
<td>85</td>
<td>40</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>141c</td>
<td>93</td>
<td>43</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>141d</td>
<td>96</td>
<td>67</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>141e</td>
<td>81</td>
<td>31</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>141f</td>
<td>78</td>
<td>59</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>141g</td>
<td>20</td>
<td>55</td>
<td>R</td>
</tr>
<tr>
<td>8</td>
<td>141h</td>
<td>53</td>
<td>9</td>
<td>S</td>
</tr>
<tr>
<td>9</td>
<td>141i</td>
<td>62</td>
<td>64</td>
<td>R</td>
</tr>
<tr>
<td>10</td>
<td>141j</td>
<td>45</td>
<td>21</td>
<td>S</td>
</tr>
</tbody>
</table>

a isolated yields. b determined by chiral-phase HPLC analysis. c determined X-ray and comparison with literatures.22
The absolute configuration of the desired product 146 was determined by using single-crystal X-ray diffraction (Figure 3.6). As discussed before, these catalysts have two chiral units processing the C–N axial chirality in the backbones and the stereogenic carbon in the lactate moiety. Furthermore, the chiral induction of the desired products 146 was influenced by the C–N axial chirality of the catalysts and not by the carbon stereogenic centre. Thus, the $S_C$. $N$ configuration of the catalyst always produced 146 with $(R)$-configuration. This reaffirmed that enantioselective induction was mostly dominated by the axial chirality and not by the stereogenic carbon in the lactate moiety.

![Figure 3.6. X-ray structure of α-oxytosylated propiophenone 146a.](image)

### 3.3.5.2. Enantioselective Lactonization of Acids

Hypervalent iodine catalysts were also investigated for oxylactonization of acyclic keto carboxylic acids to obtain a useful five membered $o$-heterocyclic compounds. The enantioselective lactonization of 5-oxo-5-phenylpentanoic acid was selected for the investigation of the influence on the stereogenic carbon and the axial chirality of the prepared C–N axial chiral iodine catalysts by applying the reported method. 5-Oxo-5-phenylpentanoic acid 147 was reacted
with 0.1 equivalents of chiral iodine catalysts 141a–j, using 1.2 equivalents of mCPBA as the oxidant in the presence of a catalytic amount of $\rho$TsOH·H₂O. Noted that the direct oxidative cyclization required longer reaction times, and the use of the catalytic amount of $\rho$TsOH·H₂O was needed to form an active catalyst of the hypervalent iodine species via the ligand exchange pathway. The desired product 5-benzoyldihydrofuran-2(3H)-one 148 was obtained in low to moderate yields (up to 43%) and in acceptable to good enantioselectivities (up to 70% $ee$). The results are summarised in Table 3.4. The best results were obtained using catalyst 141h, where the (S)-ketolactone (entry 8) was obtained in moderate yield (43%) and with good enantioselectivity (70% $ee$). In contrast, the opposite enantiomer $R$ configuration of the ketolactone was obtained in trace or low yield in most cases, but with moderate enantioselectivities (up to 50% $ee$). However, the best result so far for the desired ($R$)-ketolactone was observed 28% yield with 50% $ee$ using the catalyst 141c. Interestingly, the provision of both the enantiomers of ketolactone 148 was again dominated by the axial chirality of the catalysts, where catalysts with the $R_{C-N}$ configuration always formed the (S)-enantiomers and the (R)-enantiomers were generated by the catalysts featuring the $S_{C-N}$ configuration. As with the catalytic enantioselective α-oxytosylation of ketone, the configuration of the desired lactone seemed to be controlled by the C–N axial chirality and not by the stereogenic carbon in the lactate moiety. This provided further proof in terms of the chiral induction of the C–N axial chirality, which controlled the stereogenic centre of the obtained ketolactone compared with the stereocentre in the lactate moiety of the design catalysts.
Table 3.4. Catalytic enantioselective lactonization of acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar*I</th>
<th>Yield [%]a</th>
<th>ee [%]b</th>
<th>Configurationc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>141a</td>
<td>trace</td>
<td>6</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>141b</td>
<td>18</td>
<td>37</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>141c</td>
<td>28</td>
<td>50</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>141d</td>
<td>20</td>
<td>45</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>141e</td>
<td>26</td>
<td>32</td>
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<tr>
<td>6</td>
<td>141f</td>
<td>12</td>
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<td>7</td>
<td>141g</td>
<td>17</td>
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<td>R</td>
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<tr>
<td>8</td>
<td>141h</td>
<td>43</td>
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<tr>
<td>9</td>
<td>141i</td>
<td>trace</td>
<td>38</td>
<td>R</td>
</tr>
<tr>
<td>10</td>
<td>141j</td>
<td>24</td>
<td>1</td>
<td>S</td>
</tr>
</tbody>
</table>

*a isolated yields. *b determined by chiral-phase HPLC analysis. *c determined by comparison with literatures.25
3.3.5.3. Enantioselective Dearomatisation of Phenols

Oxidative dearomatisation reactions are very remarkable and highly useful in total synthesis, particularly in the enantioselective manner. Many natural products are prepared using the dearomatisation methodologies of arenes, phenols, and heteroaromatic compounds. Hypervalent iodine reagents can be used in the enantioselective phenol dearomatisation reaction under mild reaction conditions compared to explored common oxidants. However, a limited number of hypervalent iodine reagents control the catalytic enantioselective dearomatisation of phenols. Thus, the enantioselective synthesis of \( p \)-quinol derivative was investigated by using C–N axial chiral iodine catalysts 141a–j to determine their potential in oxidative dearomatisation reactions. 2-Bromo-4-methylphenol 149 was dearomatised to the corresponding \( p \)-quinol derivatives 150 by using 2.2 equivalents of the oxidant \( m \)CPBA in the presence of 0.1 equivalents of chiral iodine catalysts 141a–j in a mixture of acetone and water solvent, using a reported procedure. The results are summarised in Table 3.5. The desired dearomatized phenols 150 were obtained in moderate to good yields (31%–89%), but with a low enantioselectivities (maximum up to 21% \( ee \)). Among the screened catalyst, 141d provided the highest yield of 89% and 141c 81% respectively. Similarly, the maximum stereoselectivity for the dearomatized product 150, was observed for 141c (20% \( ee \)) and 141h (21% \( ee \)). It is interesting to note that, the product 150 had the same configuration and is independent of the configurations of \( R_{C:N} \) and \( S_{C:N} \) in the catalyst.
Table 3.5. Catalytic enantioselective dearomatisation of phenols

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar*I</th>
<th>Yield [%]</th>
<th>ee [%]b</th>
<th>Configuration[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>141a</td>
<td>50</td>
<td>10</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>141b</td>
<td>72</td>
<td>15</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>141c</td>
<td>81</td>
<td>20</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>141d</td>
<td>89</td>
<td>16</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>141e</td>
<td>31</td>
<td>6</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>141f</td>
<td>42</td>
<td>18</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>141g</td>
<td>49</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>8</td>
<td>141h</td>
<td>45</td>
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<td>41</td>
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<td>S</td>
</tr>
<tr>
<td>10</td>
<td>141j</td>
<td>35</td>
<td>16</td>
<td>S</td>
</tr>
</tbody>
</table>

*a* isolated yields. *b* determined by chiral-phase HPLC analysis. *c* determined by comparison with literatures.²⁷
3.4. Conclusion and Outlook

A novel class of chiral hypervalent iodine reagents possessing the axial and centre chirality was established using a simple chiral pool strategy. The design of these chiral reagents was mainly focused on the establishment of a restricted rotation around a C–N axis where the centre chirality was demonstrated to solve the separation issue of generating C–N-enriched pure reagents. The treatment of 2-iodo aniline derivatives with chiral lactates successfully generated the C–N axial chiral iodine reagents in enriched forms. Different substituents R, R¹, and R² were used for studying their influence on enantioselective transformations. As shown in Figure 3.7, the substituents R¹ were close to the iodine atom and both R and R² were investigated to determine the change in the electron density on the aromatic ring along with the effect of another substituent on the chiral carbon.

![Diagram of C–N axial chiral iodine compounds](image)

Figure 3.7. Design of C–N axial chiral iodine compounds.
These reagents were oxidised to their corresponding hypervalent iodine reagents, which were applied to the oxidative rearrangement of alkenes. The enantioselectivity of the rearranged products proved the potential of these reagents to be used as stoichiometric oxidants and to induce stereoselective reactions. Alternatively, the C–N axial chiral iodine reagents were examined as catalytic oxidants for the α-oxytosylation of ketones, lactonization of acids, and dearomatisation of phenols. Although the stereoselectivity remained low to moderate in the lactonization of acids and the dearomatisation of phenols, the α-oxytosylation of ketones exhibited promising results, which could be improved, as will be discussed in the following chapter. Interestingly, the obtained enantiomers of the enantioselective transformations were affected by the C–N axial chirality of the reagents, whereas the centre chirality in the lactate moieties did influence the configuration of the enantiomers. However, there are still possibilities to obtain highly enantioenriched products by optimising the reaction conditions for the lactonization of acids, dearomatisation of phenols, and the α-oxytosylation of ketones.

Axial chiral iodoarenes containing a chiral C–N axis have rarely been explored in the area of hypervalent iodine chemistry. Thus, C–N axial chiral iodoarenes open up an opportunity to explore further in the context of other enantioselective transformations either in stoichiometric amount or in the catalytic applications.
Because the synthetic method for designing C–N axial chiral iodoarenes is facile and rapid, a wide range of chiral iodoarenes containing the chiral C–N axis could be furnished by the variety of R, R¹, R², R³ and R⁴. Different stereogenic centres could be introduced into the substituted anilines to enhance the chiral environment surrounding the iodine, and then, their effects on enantioselective transformations could be investigated.
3.5. References


Chapter 4

Catalytic Stereoselective α-Oxytosylation of Ketones

This work has been published

4.1. Introduction of Stereoselective α-Oxytosylation of Ketones

Chiral hypervalent iodine reagents have been used in a broad range of useful oxidative transformations. In particular, the enantioselective α-oxytosylation of ketones is a very important building block to access numerous natural products, pharmaceuticals, heterocyclic systems, and useful synthetic intermediates in organic synthesis.\textsuperscript{1-4} The introduction of a good leaving group such as tosyl in the α-position of ketones can be followed by nucleophilic displacement to access important building blocks. The α-oxytosylation reaction was initially established by Koser and co-workers using [hydroxy-(tosyloxy)iodo] benzene (HTIB) with ketone 151 to form the desired oxytosylated product 152 (Scheme 4.1).\textsuperscript{5,6}

\begin{center}
\textbf{Scheme 4.1.} First α-oxytosylation reaction.
\end{center}

Following Koser’s procedure, Wirth and co-workers designed a chiral hypervalent iodine reagent 153, which was similar to an HTIB structure and promoted the first asymmetric α-oxytosylation of ketones (Scheme 4.1).\textsuperscript{7} However, the desired oxytosylated ketone 146 suffered from a low stereoinduction, which led to many efforts to develop alternative hypervalent iodine reagents or other synthetic methods. Accordingly, the catalytic utilisation of chiral hypervalent iodine reagents and their design have been demonstrated to improve the enantioselectivity of the desired α-oxytosylated ketones. Increasing efforts have been reported for reaching high
enantioselectivities, and the α-oxytosylation of ketones has been demonstrated to be the most challenging and explored transformation.\(^8\)

![Scheme 4.2. Asymmetric α-oxytosylation of ketone.](image)

A seminal effort was reported by Legault and co-workers which reached high enantioselectivities of up to 90 % \(ee\) of the α-oxytosylated ketones, like 146, using the enol ester 154 instead of the ketone (Scheme 4.3).\(^9\) Currently, the highest enantioselectivity of the direct α-oxytosylation of ketones is 88% \(ee\), which was achieved by Nachtsheim and co-workers (Scheme 4.5.).\(^{10}\)

![Scheme 4.3. Enantioselective iodine (III)-mediated synthesis of α-oxytosylerd ketones.](image)
4.1.1. Stoichiometric Stereoselective α-Oxytosylation of Ketones

The stoichiometric utilisation of hypervalent iodine reagents is broadly applicable to various useful transformations. In the stoichiometric process, the oxidation step is required for the conversion of iodine(I) reagents into their corresponding hypervalent iodine reagents before performing the aimed transformation. To the best of our knowledge, a limited number of chiral hypervalent iodine reagents as a stoichiometric oxidant to promote the asymmetric α-oxytosylation of ketones was investigated.\textsuperscript{7,11} Wirth and co-workers designed and modified a series of ortho-substituted chiral hypervalent iodine reagents in order to improve the enantioselectivity from 10% ee to up to 40% ee (Scheme 4.4). The improvements were claimed to be the result of supportive effects between the ortho substituent to the iodine atom and the size of the substituent, where the best enantioselectivity was achieved with reagent 153, which bore the ortho ethyl substituent.

\begin{center}
\textbf{Scheme 4.4.} Stoichiometric stereoselective α-oxytosylation of ketone.
\end{center}
To date, there have been no further studies on the use of chiral hypervalent iodine reagents as stoichiometric oxidants towards this reaction. Instead, the efforts have been focused on the catalytic utilisation of these reagents because stoichiometric oxidants are a disadvantage in terms of the principles of Green Chemistry.

4.1.2. Catalytic Stereoselective $\alpha$-Oxytosylation of Ketones

As discussed in the previous section, an additional oxidation step is required to obtain hypervalent iodine reagents after the synthesis of iodine(I) reagents in stoichiometric transformation reactions. Moreover, stoichiometric amounts of iodine(III) reagents are required to perform the reactions. Thus, a large amount of waste, in terms of iodine reagents, is often problematic. Consequently, researchers have recognised the catalytic use of iodine reagents can help to avoid the cost, waste, and toxicity issues. The first catalytic performance was demonstrated by both Ochiai and Kita through the in situ generation of hypervalent iodine reagents, where a catalytic amount of iodine reagent was oxidised by mCPBA as a co-oxidant.\textsuperscript{12,13} With respect to the enantioselective $\alpha$-oxytosylation, Wirth and co-workers disclosed the first catalytic use of chiral iodine reagents towards this reaction, and 39% ee of $\alpha$-oxytosylated ketone 146 was obtained.\textsuperscript{14} After this achievement, numerous chiral iodine catalysts have been designed to achieve the high enantioselectivity of the $\alpha$-oxytosylation of ketones, and different strategies have been explored. To briefly demonstrate the catalytic performance of chiral hypervalent iodine reagents towards the enantioselective $\alpha$-oxytosylation of ketones, a series of the most selective catalysts is shown in Scheme 4.5.\textsuperscript{10,14-18} The highest enantioselectivity was obtained as 90% ee of $\alpha$-oxytosylated ketone 146 by Legault and co-workers using enol esters 154 instead of ketones as the
starting substrates.\textsuperscript{9} Even though the \textit{in situ} generation methodology of hypervalent iodine reagents was applied, a stoichiometric amount of chiral iodine reagents was required to access this enantioselectivity besides the use of enol esters. Furthermore, Nachtsheim and co-workers reported the highest enantioselectivity (up to 88\% \textit{ee}) towards the direct enantioselective α-oxytosylation of ketones by using the triazole-substituted aryl iodide catalyst 164.\textsuperscript{10}

\begin{center}
\textbf{Scheme 4.5.} Series of most selective catalysts for stereoselective α-oxytosylation of ketone.
\end{center}
4.2. Use of Axial Chiral Hypervalent Iodine Reagents for α-Oxytosylation

As a part of the research interest on axial chirality, the efforts to control the stereoselective α-oxytosylation of ketones, achieved by using axial chiral iodine reagents, will be summarised. The first attempt for designing axial chiral iodine reagents was reported by Zhang and co-workers to control the stereoselective α-oxytosylation of ketones.\(^{19}\) The rigid spiroindane backbone \(^{157}\) was introduced to construct the chiral iodine reagents through several steps, where two rings in 1,1′-spirobiindane were rigidly linked via σ bonds at a quaternary centre. The rigid structure of the chiral iodine reagents delivered 58% \(ee\) of the desired α-oxytosylated ketones \(^{146}\) by using the catalytic process described in the previous section. Subsequently, other axial chiral iodine reagents were designed by Berthiol, Einhorn, and co-workers to improve the enantioselectivity of the α-oxytosylated ketones. Such catalysts possessed restricted rotation around the C–C of the biaryl skeletons \(^{162, 163}\) and \(^{165–171}\).\(^{17, 20}\) The influence of the different modifications of the structure of the axial chiral iodine reagents was examined to enhance chiral induction, including the maleimide, the BINOL, and biphenol moieties, and the close substituents to iodine. With these modifications, the desired α-oxytosylated ketones were obtained in 46% \(ee\) by using the axial chiral iodine reagent with BINOL-fused maleimides. Recently, a notable improvement was reported by Masson and co-workers where the desired enantioenriched ketone was furnished in 67% \(ee\).\(^{18}\) This achievement was delivered by using the chiral iodine reagent \(^{163}\), which contains the restricted rotation around biphenyl skeletons. Despite this significant progress, only the axial chiral iodine reagents, briefly described in Scheme 4.6, have been reported to date.
Scheme 4.6. Axial chiral iodine catalyst for enantioselective α-oxytosylation of ketones
4.3. Possible Mechanism of Catalytic α-Oxytosylation of Ketones

There are two possible paths to promote the catalytic α-oxytosylation of ketones, which have been reported for accessing the higher enantioselectivity of the α-oxytosylated ketones.9,8 After the generation of hypervalent iodine reagents by reacting with mCPBA and pTsOH·H2O, the ketones in two different forms, 172 and 173, could react with the iodine(III) reagents through two possible pathways. The first pathway proceeds through an O-bonded intermediate, 174a, using an iodine (III)-mediated ketone form. The second pathway involves the iodine(III)-mediated enol form of the ketone acting through the C-bonded intermediate 174b (Figure 4.1). In both pathways, the intermediates react with an oxytosylated anion via nucleophilic substitution, of the types SN2' and SN2, to form the chiral α-oxytosylated ketones 175. Simultaneous regeneration of the iodine precatalysts in the following reductive elimination step also occurs.

![Figure 4.1. Plausible mechanism for catalytic α-oxytosylation of ketones.](image-url)
4.4. Objectives

Various chiral iodine reagents have been explored to reach the highest enantioselectivity of α-oxytosylated ketones, and this has become a challenging transformation.

The highest enantioselectivity recently achieved was 88% ee by using the triazole-substituted aryl iodide catalysts, but noticeable progress has been achieved for this reaction by using axial chiral iodine catalysts. Although, the design of axial chiral compounds, processing restricted rotation around binaphthyl and biphenyl backbones bearing iodine, is still highly desirable. Other axial chiral compounds, different from biaryl systems, could also be used to achieve high stereoinduction. The aim was to investigate the potential of alternative types of axial chirality in chiral iodine catalysts, possessing the C–N stereogenic axis, towards the catalytic enantioselective
α-oxytosylation of ketones. According to the previous chapter, the promising results of the α-oxytosylated ketones, obtained using C–N axial chiral iodine catalysts, encouraged the evaluation of various other reaction parameters to achieve superior results. These investigations included the optimisation of the reaction parameters such as solvents, temperature, and the use of different equivalents of both the oxidant and the nucleophile. Accordingly, the scope of this reaction was explored under the optimal conditions, including a range of aromatic and aliphatic ketones with different substituents in different positions. Because C–N axial chiral iodine catalysts have two chiral sources, namely axial and centre, their influence on the configuration of the obtained ketones was examined. Finally, the use of other sulfonic acids and nucleophiles will also be discussed.

4.5. Results and Discussion

4.5.1. Evaluation of C–N Axial Chiral Iodine Catalyst

![Library of novel C–N axial chiral iodoarenes](image)

Figure 4.3. Library of novel C–N axial chiral iodoarenes 141a–j.
The potential of novel optically active C–N axial chiral iodoarenes (141a–j), whose synthesis was discussed in the previous chapter, as organocatalysts for the stereoselective α-oxytosylation of ketones, was analysed. They could successfully control the desired α-oxytosylated ketones by using a procedure reported in the literature. Propiophenone 145 was treated with 3 equivalents of mCPBA and 3 equivalents of pTsOH·H₂O in the presence of 0.1 equivalents of the C–N chiral iodine catalysts 141a–j in MeCN at room temperature for 72 h.¹⁵ The desired α-oxytosylated ketones 146 were generated in good to excellent yields, except for catalyst 141j (entry 10). Accordingly, the enantiomeric excess of the desired α-oxytosylated ketones 146 was obtained with moderate to good enantiomeric excess (31%–67% ee), except for catalysts 141g and 141i, which just returned 21% ee and 9% ee, respectively (entries 7 and 9). The results are summarised in Table 4.1. The best results were achieved using reagent 141d (entry 4), where (S)-146 was generated in excellent yield (96%) and with good enantioselectivity (67% ee). In contrast, reagent 141c (entry 3) provided the best results for the opposite enantiomer (R)-146. The chiral induction of the desired products 146 was only influenced by the C–N axial chirality of the catalysts and not by the carbon stereogenic centre. Thus, the $S_{\text{C-N}}$ configuration of the catalyst always produced 146 with the (R)-configuration. This demonstrated that enantioselective induction was mostly dominated by axial chirality and not by the stereogenic carbon in the lactate moiety.
Table 4.1. Evaluation of axial chiral iodine catalyst under literature conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar*I</th>
<th>Yield [%]&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee [%]&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Configuration&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>141a</td>
<td>40</td>
<td>47</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>141b</td>
<td>85</td>
<td>40</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>141c</td>
<td>93</td>
<td>43</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>141d</td>
<td>96</td>
<td>67</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>141e</td>
<td>81</td>
<td>31</td>
<td>R</td>
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<tr>
<td>6</td>
<td>141f</td>
<td>78</td>
<td>59</td>
<td>S</td>
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<tr>
<td>7</td>
<td>141g</td>
<td>20</td>
<td>55</td>
<td>R</td>
</tr>
<tr>
<td>8</td>
<td>141h</td>
<td>53</td>
<td>9</td>
<td>S</td>
</tr>
<tr>
<td>9</td>
<td>141i</td>
<td>62</td>
<td>64</td>
<td>R</td>
</tr>
<tr>
<td>10</td>
<td>141j</td>
<td>45</td>
<td>21</td>
<td>S</td>
</tr>
</tbody>
</table>

<sup>a</sup>isolated yields.  <sup>b</sup>determined by chiral-phase HPLC analysis.  <sup>c</sup>determined by comparison with literature.
4.5.2. Evaluation of Absence of Axial Chirality

This type of new C–N axial chiral iodine catalysts 141a–j used both axial chirality and central chirality, which provided sufficient stereocontrol in the enantioselective α-oxytosylation of ketones. Moreover, the axial chirality only controlled the configuration of the obtained α-oxytosylated ketones and not the stereogenic carbon of the lactate moiety. It is worth designing a similar structure to these reagents without axial chirality where the ortho or ortho’ substituents are removed, using the free rotation around the C–N bond (Figure 4.5). Thus, a comparison can be made to determine the role of the presence of axial chirality in the design. The synthesis of chiral iodine reagents was accomplished by using the same synthetic route via the formation of sulfonamides and the Mitsunobu reaction (Scheme 4.7). 21 2-Iodoaniline 176 was treated with sulfonyl chloride derivatives, either a tosyl group or a nosyl group, in the presence of pyridine to obtain sulfonated aniline skeletons 177a and 177b in good yields of 85% and 81%, respectively. Then, the treatment of sulfonated aniline skeletons with enantiomerically pure methyl (S)-(−)-
lactate was carried out smoothly using the Mitsunobu reaction to generate the desired catalysts \textbf{178a} and \textbf{178b}. The chiral iodine reagents processing the stereogenic carbon were obtained in good yields 76\% and 73\%, respectively.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme4.7.png}
\caption{Scheme 4.7. Synthesis of chiral iodine reagents.}
\end{figure}

Back to the aim of the synthesis, the reactivity and the selectivity of the obtained chiral iodine catalysts \textbf{178a} and \textbf{178b} were evaluated with respect to the direct enantioselective $\alpha$-oxtosylation of ketones by using the standard reaction conditions. Propiophenone \textbf{145} was treated with 3 equivalents of $m$CPBA and 3 equivalents of $p$TsOH·H$_2$O in the presence of 10 mol\% of the chiral iodine catalysts \textbf{178a} and \textbf{178b} in MeCN at room temperature.\textsuperscript{15} The chiral iodine catalysts \textbf{178a} and \textbf{178b} successfully catalysed the $\alpha$-oxtosylation reaction in moderate yields of 67\% and 60\%, respectively, as shown in Table 4.2 (entries 1 and 2). However, the chiral induction of these catalysts, \textbf{178a} and \textbf{178b}, was found to be low at 29\% and 37\%, respectively, with respect to the $\alpha$-oxtosylation of ketones. Here, the use of the chiral iodine catalyst \textbf{178b} with a nosylated aniline led to a slight increase in the enantiomeric excess as compared to catalyst \textbf{178a}. Despite the low stereoinduction, this proved the importance of the presence of the axial chirality in catalysts \textbf{141a}--
j, where (40%–67%) of the enantiomeric excesses was observed using the C–N axial chiral iodine catalysts 141a-d (entries 3–6). Notably, the stereocontrol of the C–N axial chiral iodine catalysts 141a–j was more efficient than that of the chiral catalysts, 178a and 178b, possessing the only stereogenic carbon.

**Table 4.2. Evaluation of type of chirality of catalysts.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar*I</th>
<th>Yield [%]a</th>
<th>ee [%]b</th>
<th>Configurationc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>178a</td>
<td>57</td>
<td>29</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>178b</td>
<td>60</td>
<td>37</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>141a</td>
<td>40</td>
<td>47</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>141b</td>
<td>85</td>
<td>40</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>141c</td>
<td>93</td>
<td>43</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>141d</td>
<td>96</td>
<td>67</td>
<td>S</td>
</tr>
</tbody>
</table>

a isolated yields. b determined by chiral-phase HPLC analysis. c determined by comparison with literature.
4.5.3. Evaluation of Reaction Parameters

The effects of other reaction parameters, such as solvent, equivalents of the terminal oxidant and tosylic acid, and temperature were investigated using catalyst 141d, which gave the best results reported in the previous section (Table 4.3). Initially, the enantiomeric excess was increased slightly (70% ee) with unfortunately a significant decrease in the yield (26%) when the reaction was performed at 0 °C (entry 2). In contrast, performing the reaction at 50 °C (entry 3) did not improve the reaction outcome. Reducing the number of equivalents of both mCPBA and TSA (tosylic acid) to 2 (entry 4) did not change the reactivity, but the enantiomeric excess decreased to 52% ee. Increasing the number of equivalents of both mCPBA and TSA to 5 (entry 5) did not significantly affect the yield or the ee. Then, the effects of the most effective reaction parameter, which was the solvent, was evaluated. The use of both dichloromethane (DCM) and diethyl ether (Et2O) increased the ee to 73% and 76%, respectively, however with a significant decrease in the yield (entries 6,7). A notable decrease in both the yield and the ee with the use of ethyl acetate (EtOAc) (entry 8) was observed. Then, a mixture of acetonitrile and dichloromethane was used with different ratios (entries 9–11), which showed a significant improvement in the reaction outcome compared with the use of any of these two solvents alone. The best results were achieved using the MeCN-DCM mixture (1:1), where the desired α-oxytosylated ketones were formed in 94% yield and 75% ee. Thus, the use of this solvent mixture was chosen for the formation of the enantiomer (S)-146.
Table 4.3. Evaluation of reaction parameters (reaction condition A)

\[
\begin{align*}
\text{Entry} & \quad \text{Solvent} & \quad X \text{ (Equiv.)} & \quad \text{Temp.} & \quad \text{(S)-146} \\
1 & \text{MeCN} & 3 & \text{RT} & 96 & 67 \\
2 & \text{MeCN} & 3 & 0 \degree \text{C} & 26 & 70 \\
3 & \text{MeCN} & 3 & 50 \degree \text{C} & 94 & 66 \\
4 & \text{MeCN} & 2 & \text{RT} & 92 & 52 \\
5 & \text{MeCN} & 5 & \text{RT} & 96 & 64 \\
6 & \text{DCM} & 3 & \text{RT} & 70 & 73 \\
7 & \text{Et}_2\text{O} & 3 & \text{RT} & 40 & 76 \\
8 & \text{EtOAc} & 3 & \text{RT} & 64 & 56 \\
9 & \text{MeCN-DCM (1:1)} & 3 & \text{RT} & 94 & 75 \\
10 & \text{MeCN-DCM (1:2)} & 3 & \text{RT} & 90 & 73 \\
11 & \text{MeCN-DCM (2:1)} & 3 & \text{RT} & 93 & 72 \\
\end{align*}
\]

\(a\) determined by chiral-phase HPLC analysis
In contrast, the formation of the opposite enantiomer (R)-146 was investigated by screening different solvents or solvent mixtures. The use of both dichloromethane (DCM) and diethyl ether (Et₂O) increased the ee to 54% and 59%, respectively, however with a significant decrease in the yield (entries 2,3). A decrease in the yield was observed with the use of ethyl acetate (EtOAc) but with a significant increase in ee to 69% (entry 4). A significant drop in yields and enantiomeric excesses was observed when TFE or HFIP was used. Then, a mixture of acetonitrile, dichloromethane, ethyl acetate, and diethyl ether was applied (entries 8–10) which gave a significant improvement in the ee compared with the use of any of the two solvents alone. The best results were achieved using the EtOAc-DCM mixture (1:1) where the desired α-oxytosylated ketones were formed in 72% yield and 75% ee. Thus, the use of this solvent mixture was chosen for the formation of the enantiomer (R)-146.
Table 4.4. Solvent screening for catalyst 141c (reaction condition B)

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield [%]</th>
<th>ee [%]a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>93</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>68</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>Et₂O</td>
<td>25</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>EtOAc</td>
<td>53</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>DCM-TFE (1:1)</td>
<td>67</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>TFE</td>
<td>63</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>HFIP</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>EtOAc-DCM (1:1)</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>EtOAc-Et₂O (1:2)</td>
<td>46</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>MeCN-DCM (1:1)</td>
<td>92</td>
<td>49</td>
</tr>
</tbody>
</table>

a determined by chiral-phase HPLC analysis
4.5.4. Scope of Reaction

The scope of the reaction was explored after establishing the optimised reaction conditions for both enantiomers of product 146a (Scheme 4.7). The desired α-oxytosylated ketones were obtained in satisfactory to excellent yields (31%–96%) under both conditions A and B. However, the α-oxytosylated product of the thiophene derivative 146m was obtained in poor yields under both conditions, and 1-benzosuberone was not reactive under either condition, producing only trace amounts of the aimed product 146p. In terms of chiral induction, the desired α-oxytosylated ketones were achieved with moderate to very good enantiomeric excesses under both reaction conditions ranging from 48% to 80% under condition A, and from 60% to 80% under condition B. Furthermore, the α-oxytosylation of the α-tetralone derivative 146o was obtained in a racemic mixture under condition A and 20% ee under condition B, and the 2-phenylacetophenone derivative 146k was produced as a racemic mixture under both the conditions. An electron withdrawing group in the phenyl ring of propiophenone such as (Cl, CF₃, NO₂) furnished the corresponding products 146b, 146c, 146d, and 146e in very good yields and good enantioselectivities under both the conditions. In contrast, propiophenone derivatives with electron donating groups such as Me, OMe or tBu gave the corresponding products 146f, 146g, and 146h in lower yields but good enantioselectivities. Additionally, the naphthyl derivative 146i was formed in good enantioselectivity and an acceptable yield. Heterocyclic ketones such as furan and thiophene were evaluated under both the conditions to form the corresponding products 146l and 146m in good to high enantioselectivities ranging from 57% to 80% with high yields in the case of the furan derivative 146l but with low yields in the case of 146m. Thiophene was known to be the least reactive among the five membered heteroatomic rings in some reactions, and that could be explained the low yield in the case of 146m. The application of various substituents at the α-
carbon of ketones (either aliphatic or aromatic group) was also explored under both the conditions. With the replacement of methyl at the α-carbon with an ethyl group delivered the corresponding products 146j in excellent yields (94% and 90%) and good enantioselectivities (77% and 80% ee) under both conditions A and B. However, placing a phenyl group at the α-carbon unfortunately led to a loss of enantioselectivity and the corresponding products 146k were obtained as a racemic mixture in high yields. The cyclic ketones were also evaluated under both conditions A and B with different sized rings. The reactivities and enantioselectivities demonstrated dependence on the ring size of the cyclic ketones. The use of 1-indanone derivatives obtained the corresponding product 146n in high yields with acceptable enantiomeric excess. In contrast, the use of α-tetralone derivatives formed the corresponding products 146o in poor yields and enantiomeric excess. The poor reactivity of tetralone could be because the desired product was unstable under these reaction conditions where Legault found the desired product was eliminated TsOH followed by aromatization to form 1-naphthol.22 Use of 1-benzosuberone displayed that the seven-member-ring ketone was not reactive under both the reaction conditions. These results showed a considerable improvement to the catalytic enantioselective α-oxytosylation of ketones compared with the reported methods using various classes of chiral iodoarenes. Additionally, the novel C–N axial chiral iodoarenes 141a–j, particularly 141d and 141c proved their potential as organocatalysts in enantioselective oxidative transformations. The application of other sulfonic acids was also investigated by using either benzenesulfonic acid or methanesulfonic acid rather than p-toluenesulfonic acid. The reactivity and selectivity remained good under both the conditions, furnishing the corresponding products 146q and 146r in the range of 82% to 96% product yield with up to 77% ee.
Scheme 4.7. Scope of reaction of catalytic stereoselective \(\alpha\)-oxytosylation of ketones.
4.6. Further α-Functionalisation of Ketones

It has been reported that iodoarenes can control the catalytic enantioselective α-functionalisation of ketones with the in situ generation of hypervalent iodine reagents by a co-oxidant. Therefore, the novel C–N axial chiral iodoarenes 141a–j, particularly 141d and 141c, were evaluated towards various functionalisations of ketones after the achievement of good results for the catalytic enantioselective α-oxytosylation of ketones. The catalytic use of the novel C–N axial chiral iodoarenes was initially aimed towards the enantioselective α-acetoxylation of propiophenone under the developed conditions A and B for the further functionalisation of ketones. The replacement of sulfonic acids was examined under the developed conditions with acetic acid as a nucleophile, in the presence of BF₃·OEt₂ as an additive, to furnish the α-acetoxylated ketone (Scheme 4.8). The formation of the α-acetoxylated ketones was achieved in satisfactory yields (69% and 54%) and enantiomeric excesses (50% and 34%). The use of the iodine catalyst 141d led to a slightly increased yield with good enantioselectivity compared with that of the iodine catalyst 141d, that delivered (R)-179. Here, it is important to mention that the obtained enantiomers 179 were affected by the configuration of the C–N axial chirality, where the \( R_{C-N} \) configuration always formed 179 with the (S)-configuration. This indicated that enantioselective induction was mostly dictated by the axial chirality and not by the stereogenic carbon in the lactate moiety.
The α-hydroxylation of ketones 180 was explored under the developed conditions A and B by using either 141d or 141c to investigate their ability to introduce another nucleophile (OH) into the α-position of carbonyls. Propiophenone 145 was treated with 3 equivalents of mCPBA and 3 equivalents of water, instead of sulfonic acid, in the presence of 10 mol% of the chiral iodine catalysts 141d or 141c (Scheme 4.9). Unfortunately, the introduction of hydroxyl group (OH) failed, even replacing water with methanol did not give α-alkoxylated ketone.
4.7. Conclusion and Outlook

A small library of chiral iodine catalysts, possessing the C–N stereogenic axis, was investigated for the stereoselective α-oxytosylation of ketones, which is known as a challenging transformation. A wide range of both the enantiomers of the α-oxygenated ketones were furnished in generally high enantioselectivities of up to 80% ee and good yields of up to 96% under the developed conditions. The enantioselectivity of the α-oxygenated ketones proved the potential of these reagents as efficient chiral organocatalysts. Importantly, the chiral induction was controlled by the axial chirality, where the alteration of the configuration of the chiral C–N axis was investigated. The absence of axial chirality was explored by designing a similar structure to that of the chiral C–N reagents. Mainly, the ortho, ortho' substituents were removed by using the free rotation around the C–N bond. However, the stereocontrol of the C–N axial chiral iodine catalysts 141a–j was more efficient than that of the chiral catalysts 178a–b, employing only a stereogenic carbon.

- Yields up to 96%
- Enantioselectivity up to 80% ee
- 18 examples with both enantiomers
The further functionalisation of ketones was examined in the \( \alpha \)-position of carbonyls using different nucleophiles. The novel C–N axial chiral iodoarenes were mediated by the enantioselective \( \alpha \)-acetoxylation of propiophenone in acceptable yield and selectivity. Both the enantiomers were formed, which again proved that enantioselective induction was mostly dominated by the axial chirality and not by the stereogenic carbon in the lactate moiety. Unfortunately, the functionalisation of ketones through the introduction of (OH) or (OMe) failed with the use of C–N axial chiral iodoarenes under the developed conditions A and B.

Screening different additives to the developed conditions should be examined in order to control the enantioselective \( \alpha \)-hydroxylation or \( \alpha \)-alkoxylation of ketones. The developed conditions did not yield the hydroxylated or alkoxyled ketones, and further optimisation is required in this case. Further investigations in the future could enable functionalisation of ketones for \( \alpha \)-halogenation such as fluorination, chlorination, bromination, and iodination using C–N axial chiral iodoarenes. Moreover, other groups could be introduced at the \( \alpha \) position of ketones, such as CF\(_3\), NTs, N\(_3\), and Ar, where some of them form important building blocks to access numerous natural products, pharmaceuticals, and useful synthetic intermediates in organic synthesis.
4.8. References


Chapter 5
Synthesis of Chiral Hypervalent Iodine Reagents
based on Sulfoximine

Parts of this work have been published


DOI: 10.1055/a-1508-9593
5.1. General Considerations about Sulfur

Sulfur-containing molecules have been widely used in many various areas such as agriculture, industries, and synthetic chemistry.\textsuperscript{1,2} The number of valence electrons of a sulfur atom is the same as that of oxygen, but unlike oxygen, the sulfur atom can use its unoccupied d-orbitals.\textsuperscript{2,3} In addition, the lone pair of electrons on the sulfur atom has higher nucleophilicity than that of oxygen, so the chemical properties of sulfur are somewhat different from those of oxygen.\textsuperscript{3} The readily accessible 3d orbitals of sulfur contribute to the chemical bonding. Here, sulfur has a strong tendency to extend its valence shell from an octet structure to a hypervalent sulfur compound, which have an electron decet or dodecet (Figure 5.1).\textsuperscript{4} Therefore, sulfur compounds can form stable highly-coordinated compounds such as sulfones and sulfoximines, which can exist as four coordinate structures as well as hexacoordinate structures such as SF\textsubscript{6}.

![Sulfur electronic structures](image)

**Figure 5.1.** Sulfur electronic structures.

5.2. Stereochemistry of Sulfur Compounds

Sulfur compounds were found to have optical activity similar to that of carbon compounds when the first stereochemistry of sulfur compounds was reported by Pope and Peachey in 1900.\textsuperscript{5} Then, Smiles resolved the sulfonium salt into its enantiomeric forms by the formation of diastereoisomers using chiral acids.\textsuperscript{6} Chiral sulfur compounds can present in a variety of geometries based on the
lone pair of electrons and the number of substituents attached at the sulfur atom; these geometries are shown in Figure 5.2. In the case of a pyramidal geometry, sulfur compounds 181a having three different substituents with the lone pair of electrons are observed in sulfoxides or similar compounds where the lone pair of electrons is located in the fourth quadrant. The oxygen and sulfur do not share a common π bond, but the oxygen provides electrons from the lone pair to a d-orbital of sulfur. As a result, the overlap between a p-orbital of oxygen and the d-orbital of sulfur results in d–π bonding. In the case of a tetrahedral geometry, sulfur compounds 181b having four different substituents without the lone pair of electrons are similar to tetrahedral sp<sup>3</sup> carbon compounds. This type of geometry is observed in sulfoximines. Additionally, other highly co-ordinated sulfur compounds can exceed this number of substitutes, by up to 6. Sulfur compounds 181c having four different substituents with the lone pair of electrons have a seesaw geometry. Accordingly, this type of structure is observed in sulfurane compounds where two substituents occupy the apical positions and the others occupy the equatorial positions. Different from that of sulfur compounds 181d, having six different substituents, the geometry of these compounds is an octahedral structure and these compounds have been less explored as optically active compounds.

![Figure 5.2. Chiral structure in sulfur compounds.](image-url)
The most common chiral sulfur compounds $182a-f$ containing a stereogenic sulfur centre are sulfoxides, sulfinamides, sulfinates, sulfoximines, sulfonimidamides, and sulfonimidates (Figure 5.3).$^8$

![Chemical structures](image)

Figure 5.3. Chiral sulfur compounds.

### 5.3. Chemistry of Chiral Sulfoxides

Chiral sulfoxides are interesting moieties in medical chemistry and asymmetric synthesis and they are found in many natural products and bioactive compounds.$^9$ Their chiral induction was recognised to be high to excellent along with their efficiency as catalysts in numerous asymmetric syntheses.$^9$ Because of their high configurational stability and their strong coordinating features, both sulfur and oxygen have lone pairs of electrons accessible to coordinate.$^9,10$ Moreover, the stabilisation of their reactive conformation results from the interaction between the polarised S–O bond and the other electronegative groups present in the substituents.$^9,10$ In addition, the large
differences between substituents along with the sulfinyl oxygen atom and the free electron pair around the sulfur atom, in terms of steric and stereoelectronic effects, generate a distinct chiral environment.\textsuperscript{9,10} All of these above mentioned unique properties of sulfoxides are responsible for their high chiral induction. A widely applied method to provide enantiomerically pure sulfoxides is the conversion of sulfinic chloride 183 into the chiral sulfinate using (\(-\)-menthol, which is transformed into a mixture of chiral menthylsulfinates 184\textsubscript{a} and 184\textsubscript{b}.\textsuperscript{11} In the case of menthyl \textit{p}-tolylsulfinate 184\textsubscript{a}, an enantiomerically pure compound is obtained by crystallisation with acetone and HCl. Further modification can be achieved with Grignard reagents or organometallic reagents by using the Andersen method to introduce different substituents at the sulfur atom 185 as shown in Scheme 5.1.\textsuperscript{11}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_5.1.png}
\end{center}

\textbf{Scheme 5.1.} Synthesis of chiral sulfoxides.
Another typical method is the asymmetric oxidation of sulfides \( \text{186} \) using chemical or enzymatic approaches and kinetic resolution to provide the desired optically active sulfoxides \( \text{187a} \) or \( \text{187b} \) (Scheme 5.2).\(^{12}\)

\[
\begin{align*}
\text{186} & \xrightarrow{\text{Chiral Oxidant}} \text{187a} \quad \text{or} \quad \text{187b} \\
\end{align*}
\]

**Scheme 5.2.** Synthesis of chiral sulfoxides from sulfides.

### 5.4. Chemistry of Chiral Sulfoximines

Sulfoximines are classified as hexavalent sulfur atoms bearing one oxygen, one nitrogen, and two carbon substituents. They were discovered in 1950 by Whitehead and Bentley.\(^{13,14}\) The known strategies for the synthesis of sulfoximines \( \text{189} \) are the imination of sulfoxides \( \text{187} \), the oxidation of sulfilimines \( \text{188} \), and the oxidative imination of sulfides (Figure 5.4).\(^{15-16}\)

\[
\begin{align*}
\text{186} & \xrightarrow{\text{[O]}} \text{187} \quad \text{Sulfoxides} \\
\text{186} & \xrightarrow{\text{[N]+}} \text{188} \quad \text{Sulfilimines} \\
\text{187} & \xrightarrow{\text{[O]}} \text{189} \quad \text{Sulfoximines} \\
\end{align*}
\]

**Figure 5.4.** Synthesis of sulfoximines.
The sulfoximine moieties serve as chiral auxiliaries where the stereogenic centre at the sulfur atom bears two non-identical carbon substituents. Chiral sulfoximines have been utilised as chiral ligands in various asymmetric catalytic transformations or as building blocks of pseudopeptides. Accordingly, they have attracted considerable attention in synthetic organic chemistry, applied biosciences, and medicinal chemistry. Furthermore, these compounds have ideal properties such as being highly solubile in polar solvents and the ability for further functionalization through the nitrogen or carbon atoms. The first use of chiral sulfoximines as ligands was reported by Johnson in 1979 for the ligand mediated the enantioselective reduction of ketones. To date, a wide range of enantiopure sulfoximines has been used successfully for various asymmetric reactions such as enantioselective allylic substitution, asymmetric cycloaddition and asymmetric hydrogenation of imines or ketones.

![Figure 5.5. Common strategies for the enantioselective synthesis of chiral sulfoximines.](image-url)
Common synthetic strategies to design chiral sulfoximines depend on the resolution of racemic sulfoximines into their enantiomeric forms. Such procedures such as the imination of chiral sulfoxides, the oxidation of chiral sulfilimines, and the S-alkylation of chiral sulfonamides with alkyl halides exist (Figure 5.5).

5.5. Synthesis of Chiral Sulfoxides Based on Iodine Reagents

The synthesis of chiral N-sulfinyl imines bearing an iodine atom is achieved by the condensation of carbonyl compounds with commercially available chiral sulfonamide derivatives. Following the reported procedure, 2-iodobenzaldehydes were treated with optically pure (+)-2-methyl-2-propanesulfonamide in the presence of titanium (IV) ethoxide to form the desired chiral iodine reagent, containing stereogenic sulfur as a source of chirality, in an excellent yield (95%) (Scheme 5).

![Scheme 5.3. Synthesis of chiral N-sulfinyl imine-based iodine reagent.](image)

The further modification of the chiral structure was investigated as well the reduction of the imine to a secondary amine or a tertiary amine. The reduction step was operationally straightforward with the use of sodium borohydride (NaBH₄) as the reducing agent to produce 93% of the chiral...
iodine reagent 197, containing the secondary amine without the loss of chirality of sulfur (Scheme 5.3). For the methylation step, the deprotonation of the sulfinamine was achieved using sodium hydride (NaH) as the base and methyl iodide (MeI) as the alkylating agent to access the chiral iodine structure 198 containing the tertiary amine in a good yield (84%) (Scheme 5.4).

Scheme 5.4. Synthesis of chiral N-sulfinyl amines-based iodine reagents.

5.6. Oxidation of Chiral Sulfoxides Based on Iodine Reagents

In theory, all the previously chiral iodine reagents possessing the sulfur-stereogenic centre can be oxidised to the corresponding hypervalent iodine reagents by using typical oxidation methods. Different oxidants were investigated to obtain the hypervalent iodine regents, which could be used for stereoselective transformations. Starting with sodium perborate (NaBO$_3$$\cdot$4H$_2$O) as an oxidant, the chiral sulfoxide based iodine reagents were treated with the oxidant in the presence of acetic acid. Unfortunately, the chiral sulfinimide oxidised easily to the corresponding sulfonamide 199 or 200 with a loss of their chirality. Hence, selective oxidation of iodine (I) to the corresponding iodine (III) was problematic (Scheme 5.5).
Other oxidants such as Oxone or Koser’s reagent could be investigated towards the selective oxidation of iodine reagents without the loss of chirality. The use of Oxone was explored in a mixture of chloroform and trifluoroacetic acid, again resulting in the formation of the corresponding sulfones 199, which included a loss of chirality. Surprisingly, the chiral iodine reagent containing the tertiary amine 198 exhibited not only the loss of chirality but also the cleavage of the S–N bond to generate the secondary amine 201 as a major product.25

**Scheme 5.5.** Oxidation of chiral N-sulfinyl amine-based iodine reagents with sodium perborate.

**Scheme 5.6.** Oxidation of chiral N-sulfinyl amines-based iodine reagents with Oxone.
Finally, the use of Koser’s reagent did not solve the problem, even when the chiral iodine reagents were treated with Koser’s reagent for a long reaction time. Unlike the other results, no oxidation process was observed and the recovery of the starting iodine reagents was possible.

![Scheme 5.7. Oxidation of chiral N-sulfinyl amine-based iodine reagents with Koser’s reagent.](image)

These results clearly stated the major issue during the oxidation of the iodine compounds into the hypervalent iodine reagents was the loss of chirality. The hypervalent iodine reagents were never observed without the destruction of the stereogenic centre due to the easier oxidation of sulfoxides under any oxidation conditions.

### 5.7. Introduction of Carbon Stereogenic Centre

Since the chirality of sulfur was destroyed during the oxidation of iodine reagents, the addition of another stereogenic centre to the previously prepared chiral iodine reagents was examined to solve the problem. The structure of the chiral N-sulfinyl imine-based iodine reagent 196 was modified
by treating with the Grignard reagent, phenylmagnesium bromide (PhMgBr), to form a chiral iodine reagent 203 with two stereogenic centres (Scheme 5.8).\textsuperscript{25}

\begin{center}
\begin{tikzpicture}

\node at (0,0) {\includegraphics[width=\textwidth]{Scheme5.8.png}};

\end{tikzpicture}
\end{center}

\textbf{Scheme 5.8.} Synthesis of chiral iodine reagents with two stereogenic centres.

As for the determination of the new stereocentre, the \textsuperscript{1}H NMR shows the presence of one diastereoisomer and the absolute configuration was determined using X-ray crystallography (Figure 5.6.).

\begin{center}
\begin{tikzpicture}

\node at (0,0) {\includegraphics[width=\textwidth]{Figure5.6.png}};

\end{tikzpicture}
\end{center}

\textbf{Figure 5.6.} X-ray structure of chiral iodine reagents with two stereogenic centres.

Before the investigation of the oxidation process towards I(III) compounds, the secondary amine structure 203 was converted into a tertiary amine to ensure that no other oxidation could occur to the amine. This step was performed by the methylation of the secondary amine based on the iodine reagent 203 using methyl iodide to afford the tertiary amine structure 204 in a good yield (82\%).\textsuperscript{25}
The use of sodium perborate (NaBO$_3$·4H$_2$O) as the oxidant when treating the chiral sulfoxide based iodine reagent 203 formed the corresponding sulfones 205 within 2.5 h with the loss of chirality. However, extended reaction times (12 h) generated the chiral cyclic iodine(III) compound 206 with only the stereogenic carbon centre (Scheme 5.10).$^{25}$

Scheme 5.9. Synthesis of $N$-methyl amine based iodine reagents.

Scheme 5.10. Oxidation of chiral iodine reagent 203.

Accordingly, the obtained chiral iodine reagent 204, with a carbon and sulfur stereogenic centre, was oxidised using Koser’s reagent as an oxidant. Sodium perborate and Oxone were not investigated since they are strong oxidants and the further oxidation of sulfoxides could occur. However, with the use of Koser’s reagent, the cleavage of the S–N bond was observed to form a
chiral iodine reagent 207 possessing the chiral carbon with the failure of generating an I(III) compound (Scheme 5.11). 25

Scheme 5.11. Oxidation of chiral iodine reagents with two stereogenic centres.

5.8. Objectives

Researchers have investigated the synthesis of chiral reagents by using either chiral carbons or chiral rigid compounds, but other chiral atoms have been only rarely examined in the field of hypervalent iodine chemistry. It is worth exploring the potential of a stereogenic sulfur centre towards different asymmetric transformations and reaching high enantioselectivity for challenging stereoselective reactions. A new family of chiral hypervalent iodine reagents, based on the chiral sulfur auxiliary, could be accessible by using commercially available and optically pure sulfur compounds or resolving enantiomeric sulfur compounds. However, the use of chiral sulfoxides in the design of the backbone of iodine reagents could not successfully access the chiral hypervalent iodine reagents. The chirality of sulfur was lost during the oxidation reaction where the sulfoxides were oxidised to sulfones resulting in the loss of chirality. Moreover, sulfur compounds can be easily oxidised under oxidative conditions, which is needed to generate the corresponding hypervalent iodine reagents.
Sulfoximines are another class of sulfur compounds which could be synthesised by using the known procedures. The iodine atom could be introduced later to the backbones. Further modification could be achieved by functionalization through the nitrogen or carbon atoms to access a wide range of chiral iodine reagents possessing the stereogenic sulfur centre. Hence, the synthesis of chiral sulfoximines could be achieved by using one of these possible procedures: the resolution of sulfoximine salts in their diastereomeric forms or the imination of chiral sulfoxides. Then, the chiral induction of sulfoximines was investigated toward different stereoselective transformations as reagents or catalysts (Figure 5.8). The synthesis of chiral iodine reagents bearing a stereogenic sulfur centre would be unprecedented in hypervalent iodine chemistry.
5.9. Results and Discussion

5.9.1. Synthesis of Chiral Sulfoxide Auxiliaries

Among the different types of chiral sulfur compounds containing a stereogenic sulfur, chiral sulfoxides are the most used and have been well-recognised in stereoselective synthesis. The preparation of enantiomerically pure sulfoxides would be easily affordable by various chiral pool strategies using commercially available chiral reagents to establish a stereogenic centre at sulfur. The synthesis of optically active sulfoxides could be easily accessible by the known asymmetric oxidation of sulfides. However, a diastereoselective strategy is the typical method used to achieve chirality at sulfur and does not need expensive catalysts. Thus, diastereomerically pure sulfoxides were obtained by using inexpensive reagents. When enantiopure (−)-menthol was used as the chiral source, the chirality of menthol was transferred to the desired menthyl-p-toluenesulfinate \(^{209}\). Initially, the corresponding p-toluenesulfinic chloride was prepared from the reaction of anhydrous sodium p-toluenesulfinate \(^{208}\) with thionyl chloride in toluene at room temperature. Then, the chirality of sulfur was furnished by using a simple protocol where the obtained p-toluenesulfinic chloride was reacted with enantiopure (−)-menthol in the presence of triethylamine (Et\(_3\)N). The resulting diastereoisomers of menthyl-p-toluenesulfinites were easily separable by recrystallization from acetone and catalytic HCl at (−20 °C), delivering the (S) configuration at the sulfur as the major diastereomer \(^{209}\) in an acceptable yield of 48% (Scheme 5.12).\(^{28}\)
After generating the stereogenic sulfur centre using auxiliary menthol, further functionalization was performed to obtain the resulting chiral menthyl sulfinate to demonstrate a small library of enantiomerically pure sulfoxide compounds. However, the retention of the chirality at the sulfur atom was necessary to design chiral iodine reagents featuring a stereogenic sulfur. The sulfinylation of bromo aromatic compounds was conducted by a nucleophilic substitution strategy using organolithium or Grignard reagents to establish different chiral sulfoxides, which were utilised to introduce an iodine atom in the ortho-position of the sulfoxide moieties. Commercially available bromo aromatic compounds 210a-c were ortho-lithiated through the bromo-lithium exchange process with n-butyllithium in THF to react then with (S₃)-menthyl-p-tolylsulfinate 209 (Scheme 5.13). The desired sulfoxides 211a-c were achieved in acceptable yields (18-36%) with different enantiomeric excesses (8%–89% ee).
Initially, 2-bromo-N-acetanilide 210a was lithiated with nBuLi to react with (S₃)-menthyl-p-tolylsulfinate 209 via the nucleophilic substitution strategy. Then, the hydrolysis of the acetyl substituent was conducted using an excess amount of potassium hydroxide in a mixture of water and ethanol to obtain the chiral sulfoxide 211a, based on the aniline moiety, in 18% yield and a good degree of enantioselectivity (89% ee). The use of the aniline moiety aimed to later convert the amine to iodine via the Sandmeyer reaction to ensure a chiral environment of sulfur near iodine.

Two different substituted sulfoxide auxiliaries were obtained by using the lithiation method with nBuLi, where 3-bromoanisole 210b and 1-bromo-3,5-dimethoxybenzene 210c were used with (S₃)-menthyl-p-tolylsulfinate 209 (Scheme 5.13). The resulting chiral sulfoxides 211b and 211c were formed in acceptable yields of 21% and 36%, respectively, but racemisation was observed (10% ee, 8% ee). However, these obtained sulfoxides can be used to synthesise iodine reagents to study the reactivities of such compounds irrespective of the selectivity.
The Grignard reagent was examined as a nucleophilic substitution strategy to yield the sulfoxide auxiliary. With a simple aliphatic derivative, methylmagnesium bromide 212 was treated with the previously obtained chiral sulfoxide 209 in toluene to form (R,S)-methyl-p-tolylsulfoxide 213 in a good yield of 81% and excellent enantioselectivity of 99% ee (Scheme 5.14). Applying this procedure resulted the sulfoxide 213 with the opposite configuration (R,S) at the sulfur centre, where the (S,S) configuration was used in the starting menthyl-p-tolylsulfinate 209.


5.9.2. Synthesis of Chiral Iodine Reagents with Stereogenic Sulfoxide

After the successful synthesis of stereogenic sulfoxides, an iodine atom was introduced by different methods depending on the sulfoxide moieties: the Sandmeyer reaction, deprotonation with LDA, or palladium-mediated deprotonation. Starting with the Sandmeyer reaction, the aniline substituent of the prepared sulfoxide was transformed to iodine by using a simple two-step reaction. The aniline 211a was diazotized by sodium nitrate (NaNO₂) in the presence of hydrochloric acid followed by the decomposition of the diazonium salt by potassium iodide (KI) in the presence of HCl in a mixture of water and acetonitrile (Scheme 5.15). The use of the
enantiopure 2-(p-tolysulfinyl) aniline 211a in the Sandmeyer reaction moderately decreased the degree of enantiopurity to 70% ee, but 1-iodo-2-(p-tolysulfinyl) benzene 214a was obtained in low yield (18%).

\[
\begin{align*}
\text{NaNO}_2, \text{HCl, KI} & \quad \text{MeCN:H}_2\text{O, 90 °C} \\
\begin{array}{c}
\text{S} \\
\text{O} \\
\text{N} \text{H}_2 \\
\end{array} & \quad \begin{array}{c}
\text{S} \\
\text{O} \\
\text{I} \\
\end{array}
\end{align*}
\]

**Scheme 5.15.** Synthesis of chiral iodine reagent 214a.

The second method to introduce iodine was the deprotonation with lithium diisopropylamide (LDA); in this case, both the obtained sulfoxides 211b and 211c were transformed into the iodoarene, containing a chiral sulfoxide. The deprotonation of the prepared sulfoxide moieties with LDA generated the ortho-lithiated intermediates. LDA was freshly prepared by adding nBuLi with isopropyl amine in THF at −78 °C (Scheme 5.16). Then, the ortho-lithiated intermediates were treated with iodine to furnish the iodine reagents 214b and 214c in good yields of 63% and 58%, respectively, but the enantiopurities decreased slightly to 7% ee.

\[
\begin{align*}
\text{S} \\
\text{O} \\
1. \text{LDA, THF, -78 °C} & \quad 2. \text{I}_2, \text{THF} \\
\begin{array}{c}
\text{S} \\
\text{O} \\
\text{R} \\
\end{array} & \quad \begin{array}{c}
\text{S} \\
\text{O} \\
\text{I} \\
\text{R} \\
\end{array}
\end{align*}
\]

**Scheme 5.16.** Synthesis of chiral iodine reagents 214b and 214c.
The last method was the palladium-catalysed C–H iodination where iodine was selectively introduced in the ortho-position while the sulfinyl group was used as a directing group.\(^{30}\) The iodination of enantiopure methyl-\(p\)-tolylsulfoxide 213 was achieved by using palladium (II) acetate [Pd(OAc)\(_2\)] as a catalyst in the presence of \(N\)-iodosuccinimide (NIS) as the iodine source in a mixture of DCE and HFIP (11:1) at 100°C overnight (Scheme 5.17). The desired iodine reagent 215 was formed in an acceptable yield (47%), but unfortunately, the enantioselectivity decreased significantly to 19\% ee.

![Scheme 5.17. Synthesis of chiral iodine reagent 215.](image)

The demonstration of all of these methods furnished a small library of chiral iodine reagents possessing a stereogenic sulfur centre in the sulfoxide form. However, chiral iodine reagents based on sulfoxide could not be used as hypervalent iodine reagents because of the problematic oxidation of the sulfoxide moieties. In order to maintain the chirality on the sulfur atom, the synthesis to the sulfoximine was carried out to avoid further oxidation processes.
5.9.3. Synthesis of Chiral Iodine Reagents with Stereogenic Sulfoximine

As discussed earlier, sulfoximine moieties are a recognised class of the sulfur(VI) family, and they can serve as a chiral auxiliary. Accordingly, the design of hypervalent iodine reagents based on chiral sulfoximines is a good alternative to investigate the potential of a stereogenic sulfur along with their chemical stability toward any further oxidations. In general, sulfoximines can be synthesised by the direct oxidative imination of commercially available sulfides and the iminaton of sulfoxides (Figure 5.9). The direct oxidative imination route will afford sulfoximines in racemic forms, which can be converted into enantio-enriched sulfoximines by resolving the enantiomers via kinetic resolution. Another method is the imination of optically active sulfoxides, which transfers the chirality to the resulting sulfoximines without the need for expensive chiral reagents.

As discussed earlier, chiral sulfoxides can be oxidised easily and lose the chirality under any oxidation conditions. Therefore, the chiral sulfur needs to be protected by the conversion of chiral sulfoxides into a highly stable structure of chiral sulfoximines to withstand oxidation reactions.

Figure 5.9. Synthesis of chiral iodine reagents processing chiral sulfoxides.
Thus, the obtained optically active sulfoxide compounds 214a-c, 213 and 215 could be transformed into chiral sulfoximines by using the imination reaction with the simple combination of PIDA and N-sources. The synthesis of enantiopure sulfoximines was achieved using the simple imination procedure, which was the combination of 3 equivalents of PIDA and 4 equivalents of ammonium carbamate as the N-source in methanol at room temperature. The desired chiral sulfoximine moieties 219a-e were obtained in acceptable yields (26%–85%) (Scheme 5.18). This imination reaction was reported to be stereospecific with the retention of the configuration of the obtained sulfoximines. The degree of enantioselectivities decreased very slightly (7%–88% ee).

![Scheme 5.18. Synthesis of chiral iodine reagents based on sulfoximine moiety.](image-url)
The application of the imination procedure to 2-iodo-4-methyl-1-(methylsulfinyl) benzene (19% ee) 215 generated the desired chiral sulfoximine 219a in a moderate yield 51% with a small decrease in enantiopurity to 16% ee. However, the enantiopurity of 1-iodo-2-(p-tolylsulfinyl) benzene 214a was maintained as 70% ee for the obtained sulfoximine 219b with an acceptable yield (26%). The use of both 1-methoxy and 1,5-dimethoxy sulfoxide derivatives 214b and 214c retained the enantiopurity at 7% ee for both sulfoxides, and the sulfoximines 219c and 219d were obtained in moderate yields of 46% and 36%, respectively. Since the palladium-catalysed C–H iodination failed to obtain a high chiral induction of the iodine reagent, the enantiopure (R,S)-methyl-p-tolylsulfoxide 213 was used to reach a high enantiopurity of the sulfoximine. The conversion of (R,S)-methyl-p-tolylsulfoxide into NH-sulfoximine 219e was achieved in a good yield (85%) and excellent selectivity (88% ee). Consequently, the idea of using chiral sulfoximines possessing a sulfur (VI) instead of chiral sulfoxides, in order to maintain the chirality of sulfur, seemed to be well implemented. Further exploration of hypervalent iodine reagents bearing a stereogenic sulfur atom seems feasible in this manner.

5.9.4. Resolution of Sulfoximine Salts Based on Iodine Reagents

The kinetic resolution process could afford sulfoximines in an enantioenriched form using a chiral inexpensive acid such as, (+)-10-camphorsulfonic acid (CSA). Initially, the racemic sulfoximines were obtained using the direct oxidative imination of sulfide derivatives, which transferred both NH and O to sulfides using simple and direct methods. Interestingly, the most efficient method was the combination of ammonium carbonate \((\text{NH}_4)_2\text{CO}_3\) as the N-source and (diacetoxyiodo) benzene \([\text{PhI(OAc)}_2]\) as the O-source; this method is metal, base, and additive-free.31 2-
Iodothioanisole $220$ was selected to work the racemic sulfoximine-based iodine reagents $221$. The conversion of the racemic iodine reagents into optically active iodine reagents was carried out using kinetic resolution with the chiral acid (CSA). $2$-Iodothioanisole $220$ was reacted with 1.5 equivalents of ammonium carbonate and 2.3 equivalents of PhI(OAc)$_2$ in methanol at room temperature, affording $S$-methyl-$S$-phenylsulfoximine $221$ in a good yield (68%). (Scheme 5.19).

**Scheme 5.19.** Synthesis of racemic sulfoximine-bearing iodine reagent.

In terms of chiral induction, the resulting racemic sulfoximine $221$ was converted to its enriched forms by using 0.5 equivalents of (+)-camphorsulfonic acid to generate diastereoisomeric salts $222$ in a 6:3 ratio (Scheme 5.20).$^{32}$ Before the basic hydrolysis of the salt, the diastereoisomers were separated by using multi-recrystallisation from hot acetonitrile to reach high enantiopurity, where the desired chiral reagent $223$ was formed in 56% ee with a good yield (85%).

**Scheme 5.20.** Synthesis of chiral iodine reagent-based chiral sulfur (VI).
This was also the first example of a chiral iodine reagent possessing a stereogenic sulfur which has not yet been investigated in hypervalent iodine chemistry. It is worth examining the chiral induction of the sulfur atom towards different catalytic stereoselective transformations.

5.9.5. Functionalisation of NH-Sulfoximines

The further functionalization through the NH of the sulfoximines was carried out using the acylation method where the introduction of substrates through NH generated rigid backbones. The design of such chiral compounds was the intended modification to locate the chiral environment in close proximity to the central iodine. The synthesis of the N-acylated sulfoximine-based iodine reagents 225-227 was achieved by the treatment of 2-benzoyl chloride derivatives with chiral NH-sulfoximines in the presence of pyridine in good to excellent yields (85%-95%) with retained enantiopurities (46-70% ee) (Scheme 5.21).

Scheme 5.21. Synthesis of N-sulfoximines.
The benzoyl chloride 224a was introduced to optically active imino(2-iodophenyl) (p-tolyl)-\(\lambda^6\)-sulfanone 219b and S-methyl-S-2-iodophenylsulfoximine 223 to form N-sulfoximines 226 and 227 in excellent yields of 95% and 93%, respectively. The enantioselectivity slightly decreased in the methyl-based sulfoximine 227 to 46% ee and was maintained in p-tolyl-based sulfoximine 226 at 70% ee. Imino(methyl)(p-tolyl)-\(\lambda^6\)-sulfanone 219e was treated with 2-iodobenzoyl chloride 224b to form the chiral iodine based on sulfoximine 225 in a good yield and selectivity (85%, 57% ee).

5.9.6. Oxidation of Chiral Iodine Reagent-Based Sulfoximine

The oxidation of the chiral iodine reagent to the corresponding hypervalent iodine reagent was investigated using sodium perborate as the oxidant in the presence of acetic acid at 50 °C for 24 h (Scheme 5.22). However, the use of 10 equivalents of NaBO\(_3\)·4H\(_2\)O failed to oxidise any of the newly prepared iodine reagents. The excess amount of the oxidant (30 equivalents) oxidised only the chiral NH-sulfoximine containing iodine reagent 223 in a good yield (81%).

![Scheme 5.22. Oxidation of chiral iodine reagent based on N-sulfoximines.](image)
The structural configuration of this chiral hypervalent iodine reagent 228 based on \(N\)-sulfoximine was assigned by solving the X-ray crystal structures where the nitrogen atom interacted strongly with the iodine (2.100 Å). The N–I bond was shorter than the iodine oxygen bond [I(1)–O (2), 2.249 Å] (Figure 5.10). The structure of this chiral reagent possessing a stereogenic sulfur is known as a pseudo-cyclic structure because of the intramolecular I···N interaction. This structure is commonly found in the case where the \textit{ortho}-substituent of the aromatic ring interacts with iodine. Ordinarily, the presence of the pseudo-cyclic structure in hypervalent iodine reagents is responsible for high thermal stability along with an improvement in the solubility and reactivity.\(^{36}\)

![Figure 5.10. X-ray structure of chiral iodine reagents processing stereogenic sulfur center.](image)

However, the other chiral iodine reagents (219a-d, 225-227) were examined with excess equivalents of NaBO\(_3\)·4H\(_2\)O (up to 30) in order to fully oxidise them along with more reaction time (24 h). The target chiral hypervalent iodine reagents were not formed with the applied conditions. Alternative oxidants were applied to the remaining chiral iodine catalyst including 10 equivalents of Selectfluor\textsuperscript{®} in acetonitrile, used in the presence of acetic acid for 24 h. Regrettably, the aimed hypervalent iodine reagents were not formed even when increasing equivalents of
Selectfluor® were used. Consequently, the chiral iodine reagent possessing a stereogenic sulfur seemed to be difficult to oxidise.

5.9.7. Catalytic Enantioselective Reactions

The chiral induction of the stereogenic sulfur centre was examined in different catalytic enantioselective reactions through in situ generated hypervalent iodine compounds.

5.9.7.1. Enantioselective α-Oxytosylation of Ketones

For the catalytic stereoselective α-oxytosylation of ketones, the chiral sulfoximine-based iodine reagents catalysed the reaction of propiophenone 145 with 3 equivalents of mCPBA and 3 equivalents of pTsOH·H2O in MeCN at room temperature for 72 h.33 In general, the desired product 146 was formed in low yields (13% or 15%) or in trace amounts. Some of these reagents unfortunately failed to introduce OTs stereoselectively in the α-position of propiophenone (entries 1-4 and 6). However, catalysts 219c and 219d were delivered the desired product in 3% and 2% ee although these catalysts had low enantiopurity (7% ee). Catalyst 223 was able to transfer some chirality (12% ee) to the desired product, which was obtained in trace amounts (entry 5). Interestingly, the selectivity was increased slightly (18% ee) using catalyst 226, which contains a N-sulfoximine backbone (entry 7). Similarly, catalyst 227 achieved 18% ee of the desired product with no improvement in the yield (entry 8). These chiral reagents seemed to be difficult to oxidise to the corresponding hypervalent iodine reagents in order to perform this reaction.
Table 5.1. Catalytic enantioselective α-oxytosylation of ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar*I</th>
<th>Enantiomeric Purity of Ar*I</th>
<th>146</th>
<th>146</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>219a</td>
<td>16</td>
<td>trace</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>219b</td>
<td>70</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>219c</td>
<td>7</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>219d</td>
<td>7</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>223</td>
<td>56</td>
<td>trace</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>225</td>
<td>57</td>
<td>trace</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>226</td>
<td>70</td>
<td>trace</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>227</td>
<td>46</td>
<td>trace</td>
<td>18</td>
</tr>
</tbody>
</table>

*a*Isolated yield. *b* Determined by HPLC.
5.9.7.2. Enantioselective Lactonization of Acids

In order to further investigate the reactivity and selectivity of chiral iodine reagents, the catalytic stereoselective lactonization of acids was examined using the reported procedure. Chiral iodine reagents based on sulfoximine catalysed the reaction of 5-oxo-5-phenylpentanoic acid 147 with 3 equivalents of mCPBA as the oxidant in the presence of a catalytic amount of pTsOH·H₂O. The desired product 148 was obtained in low yields for catalysts 219c and 219d, where methoxy groups are substituents on the iodoarene (entries 3 and 4). However, trace amounts of 148 were observed in most cases. This further demonstrated that these chiral iodoarenes were difficult to oxidise to the corresponding hypervalent iodine reagents. Unfortunately, these chiral iodine reagents typically failed to transfer their chirality to the desired product. However, catalyst 219c was able to deliver the desired product in 6% ee although enantiomeric purity of catalysts 219c was low (7% ee) (entry 3). Similarity, catalyst 219d was achieved 3% ee of the desired product even though this catalyst had low enantiomeric purity (7% ee). Catalyst 227, which contained the N-benzoyl group, was able to induce 16% ee to the product (entry 8).
Table 5.2. Catalytic enantioselective lactonization of acids

```
<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar*I</th>
<th>Purity of Ar*I</th>
<th>Yield [%]^a</th>
<th>ee [%]^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>219a</td>
<td>16</td>
<td>trace</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>219b</td>
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<td>219d</td>
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<td>11</td>
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<td>56</td>
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<td>70</td>
<td>trace</td>
<td>5</td>
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<td>46</td>
<td>6</td>
<td>16</td>
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```

^aIsolated yield. ^bDetermined by HPLC.
5.9.7.3. Enantioselective Dearomatisation of Phenols

The dearomatisation of phenols was then investigated to explore the reactivity of the new chiral iodine reagents based on sulfoximine. The known procedure was applied using 2-bromo-4-methylphenol 149, which was dearomatized into the corresponding p-quinol derivative 150 with 2.2 equivalents of mCPBA in a mixture of acetone and water. This type of reaction seemed to be suitable for examining the reactivity of chiral iodine reagents, where the desired product 150 was obtained in acceptable yields in some cases (entries 2–4, 6 and 8). The best result achieved was 44% of the desired product using catalyst 219d, which contained two substituted methoxy groups (entry 4). Though, the dearomatized phenol 150 was obtained as a racemic product in all the cases where the chiral indication by the sulfur centre was failed in the desired product. However, only catalyst 219c achieved the desired product in 7% ee where enantiomeric purity of catalyst 219c was 7% ee. Interesting, improving enantiomeric purity of this catalyst could improve stereoinduction of the desired product. Also, catalyst 219c with one substituted methoxy group achieved 43% of the desired product (entry 3). Similarly, catalysts 225 and 227 returned the desired product in 40% and 41% yields, respectively. However, the yield of the desired product decreased steeply when the chiral iodine catalysts had one aromatic ring such as reagents 219a and 223 (entries 1 and 5). Also, trace amounts of the desired product were observed when the iodine catalyst 226 was used (entry 7).
### Table 5.3. Catalytic enantioselective dearomatisation of phenols

![Chemical structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar*I</th>
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<th>Yield [%]a</th>
<th>ee [%]b</th>
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<tr>
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*a*Isolated yield.  *b*Determined by HPLC.
5.10. Conclusion and Outlook

This chapter introduced a novel class of chiral iodoarenes possessing a stereogenic sulfoximine, which have thus far never been investigated in the area of hypervalent iodine chemistry. The aim was to investigate the stereogenic sulfur as a new source of chirality. Though the chirality of the sulfoxide skeletons was typically destroyed during the oxidation reaction because of the further oxidation to sulfones. Despite well-known oxidation methods for sulfur compounds, enantioselective oxidation of sulfur compounds for application in hypervalent iodine chemistry proved to be difficult. A chiral sulfoximine was investigated to retain the chirality of sulfur without any distractions, and they were synthesised using the known procedures. Hence, the synthesis of chiral sulfoximines was achieved by using one of these possible procedures: the resolution of sulfoximine salts in their diastereomeric forms or the imination of chiral sulfoxides. Moreover, further modification was achieved by functionalization through the NH of sulfoximine to ensure that the chiral environment was close enough to that of iodine with the provision of rigid reagents. Then, the chiral induction of sulfoximines of these novel chiral iodine reagents was investigated in various asymmetric catalytic reactions, particularly the catalytic enantioselective α-oxytosylation of a ketone, lactonization of an acid, and dearomatization of a phenol. The oxidation of these chiral iodoarenes was examined, but they seemed to be difficult to oxidise to the corresponding hypervalent iodine reagents. In the future, an effective oxidation pathway could be used to access the chiral hypervalent iodine reagent-based sulfoximine. The use of sodium hypochlorite pentahydrate as an oxidant in the presence of acetic acid could feasibly provide access to the target hypervalent iodine reagents, and then, the examination of their reactivity would be worth investigating with respect to enantioselective transformations.
The enantioselective oxidation or iminination of sulfides could be a strategy to obtain chiral iodoarenes by using a chiral catalyst. Then, a further step will be required for the protection sulfur, to avoid destroying the chirality during the oxidation reaction by synthesising sulfoximines either by the imination of sulfoxides or by the oxidation of sulfilimines (Scheme 5.23).

**Scheme 5.23.** The enantioselective oxidation or imination of sulfide.
5.11. References


Chapter 6

Experimental Part
6.1. General Methods

All reactions were performed using standard laboratory equipment. Any air and moisture sensitive reactions were carried out under an inert atmosphere of argon or nitrogen using oven dried glassware and freshly distilled and dried solvents. All reactions were stirred using magnetic stirring, and for the need of heating, over a hotplate with a temperature probe control and an adapted heating block. Lower temperatures were achieved using ice/water bath (0 °C), dry ice/ acetonitrile bath (– 40 °C), dry ice/acetone bath (– 78 °C) or using a chiller (0 to – 20 °C). Büchi rotavapors were used for solvent evaporations, and a high vacuum apparatus was used to further dry the products.

All reagent-grade chemicals and solvents were obtained from Sigma Aldrich, Alfa Aesar, Acros Organics, Fisher Scientific, TCI, and FluoroChem and were used as received without purification unless mentioned otherwise. Dry diethyl ether, tetrahydrofuran, toluene, and acetonitrile were collected from a solvent purification system (SPS) stored under a nitrogen atmosphere, which is from the company M BRAUN (MB SPS-800). Dry dichloromethane was freshly distilled from P₂O₅ under a or dried nitrogen atmosphere.

Thin layer chromatography (TLC) was performed on precoated aluminium sheets of Merck silica gel 60 F254 (0.20 mm) and visualized by UV radiation (254 nm). Manual column chromatography was carried out using silica gel 60 (Merck, 230-400 mesh) under increased pressure. Automated column chromatography was performed on a Biotage® Isolera Four using Biotage® cartridges SNAP Ultra 10 g, SNAP Ultra 25 g, SNAP Ultra 50 g, and SNAP Ultra 100 g. The eluting solvents used for the purification are indicated in the text.
HPLC measurements were performed on a Shimadzu apparatus. The different modules were SIL-10ADVP (auto injector), LC-10ATVP (liquid chromatograph), FCV-10ALVP (pump), DGU-14A (degasser), CTO-10ASVP (column oven), SCL-10AVP (system controller) and SPD-M10A (diode array detector). The solvents used were n-hexane and 2-propanol as HPLC grade. The chiral columns used for the separation of enantiomers were YMC Chiral Amylose-C S-5µm (0.46 cm Ø x 25 cm), Daicel Chiralcel OD-H (0.46 cm Ø x 25 cm), and Regis® Pirkle Covalent (S,S) Whelk-O1 (0.46 cm Ø x 25 cm).

$^1$H and $^{13}$C NMR spectra were measured at 298 K on Bruker DPX 300, 400 or 500 MHz apparatus and were referenced to residual proton solvent peaks: ($^1$H: CDCl$_3$, $\delta=$ 7.26 ppm; DMSO-d$_6$, $\delta=$ 2.54 ppm; Acetone-d$_3$, $\delta=$ 2.05; methanol-d$_4$, $\delta=$ 4.87) and the residual $^{13}$C solvent peaks: ($^{13}$C: CDCl$_3$, $\delta=$77.2 ppm; DMSO-d$_6$, $\delta=$ 39.5 ppm; CD$_3$COCD$_3$-d$_3$, $\delta=$ 206.3; CD$_3$OD-d$_4$, $\delta=$ 49). Chemical shifts $\delta$ were given in ppm and the multiplicity of the signals was reported as: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplet, m = multiplet, b = broad. The coupling constants (J) in Hertz. Mass spectrometric measurements were performed by R. Jenkins, R. Hick, T. Williams and S. Waller at Cardiff University on a Water LCR Premier XE. Ions were generated by Electrospray (ES) or Electron Ionisation (EI). The molecular ion peak values quoted for either molecular ion plus or minus hydrogen [M+H]$^+$, [M-H]$^+$ or molecular ion plus sodium [M+Na]$^+$.

IR spectra were recorded on a Shimadzu FTIR Affinity-1S apparatus and wavenumbers are quoted in cm$^{-1}$. All compounds were measured neat directly on the crystal of the IR machine. Melting points were measured using a Gallenkamp variable heater with samples in open capillary tubes. Optical rotations were measured with a SCHMIDT and HAENSCH UniPol L polarimeter at 20 °C in a cuvette of 50 mm length with a sodium light (589.30 nm).
X-Ray crystallographic studies were carried out at the X-Ray Crystallography Service at Cardiff University. The data were collected on an Agilent SuperNova Dual Atlas diffractometer with a mirror monochromator, equipped with an Oxford cryosystems cooling apparatus. Crystal structures were solved and refined using SHELX. Nonhydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted in idealised positions. The structure was solved by a direct method and refined by a full matrix least-squares procedure on F2 for all reflections (SHELXL-97).
6.2. Experimental Data for Chapter 2

6.2.1. Synthesis of Axially Chiral Iodine Compounds in Racemic Forms

6.2.1.1. Synthesis of 2-iodo-4,6-dimethylaniline (GP1)

Prepared according to a literature procedure.\textsuperscript{1} 2,4-Dimethyl aniline \textbf{107} (40 mmol), iodine (40 mmol) and sodium bicarbonate (60 mmol, 1.5 equiv.) were dissolved in a mixture of toluene and H\textsubscript{2}O (50 mL, 9:1), the mixture was stirred at room temperature for 16 h. The reaction mixture was then diluted with ethyl acetate and washed with aqueous solution of Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} (2 x 50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine and dried over MgSO\textsubscript{4}, filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (n-hexane/EtOAc 9:1).

\textbf{2-Iodo-4,6-dimethylaniline 108}

Following \textbf{GP 1}: 2,4-Dimethyl aniline \textbf{107} (4.95 mL, 40.0 mmol), I\textsubscript{2} (10.2 g, 40.0 mmol), and NaHCO\textsubscript{3} (5.0 g, 60.0 mmol) to afford \textbf{108} as a light brown solid (8.70 g, 88\%). \textbf{M.p.}: 65–66 °C. \textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})}: \(\delta = 7.36\) (s, 1H), 6.84 (s, 1H), 3.93 (bs, 2H), 2.19 (s, 6H) ppm. \textbf{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})}: \(\delta = 142.5, 137.0, 131.5, 129.4, 122.6, 84.9, 20.0, 19.0\) ppm. The spectroscopic data are in agreement with the literature.\textsuperscript{1,2}
6.2.1.2. Synthesis of 2° N-aryl amides based on iodine reagents (GP2)

Prepared according to a literature procedure.³ Into a dried round flask, one drop of dry DMF was added to a mixture of the aromatic acids 109 or 110 (0.5 mmol) in SOCl₂ (6.85 mmol, 13.7 equiv.), and the mixture was stirred at 74 °C for 6 h under argon atmosphere. The solvents were then evaporated under reduced pressure to obtain the crude acid chlorides which were dissolved in anhydrous DCM (5 mL) under argon atmosphere. The mixture was cooled to 0 °C followed by dropwise addition of NEt₃ (0.75 mmol, 1.5 equiv.) and 2-iodo-4,6-dimethyl aniline 108 (0.75 mmol, 1.5 equiv.) in anhydrous DCM, and the mixture was stirred overnight at room temperature under argon atmosphere. After completion, the mixture was washed with 1M HCl (2x 10 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (2x 20 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (n-hexane/EtOAc 8:2).

**N-(2-Iodo-4,6-dimethylphenyl) benzamide 111**

Following **GP 2**: Benzoyl chloride (0.06 mL, 0.5 mmol), NEt₃ (0.1 mL, 0.75 mmol) and 2-iodo-4,6-dimethyl aniline 108 (184 mg, 0.75 mmol) to afford 111 as a white solid (170.3 mg, 97%). **M.p.**: 179– 181 °C. **¹H NMR** (500 MHz, CDCl₃): δ= 7.99 – 795 (m, 2H), 7.56 (s, 1H), 7.53 – 7.47 (m, 3H), 7.07 (s, 1H),
2.32 (s, 3H), 2.30 (s, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 165.9, 139.3, 137.5, 137.2, 134.6, 134.3, 132.1, 132.0, 128.9, 127.6, 99.5, 20.6, 19.8$ ppm. The spectroscopic data are in agreement with the literature.$^4$

$N$-(2-Iodo-4,6-dimethylphenyl) picolinamide 112

Following GP 2: Picolinic acid 110 (62 mg, 0.5 mmol) in SOCl$_2$ (0.49 mL, 6.85 mmol), NEt$_3$ (0.1 mL, 0.75 mmol) and 2-iodo-4,6-dimethyl aniline 108 (184 mg, 0.75 mmol) to afford 112 as a light yellow solid (112.7 mg, 64%). M.p.: 128 – 129 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 9.55$ (s, 1H), 8.67 (ddd, $J = 4.8, 1.7, 0.9$ Hz, 1H), 8.29 (dt, $J = 7.9, 1$ Hz, 1H), 7.91 (td, $J = 7.7, 1.7$ Hz, 1H), 7.58 (s, 1H), 7.54 – 7.44 (m, 1H), 7.07 (s, 1H), 2.31 (s, 3H), 2.30 (s, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 162.3, 149.5, 148.3, 138.9, 137.5, 137.2, 137.0, 134.6, 131.8, 126.6, 122.7, 98.8, 20.5, 19.7$ ppm.

HRMS (ESI): [M+H]$^+$ calc. 353.0151, found 353.0147 [C$_{14}$H$_{14}$IN$_2$O$^+$]. IR (neat): $\nu = 3280, 3105, 1527, 1465, 1334, 1161, 738, 626$ cm$^{-1}$. 

164
6.2.1.2. Synthesis of 3° N-aryl amides based on iodine reagents (GP3)

Prepared according to a literature procedure. To a stirred solution of the obtained 2° N-aryl amides 111 or 112 (0.5 mmol) in dry THF (5.0 mL), 60 % NaH (1.25 mmol, 2.5 equiv.) was added at 0 °C under nitrogen atmosphere. The mixture was then allowed to warm to room temperature before dropwise addition of methyl iodide (1.5 mmol, 3.0 equiv.). The mixture was stirred overnight at room temperature under argon atmosphere, and the solvents were evaporated under reduced pressure after the completing of the reaction. The reaction mixture was then diluted with Et₂O and washed with 10 % Na₂S₂O₃ (2x 5 mL). The organic layer was separated, and the aqueous layer was extracted with Et₂O (2x 10 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (n-hexane/EtOAc 8:2).
N-(2-Iodo-4,6-dimethylphenyl)-N-methylbenzamide 113

Following GP 3: N-(2-Iodo-4,6-dimethylphenyl) benzamide 111 (175 mg, 0.5 mmol), 60 % NaH (52 mg, 1.30 mmol) and MeI (0.10 mL, 1.5 mmol) to afford 113 as a light yellow solid (149 mg, 82%). M.p.: 99–101°C.

C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.46 (s, 1H), 7.42 – 7.38 (m, 2H), 7.26 – 7.23 (m, 1H), 7.18 – 7.13 (m, 2H), 6.87 (s, 1H), 3.30 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 170.6, 142.7, 139.7, 138.4, 137.0, 135.8, 132.2, 130.0, 128.1, 127.6, 100.6, 36.5, 20.5, 19.4 ppm. HRMS (ESI): [M+H]$^+$ calc. 366.0349, found 366.0353 [C$_{16}$H$_{17}$INO]$^+$. IR (neat): $\nu$ = 1642, 1357, 786, 695 cm$^{-1}$.

N-(2-Iodo-4,6-dimethylphenyl)-N-methylpicolinamide 114

Following GP 3: N-(2-Iodo-4,6-dimethylphenyl) picolinamide 112 (175 mg, 0.5 mmol), 60 % NaH (52 mg, 1.30 mmol) and MeI (0.10 mL, 1.5 mmol) to afford 114 as a light yellow solid (144 mg, 79%). M.p.: 108–107 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.20 (ddd, $J$ = 4.8, 2, 1.2 Hz, 1H), 7.76 (dt, $J$ = 7.9, 1 Hz, 1H), 7.60 (td, $J$ = 7.7, 1.7 Hz, 1H), 7.34 (s, 1H), 7.10 (ddd, $J$ = 7.6, 4.8, 1.2 Hz, 1H), 6.91 (s, 1H), 3.29 (s, 3H), 2.36 (s, 3H), 2.18 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 168.6, 153.8, 147.8, 142.6, 139.4, 138.4, 137.4, 135.9, 131.7, 124.3, 123.6, 99.8, 35.9, 20.5, 19.8 ppm. HRMS (ESI): [M+H]$^+$ calc. 367.0302, found 367.0304 [C$_{15}$H$_{16}$IN$_2$O]$^+$. IR (neat): $\nu$ = 1627, 740, 702, 592 cm$^{-1}$.
6.2.2. Oxidation of Axially Chiral Iodine Reagents (GP 4)

**Method A**

Prepared according to a literature procedure.\(^5\) To a stirred solution of iodoarene 112 or 114 (0.53 mmol) in dichloromethane/trifluoroethanol (TFE) (1:1, 4.0 mL), m-CPBA (77% pure, 0.64 mmol, 143 mg, 1.2 equiv.) was added, followed by the addition of \(p\)-TsOH hydrate (0.53 mmol, 53 mg). The resulting solution was stirred at room temperature for 16 h till the reaction completed. The solvents were evaporated under reduced pressure, and the resulting solid was filtered off, washed with diethyl ether several times to obtain the desired product.

**Method B**

Prepared according to a modified procedure.\(^6\) To a stirred solution of iodoarene 111 or 113 (0.50 mmol) in acetic acid (3.0 mL), peracetic acid solution 32 wt.% in dilute acetic acid (2.70 mmol, 0.20 mL, 5.4 equiv.) was added. The resulting solution was stirred at 30 °C for 16 h till the reaction completed. The solvents were evaporated under reduced pressure, and the resulting crude was washed with hexane several times to obtain the desired product.
(3,5-Dimethyl-2-(picolinamido) phenyl)(hydroxy)-λ³-iodaneyl-4-methylbenzenesulfonate 115

Following GP 4, method A, N-(2-Iodo-4,6-dimethylphenyl) picolinamide 112 (187 mg, 0.53 mmol), to afford 115 as a yellow oil (257 mg, 90%). ¹H NMR (500 MHz, CDCl₃): δ= 9.82 (bs, 1H), 8.85 – 8.82 (m, 1H), 8.48 – 8.45 (m, 1H), 8.16 – 8.09 (m, 1H), 8.03 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.55 (s, 1H), 7.09 (d, J = 8.0 Hz, 9H), 2.32 (s, 13H), 2.29 (s, 5H), 2.27 (s, 6H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ= 170.2, 168.3, 153.6, 146.9, 140.9, 139.4, 137.4, 137.2, 134.7, 133.6, 131.9, 130.3, 129.9, 129.0, 128.4, 126.2, 21.5, 20.6, 19.7 ppm. IR (neat): ν= 3280, 3105, 2710, 1527, 1653, 1334, 1161, 738, 626 cm⁻¹.

(3,5-Dimethyl-2-(N-methylpicolinamido)phenyl)(hydroxy)-λ³-iodaneyl methylbenzenesulfonate 116

Following GP 4, method A: N-(2-Iodo-4,6-dimethylphenyl)-N-methylpicolinamide 114 (194 mg, 0.53 mmol) to afford 116 as a yellow solid (270 mg, 92%). M.p.: 94–96 °C. ¹H NMR (500 MHz, CDCl₃): δ= 8.70 – 8.66 (m, 1H), 8.14 (s, 1H), 7.92 – 7.87 (m, 1H), 7.75 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 7.7 Hz, 1H), 7.40 – 7.30 (m, 1H), 7.09 (d, J = 8.0 Hz, 2H), 7.06 (s, 1H), 3.43 (s, 3H), 2.30 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ= 171.3, 167.6, 166.1, 146.9, 142.2, 140.0, 137.3, 136.1, 133.8, 132.9, 130.0, 129.7, 128.9, 128.2, 127.3, 126.2, 36.9, 21.4, 21.1, 20.9 ppm. IR (neat): ν= 2700, 1650, 1653, 1100, 1115, 740, 555 cm⁻¹.
(2-Benzamido-3,5-dimethylphenyl)-$\lambda^3$-iodanediyl diacetate 117

Following **GP 4.** method B: $N$-(2-Iodo-4,6-dimethylphenyl) benzamide 111 (176 mg, 0.50 mmol), to afford 117 as a yellow oil (213 mg, 91%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 8.09 (s, 1H), 8.00 – 7.95 (m, 2H), 7.83 – 7.79 (m, 2H), 7.52 – 7.44 (m, 2H), 2.36 (s, 6H), 2.05 (s, 6H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = 176.2, 170.9, 140.1, 139.3, 137.6, 137.4, 134.5, 131.9, 130.1, 127.5, 21.1, 20.8, 20.5 ppm. IR (neat): $\nu$ = 3560, 2970, 2358, 1739, 1558, 1507, 1374, 1217, 913 cm$^{-1}$.

(3,5-Dimethyl-2-(N-methylbenzamido)phenyl)-$\lambda^3$-iodanediyl diacetate 118

Following **GP 4.** method B: $N$-(2-Iodo-4,6-dimethylphenyl)-N-methylbenzamide 113 (183 mg, 0.50 mmol) to afford 118 as a yellow oil (227 mg, 94%).$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.99 (s, 1H), 7.85 (s, 1H), 7.58 – 7.54 (m, 1H), 7.48 – 7.38 (m, 4H), 3.43 (s, 3H), 2.41 (s, 3H), 2.40 (s, 3H), 2.36 (s, 3H), 2.29 (s, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = 176.5, 169.5, 141.6, 140.9, 137.2, 136.9, 136.6, 134.5, 130.6, 129.3, 127.7, 127.0, 38.8, 20.9, 20.5, 19.6 ppm. IR (neat): 2970, 2358, 1734, 1558, 1217, 1007, 668 cm$^{-1}$.
6.2.3. Symmetric Reactions

6.2.3.1. Oxidation of sulfide (GP 5)

Prepared according to a literature procedure. Thioanisole 119 (0.125 mmol) was added to a solution of hypervalent iodine (0.15 mmol, 1.2 equiv.) in acetonitrile (2.0 mL). The mixture was stirred at room temperature for overnight. After completion of the reaction, 5% aqueous Na$_2$S$_2$O$_3$ (5.0 mL) and saturated NaHCO$_3$ (5.0 mL) were added. The organic layer was separated, and the aqueous layer was extracted with DCM (2x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (n-hexane/EtOAc 1:1).

Methyl phenyl sulfoxide 120

Following GP 5: Thioanisole 119 (16 mg, 0.125 mmol), (3,5-dimethyl-2-(picolinamido) phenyl) (hydroxy)-$\lambda^3$-iodaneyl 4-methylbenzenesulfonate 116 (83.0 mg, 0.15 mmol) to afford 120 as a yellow oil (11.0 mg, 63%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta= 7.68 - 7.63$ (m, 2H), 7.57 – 7.48 (m, 3H), 2.73 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta= 145.9, 131.2, 129.5, 123.7, 44.2$ ppm. The spectroscopic data are in agreement with the literature.
6.2.3.2. Hoffman Rearrangement (GP 6)

Prepared according to a literature procedure.\(^8\) Benzamide **121** (0.125 mmol) was added to a solution of hypervalent iodine (0.20 mmol, 1.6 equiv.) in MeOH (3.0 mL). The reaction was stirred at reflux for overnight. After completion of the reaction, 5% aqueous Na\(_2\)S\(_2\)O\(_3\) (5.0 mL) and saturated NaHCO\(_3\) (5.0 mL) were added. The organic layer was separated, and the aqueous layer was extracted with DCM (2x 10 mL). The combined organic layers were dried over MgSO\(_4\), filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (\(n\)-hexane/EtOAc 7:3).

**Methyl phenylcarbamate 122**

Following **GP 6**: Benzamide **121** (15 mg, 0.125 mmol), (3,5-dimethyl-2-(picolinamido) phenyl) (hydroxy)-\(\lambda^3\)-iodaneyl 4-methylbenzenesulfonate **116** (0.111g, 0.20 mmol) to afford **122** as a yellow oil (10.7 mg, 57%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta=7.38\) (d, \(J=7.9\) Hz, 2H), 7.34 – 7.27 (m, 2H), 7.09 – 7.03 (m, 1H), 6.62 (bs, 1H), 3.78 (s, 3H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta=154.1, 138.0, 129.2, 123.6, 118.8, 52.5\) ppm. The spectroscopic data are in agreement with the literature.\(^8\)
6.2.3.3. Dearomatization of phenols (GP 7)

![Chemical structure diagram]

Prepared according to a literature procedure.\(^7\) 2,4-dimethylphenol 123 (0.125 mmol) was added to a solution of hypervalent iodine (0.15 mmol, 1.2 equiv.) in Acetonitrile (2.0 mL) and water (1.0 mL). The reaction was stirred at 0 °C to room temperature for overnight. After completion of the reaction, 5% aqueous Na\(_2\)S\(_2\)O\(_3\) (5.0 mL) and saturated NaHCO\(_3\) (5.0 mL) were added. The organic layer was separated, and the aqueous layer was extracted with DCM (2x 10 mL). The combined organic layers were dried over MgSO\(_4\), filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (n-hexane/EtOAc 6:4).

4-Hydroxy-2,4-dimethylcyclohexa-2,5-dien-1-one 124

Following GP 7: 2,4-dimethylphenol 123 (15 mg, 0.125 mmol), (3,5-dimethyl-2-(picolinamido) phenyl) (hydroxy)-\(\lambda^3\)-iodaneyl 4-methylbenzenesulfonate 116 (83.0 mg, 0.15 mmol) to afford 124 as a colorless oil (7.0 mg, 42%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta=6.84\) (dd, \(J=10.0, 3.1\) Hz, 1H), 6.64 (dd, \(J=3.0, 1.5\) Hz, 1H), 6.11 (d, \(J=9.9\) Hz, 1H), 2.29 – 2.15 (bs, 1H), 1.87 (s, 3H), 1.46 (s, 3H) ppm. \(^13\)C NMR (101 MHz, CDCl\(_3\)): \(\delta=186.1, 151.8, 147.4, 134.0, 127.2, 67.7, 27.0, 15.7\) ppm. The spectroscopic data are in agreement with the literature.\(^7\)
6.2.3.4. Oxidative dimerization (GP 8)

Prepared according to a literature procedure. Benzaldoxime 125 (0.125 mmol) was added to a solution of hypervalent iodine (0.20 mmol, 1.6 equiv.) in acetonitrile (2.0 mL). The reaction was stirred at room temperature for overnight. After completion of the reaction, 5% aqueous Na$_2$S$_2$O$_3$ (5.0 mL) and saturated NaHCO$_3$ (5.0 mL) were added. The organic layer was separated, and the aqueous layer was extracted with DCM (2x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel ($n$-hexane/EtOAc 7:3).

3,5-Diphenyl-1,2,4-thiadiazole 126

Following GP 8: Benzaldoxime 125 (17 mg, 0.125 mmol), (3,5-dimethyl-2-(picolinamido) phenyl) (hydroxy)-$\lambda^3$-iodaneyl 4-methylbenzenesulfonate 116 (0.111g, 0.20 mmol) to afford 126 as a white solid (10.8 mg, 77%). M.P.: 90 – 91 ºC. $^1$H NMR (400 MHz, d$_6$-acetone): $\delta$= 8.44 – 8.37 (m, 2H), 8.20 – 8.13 (m, 2H), 7.66 – 7.53 (m, 6H) ppm. $^{13}$C NMR (101 MHz, d$_6$-acetone): $\delta$ =189.3, 174.4, 133.8, 133.2, 131.4, 130.4, 129.7, 129.0, 128.3 ppm. The spectroscopic data are in agreement with the literature.
6.3. Experimental Data for Chapter 3

6.3.1. Synthesis of Axially Chiral Iodine Reagents in Diastereomeric Forms

6.3.1.1. Synthesis of 2-iodoaniline derivatives (GP 9)

Prepared according to a literature procedure.™ 2-Methyl aniline derivative 107 or 138 (40 mmol), iodine (40 mmol) and sodium bicarbonate (60 mmol, 1.5 equiv.) were dissolved in a mixture of toluene and H₂O (50 mL, 9:1), the mixture was stirred at room temperature for (5-24) h. The reaction mixture was then diluted with ethyl acetate and washed with aqueous solution of Na₂S₂O₃ (2x 20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2x 20 mL). The combined organic layers were washed with brine and dried over MgSO₄, filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (n-hexane/EtOAc 9:1).
2-Iodo-4,6-dimethylaniline 108

Following **GP 9**: 2,4-Dimethyl aniline 107 (4.95 ml, 40 mmol), I$_2$ (10.2 g, 40 mmol), and NaHCO$_3$ (5.0 g, 60 mmol) to afford 108 as a light brown solid (8.7 g, 88%). **M.p.**: 65 – 66 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$= 7.35 (s, 1H), 6.84 (s, 1H), 3.92 (bs, 2H), 2.19 (s, 6H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$= 142.5, 136.9, 131.5, 129.4, 122.6, 84.9, 19.9, 19.0 ppm. The spectroscopic data are in agreement with the literature.\(^1\)\(^2\)

4-Chloro-2-iodo-6-methylaniline 139

Following **GP 9**: 4-Chloro-2-methylaniline 137 (1.0 g, 7.0 mmol), I$_2$ (1.77 g, 7.0 mmol), and NaHCO$_3$ (0.88 g, 10.5 mmol) to afford 139 as a light yellow solid (0.73 g, 39 %). **M.p.**: 49 – 50 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$= 7.49 (d, $J$ = 2.2 Hz, 1H), 7.01 (d, $J$ = 1.8 Hz, 1H), 4.06 (bs, 2H), 2.20 (s, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = 143.8, 135.7, 130.4, 123.4, 123.0, 83.8, 19.0 ppm The spectroscopic data are in agreement with the literature.\(^9\)
6.3.1.2. Synthesis of N-substituted 2-iodoaniline (GP 10)

Prepared according to a literature procedure.\textsuperscript{10} To a stirred solution of 2-iodoaniline derivative 108 or 139 (12 mmol) and pyridine (1.45 mL, 18 mmol, 1.5 equiv.) in dry dichloromethane (25 mL), the appropriate sulfonyl chloride derivative (12 mmol) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 16 h, then washed with HCl (1 M, 3x 10 mL). The combined acid wash was extracted with dichloromethane (4x 10 mL). The combined organic layers were dried over MgSO\textsubscript{4}, filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (n-hexane/EtOAc 8:2).

\textit{N-}(2-Iodo-4,6-dimethylphenyl)-4-methylbenzenesulfonamide 140a

Following \textbf{GP 10}: 2-Iodo-4,6-dimethyl aniline 108 (2.97 g, 12 mmol), 4-methylbenzenesulfonyl chloride (2.29 g, 12 mmol), and pyridine (1.45 mL, 18 mmol) to afford 140a as a white solid (3.66 g, 76%). \textbf{M.p.:} 157 – 158 °C. \textit{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})}: \(\delta= 7.56\) (d, \(J = 8.1\) Hz, 2H), 7.39 (s, 1H), 7.25 (d, \(J = 8.1\) Hz, 2H), 7.07 (s, 1H), 6.04 (bs, 1H), 2.49 (s, 3H), 2.44 (s, 3H), 2.26 (s, 3H) ppm. \textit{\textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3})}: \(\delta= 144.1, 139.6, 139.4, 137.7, 137.4, 133.4, 132.9, 129.7, 128.1, 100.3, 21.8, 20.9, 20.5\) ppm. The spectroscopic data are in agreement with the literature.\textsuperscript{11}
**N-(2-Iodo-4,6-dimethylphenyl)-4-nitrobenzenesulfonamide 140b**

Following **GP 10**: 2-Iodo-4,6-dimethyl aniline **108** (2.97 g, 12 mmol), 4-nitrobenzenesulfonyl chloride (2.66 g, 12 mmol), and pyridine (1.45 mL, 18 mmol) to afford **140b** as a white solid (3.47 g, 67%). **M.p.**: 138 – 139 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.30\) (d, \(J = 7.9\) Hz, 2H), 7.87 (d, \(J = 7.8\) Hz, 2H), 7.39 (s, 1H), 7.11 (s, 1H), 6.19 (bs, 1H), 2.52 (s, 3H), 2.26 (s, 3H) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = 150.6, 145.8, 140.4, 140.2, 137.9, 133.3, 132.3, 129.5, 124.4, 100.1, 21.0, 20.6\) ppm. HRMS (ESI): [M-H]^- calc. for \([\text{C}_{14}\text{H}_{12}\text{IN}_{2}\text{O}_{4}\text{S}]^-\) 430.9568, found 430.9548. IR (neat): \(\nu = 3281, 3105, 1527, 1465, 1334, 1163, 1087, 854, 738, 628\) cm\(^{-1}\).

**N-(2-Iodo-4,6-dimethylphenyl)-4-methoxybenzenesulfonamide 140c**

Following **GP 10**: 2-Iodo-4,6-dimethyl aniline **108** (2.97 g, 12 mmol), 4-methoxybenzenesulfonyl chloride (2.48 g, 12 mmol), and pyridine (1.45 mL, 18 mmol) to afford as a white solid **140c** (3.25 g, 65%). **M.p.**: 176 – 177 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.62 – 7.57\) (m, 2H), 7.38 (d, \(J = 1.1\) Hz, 1H), 7.06 (s, 1H), 6.93 – 6.88 (m, 2H), 6.02 (bs, 1H), 3.87 (s, 3H), 2.49 (s, 3H), 2.25 (s, 3H) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = 163.6, 139.7, 139.4, 137.7, 133.5, 133.0, 132.1, 130.2, 114.2, 100.2, 55.8, 20.9, 20.5\) ppm. HRMS (ESI): [M+H]^+ calc. 417.9974, found 417.9978 [C\(_{15}\)H\(_{17}\)INO\(_3\)S]^+. IR (neat): \(\nu = 3280, 3105, 1527, 1465, 1346, 1334, 1161, 1087, 852, 738, 621\) cm\(^{-1}\).
N-(4-Chloro-2-iodo-6-methylphenyl)-4-methylbenzenesulfonamide 140d

Following GP 10: 4-Chloro-2-iodo-6-methylaniline 139 (3.20 g, 12 mmol), 4-methylbenzenesulfonyl chloride (2.29 g, 12 mmol), and pyridine (1.45 mL, 18 mmol) to afford as a white solid 140d (2.32 g, 46%). M.p.: 101 – 102 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.57 – 7.56 (m, 1H), 7.55 – 7.53 (m, 2H), 7.28 – 7.25 (m, 3H), 6.06 (bs, 1H), 2.51 (s, 3H), 2.43 (s, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = 144.5, 141.2, 137.1, 136.5, 135.0, 133.9, 132.0, 129.9, 128.1, 100.4, 21.8, 21.1 ppm. HRMS (ESI): [M-H]$^+$ calc. 419.9322, found 419.9328 [C$_{14}$H$_{12}$ClINO$_2$S]$^+$. IR (neat): $\nu$ = 3267, 3010, 2358, 1757, 1456, 1336, 1149, 1087, 857, 732, 588 cm$^{-1}$. 
6.3.1.3. Synthesis of Diastereomers of Axial Chiral Iodine Reagents (GP 11)

Prepared according to a modified literature procedure.\textsuperscript{12} To a stirred solution of \(N\)-substituted 2-iodoaniline \(140\mathbf{a-d}\) (5.6 mmol), triphenylphosphine (8.4 mmol, 1.5 equiv.), and \(S\)-lactate derivative (8.4 mmol, 1.5 equiv.) in dry toluene (30 mL), diisopropyl azodicarboxylate (8.4 mmol, 1.5 equiv.) was added at 0 °C. The reaction mixture was warmed up to room temperature and then stirred at 50 °C for 6 h. The solvent was then removed under reduced pressure and \(\text{Et}_2\text{O}\) was added. The precipitated triphenylphosphine oxide was removed by filtration and the filtrate was concentrated under reduced pressure. The formed diastereoisomers were separated by flash column chromatography multiple times (\(n\)-hexane: \(\text{EtOAc}\) 9:1).
(Methyl \textit{N}-\textit{(2-iodo-4,6-dimethylphenyl)}-\textit{N}-\textit{((4-nitrophenyl) sulfonyl)}-alaninate)

Following \textbf{GP 11}: \textit{N}-\textit{(2-Iodo-4,6-dimethylphenyl)}-4 nitrobenzenesulfonamide 140b (2.42 g, 5.6 mmol), \textit{pph}_3 (2.20 g, 8.4 mmol), S-lactic acid methyl ester (0.80 mL, 8.4 mmol), and DIAD (1.65 mL, 8.4 mmol) to afford two diastereoisomers (55:45) (2.84 g, 98%); major diastereomer \textit{R, S}_\textit{N-C}: minor diastereomer \textit{R, R}_\textit{N-C}.

(R, \textit{S}_\textit{N-C}) (Methyl \textit{N}-\textit{(2-iodo-4,6-dimethylphenyl)}-\textit{N}-\textit{((4-nitrophenyl) sulfonyl)}-alaninate)

\textbf{141a}: White solid. \textbf{M.p.} 148 – 147 °C. \textbf{[\alpha] D}_{20} = +10.2 (c=0.19, CHCl_3).

\textbf{1H NMR (500 MHz, CDCl}_3): \delta = 8.33 – 8.27 (m, 2H), 7.91 – 7.80 (m, 2H), 7.53 (d, \textit{J} = 1.5 Hz, 1H), 7.05 (s, 1H), 4.90 (q, \textit{J} = 7.2 Hz, 1H), 3.88 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H), 1.10 (d, \textit{J} = 7.2 Hz, 3H) ppm.

\textbf{13C NMR (126 MHz, CDCl}_3): \delta = 173.6, 150.4, 145.8, 144.2, 141.3, 139.2, 134.7, 132.7, 130.3, 123.9, 104.2, 58.3, 52.8, 20.6, 19.9, 17.8 ppm. \textbf{HRMS} (ESI): [\textbf{M+H}]^+ \textit{calc.} 519.0087, found 519.0084 [\textit{C}_{18}\textit{H}_{26}\textit{IN}_{2}\textit{O}_6\textit{S}]^+. \textbf{IR (neat)}: \nu = 2949, 1751, 1525, 1456, 1344, 1315, 1205, 1163, 1085, 950, 850, 738, 684, 619, 582, 547 cm\textsuperscript{-1}.
**(R, R<sub>N</sub>C)** -(Methyl N-(2-iodo-4,6-dimethylphenyl)-N-((4-nitrophenyl) sulfonyl)-alaninate)

**141b**: White solid. **M.p.** 156 – 157 °C. \[\alpha\]D
20 = −25.6 (c=0.31, CHCl3).

**1H NMR (500 MHz, CDCl3)**: \(\delta= 8.30 \text{ (d, } J = 8.9 \text{ Hz, 2H}), 7.94 \text{ (d, } J = 8.9 \text{ Hz, 2H}), 7.53 \text{ (s, 1H)}, 7.10 \text{ (s, 1H)}, 4.86 \text{ (q, } J = 7.2 \text{ Hz, 1H}), 3.80 \text{ (s, 3H)}, 2.42 \text{ (s, 3H)}, 2.29 \text{ (s, 3H)}, 1.21 \text{ (d, } J = 7.2 \text{ Hz, 3H}) \text{ ppm.}**

**13C NMR (125 MHz, CDCl3)**: 173.4, 145.6, 144.0, 141.2, 139.4, 134.5, 132.8, 130.6, 123.6, 104.1, 58.8, 52.4, 21.0, 20.4, 17.2 ppm. **HRMS (ESI)**: [M+H]+ calc. 519.0087, found 519.0093 [C18H20IN2O6S]+. **IR (neat)**: \(\nu=2949, 1751, 1525, 1456, 1344, 1315, 1205, 1163, 1085, 950, 850, 738, 684, 619, 582, 547 \text{ cm}^{-1}.

**Methyl N-(2-iodo-4,6-dimethylphenyl)-N-tosyl-alaninate**

Following **GP 11**: \(N\)-(2-Iodo-4,6-dimethylphenyl)-4-methylbenzenesulfonamide 140a (2.25 g, 5.6 mmol), pph3 (2.20 g, 8.4 mmol), S-lactic acid methyl ester (0.80 mL, 8.4 mmol), and DIAD (1.65 mL, 8.4 mmol) to afford two diastereoisomers (65:35) (1.85 g, 68%); major diastereomer **R, SN-C**: minor diastereomer **R, RN-C**.
\((R, S_{N-C})\)-Methyl \(N\)-(2-iodo-4,6-dimethylphenyl)-\(N\)-tosyl-alaninate

\(141c\): White foam. \([\alpha]_D^{20} = +9.1\) (c=0.22, CHCl\(_3\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.56\) (d, \(J = 8.3\) Hz, 2H), 7.50 (s, 1H), 7.24 (d, \(J = 8.2\) Hz, 2H), 7.01 (s, 1H), 4.88 (q, \(J = 7.1\) Hz, 1H), 3.86 (s, 3H), 2.41 (s, 3H), 2.26 (s, 3H), 2.25 (s, 3H), 1.07 (d, \(J = 7.2\) Hz, 3H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 173.8, 144.6, 143.7, 140.4, 138.8, 137.4, 135.4, 132.2, 129.3, 128.8, 104.1, 57.6, 52.5, 21.6, 20.4, 19.9, 17.8\) ppm.

HRMS (ESI): [M+H]\(^+\) calc. 488.0393, found 488.0383 [C\(_{19}\)H\(_{23}\)INO\(_4\)S]\(^+\). IR (neat): \(\nu = 2951, 1751, 1597, 1452, 1344, 1161, 1085, 916, 592\) cm\(^{-1}\).

\((R, R_{N-C})\)-Methyl \(N\)-(2-iodo-4,6-dimethylphenyl)-\(N\)-tosyl-alaninate

\(141d\): White solid. M.p.: 102 – 103 °C. \([\alpha]_D^{20} = -6.0\) (c=1, CHCl\(_3\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.64\) (d, \(J = 8.3\) Hz, 2H), 7.56 (s, 1H), 7.29 – 7.22 (m, 2H), 7.02 (s, 1H), 4.74 (q, \(J = 7.2\) Hz, 1H), 3.77 (s, 3H), 2.42 (s, 3H), 2.26 (s, 3H), 2.23 (s, 3H), 1.19 (d, \(J = 7.2\) Hz, 3H) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = 172.4, 143.9, 142.3, 140.5, 139.4, 137.8, 136.2, 132.6, 129.3, 129.2, 105.0, 58.5, 52.3, 21.8, 20.8, 20.5, 17.5\) ppm.

HRMS (ESI): [M+H]\(^+\) calc. 488.0393, found 488.0393 [C\(_{19}\)H\(_{23}\)INO\(_4\)S]\(^+\). IR (neat): \(\nu = 2949, 1759, 1597, 1456, 1338, 1161, 1085, 916, 592\) cm\(^{-1}\).
Methyl $N$-(2-iodo-4,6-dimethylphenyl)-$N$-((4-methoxyphenyl) sulfonyl)-D-alaninate

Following **GP 11**: $N$-(2-Iodo-4,6-dimethylphenyl)-4-methoxybenzenesulfonamide 140c (2.34 g, 5.6 mmol), pph$_3$ (2.20 g, 8.4 mmol), S-lactic acid methyl ester (0.80 mL, 8.4 mmol), and DIAD (1.65 mL, 8.4 mmol) to afford two diastereoisomers (65:35) (1.49 g, 53%); major diastereomer $R$, $S_{N-C}$: minor diastereomer $R$, $R_{N-C}$.

(R, $S_{N-C}$)-Methyl $N$-(2-iodo-4,6-dimethylphenyl)-$N$-((4-methoxyphenyl) sulfonyl)-D-alaninate

**141e**: White solid. **M.p.**: 124 – 125 °C. [α]$_D^{20}$ = +3.3 (c=1.8, CHCl$_3$).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$= 7.63 – 7.58 (m, 2H), 7.52 – 7.48 (m, 1H), 7.02 – 7.00 (m, 1H), 6.93 – 6.89 (m, 2H), 4.87 (q, $J$ = 7.2 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H), 1.07 (d, $J$ = 7.2 Hz, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$= 174.1, 163.4, 144.8, 140.6, 138.9, 135.5, 132.4, 132.3, 131.0, 113.9, 104.1, 57.7, 55.7, 52.6, 20.6, 19.9, 17.9 ppm. **HRMS (ESI)**: [M+H]$^+$ calc. 504.0342, found 504.0347 [C$_{19}$H$_{22}$INO$_5$S]$^+$. **IR (neat)**: $\nu$= 2360, 2341, 1743, 1458, 1344, 1257, 1195, 1157, 680, 592, 545 cm$^{-1}$. 

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(R, R\textsubscript{N,C})-Methyl N-(2-iodo-4,6-dimethylphenyl)-N-((4-methoxyphenyl) sulfonyl)-D-alaninate

141f: White solid. M.p.: 119 – 120 °C. [α]\textsubscript{D} = –1.7 (c=2.4, CHCl\textsubscript{3}).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ= 7.70 – 7.66 (m, 2H), 7.56 – 7.54 (m, 1H), 7.03 – 7.01 (m, 1H), 6.94 – 6.91 (m, 2H), 4.74 (q, J = 7.2 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 2.26 (s, 6H), 1.17 (d, J = 7.2 Hz, 3H) ppm. \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): δ= 172.5, 163.4, 142.3, 140.5, 139.4, 136.1, 132.6, 132.5, 131.3, 113.8, 105.0, 58.4, 55.7, 52.3, 20.8, 20.5, 17.5 ppm. HRMS (ESI): [M+H]\textsuperscript{+} calc. 504.0342, found 504.0342 [C\textsubscript{19}H\textsubscript{22}INO\textsubscript{5}S]\textsuperscript{+}. IR (neat): ν = 2360, 2341, 1743, 1593, 1346, 1257, 1157, 682, 592, 543 cm\textsuperscript{-1}.

(R)-Methyl N-(4-chloro-2-iodo-6-methylphenyl)-N-tosyl-L-alaninate

Following GP 11: N-(4-Chloro-2-iodo-6-methylphenyl)-4-methylbenzenesulfonamide 140d (2.0 g, 4.7 mmol), pph\textsubscript{3} (1.84 g, 7 mmol), S-lactic acid methyl ester (0.67 mL, 7.0 mmol), and DIAD (1.38 mL, 7.0 mmol) to afford two diastereoisomers (65:35) (2.22 g, 93%); major diastereomer R, S\textsubscript{N,C}: minor diastereomer R, R\textsubscript{N,C}. 
(S, R<sub>N</sub>C)-Methyl N-(4-chloro-2-iodo-6-methylphenyl)-N-tosyl-L-alaninate

141g: White foam. \([\alpha]_D^{20} = +2.2\) (c=2.7, CHCl<sub>3</sub>). \(^1\)H NMR (500 MHz, CDCl<sub>3</sub>): \(\delta = 7.66\) (dd, \(J = 2.5, 0.6\) Hz, 1H), 7.58 – 7.54 (m, 2H), 7.27 – 7.24 (m, 2H), 7.21 (dd, \(J = 2.5, 0.6\) Hz, 1H), 4.87 (q, \(J = 7.2\) Hz, 1H), 3.86 (s, 3H), 2.42 (s, 3H), 2.30 (s, 3H), 1.08 (d, \(J = 7.2\) Hz, 3H) ppm. \(^{13}\)C NMR (126 MHz, CDCl<sub>3</sub>): \(\delta = 173.7, 146.5, 144.2, 137.6, 137.24, S10 137.18, 135.1, 131.4, 129.6, 128.9, 104.5, 57.7, 52.7, 21.8, 20.1, 17.9\) ppm. HRMS (ESI): [M+Na]<sup>+</sup> calc. 529.9666, found 529.9671 \([C_{18}H_{19}ClINO_4SNa]^+\). IR (neat): \(\nu = 2358, 1749, 1456, 1346, 1155, 1083, 669, 586, 540\) cm<sup>–1</sup>.

(R, R<sub>N</sub>C)-Methyl N-(4-chloro-2-iodo-6-methylphenyl)-N-tosyl-L-alaninate

141h: White solid. M.p.: 117 – 118 °C. \([\alpha]_D^{20} = –3.8\) (c=3.2, CHCl<sub>3</sub>). \(^1\)H NMR (500 MHz, CDCl<sub>3</sub>): \(\delta = 7.72\) (dd, \(J = 2.5, 0.6\) Hz, 1H), 7.65 – 7.61 (m, 2H), 7.30 – 7.26 (m, 2H), 7.23 (dd, \(J = 2.5, 0.6\) Hz, 1H), 4.74 (q, \(J = 7.2\) Hz, 1H), 3.78 (s, 3H), 2.43 (s, 3H), 2.28 (s, 3H), 1.20 (d, \(J = 7.2\) Hz, 3H) ppm. \(^{13}\)C NMR (126 MHz, CDCl<sub>3</sub>): \(\delta = 172.1, 144.2, 144.1, 138.1, 137.8, 137.5, 135.1, 131.6, 129.4, 129.2, 105.4, 58.5, 52.4, 21.8, 20.9, 17.5\) ppm. HRMS (ESI): [M+Na]<sup>+</sup> calc. 529.9666, found 529.9667 \([C_{18}H_{19}ClINO_4SNa]^+\). IR (neat): \(\nu = 2360, 1757, 1456, 1338, 1153, 1085, 673, 588, 538\) cm<sup>–1</sup>.
Benzyl N-(2-iodo-4,6-dimethylphenyl)-N-((4-nitrophenyl) sulfonyl)-D-alaninate

Following GP 11: N-(2-Iodo-4,6-dimethylphenyl)-4 nitrobenzenesulfonamide 140b (2.42 g, 5.6 mmol), pph3 (2.20g, 8.4 mmol), L-lactic acid benzyl ester (1.35 mL, 8.4 mmol), and DIAD (1.65 mL, 8.4 mmol) to afford two diastereoisomers (60:40) (2.32 g, 68%); major diastereomer R, S_{N-C}: minor diastereomer R, R_{N-C}.

(R, S_{N-C})-(Benzyl N-(2-iodo-4,6-dimethylphenyl)-N-((4-nitrophenyl) sulfonyl)- alaninate

141i: Colorless oil. [α]_D^{20} = +20 (c=0.20, CHCl3). \(^1\)H NMR (500 MHz, CDCl3): δ= 8.26 – 8.20 (m, 2H), 7.78 – 7.73 (m, 2H), 7.53 (dd, \(J = 1.4\), 0.6 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.44 – 7.40 (m, 2H), 7.40 – 7.36 (m, 1H), 7.02 (dd, \(J = 1.4, 0.7\) Hz, 1H), 5.34 – 5.24 (m, 2H), 4.96 (q, \(J = 7.2\) Hz, 1H), 2.28 (s, 3H), 2.19 (s, 3H), 1.09 (d, \(J = 7.2\) Hz, 3H) ppm. \(^13\)C NMR (126 MHz, CDCl3): δ= 172.9, 150.3, 145.8, 144.0, 141.3, 139.2, 135.6, 134.7, 132.6, 130.2, 128.8, 128.7, 128.7, 123.9, 104.4, 67.8, 58.4, 20.6, 19.9, 17.8 ppm. HRMS (ESI): [M+H]^+ calc. 595.0400, found 595.0419 [C_{24}H_{24}IN_{2}O_{6}S]^+. IR (neat): ν= 2360, 1747, 1529, 1348, 1166, 854, 738, 617 cm \(^{-1}\).
**(R, R-N-C)-(Benzyl N-(2-iodo-4,6-dimethylphenyl)-N-((4-nitrophenyl) sulfonyl)- alaninate**

**141j:** White foam. \([\alpha]_D^{20} = -25 \ \text{(c} = 0.16, \ \text{CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.24 - 8.18 \ (m, 2H), 7.86 - 7.81 \ (m, 2H), 7.52 \ (dd, J = 1.4, 0.6 \ \text{Hz, 1H}), 7.43 - 7.34 \ (m, 5H), 7.09 \ (dd, J = 1.4, 0.7 \ \text{Hz, 1H}), 5.28 - 5.19 \ (m, 2H), 4.91 \ (q, J = 7.2 \ \text{Hz, 1H}), 2.42 \ (s, 3H), 2.28 \ (s, 3H), 1.21 \ (d, J = 7.3 \ \text{Hz, 3H}) \ \text{ppm.} \)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = 171.4, 150.3, 146.2, 142.9, 141.3, 139.6, 135.5, 135.4, 132.9, 130.8, 128.8, 128.7, 128.6, 123.7, 103.8, 67.5, 59.0, 21.1, 20.5, 17.4 \ \text{ppm.} \)

**HRMS (ESI):** [M+H]\(^+\) calc. 595.0400, found 595.0402 \([\text{C}_{24}\text{H}_{24}\text{IN}_{2}\text{O}_{6}\text{S}]^+\). **IR (neat):** \(\nu = 2360, 1751, 1529, 1348, 1166, 740 \ \text{cm}^{-1}\). 


6.3.2. Oxidation of Axially Chiral Iodine Reagents (GP 12)

Prepared according to a literature procedure.\textsuperscript{13} To a stirred solution of iodoarene 141a-j in acetic acid (10.0 mL) and acetonitrile (32.0 mL), Selectfluor\textsuperscript{®} (10 equiv.) was added to the reaction mixture. The mixture was stirred at room temperature overnight till the reaction completed. The solvents were evaporated under reduced pressure, and the residue then was washed with water. The organic layer was separated, and the aqueous layer was extracted with DCM (2x 10 mL). The combined organic layers were dried over MgSO\textsubscript{4}, filtered, concentrated under reduced pressure. The residue was washed with \textit{n}-hexane to afford the pure product.

\textbf{\((R, S_{N-C})-\) Methyl (2R)-2-(1-acetoxy-5,7-dimethyl-3-(4-nitrophenyl)-3-oxido-1\(\lambda^3\),2\(\lambda^3\),3\(\lambda^4\)-benzo[e] \[1,2,3,4\] iodoxathiazin-4(1H)-yl) propanoate 142a}

Following GP 12: \((R, S_{N-C})\) - (Methyl \(N\)-(2-iodo-4,6-dimethylphenyl)-\(N\)-(4-nitrophenyl) sulfonyl)-alaninate 141a (0.174 g, 0.33 mmol) and Selectfluor\textsuperscript{®} (1.17 g, 3.3 mmol) to afford 142a as a yellow oil (166 mg, 87%). \([\alpha]_D^{20} = +17.4\) (c= 0.69, CHCl\textsubscript{3}). \textbf{\(^1H\) NMR (500 MHz, CDCl\textsubscript{3})}: \(\delta\) = 8.29 – 8.25 (m, 2H), 8.15 (d, \(J = 1.7\) Hz, 1H), 7.87 – 7.84 (m, 2H), 7.28 (s, 1H), 4.82 – 4.74 (m, 1H), 3.82 (s, 3H), 2.43 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.18 (d, \(J = 7.2\) Hz, 3H) ppm. \textbf{\(^{13}C\) NMR (126 MHz, CDCl\textsubscript{3})}: \(\delta\) =
176.7, 173.2, 150.3, 145.7, 142.7, 139.7, 136.8, 130.3, 129.0, 124.6, 123.9, 123.6, 61.4, 52.9, 21.0, 20.6, 20.0, 17.6 ppm. IR (neat): \( \nu = 2925, 1746, 1527, 1345, 1159, 1084, 680, 546 \text{ cm}^{-1}. \)

\[ (R, R_{N-C})- \text{Methyl (2R)-2-(1-acetoxy-5,7-dimethyl-3-(4-nitrophenyl)-3-oxido-1\lambda^3,2\lambda^3,3\lambda^4-benzo[e] [1,2,3,4] iodoaxathiazin-4(1H)-yl) propanoate} \]

\[ 142b \]

Following GP 12: \((R, R_{N-C})-(\text{Methyl } N-(2-\text{iodo-4,6-dimethylphenyl})-N-(4-\text{nitrophenyl}) \text{ sulfonyl})-\text{alaninate} \]

\[ 141b \text{ (0.174 g, 0.33 mmol)} \) and Selectfluor\(^{\circledast} \text{ (1.17 g, 3.3 mmol)} \) to afford \[ 142b \text{ as a yellow oil (166 mg, 87\%)} \). [\( \alpha \Texto{D}^{20} = -76.5 \text{ (c= 0.68, CHCl}_3 \text{)} \).

**H NMR (500 MHz, CDCl\(_3\)):** \[ \delta = 8.29 - 8.26 \text{ (m, 2H)}, 8.11 \text{ (s, 1H)}, 7.83 - 7.80 \text{ (m, 2H)}, 7.27 \text{ (s, 1H)}, 4.73 \text{ (q, } J = 7.2 \text{ Hz, 1H)}, 3.62 \text{ (s, 3H)}, 2.39 \text{ (s, 3H)}, 2.03 \text{ (s, 3H)}, 1.95 \text{ (s, 3H)}, 1.21 \text{ (d, } J = 7.4 \text{ Hz, 3H)} \text{ ppm.} \]

\[ 13C \text{ NMR (126 MHz, CDCl\(_3\)):} \delta = 176.6, 173.0, 150.5, 145.5, 144.5, 142.6, 138.8, 136.8, 130.4, 130.1, 123.9, 123.8, 123.5, 61.3, 52.7, 20.8, 20.5, 19.9, 17.4 \text{ ppm. IR (neat):} \nu = 1738, 1524, 1346, 1164, 1084, 853, 738, 609 \text{ cm}^{-1}. \]

\[ (R, S_{N-C})- \text{Methyl (2R)-2-(1-acetoxy-5,7-dimethyl-3-oxido-3-(p-tolyl)-1\lambda^3,2\lambda^3,3\lambda^4-benzo[e]} \]

\[ 142c \text{ (0.11 g, 0.22 mmol), Selectfluor}^{\circledast} \text{ (0.78 g, 2.2 mmol)} \) to afford \[ 142c \text{ as a yellow oil (0.10 g, 91\%)} \). [\( \alpha \Texto{D}^{20} = +95.0 \text{ (c=0.40, CHCl}_3 \text{)} \).

**H NMR (500 MHz, CDCl\(_3\)):** \[ \delta = 8.09 \text{ (s, 1H)}, 7.40 \text{ (d, } J = 8.3 \text{ Hz, 2H)}, 7.24 \text{ (d, } J = 8.2 \text{ Hz, 2H)}, 7.14 \text{ (s, 1H)}, 4.93 \text{ (q, } J = 7.2 \text{ Hz, 1H)}, 3.84 \text{ (s, 3H)}, 2.42 \text{ (s, 3H)}, 2.41 \text{ (s, 3H)}, 2.35 \text{ (s, 3H)}, 1.73 \text{ (s, 3H)}, 1.17 \text{ (d, } J = 7.4 \text{ Hz, 3H)} \text{ ppm.} \]

\[ 13C \text{ NMR (126 MHz, CDCl\(_3\)):} \delta = 176.3, 172.6, 145.8, 142.6, 138.8, 136.8, 130.4, 130.1, 123.9, 123.8, 123.5, 61.3, 52.7, 20.8, 20.5, 19.9, 17.4 \text{ ppm.} \]
143.6, 143.2, 136.8, 134.9, 131.5, 129.7, 129.1, 128.7, 126.3, 66.0, 52.9, 21.9, 21.5, 21.2, 18.6, 16.4 ppm. IR (neat): ν = 1751, 1344, 1160, 1085, 916, 687, 590 cm⁻¹.

(R, R₅-C)- Methyl (2R)-2-(1-acetoxy-5,7-dimethyl-3-oxido-3-(p-tolyl)-1λ³,2λ³,3λ⁴-benzo[e] [1,2,3,4] iodaoxathiazin-4(1H)-yl) propanoate 142d

Following GP 12: (R, R₅-C)-Methyl N-(2-iodo-4,6-dimethylphenyl)-N-tosyl-alaninate 141d (0.11 g, 0.22 mmol), Selectfluor® (0.78 g, 2.2 mmol) to afford 142d as a yellow oil (0.10 g, 91 %). [α]D²⁰ = –87.5 (c = 0.16, CHCl₃).

¹H NMR (500 MHz, CDCl₃): δ = 7.96 (s, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.53 (s, 1H), 7.32 (d, J = 8.1 Hz, 2H), 4.65 (q, J = 7.2 Hz, 1H), 3.88 (s, 3H), 2.46 (s, 3H), 2.37 (s, 3H), 2.36 (s, 3H), 1.75 (s, 3H), 1.16 (d, J = 7.2 Hz, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 175.3, 172.4, 146.1, 143.5, 141.5, 136.7, 134.8, 132.6, 130.4, 129.0, 128.4, 126.4, 66.0, 54.1, 21.9, 21.5, 21.2, 19.3, 17.1 ppm. IR (neat): ν = 1734, 1451, 1193, 1162, 725, 591 cm⁻¹.

(R, S₅-C)- Methyl (2R)-2-(1-acetoxy-3-(4-methoxyphenyl)-5,7-dimethyl-3-oxido-1λ³,2λ³,3λ⁴-benzo[e] [1,2,3,4] iodaoxathiazin-4(1H)-yl) propanoate 142e

Following GP 12: (R, S₅-C)-methyl N-(2-iodo-4,6-dimethylphenyl)-N-((4-methoxyphenyl) sulfonyl)-D-alaninate 141e (0.135 g, 0.27 mmol), Selectfluor® (0.96 g, 2.7 mmol) to afford 142e as a yellow oil (0.14 g, 93 %). [α]D²⁰ = +60.0 (c=0.10, CHCl₃).

¹H NMR (500 MHz, CDCl₃): δ = 8.11 (s, 1H), 7.65 – 7.62 (m, 2H), 7.24 (s, 1H), 6.90 – 6.88 (m, 2H), 6.80 – 6.72 (m, 2H), 6.57 (d, J = 8.5 Hz, 1H).
4.68 (q, $J = 7.2$ Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 2.40 (s, 3H), 1.99 (s, 6H), 1.19 (d, $J = 7.1$ Hz, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 177.1, 173.7, 163.8, 156.5, 142.0, 139.4, 136.8, 133.9, 133.3, 131.9, 129.7, 114.6, 62.7, 60.8, 54.1, 21.4, 20.9, 20.2, 18.3 ppm. IR (neat): $\nu = 1748, 1595, 1340, 1258, 1156, 1085, 803, 692, 591 \text{ cm}^{-1}$.

(R, $R_{N-C}$)- Methyl (2R)-2-(1-acetoxy-3-(4-methoxyphenyl)-5,7-dimethyl-3-oxido-1$\lambda^3,2\lambda^3,3\lambda^4$-benzo[e] [1,2,3,4] iodoaxathiazin-4(1H)-yl) propanoate 142f

Following GP 12: (R, $R_{N-C}$)-methyl N-(2-ido-4,6-dimethylphenyl)-N-((4-methoxyphenyl) sulfonyl)-D-alaninate 142f (0.135 g, 0.27 mmol), Selectfluor® (0.96 g, 2.7 mmol) to afford 142f as a yellow oil (0.137 g, 90%). $[\alpha]_D^{20} = -30.7$ (c=0.13, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.78 – 7.74$ (m, 2H), 7.72 (s, 1H), 7.24 (s, 1H), 6.95 – 6.93 (m, 2H), 5.15 (q, $J = 7.2$ Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.43 (s, 3H), 2.42 (s, 3H), 2.02 (s, 3H), 1.20 (d, $J = 7.3$ Hz, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 176.8, 172.7, 163.9, 143.4, 142.0, 141.6, 136.9, 134.6, 133.8, 131.3, 129.6, 114.2, 58.5, 55.8, 52.8, 21.4, 21.2, 20.2, 18.2 ppm. IR (neat): $\nu = 1739, 1386, 1217, 1147, 682, 592 \text{ cm}^{-1}$.
(R, S_{N-C})- Methyl (2R)-2-(1-acetoxy-7-chloro-5-methyl-3-oxido-3-(p-tolyl)-1\lambda^3,2\lambda^3,3\lambda^4-benzo[e] [1,2,3,4] iodoaxathiazin-4(1H)-yl) propanoate 142g

Following GP 12: (S, R_{N-C})-methyl N-(4-chloro-2-iodo-6-methylphenyl)-N-tosyl-L-alaninate 141g (0.14 g, 0.27 mmol), Selectfluor\textsuperscript{®} (0.96 g, 2.70 mmol) to afford 142g as a yellow oil (0.14 g, 94%). \([\alpha]_D^{20} = +60.0\) (c=0.10, CHCl\textsubscript{3}). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \[\delta = 8.27\) (dd, \(J = 2.5, 0.5\) Hz, 1H), 7.64 – 7.61 (m, 2H), 7.40 (dd, \(J = 2.5, 0.5\) Hz, 1H), 7.29 – 7.27 (m, 2H), 4.74 – 4.71 (m, 1H), 3.58 (s, 3H), 2.45 (s, 3H), 2.44 (s, 3H), 2.19 (s, 3H), 1.29 (d, \(J = 7.6\) Hz, 3H) ppm. \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): \[\delta = 176.9, 172.3, 145.1, 144.0, 138.1, 137.6, 136.4, 136.0, 135.5, 131.5, 129.8, 127.4, 59.9, 52.9, 21.8, 20.7, 18.2, 16.7\) ppm. IR (neat): \(\nu = 1747, 1463, 1155, 1083, 586\) cm\textsuperscript{-1}.

(R, S_{N-C})- Methyl (2R)-2-(1-acetoxy-7-chloro-5-methyl-3-oxido-3-(p-tolyl)-1\lambda^3,2\lambda^3,3\lambda^4-benzo[e] [1,2,3,4] iodoaxathiazin-4(1H)-yl) propanoate 142h

Following GP 12: (R, R_{N-C})-methyl N-(4-chloro-2-iodo-6-methylphenyl)-N-tosyl-L-alaninate 141h (0.11 g, 0.22 mmol), Selectfluor\textsuperscript{®} (0.78 g, 2.20 mmol) to afford 142h as a yellow oil (0.12 g, 93 %). \([\alpha]_D^{20} = -50.0\) (c=0.12, CHCl\textsubscript{3}). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \[\delta = 8.20\) (dd, \(J = 2.5, 0.5\) Hz, 1H), 7.66 – 7.63 (m, 2H), 7.34 (dd, \(J = 2.5, 0.5\) Hz, 1H), 7.28 – 7.25 (m, 2H), 4.69 – 4.64 (m, 1H), 3.52 (s, 3H), 2.39 (s, 3H), 2.37 (s, 3H), 1.94 (s, 3H), 1.14 (d, \(J = 7.3\) Hz, 3H) ppm. \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): \[\delta = 176.9, 172.9, 145.4, 144.4, 138.2, 136.9, 136.5, 136.3, 135.5, 131.5, 129.8, 127.4, 59.9, 52.9, 21.8, 20.7, 18.2, 16.8\) ppm.
136.4, 136.0, 135.6, 130.2, 129.8, 127.4, 60.7, 54.3, 21.8, 20.6, 20.2, 16.7 ppm. **IR (neat):** ν= 2952, 1739, 1595, 1336, 1151, 1084, 586 cm$^{-1}$.

(R, S$_{N-C}$)- Benzyl (2R)-2-(1-acetoxy-5,7-dimethyl-3-(4-nitrophenyl)-3-oxido-1$\lambda^3$2$\lambda^3$,3$\lambda^4$-benzo[e] [1,2,3,4] iodoaxathiazin-4(1H)-yl) propanoate 142i

Following GP 12: (R, S$_{N-C}$)-(Benzyl N-(2-iodo-4,6-dimethylphenyl)-N-((4-nitrophenyl) sulfonfonyl)- alaninate 141i (0.196 g, 0.33 mmol), Selectfluor® (1.17 g, 3.3 mmol) to afford 142i as a yellow oil (0.185 g, 86%). [α]$^D_{20}$ = +40.0 (c=0.10, CHCl$_3$). **$^1$H NMR (300 MHz, CDCl$_3$):** δ= 8.20 – 8.15 (m, 2H), 8.09 (s, 1H), 8.02 – 7.94 (m, 2H), 7.42 – 7.37 (m, 5H), 7.31 (s, 1H), 5.28 – 5.18 (m, 2H), 5.00 – 4.92 (m, 1H), 2.41 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.27 – 1.23 (m, 3H) ppm. **$^{13}$C NMR (101 MHz, CDCl$_3$):** δ= 176.6, 170.9, 144.6, 142.1, 139.4, 138.7, 136.7, 135.2, 133.9, 130.4, 128.7, 128.6, 128.5, 123.7, 123.6, 119.7, 67.5, 61.0, 21.0, 20.9, 20.8, 17.3 ppm. **IR (neat):** ν= 1746, 1348, 1166, 617 cm$^{-1}$.

(R, R$_{N-C}$)- Benzyl (2R)-2-(1-acetoxy-5,7-dimethyl-3-(4-nitrophenyl)-3-oxido-1$\lambda^3$,2$\lambda^3$,3$\lambda^4$-benzo[e] [1,2,3,4] iodoaxathiazin-4(1H)-yl) propanoate 142j

Following GP 12: (R, R$_{N-C}$)-(Benzyl N-(2-iodo-4,6-dimethylphenyl)-N-((4-nitrophenyl) sulfonfonyl)- alaninate 141j (0.196 g, 0.33 mmol), Selectfluor® (1.17 g, 3.3 mmol) to afford 142j as a yellow oil (0.188 g, 87%). [α]$^D_{20}$ = −65.7 (c=0.70, CHCl$_3$). **$^1$H NMR (300 MHz, CDCl$_3$):** δ= 8.20 – 8.15 (m, 2H), 8.09 (s, 1H), 8.02 – 7.94 (m, 2H), 7.42 – 7.37 (m, 5H), 7.31 (s, 1H), 5.28 – 5.18 (m, 2H), 5.00 – 4.92 (m, 1H), 2.41 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.27 – 1.23 (m, 3H) ppm. **IR (neat):** ν= 2952, 1739, 1595, 1336, 1151, 1084, 586 cm$^{-1}$.
MHZ, CDCl$_3$): δ = 8.26 – 8.21 (m, 2H), 8.14 (s, 1H), 7.66 – 7.60 (m, 2H), 7.48 – 7.44 (m, 5H), 7.27 (s, 1H), 5.32 – 5.18 (m, 2H), 4.84 (q, $J = 7.2$ Hz, 1H), 2.42 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.15 (d, $J = 7.2$ Hz, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ = 176.4, 172.9, 159.2, 150.1, 145.7, 142.7, 139.6, 139.1, 136.8, 134.7, 130.2, 128.8, 128.7, 128.5, 123.9, 123.5, 119.9, 67.8, 61.2, 21.0, 20.7, 19.9, 17.5 ppm. IR (neat): ν = 2360, 1734, 1349, 1160, 588 cm$^{-1}$.

6.3.3. Asymmetric Applications of C-N Axially Chiral Hypervalent Iodine Reagents in Stoichiometric Manner

6.3.3.1. Enantioselective oxidative rearrangement of alkenes (GP 13)

Prepared according to a literature procedure.$^{14}$ To a solution of alkene 143 (20 mg, 0.09 mmol), iodine(III) reagent (0.11 mmol, 1.2 equiv.), and methanol (11 μL, 0.26 mmol, 3 equiv.) in CH$_2$Cl$_2$:TFE (10:1 v/v) (3.0 mL) at −78 °C, p-TsOH hydrate (20 mg, 0.11 mmol, 1.2 equiv.) was added. The mixture was stirred at −78 °C for 4 h, and the mixture was then stirred at room temperature for 16 h. After completion of the reaction, the mixture was washed with sat. aq. NaHCO$_3$ solution and sat. aq. Na$_2$S$_2$O$_3$ solution and extracted with DCM (3x 5 mL). The combined organic layers were dried over MgSO$_4$, filtered, concentrated under reduced pressure. The crude products were purified by flash chromatography on silica gel ($n$-hexane/EtOAc 9:1) to afford the desired pure products.
Following GP 13: Methyl (2R)-2-(1-acetoxy-5,7-dimethyl-3-oxido-3-(p-tolyl)-1λ3,2λ3,3λ4-benzo[e] [1,2,3,4] iodoxathiazin-4(1H)-yl) propanoate 142g (60.0 mg, 0.11 mmol) or (R, Rκ-C)-methyl (2R)-2-(1-acetoxy-7-chloro-5-methyl-3-oxido-3-(p-tolyl)-1λ3,2λ3,3λ4-benzo[e] [1,2,3,4] iodoxathiazin-4(1H)-yl) propanoate 142h (62.0 mg, 0.11 mmol) to afford 144 as a colorless oil. 1H NMR (500 MHz, CDCl3): δ = 7.88 (d, J = 7.9 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 7.30 (t, J = 7.6 Hz, 2H), 7.26 – 7.16 (m, 4H), 7.11 (t, J = 7.0 Hz, 1H), 4.48 (t, J = 7.2 Hz, 1H), 2.14 – 2.03 (m, 1H), 1.79 – 1.68 (m, 1H), 1.32 – 1.11 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H) ppm. 13C NMR (126 MHz, CDCl3): δ = 200.3, 140.0, 137.2, 132.9, 129.0, 128.8, 128.6, 128.4, 127.1, 53.6, 36.3, 21.0, 14.2 ppm. The spectroscopic data are in agreement with the literature.

(S)-144: colorless oil (10.0 mg, 47%), Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), n-hexane/i-PrOH = 95.5:0.5, 1.0 mL/min, 245 nm t R (major) = 9.8 min, t R (minor) = 12.8 min, ee = 81%.

(R)-144: colorless oil (13.0 mg, 62%), Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), n-hexane/i-PrOH = 95.5:0.5, 1.0 mL/min, 245 nm t R (major) = 12.6 min, t R (minor) = 9.8 min, ee = 84%.
6.3.4. Asymmetric Applications of C-N axially Chiral Hypervalent Iodine Reagents in Catalytic Manner

6.3.4.1. Enantioselective α-oxytosylation of ketones (GP 14)

![Chemical structure](image)

Prepared according to a literature procedure.\textsuperscript{15} Propiophenone 145 (36.4 mg, 0.271 mmol), iodine catalyst 141a-j (14 mg, 0.027 mmol), and \textit{m}-CPBA (184 mg, 0.81 mmol, 3 equiv.) were dissolved in MeCN (3.0 mL), and \textit{p}-TsOH hydrate (154 mg, 0.81 mmol, 3.0 equiv.) was added to the mixture and stirred at room temperature for 72 h. After completion of the reaction, the mixture was washed with sat. aq. NaHCO\textsubscript{3} solution and sat. aq. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution and extracted with DCM (3x 5 mL). The combined organic layers were dried over MgSO\textsubscript{4}, filtered, concentrated under reduced pressure. The crude products were purified by flash chromatography on silica gel (\textit{n}-hexane/EtOAc 8:2) to afford the desired pure products.
1-Oxo-1-phenylpropan-2-yl 4-methylbenzenesulfonate 146a

Following **GP 14:** Chiral iodine catalyst 141c or 141d (13 mg, 0.027 mmol), *m*-CPBA (184 mg, 0.81 mmol), *p*-TsOH hydrate (154 mg, 0.81 mmol), and propiophenone 145a (36.4 mg, 0.27 mmol) to afford 146a as a white solid. **M.p.:** 68 – 69 °C. **^1H NMR (400 MHz, CDCl$_3$):** $\delta = 7.89 – 7.86$ (m, 2H), 7.77 – 7.73 (m, 2H), 7.62 – 7.56 (m, 1H), 7.48 – 7.43 (m, 2H), 7.28 – 7.24 (m, 2H), 5.78 (q, $J = 6.9$ Hz, 1H), 2.41 (s, 3H), 1.6 (d, $J = 6.9$ Hz, 3H) ppm. **^13C NMR (101 MHz, CDCl$_3$):** $\delta = 195.0, 145.2, 134.0, 133.9, 133.7, 129.9, 128.9, 128.1, 77.5, 21.8, 18.9$ ppm. The spectroscopic data are in agreement with the literature.$^{15}$

**(S)-146a:** white solid (79 mg, 96%). $[\alpha]_D^{20} = -12$ (c=2.0, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5$\mu$m (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 9.84$ min, minor isomer: $t_R = 8.96$ min, $ee = 67%$.

**(R)-146a:** white solid (76 mg, 93%). $[\alpha]_D^{20} = +8.33$ (c=1.2, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5$\mu$m (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 8.97$ min, minor isomer: $t_R = 9.86$ min, $ee = 43%$.
6.3.4.2. Enantioselective lactonization of acids (GP 15)

Prepared according to a literature procedure. \(^{16}\) Chiral iodine catalyst 141a-j (0.027 mmol), 5-Oxo-5-phenylpentanoic acid 147 (0.27 mmol, 52.0 mg), \(p\)-TsOH hydrate (0.054 mmol, 10.0 mg, 0.2 equiv.), and \(m\)-CPBA (0.32 mmol, 72.0 mg, 1.20 equiv.) were dissolved in DCM (3.0 mL). The reaction mixture was stirred at room temperature for 48 h. After completion of the reaction, the mixture was washed with sat. aq. NaHCO\(_3\) solution and sat. aq. Na\(_2\)S\(_2\)O\(_3\) solution and extracted with DCM (3x 5 mL). The combined organic layers were dried over MgSO\(_4\), filtered, concentrated under reduced pressure. The crude products were purified by flash chromatography on silica gel (\(n\)-hexane/EtOAc 7:3) to afford the desired pure products.

5-Benzoyldihydrofuran-2(3H)-one 148

Following GP 15: Chiral iodine catalyst 141c or 141h (14 mg, 0.027 mmol) to afford 148 as a white solid. M.p.: 64 – 65 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta= 8.02 – 7.96\) (m, 2H), 7.68 – 7.60 (m, 1H), 7.56 – 7.48 (m, 2H), 5.82 – 5.77 (m, 1H), 2.65 – 2.43 (m, 4H) ppm. \(^1\)C NMR (126 MHz, CDCl\(_3\)): \(\delta= 194.4, 176.3, 134.4, 133.8, 129.2, 128.9, 78.4, 26.9, 25.1\) ppm. The spectroscopic data are in agreement with the literature.\(^{16}\)
(S)-148: white solid (22.0 mg, 43 %), $[\alpha]_D^{20} = +60$ (c=0.1, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), ($n$-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 12.51$ min, minor isomer: $t_R = 10.76$ min, $ee = 70\%$.

(R)-148: Prepared: white solid (14.5 mg, 28%). $[\alpha]_D^{20} = -33.3$ (c=0.12, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), ($n$-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 10.67$ min, minor isomer: $t_R = 12.45$ min, $ee = 50\%$.

The assignation of the product’s configuration $R$ and $S$ is based on the data previous reports.$^{17}$

6.3.4.3. Enantioselective dearomatization of phenols (GP 16)

Prepared according to a modified literature procedure.$^{18}$ Chiral iodine catalyst 141a-j (0.027 mmol), and $m$-CPBA (132.0 mg, 0.59 mmol, 2.2 equiv.) were dissolved in mixture of acetone (4.0 mL) and water (2.0 mL) at 0 °C. 2-Bromo-4-methylphenol 149 (0.50 mL, 0.27 mmol, 1.0 equiv.) was added to the mixture, and the mixture was then stirred at 0 °C for 4 h, and at room
temperature overnight. After completion of the reaction, the mixture was washed with sat. aq.
NaHCO₃ solution and sat. aq. Na₂S₂O₃ solution and extracted with EtOAc (3x 5 mL). The
combined organic layers were dried over MgSO₄, filtered, concentrated under reduced
pressure. The crude products were purified by flash chromatography on silica gel (n-
hexane/EtOAc 6:4) to afford the desired pure products.

2-Bromo-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one 150

Following GP 16: Chiral iodine catalyst 141d (13.0 mg, 0.027 mmol) to
afford 150 as a yellow solid. M.p.: 104 – 107 °C. ¹H NMR (500 MHz,
CDCl₃): δ= 7.33 (dd, J = 2.8, 1.6 Hz, 1H), 6.95 – 6.88 (m, 1H), 6.27 – 6.20
(m, 1H), 2.31 (bs, 1H), 1.52 (d, J = 1.5 Hz, 3H) ppm. ¹³C NMR (126 MHz,
CDCl₃): δ= 178.2, 152.3, 152.1, 125.8, 123.7, 70.1, 26.6 ppm. The spectroscopic data are in
agreement with the literature.¹⁹

(S)-6a: (44.4 mg, 81 %), [α]D²⁰ = +3.63 (c=1.1, CHCl₃), Enantiomeric excess is determined by
HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0
mL/min, 254 nm): major isomer: tR = 4.70 min, minor isomer: tR = 5.08 min, ee= 20 %.
6.4 Experimental Data for Chapter 4

6.4.1. Synthesis of Chiral Iodine Reagents with the Absence of Axial Chirality

6.4.1.1. Synthesis of \(\textbf{N}\)-Substituted 2-Iodoaniline (GP 17)

Prepared according to a modified literature procedure.\(^{20}\). To a stirred solution of 2-ido aniline 176 (4.57 mmol) and pyridine (0.55 mL, 6.86 mmol, 1.5 equiv.) in dry dichloromethane (15 mL), the appropriate sulfonyl chloride derivative (4.57 mmol) was added at 0 °C. The reaction mixture was stirred at ambient temperature for 16 h, then washed with HCl (1 M, 3x 5 mL). The combined acid wash was extracted with dichloromethane (4x 5 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (\(n\)-hexane/EtOAc 8:2).
**N-(2-Iodophenyl)-4-methylbenzenesulfonamide 177a**

Following **GP 17**: 2-Iodoaniline 176 (1.0 g, 4.57 mmol), 4-methylbenzenesulfonyl chloride (0.87 g, 4.57 mmol), and pyridine (0.55 mL, 6.86 mmol) to afford 177a as a white solid (1.44 g, 85%). **M.p.**: 83 – 84 °C. **\(^1\)H NMR (400 MHz, CDCl\(_3\))**: δ = 7.75 – 7.54 (m, 4H), 7.35 – 7.27 (m, 1H), 7.24 – 7.18 (m, 2H), 6.89 – 6.80 (m, 1H), 6.81 (bs, 1H), 2.36 (s, 3H) ppm. **\(^13\)C NMR (101 MHz, CDCl\(_3\))**: δ = 144.3, 139.1, 137.5, 135.9, 129.7, 129.5, 127.5, 126.9, 122.5, 92.3, 21.6 ppm. The spectroscopic data are in agreement with the literature.\(^{21}\)

**N-(2-Iodophenyl)-4-nitrobenzenesulfonamide 177b**

Following **GP 17**: 2-Iodoaniline 176 (1.0 g, 4.57 mmol), 4-nitrobenzenesulfonyl chloride (1.00 g, 4.57 mmol), and pyridine (0.55 mL, 6.86 mmol) to afford 177b as a yellow solid (1.49 g, 81%). **M.p.**: 139 – 140 °C. **\(^1\)H NMR (400 MHz, CDCl\(_3\))**: δ = 8.31 – 8.21 (m, 2H), 7.94 – 7.85 (m, 2H), 7.75 – 7.62 (m, 2H), 7.42 – 7.35 (m, 1H), 6.98 – 6.87 (m, 1H), 6.83 (bs, 1H) ppm. **\(^13\)C NMR (101 MHz, CDCl\(_3\))**: δ = 150.6, 144.6, 139.5, 136.5, 130.0, 128.9, 128.3, 124.4, 124.2, 93.5 ppm. The spectroscopic data are in agreement with the literature.\(^{20}\)
6.4.1.2. Synthesis of N-substituted 2-iodoaniline (GP 18)

Prepared according to a modified literature procedure.\textsuperscript{12} To a stirred solution of N-substituted 2-iodoaniline 177a or 177b (3.0 mmol), triphenylphosphine (4.5 mmol, 1.5 equiv.), and S-lactate derivative (4.5 mmol, 1.5 equiv.) in dry toluene (20 mL), diisopropyl azodicarboxylate (4.5 mmol, 1.5 equiv.) was added at 0 °C. The reaction mixture was warmed up to room temperature and then stirred at 50 °C for 6 h. The solvent was then removed under reduced pressure and Et\textsubscript{2}O was added. The precipitated triphenylphosphine oxide was removed by filtration and the filtrate was concentrated under reduced pressure. The crude products were purified by flash chromatography on silica gel ($n$-hexane/EtOAc 8:2) to afford the desired pure products.
Methyl N-(2-iodophenyl)-N-tosyl-L-alaninate 178a

Following GP 18: N-(2-Iodophenyl)-4-methylbenzenesulfonamide 177a (1.12 g, 3.0 mmol), pph3 (1.18 g, 4.5 mmol), S-lactic acid methyl ester (0.43 mL, 4.5 mmol), and DIAD (0.89 mL, 4.5 mmol) to afford 178a as a colorless oil (1.04 g, 76%). M.p.: 80 – 81 °C. $[\alpha]_D^{20} = +13.0$ (c=1.38, CHCl3). $^1$H NMR (400 MHz, CDCl3): $\delta$= 7.92 (dd, $J$ = 7.9, 1.5 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.57 – 7.51 (m, 2H), 7.38 – 7.29 (m, 1H), 7.28 – 7.23 (m, 1H), 7.09 – 7.02 (m, 1H), 4.98 (q, $J$ = 7.4 Hz, 1H), 3.60 (s, 3H), 2.42 (s, 3H), 1.29 (d, $J$ = 7.4 Hz, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl3): $\delta$= 172.8, 143.8, 140.6, 139.4, 137.2, 133.9, 130.6, 129.3, 128.9, 128.5, 106.6, 57.7, 52.2, 21.8, 16.8 ppm. HRMS (ESI): [M+Na]$^+$ calc. 481.9899, found 481.9913 $\left[\text{C}_{17}\text{H}_{18}\text{INO}_4\text{SNa}\right]^+$. IR (neat): $\nu$ = 2980, 1745, 1355, 1167, 714 cm$^{-1}$.

Methyl N-(2-iodophenyl)-N-((4-nitrophenyl) sulfonyl)-L-alaninate 178b

Following GP 18: N-(2-Iodophenyl)-4-nitrobenzenesulfonamide 177b (1.21 g, 3.0 mmol), pph3 (1.18 g, 4.5 mmol), S-lactic acid methyl ester (0.43 mL, 4.5 mmol), and DIAD (0.89 mL, 4.5 mmol) to afford 178b as a white solid (1.07 g, 73%). M.p.: 113 – 115 °C. $[\alpha]_D^{20} = +8.33$ (c=0.72, CHCl3). $^1$H NMR (400 MHz, CDCl3): $\delta$= 8.36 – 8.29 (m, 2H), 7.98 (d, $J$ = 8.0 Hz, 1H), 7.83 (d, $J$ = 7.3 Hz, 2H), 7.58 (d, $J$ = 8.0 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.15 – 7.08 (m, 1H), 5.03 (q, $J$ = 7.4 Hz, 1H), 3.66 (s, 3H), 1.32 (d, $J$ = 7.4 Hz, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl3): $\delta$= 172.5, 150.3, 145.5, 141.0, 138.7, 133.6, 131.1, 129.8, 129.3, 123.9, 105.9, 58.5, 52.6, 16.6 ppm. HRMS (ESI): [M+Na]$^+$ calc. 512.9699, found 512.9713 $\left[\text{C}_{16}\text{H}_{15}\text{IN}_{2}\text{O}_{6}\text{SNa}\right]^+$. IR (neat): $\nu$ = 2982, 1746, 1345, 1166, 1105, 853 cm$^{-1}$. 

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6.4.2. Catalytic Stereoselective α-Oxytosylation of Ketones (GP 19)

**Method A:** Chiral iodine catalyst 141d (0.027 mmol), \( m \)-CPBA (0.81 mmol, 3.0 equiv.), and RSO₃H (0.81 mmol, 3.0 equiv.) were dissolved in a mixture of MeCN and DCM (1:1), followed by the addition of the appropriate ketone 145a-r (0.27 mmol). The reaction mixture was stirred at room temperature for 72 h. After completion of the reaction, the mixture was washed with sat. aq. NaHCO₃ solution and sat. aq. Na₂S₂O₃ solution and extracted with DCM (3x 5 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated under reduced pressure. The crude products were purified by flash chromatography on silica gel (n-hexane/EtOAc 8:2) to afford the desired pure products.

**Method B:** Chiral iodine catalyst 141c (0.027 mmol), \( m \)-CPBA (0.81 mmol, 3.0 equiv.), and RSO₃H (0.81 mmol, 3.0 equiv.) were dissolved in a mixture of EtOAc and DCM (1:1) followed by the addition of the appropriate ketone 145a-r (0.27 mmol). The reaction mixture was stirred at room temperature for 72 h. After completion of the reaction, the mixture was washed with sat. aq. NaHCO₃ solution and sat. aq. Na₂S₂O₃ solution and extracted with DCM (3x 5 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated under reduced pressure. The crude products were purified by flash chromatography on silica gel (n-hexane/EtOAc 8:2) to afford the desired pure products.
1-Oxo-1-phenylpropan-2-yl 4-methylbenzenesulfonate 146a

Following GP 19 method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), p-TsOH hydrate (154 mg, 0.81 mmol), and propiophenone 145a (36.4 mg, 0.27 mmol) to afford 146a as a white solid. M.p.: 68 – 69 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)):\(\delta=\) 7.89 –7.86 (m, 2H), 7.77 – 7.73 (m, 2H), 7.62 – 7.56 (m, 1H), 7.48 – 7.43 (m, 2H), 7.28 – 7.24 (m, 2H), 5.78 (q, \(J=6.9\) Hz, 1H), 2.41 (s, 3H), 1.6 (d, \(J=6.9\) Hz, 3H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta=\) 195.0, 145.2, 134.0, 133.9, 133.7, 129.9, 128.9, 128.1, 77.5, 21.8, 18.9 ppm. The spectroscopic data are in agreement with the literature.

(S)-146a: Prepared by method A: white solid (78 mg, 95%), \([\alpha]_D^{20}=−12\ (c=2.0, \text{CHCl}_3)\). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (\(n\)-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R=9.84\) min, minor isomer: \(t_R=8.96\) min, \(ee= 75\%\).

(R)-146a: Prepared by method B: white solid (59 mg, 72%), \([\alpha]_D^{20}=+8.33\ (c=1.2, \text{CHCl}_3)\). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (\(n\)-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R=8.97\) min, minor isomer: \(t_R=9.86\) min, \(ee= 75\%\).
1-(4-Chlorophenyl)-1-oxopropan-2yl 4-methylbenzenesulfonate 146b

Following GP 19 method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), p-TsOH hydrate (154 mg, 0.81 mmol), and 4-chloropropiophenone 145b (46 mg, 0.27 mmol) to afford 146b as a white solid. M.p.: 106 – 108 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ= 7.87 – 7.81 (m, 2H), 7.74 (d, $J = 8.3$ Hz, 2H), 7.46 – 7.40 (m, 2H), 7.31 – 7.26 (m, 2H), 5.68 (q, $J = 6.9$ Hz, 1H), 2.42 (s, 3H), 1.58 (d, $J = 6.9$ Hz, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ= 194.0, 145.3, 140.6, 133.5, 132.2, 130.4, 129.9, 129.3, 128.1, 77.4, 21.8, 18.7 ppm. The spectroscopic data are in agreement with the literature.$^{22}$

(S)-146b: Prepared by method A: white solid (73 mg, 80%), $[\alpha]_D^{20} = -1.1$ (c=1.76, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 13.49$ min, minor isomer: $t_R = 10.01$ min, ee = 71%.

(R)-146b: Prepared by method B: white solid (73 mg, 80%), $[\alpha]_D^{20} = +11.1$ (c=0.36, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 10.00$ min, minor isomer: $t_R = 13.52$ min, ee = 77%.
1-(3-Chlorophenyl)-1-oxopropan-2-yl 4-methylbenzenesulfonate 146c

Following GP 19 Method A or Method B: chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), p-TsOH hydrate (154 mg, 0.81 mmol), and 3′-chloropropiophenone 145c (46 mg, 0.27 mmol) to afford 146c as a white solid. M.p.: 145 – 147 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.82 – 7.76 (m, 2H), 7.75 – 7.70 (m, 2H), 7.58 – 7.52 (m, 1H), 7.41 – 7.38 (m, 1H), 7.29 – 7.26 (m, 2H), 5.69 (q, $J = 7.0$ Hz, 1H), 2.42 (s, 3H), 1.60 (d, $J = 6.9$ Hz, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta =$ 194.1, 169.7, 145.4, 135.4, 135.3, 133.9, 133.4, 130.2, 130.0, 128.9, 128.1, 127.0, 77.6, 21.8, 18.8 ppm. The spectroscopic data are in agreement with the literature.$^{23}$

(S)-146c: Prepared by Method A: white solid (81 mg, 89%), $[\alpha]D^{20} = -15.4$ (c = 0.13, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm S14 (25 cm), (n-hexane/i-PrOH = 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 9.2$ min, minor isomer: $t_R = 8.2$ min, ee = 74%.

(R)-146c: Prepared by Method B: white solid (83 mg, 91%), $[\alpha]D^{20} = +20$ (c=0.1, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-hexane/i-PrOH = 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 8.2$ min, minor isomer: $t_R = 9.2$ min, ee = 60%.
1-Oxo-1-(3-(trifluoromethyl) phenyl) propan-2-yl 4-methylbenzenesulfonate 146d

Following GP 19 method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), p-TsOH hydrate (154 mg, 0.81 mmol), and 3’-(trifluoromethyl) propiophenone 145d (55 mg, 0.27 mmol) to afford 146d as a white solid. M.p.: 100 – 101 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$= 8.10 (d, $J$ = 8.1 Hz, 2H), 7.83 (d, $J$ = 7.9 Hz, 1H), 7.74 – 7.69 (m, 2H), 7.61 (t, $J$ = 7.7 Hz, 1H), 7.29 – 7.22 (m, 2H), 5.70 (q, $J$ = 6.9 Hz, 1H), 2.41 (s, 3H), 1.61 (d, $J$ = 6.9 Hz, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$= 194.2, 145.5, 134.4, 133.3, 132.1, 130.3, 130.0, 129.5, 128.1, 125.8, 77.7, 21.8, 18.7 ppm. The spectroscopic data are in agreement with the literature.$^{24}$

(S)-146d: Prepared by method A: white solid (91 mg, 91%), $[\alpha]_D^{20} = -1.2$ (c=5.0, CHCl$_3$).
Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 7.07$ min, minor isomer: $t_R = 6.38$ min, $ee = 74\%$.

(R)-146d: Prepared by method B: white solid (95 mg, 95%), $[\alpha]_D^{20} = +6.7$ (c= 0.3, CHCl$_3$).
Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 6.40$ min, minor isomer: $t_R = 7.11$ min, $ee = 77\%$. 
1-(3-Nitrophenyl)-1-oxopropan-2-yl 4-methylbenzenesulfonate 146e

Following GP 19 Method A or Method B: chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), p-TsOH hydrate (154 mg, 0.81 mmol), and 3-nitropropiophenone 145e (48 mg, 0.27 mmol) to afford 146e as a white solid. M.p.: 80 – 82 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.67$ – $8.66$ (m, 1H), 8.43 (ddd, $J = 8.2$, 2.3, 1.1 Hz, 1H), 8.27 (ddd, $J = 7.8$, 1.7, 1.1 Hz, 1H), 7.77 – 7.65 (m, 3H), 7.32 – 7.26 (m, 2H), 5.68 (q, $J = 7.0$ Hz, 1H), 2.42 (s, 3H), 1.63 (d, $J = 7.0$ Hz, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 193.6$, 148.5, 145.7, 135.2, 134.5, 133.2, 130.2, 130.1, 128.1, 128.0, 123.9, 77.8, 21.8, 18.5 ppm. The spectroscopic data are in agreement with the literature.$^{24}$

(S)-146e: Prepared by Method A: white solid (57 mg, 61%), $[\alpha]_D^{20} = -7.4$ (c=0.54, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5µm (25 cm), (n-hexane/i-PrOH = 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 19.9$ min, minor isomer: $t_R = 16.5$ min, $ee = 72%$.

(R)-146e: Prepared by Method B: white solid (50 mg, 53 %), $[\alpha]_D^{20} = +11.1$ (c=0.18, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5µm (25 cm), (n-hexane/i-PrOH = 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 16.5$ min, minor isomer: $t_R = 19.9$ min, $ee = 64%$. 

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1-Oxo-1-(p-tolyl) propan-2-yl 4-methylbenzenesulfonate 146f

Following GP 19 method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), p-TsOH hydrate (154 mg, 0.81 mmol), and 4-methylpropiophenone 145f (40 mg, 0.27 mmol) to afford 146f as a white solid. M.p.: 85 – 86 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.81 – 7.73\) (m, 4H), \(7.29 – 7.22\) (m, 4H), 5.77 (q, \(J = 6.9\) Hz, 1H), 2.41 (s, 3H), 2.40 (s, 3H), 1.58 (d, \(J = 6.9\) Hz, 3H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 194.5, 145.1\) (2 peaks), 133.7, 131.3, 129.9, 129.6, 129.0, 128.1, 77.5, 21.9, 21.8, 19.0 ppm. The spectroscopic data are in agreement with the literature.\(^{24}\)

\((S)-146f\): Prepared by method A: white solid (27 mg, 31%), \([\alpha]_D^{20} = -7.69\) (c=0.26, CHCl\(_3\)). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 11.81\) min, minor isomer: \(t_R = 10.10\) min, \(ee = 69\%\).

\((R)-146f\): Prepared by method B: white solid (54 mg, 63%), \([\alpha]_D^{20} = +2.0\) (c=1.0, CHCl\(_3\)). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 10.07\) min, minor isomer: \(t_R = 11.83\) min, \(ee = 78\%\).
1-(4-Methoxyphenyl)-1-oxopropan-2-yl 4-methylbenzenesulfonate 146g

Following GP 19 method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), p-TsOH hydrate (154 mg, 0.81 mmol), and 4-methoxypropiophenone 145g (44 mg, 0.27 mmol) to afford 146g as a white solid. M.p.: 77 – 78 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.92 – 7.86$ (m, 2H), 7.75 (d, $J = 8.3$ Hz, 2H), 7.29 – 7.24 (m, 2H), 6.95 – 6.90 (m, 2H), 5.73 (q, $J = 6.9$ Hz, 1H), 3.88 (s, 3H), 2.41 (s, 3H), 1.58 (d, $J = 6.9$ Hz, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 193.2$, 164.2, 145.1, 131.4, 129.9, 128.1, 126.7, 114.1, 77.4, 55.7, 21.8, 19.0 ppm. The spectroscopic data are in agreement with the literature.$^{24}$

(S)-$^{146g}$: Prepared by method A: white solid (28 mg, 31%), $[\alpha]_D^{20} = -20$ (c=0.1, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5$\mu$m (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 17.66$ min, minor isomer: $t_R = 15.00$ min, $ee = 71\%$.

(R)-$^{146g}$: Prepared by method B: white solid (14 mg, 15%), $[\alpha]_D^{20} = +16.7$ (c=0.12, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5$\mu$m (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 14.97$ min, minor isomer: $t_R = 17.63$ min, $ee = 74\%$. 
1-(4-(Tert-Butyl)phenyl)-1-oxopropan-2-yl 4-methylbenzenesulfonate 146h

Following GP 19 Method A or Method B, Chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), p-TsOH hydrate (154 mg, 0.81 mmol), and 3-tert-butylpropioiophenone 145h (51 mg, 0.27 mmol) to afford 146h as a white solid. M.p.: 62 – 64 °C. 1H NMR (400 MHz, CDCl3): δ = 7.85 – 7.79 (m, 2H), 7.79 – 7.72 (m, 2H), 7.48 – 7.43 (m, 2H), 7.27 – 7.22 (m, 2H), 5.78 (q, J = 6.9 Hz, 1H), 2.40 (s, 3H), 1.59 (d, J = 6.9 Hz, 3H), 1.34 (s, 9H) ppm. 13C NMR (101 MHz, CDCl3): δ = 194.4, 157.9, 145.0, 133.7, 131.1, 129.8, 128.9, 128.1, 125.8, 77.6, 35.3, 31.1, 21.8, 18.9 ppm. HRMS (ESI): [M+H] + calc. 361.1474 for [C20H25O4S] +, found 361.1472. IR (neat): ν = 2932, 1365, 1177, 1086, 921, 664 cm⁻¹.

(S)-146h: Prepared by Method A: white solid (19 mg, 20%), [α]D²⁰ = −16.7 (c=0.12, CHCl₃).

Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-hexane/i-PrOH = 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: tR = 8.7 min, minor isomer: tR = 8.1 min, ee = 53%.

(R)-146h: Prepared by Method B: white solid (63 mg, 65%), [α]D²⁰ = +5.9 (c=0.34, CHCl₃).

Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-hexane/i-PrOH = 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: tR = 8.1 min, minor isomer: tR = 8.8 min, ee = 66%.
1-(Naphthalen-2-yl)-1-oxopropan-2-yl 4-methylbenzenesulphonate 146i

Following **GP 19** method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), *m*-CPBA (184 mg, 0.81 mmol), *p*-TsOH hydrate (154 mg, 0.81 mmol), and 1-naphthalen-2-yl-propan-1-one 145i (50 mg, 0.27 mmol) to afford 146i as a colorless oil. **1H NMR (400 MHz, CDCl₃):** δ = 8.40 (s, 1H), 7.96 – 7.84 (m, 4H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.66 – 7.55 (m, 2H), 7.22 – 7.18 (m, 2H), 5.97 – 5.90 (m, 1H), 2.36 (s, 3H), 1.67 (d, *J* = 6.9, 0.8 Hz, 3H) ppm. **13C NMR (101 MHz, CDCl₃):** δ = 194.9, 145.1, 135.9, 133.6, 132.4, 131.1, 130.8, 129.9, 129.8, 129.2, 128.8, 128.0, 127.9, 127.1, 124.2, 77.6, 21.7, 19.0 ppm. The spectroscopic data are in agreement with the literature.²⁴

**(S)-146i:** Prepared by method A: white solid (58 mg, 60%), [α]D²⁰ = −10.5 (c = 0.19, CHCl₃). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (*n*-Hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: *t*ₚ = 13.68 min, minor isomer: *t*ₚ = 11.76 min, *ee* = 67%.

**(R)-146i:** Prepared by method B: white solid (46 mg, 48%), [α]D²⁰ = +12.5 (c = 0.16, CHCl₃). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (*n*-Hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: *t*ₚ = 11.75 min, minor isomer: *t*ₚ = 13.67 min, *ee* = 78%.
1-Oxo-1-phenylbutan-2-yl 4-methylbenzenesulfonate 146j

Following GP 19 method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), p-TsOH hydrate (154 mg, 0.81 mmol), and butyrophenone 145j (40 mg, 0.27 mmol) to afford 146j as a white solid. M.p.: 63 – 65 °C. \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.88 – 7.82\) (m, 2H), 7.74 (d, \(J = 8.3\) Hz, 2H), 7.59 – 7.55 (m, 1H), 7.46 – 7.42 (m, 2H), 7.24 (dd, \(J = 8.6, 0.6\) Hz, 2H), 5.56 (dd, \(J = 7.8, 5.0\) Hz, 1H), 2.40 (s, 3H), 2.04 – 1.88 (m, 2H), 0.98 (t, \(J = 7.4\) Hz, 3H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 195.0, 145.1, 134.3, 133.9, 133.5, 129.8, 128.9, 128.8, 128.2, 82.7, 26.4, 21.8, 9.7\) ppm. The spectroscopic data are in agreement with the literature.\(^{24}\)

\((S)-146j\): Prepared by method A: white solid (81 mg, 94%), \([\alpha]_D^{20} = -20\) (c= 8.1, CHCl\(_3\)). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-S 5\(\mu\)m (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 9.23\) min, minor isomer: \(t_R = 8.14\) min, \(ee = 77\%\).

\((R)-146j\): Prepared by method B: white solid (78 mg, 91%), \([\alpha]_D^{20} = +7.4\) (c= 1.08, CHCl\(_3\)). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-S 5\(\mu\)m (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 8.18\) min, minor isomer: \(t_R = 9.29\) min, \(ee = 80\%\).
2-Oxo-1,2-diphenylethyl 4-methylbenzenesulfonate 146k

Following GP 19 method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), *m*-CPBA (184 mg, 0.81 mmol), *p*-TsOH hydrate (154 mg, 0.81 mmol), and deoxy benzoin 145k (53 mg, 0.27 mmol) to afford 146k as a white solid. M.p.: 95 – 96 °C. $^1$H NMR (400 MHz, CDCl3): $\delta$= 7.85 – 7.81 (m, 2H), 7.72 (d, $J$ = 8.3 Hz, 2H), 7.54 – 7.48 (m, 1H), 7.39 – 7.33 (m, 4H), 7.32 – 7.27 (m, 3H), 7.24 – 7.20 (m, 2H), 6.67 (s, 1H), 2.39 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl3): $\delta$= 192.2, 145.0, 134.2, 133.8, 133.7, 132.8, 129.7, 129.2, 129.1, 128.8, 128.3, 128.2, 82.4, 21.8 ppm. The spectroscopic data are in agreement with the literature. $^{24}$

(S)-146k: Prepared by method A: white solid (18.8 mg, 19%), Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R$ = 15.26 min, minor isomer: $t_R$ = 18.68 min, $ee$= 3%.

(R)-146k: Prepared by method B: white solid (39.6 mg, 40%), Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R$ = 18.69 min, minor isomer: $t_R$ = 15.27 min, $ee$= 4%.
1-(Furan-2-yl)-1-oxopropan-2-yl 4-methylbenzenesulfonate 146l

Following GP 19 method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), p-TsOH hydrate (154 mg, 0.81 mmol), and 2-propionylfuran 145l (34 mg, 0.27 mmol) to afford 146l as a colourless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta= 7.78 \) (d, \(J= 8.1 \) Hz, 2H), 7.63 – 7.60 (m, 1H), 7.36 (dd, \(J= 3.6, 0.5 \) Hz, 1H), 7.30 (d, \(J= 8.0 \) Hz, 2H), 6.58 – 6.55 (m, 1H), 5.51 (q, \(J= 6.9 \) Hz, 1H), 2.42 (s, 3H), 1.55 (d, \(J= 6.9 \) Hz, 3H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta= 183.5, 149.7, 147.6, 145.3, 133.5, 130.0, 128.1, 120.2, 112.8, 77.5, 21.8, 18.6 \) ppm. The spectroscopic data are in agreement with the literature.\(^{24}\)

\((S)\)-146l: Prepared by method A: colourless oil (73.5 mg, 93%), \([\alpha]_D^{20} = -18.5 \) (c=0.54, CHCl\(_3\)). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5\(\mu\)m (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 10.5 \) min, minor isomer: \(t_R = 9.9 \) min, \(ee= 57\%\).

\((R)\)-146l: Prepared by method B: colourless oil (52 mg, 66%), \([\alpha]_D^{20} = +13.3 \) (c=0.15, CHCl\(_3\)). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5\(\mu\)m (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 10.0 \) min, minor isomer: \(t_R = 10.6 \) min, \(ee= 76\%\).
1-Oxo-1-(thiophen-2-yl) propan-2-yl 4-methylbenzenesulfonate 146m

Following GP 19 method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), p-TsOH hydrate (154 mg, 0.81 mmol), and 2-propionylthiophene 145m (38 mg, 0.27 mmol) to afford 146m as a colourless oil. \( ^1 \text{H NMR} \ (400 \text{ MHz, CDCl}_3) \): \( \delta = 7.88 \ (\text{dd}, J = 3.9, 0.9 \text{ Hz, 1H}), 7.76 \ (\text{d}, J = 8.4 \text{ Hz, 2H}), 7.71 \ (\text{dd}, J = 4.9, 1.0 \text{ Hz, 1H}), 7.28 \ (\text{d}, J = 8.0 \text{ Hz, 2H}), 7.15 \ (\text{dd}, J = 4.9, 3.9 \text{ Hz, 1H}), 5.45 \ (\text{q}, J = 6.9 \text{ Hz, 1H}), 2.42 \ (\text{s}, 3\text{H}), 1.60 \ (\text{d}, J = 6.9 \text{ Hz, 3H}) \text{ ppm.} \ \ ^{13}\text{C NMR} \ (101 \text{ MHz, CDCl}_3) \): \( \delta = 188.2, 145.4, 140.0, 135.4, 134.0, 133.3, 130.0, 128.6, 128.2, 78.7, 21.8, 19.3 \text{ ppm.} \) The spectroscopic data are in agreement with the literature.\(^{24}\)

\((S)-146m\): Prepared by method A: colourless oil (7 mg, 8%), \([\alpha]_D^{20} = -40 \ (\text{c}=0.1, \text{CHCl}_3)\). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5\(\mu\)m (25 cm), (\(n\)-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \( t_R = 10.81 \text{ min, minor isomer: } t_R = 9.57 \text{ min, ee = 65%.} \)

\((R)-146m\): Prepared by method B: colourless oil (13 mg, 15%), \([\alpha]_D^{20} = +20 \ (\text{c}=0.1, \text{CHCl}_3)\). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5\(\mu\)m (25 cm), (\(n\)-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \( t_R = 9.60 \text{ min, minor isomer: } t_R = 10.86 \text{ min, ee = 80%.} \)
1-Oxo-2,3-dihydro-1H-inden-2-yl 4-methylbenzenesulfonate 146n

Following **GP 19** method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), *m*-CPBA (184 mg, 0.81 mmol), *p*-TsOH hydrate (154 mg, 0.81 mmol), and 1-indanone 145n (36 mg, 0.27 mmol) to afford 146n as a white solid. **M.p.**: 108 – 109 °C. **^1H NMR (400 MHz, CDCl₃)**: δ= 7.93 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.65 (td, *J* = 7.7, 1,1 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.41 – 7.36 (m, 3H), 5.13 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.66 (dd, *J* = 17.3, 7.9 Hz, 1H), 3.28 (dd, *J* = 17.2, 4.7 Hz, 1H), 2.47 (s, 3H) ppm. **^13C NMR (101 MHz, CDCl₃)**: δ= 197.7, 150.1, 145.3, 136.5, 133.8, 133.4, 130.0, 128.6, 128.4, 126.8, 124.9, 78.4, 34.1, 21.9 ppm. The spectroscopic data are in agreement with the literature.¹⁵

(±)146n: Prepared by method A: white solid (77 mg, 94%), [α]D$_{20}^{20}$ = −2.1 (c=1.9, CHCl₃).

Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (*n*-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: *t*$_R$ = 18.07 min, minor isomer: *t*$_R$ = 17.07 min, *ee* = 48%.

(R)-146n: Prepared by method B: white solid (55 mg, 67%), [α]D$_{20}^{20}$ = +3.3 (c=1.2, CHCl₃).

Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (*n*-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: *t*$_R$ = 17.15 min, minor isomer: *t*$_R$ = 18.17 min, *ee* = 62%.
1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl 4-methylbenzenesulfonate 146o

Following GP 19 method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), *m*-CPBA (184 mg, 0.81 mmol), *p*-TsOH hydrate (154 mg, 0.81 mmol), and 1-tetralone 145o (39 mg, 0.27 mmol) to afford 146o as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ= 7.95 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.50 (td, *J* = 7.6, 1.4 Hz, 1H), 7.37–7.28 (m, 3H), 7.27–7.22 (m, 1H), 5.16 (dd, *J* = 12.2, 4.9 Hz, 1H), 3.15–3.10 (m, 2H), 2.60–2.52 (m, 1H), 2.48–2.35 (m, 1H), 2.45 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ= 190.6, 145.0, 143.0, 134.4, 133.8, 131.3, 129.9, 128.8, 128.3, 128.2, 127.3, 80.2, 30.7, 27.5, 21.8 ppm. The spectroscopic data are in agreement with the literature.²⁴

(R)-146o: Prepared by method A: colourless oil (27 mg, 32%). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (*n*-Hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: *t*<sub>R</sub> = 13.86 min, minor isomer: *t*<sub>R</sub> = 14.51 min, *ee* = 3%.

(S)-146o: Prepared by method B: colourless oil (14 mg, 17%). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (*n*-Hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: *t*<sub>R</sub> = 14.59 min, minor isomer: *t*<sub>R</sub> = 13.92 min, *ee* = 20%.
1-Oxo-1-phenylpropan-2-yl benzenesulfonate 146q

Following GP 19 method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), benzenesulfonic acid (128 mg, 0.81 mmol), and propiophenone 145a (36.4 mg, 0.27 mmol) to afford 146q as a white solid. M.p.: 62 – 63 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$= 7.90 – 7.85 (m, 4H), 7.64 – 7.56 (m, 2H), 7.52 – 7.43 (m, 4H), 5.83 (q, $J$ = 6.9 Hz, 1H), 1.61 (d, $J$ = 6.9 Hz, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$= 194.8, 136.7, 134.1, 134.0, 133.8, 129.3, 129.0, 128.9, 128.1, 77.7, 18.9 ppm. The spectroscopic data are in agreement with the literature.$^{15}$

(S)-146q: Prepared by method A: white solid (75 mg, 96%), $\alpha$$^D$$^20$ = –1.0 (c= 1.90, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5$\mu$m (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R$ = 9.78 min, minor isomer: $t_R$ = 9.07 min, ee = 70%.

(R)-146q: Prepared by method B: white solid (73 mg, 94%), $\alpha$$^D$$^20$ = +1.8 (c= 2.24, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5$\mu$m (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R$ = 9.07 min, minor isomer: $t_R$ = 9.78 min, ee = 77%.
1-Oxo-1-phenylpropan-2-yl methanesulfonate 146r

Following GP 19 method A and method B: Chiral iodine catalyst (13 mg, 0.027 mmol), m-CPBA (184 mg, 0.81 mmol), methanesulfonic acid (78 mg, 0.81 mmol), and propiophenone 145a (36.4 mg, 0.27 mmol) to afford 146r as a white solid. M.p.: 76 – 78 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.97 – 7.91 (m, 2H), 7.68 – 7.59 (m, 1H), 7.55 – 7.48 (m, 2H), 6.05 (q, $J$ = 7.0 Hz, 1H), 3.14 (s, 3H), 1.67 (d, $J$ = 7.0 Hz, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 193.7, 134.3, 129.2, 128.8, 77.4, 39.6, 18.9 ppm. The spectroscopic data are in agreement with the literature.$^{15}$

(S)-146r: Prepared by method A: white solid (59.5 mg, 96%), $[\alpha]_D^{20}$ = -3.0 (c= 0.66, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R$ = 18.9 min, minor isomer: $t_R$ = 19.8 min, ee= 65%.

(R)-146r: Prepared by method B: white solid (51 mg, 82%), $[\alpha]_D^{20}$ = +9.0 (c= 0.22, CHCl$_3$). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R$ = 19.8 min, minor isomer: $t_R$ = 18.9 min, ee= 66%.
6.4.3. Catalytic Stereoselective $\alpha$-Acetoxylation of Ketones (GP 20)

**Method A:** Prepared according to a modified literature procedure. Chiral iodine catalyst 141d (0.027 mmol), $m$-CPBA (0.54 mmol, 2.0 equiv.), $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.11 mL, 0.81 mmol, 3.0 equiv.) and AcOH (1.0 mL, 0.81 mmol, 3.0 equiv.) were dissolved in a mixture of MeCN and DCM (1:1), followed by the addition of the Propiophenone 145 (0.036 g, 0.27 mmol). The reaction mixture was stirred at room temperature for 72 h. After completion of the reaction, the mixture was washed with sat. aq. NaHCO$_3$ solution and sat. aq. Na$_2$S$_2$O$_3$ solution and extracted with DCM (3x 5 mL). The combined organic layers were dried over MgSO$_4$, filtered, concentrated under reduced pressure. The crude products were purified by flash chromatography on silica gel ($n$-hexane/EtOAc 9:1) to afford the desired pure products.

**Method B:** Prepared according to a modified literature procedure. Chiral iodine catalyst 141c (0.027 mmol), $m$-CPBA (0.54 mmol, 2.0 equiv.), $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.11 mL, 0.81 mmol, 3.0 equiv.) and AcOH (1.0 mL, 0.81 mmol, 3.0 equiv.) were dissolved in a mixture of EtOAc and DCM (1:1), followed by the addition of the Propiophenone 145 (0.036 g, 0.27 mmol). The reaction mixture was stirred at room temperature for 72 h. After completion of the reaction, the mixture was washed with sat. aq. NaHCO$_3$ solution and sat. aq. Na$_2$S$_2$O$_3$ solution and extracted with DCM (3x 5 mL). The combined organic layers were dried over MgSO$_4$, filtered, concentrated under reduced pressure. The crude products were purified by flash chromatography on silica gel ($n$-hexane/EtOAc 9:1) to afford the desired pure products.
1-Oxo-1-phenylpropan-2-yl acetate 179

Following GP 20: Methyl \(N\)-(2-iodo-4,6-dimethylphenyl)-\(N\)-tosyl-alaninate 141c or 141d (13.0 mg, 0.027 mmol) to afford 179 as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.93\) (d, \(J = 7.9\) Hz, 2H), 7.58 (t, \(J = 7.4\) Hz, 1H), 7.47 (t, \(J = 7.4\) Hz, 2H), 5.96 (q, \(J = 7.0\) Hz, 1H), 2.14 (s, 3H), 1.52 (d, \(J = 7.0\) Hz, 3H) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = 197.0, 170.6, 134.5, 133.7, 128.9, 128.6, 71.6, 20.9, 17.3\) ppm. The spectroscopic data are in agreement with the literature. \(^{25}\)

(S)-179: Prepared by method A: white solid (36 mg, 69%), \([\alpha]_D^{20} = -90.9\) (c=0.22, CHCl\(_3\)). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5\(\mu\)m (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 5.0\) min, minor isomer: \(t_R = 4.7\) min, \(ee = 50\%\).

(R)-179: Prepared by method B: white solid (28 mg, 54%), \([\alpha]_D^{20} = +11.8\) (c=0.17, CHCl\(_3\)). Enantiomeric excess is determined by HPLC YMC Chiral Amylose-C S-5\(\mu\)m (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 4.7\) min, minor isomer: \(t_R = 5.0\) min, \(ee = 34\%\).
6.5 Experimental Data for Chapter 5

6.5.1. Synthesis of Chiral Sulfoxide Auxiliaries

6.5.1.1. Synthesis of chiral menthyl \((S_S)-p\)-tolylsulfinate (GP 21)

Prepared according to a modified literature procedure.\textsuperscript{26,27} To a solution of sodium 4-methylbenzene-1-sulfinate 208 (5.0 g, 32.0 mmol) in toluene (50 mL), was added thionyl chloride SOCl\(_2\) (2.8 mL, 39 mmol, 1.2 equiv.) portionwise at 0 °C. The obtained yellow solution was stirred at room temperature for 4h, and the solvents were then removed under reduced pressure. \((-\)-Menthol (5.00 g, 32.0 mmol) in Et\(_2\)O (50 mL) was added to the resulting crude, and triethyl amine Et\(_3\)N (6.70 mL, 48.0 mmol, 1.5 equiv.) were added portionwise at 0 °C. The reaction mixture was stirred at room temperature for 16 h. After the completing of the reaction, the mixture was then diluted with EtOAc (20 mL) and quenched with brine (10 mL) followed by 1 M HCl (10 mL) and saturated NaHCO\(_3\). The phases were separated, and the organic layer was dried over (Na\(_2\)SO\(_4\)), filtered off and evaporated under reduced pressure. The crude mixture was diluted in acetone (50 mL) and 4 drops of concentrated HCl were added. The solution was cooled, and the obtained crystals were filtered and washed with cold acetone. The mother liquor was then concentrated to half its volume, 3 drops of concentrated HCl were added. The crystal process was repeated more times, and the obtained chiral \((S_S)\)-menthyl-\(p\)-tolylsulfinate 209 was recrystallized from hot acetone.
Experimental part

(1R, 2S, 5R)-(−)-Menthyl (Ss)-p-tolylsulfinate 209

Following GP 21: Affording 209 as a white solid (4.52 g, 48%). M.p.: 103 – 105 °C. [α]D 20 = −78.6 (c= 1.12, CHCl3). 1H NMR (500 MHz, CDCl3): δ= 7.63 – 7.58 (m, 2H), 7.32 (d, J = 7.9 Hz, 2H), 4.12 (td, J = 10.8, 4.5 Hz, 1H), 2.43 (s, 3H), 2.33 – 2.22 (m, 1H), 2.16 – 2.06 (m, 1H), 1.72 – 1.64 (m, 2H), 1.54 – 1.43 (m, 1H), 1.39 – 1.30 (m, 1H), 1.29 – 1.16 (m, 1H), 1.10 – 0.99 (m, 1H), 0.96 (d, J = 6.5 Hz, 3H), 0.88 – 0.83 (m, 4H), 0.72 (d, J = 6.9 Hz, 3H) ppm. 13C NMR (126 MHz, CDCl3): δ= 143.3, 142.6, 129.8, 125.1, 80.3, 48.0, 43.1, 34.2, 31.9, 25.4, 23.3, 22.2, 21.6, 21.0, 15.6 ppm. The spectroscopic data are in agreement with the literature.28

6.5.1.2. Synthesis of chiral sulfoxides using Grignard reagent (GP 22)

Prepared according to a literature procedure.26 To a solution of (−)-menthyl (Ss)-p-tolylsulfinate 209 (1.0 g, 3.4 mmol) in 30 mL of anhydrous toluene, methyl magnesium bromide 212 (1.70 mL, 3 M in diethyl ether, 1.5 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 5 h. After the completing of the reaction,
the mixture was quenched by saturated solution of NH₄Cl at 0 °C, and the organic layer was extracted with Et₂O. The combined organic layers were dried over MgSO₄, filtered, concentrated under reduced pressure. Crystallization from petroleum ether afforded the title compound.

(Rs)-1-Methyl-4-(methylsulfinyl) benzene 213

Following GP 22: Affording 213 as a white solid (0.42 g, 81 %).

M.p.: 74 – 76 °C. [α]D²⁰ = +155 (c= 0.4, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ= 7.57 – 7.50 (m, 2H), 7.33 (d, J = 8.0 Hz, 2H), 2.70 (s, 3H), 2.41 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ= 142.7, 141.6, 130.2, 123.7, 44.2, 21.5 ppm. The spectroscopic data are in agreement with the literature.²⁶

Enantiomeric excess was determined by CHIRALPAK® ODH, (n-Hexane/i-PrOH = 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: tR = 16.1 min, minor isomer: tR = 18.4 min, ee= 99.5 %.
6.5.1.3. Synthesis of Chiral Sulfoxides using Organolithium Reagents (GP 23)

Method A

Prepared according to a literature procedure. A stirred solution of 2-bromo-N-acetanilide 211a (6.8 mmol) in dry THF was cooled down to –78 °C, and a solution of n-butyllithium in hexanes (2.5 M, 14.9 mmol, 2.2 equiv.) was then slowly added. The reaction mixture was stirred for 1 h at the same temperature. The (–)-(S)-menthyl-p-toluenesulfinate 209 (6.8 mmol) was dissolved in dry THF and adding to the reaction mixture. Then, the reaction mixture was stirred for 3-4 h at the same temperature. After the completing of the reaction, MeOH (few drops) was added following by the addition of a saturated aqueous solution of NH₄Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2x 20 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated under reduced pressure. The crude product was dissolved in 40 mL of a 1:1 mixture of ethanol and water, and potassium hydroxide (3.0 g, 54.4 mmol, excess) was added. The resulting mixture was stirred at 90 °C for 2 h. After the completing of the reaction, solvents were removed under reduced pressure. The crude was diluted with Et₂O (20 mL) and water (20 mL), and the organic layer was separated, and the aqueous layer was extracted with EtOAc (2x 20 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated under reduced pressure. The crude products were purified by flash chromatography on silica gel (n-hexane/EtOAc 7:3) to afford the desired pure product.
**Method B**

Prepared according to a literature procedure. A solution of bromobenzene derivatives 210a or 210b (9.2 mmol) in dry THF was cooled down to −78 °C, and a solution of n-butyllithium in hexanes (2.5 M, 10.1 mmol, 1.1 equiv.) was then slowly added. The reaction mixture was stirred for 2 h at the same temperature. The (−)-(S)-menthyl-p-toluenesulfinate (9.2 mmol) was dissolved in dry toluene and adding to the reaction mixture. Then, the reaction mixture was stirred for 3–4 h at the same temperature. After the completing of the reaction, the reaction was quenched by adding a saturated aqueous solution of NH₄Cl, and the organic layer was separated, and the aqueous layer was extracted with EtOAc (2x 20 mL). The combined organic layers were dried over MgSO₄, filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (n-hexane/EtOAc 7:3).

**(S)-2-(p-Tolylsulfinyl) aniline 211a**

Following GP 23, Method A: 2-Bromo-N-acetanilide 210a (1.45 g, 6.8 mmol), n-BuLi (6.0 mL, 14.9 mmol), (−)-(S)-menthyl-p-toluenesulfinate (2.0 g, 6.8 mmol), and KOH (g, mmol) to afford 211a as a yellow oil (0.283 g, 18 %). \([\alpha]_D^{20} = +27.3 (c=0.66, \text{CHCl}_3)\). \(^1\text{H NMR} (500 \text{ MHz, CDCl}_3)\): \(\delta= 7.48 – 7.43 (m, 3H), 7.26 – 7.19 (m, 3H), 6.76 (td, J = 7.5, 1.1 Hz, 1H), 6.59 (dd, J = 8.1, 1.0 Hz, 1H), 4.89 (bs, 2H), 2.37 (s,
3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta =$ 147.6, 140.8, 140.2, 132.9, 129.8, 128.4, 124.9, 124.2, 117.7, 117.4, 21.4 ppm. The spectroscopic data in agreement with the literature.$^{29}$

Enantiomeric excess was determined by CHIRALPAK® ODH, ($n$-Hexane/$i$-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 11.8$ min, minor isomer: $t_R = 9.7$ min, $ee =$ 89%.

**1-Methoxy-3-(p-tolylsulfinyl) benzene 211b**

Following **GP 23, Method B**: 3-Bromoanisole 210b (2.0 mL, 16.5 mmol), $n$-BuLi (7.3 mL, 18.2 mmol), and (−)-(S)-menthyl-$p$-toluenesulfinate (4.86 g, 16.5 mmol) to afford 211b as a light yellow solid (0.853 g, 21%). M.p.: 62 – 64 $^\circ$C. $[\alpha]_D^{20} =$ −9.5 ($c =$ 0.42, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.55 – 7.51 (m, 2H), 7.36 – 7.31 (m, 1H), 7.26 – 7.23 (m, 3H), 7.16 – 7.12 (m, 1H), 6.96 – 6.92 (m, 1H), 3.82 (s, 3H), 2.36 (s, 3H) ppm.$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta =$ 160.5, 147.3, 142.6, 141.8, 130.3, 130.2, 125.1, 117.3, 117.0, 109.1, 55.7, 21.6 ppm. The spectroscopic data are in agreement with the literature.$^{30}$

Enantiomeric excess was determined by CHIRALPAK® ODH, ($n$-Hexane/$i$-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 7.3$ min, minor isomer: $t_R = 6.8$ min, $ee =$ 10%.
1,3-Dimethoxy-5-(p-tolylsulfinyl) benzene 211c

Following **GP 23, Method B:** 1-Bromo-3,5-dimethoxybenzene 210c (2.0 g, 9.2 mmol), n-BuLi (4.0 mL, 10.1 mmol), and (−)-(S)-menthyl-p-toluenesulfinate (2.70 g, 9.2 mmol) to afford 211c as a white solid (0.915 g, 36%). M.p.: 80 – 83 °C. \([\alpha]_{20}^D = +7.14\) (c= 0.28, CHCl3).

\(^1\)H NMR (500 MHz, CDCl3): δ = 7.55 – 7.52 (m, 2H), 7.26 – 7.23 (m, 2H), 6.77 (d, \(J = 2.3\) Hz, 2H), 6.47 – 6.45 (m, 1H), 3.79 (s, 6H), 2.37 (s, 3H) ppm. \(^13\)C NMR (126 MHz, CDCl3): δ = 161.4, 148.2, 142.6, 141.8, 130.2, 125.1, 103.3, 102.2, 55.8, 21.6 ppm. The spectroscopic data are in agreement with the literature.\(^{31}\)

Enantiomeric excess is determined by CHIRALPAK® ODH, (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 7.8\) min, minor isomer: \(t_R = 9.9\) min, ee= 8 %.
6.5.2. Iodination of Chiral Sulfoxide Auxiliaries

6.5.2.1. Palladium mediated iodination (GP 24)

Prepared according to a literature procedure.\textsuperscript{32} To a stirred solution of \((R_S)-1\text{-methyl-4-}(methylsulfinyl)benzene 213\) (0.50 g, 3.24 mmol), Pd(OAc)\(_2\) (146 mg, 0.65 mmol, 0.2 equiv.), NIS (0.36 g, 1.62 mmol, 0.5 equiv.), DCE (11.0 mL), and HFIP (1.0 mL) at 100 °C for 24 h under air. The obtained mixture was passed through a silica gel with EtOAc as an eluent, and then the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (\(n\)-hexane/EtOAc 1:1).

2-Iodo-4-methyl-1-(methylsulfinyl) benzene 215

Following GP 24: Affording 215 as a yellow oil (0.43 g, 47%). \([\alpha]_D^{20} = +3.03\) (c=0.66, CHCl\(_3\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ= 7.78 (d, \(J= 8.0\) Hz, 1H), 7.66 (s, 1H), 7.44 – 7.40 (m, 1H), 2.76 (s, 3H), 2.38 (s, 3H) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ= 145.3, 143.4, 139.9, 130.6, 125.7, 91.5, 42.5, 21.0 ppm. The spectroscopic data are in agreement with the literature.\textsuperscript{32}

Enantiomeric excess is determined by YMC Chiral Amylose-C S-5\(\mu\)m (25 cm), (\(n\)-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 6.2\) min, minor isomer: \(t_R = 6.5\) min, \(ee = 19\%\).
6.5.2.2. The Sandmeyer reaction (GP 25)

Prepared according to a modified literature procedure. To a cooled solution of \((p\text{-Tolylsulfinyl})\text{aniline 211a (0.36 g, 1.56 mmol)}\) and \text{aq. HCl (37\%, 0.20 mL)}\) in \(\text{H}_2\text{O (4.0 mL)}\) at 0 °C, a solution of sodium nitrite \(\text{NaNO}_2 (0.11 g, 1.56 mmol, 1.2 \text{ equiv.})\) in \(\text{H}_2\text{O (4.0 mL)}\) and \(\text{MeCN (4.0)}\) was added. Then, the reaction mixture was stirred for 10 min before the addition of potassium iodide \(\text{KI (0.26 g, 1.56 mmol, 1.0 \text{ equiv.})}\) at 0 °C. The reaction mixture was then stirred for 30 min at room temperature and then heated at 70 °C for 2 h. After the completing of the reaction, the solution was neutralized by a solution of \(\text{Na}_2\text{S}_2\text{O}_3\), and the aqueous layer was extracted with \(\text{EtOAc (3x 10 mL)}\). The combined organic layers were dried over \(\text{MgSO}_4\), filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (\(n\text{-hexane /EtOAc 7:3)}\).

\((S)\text{-1-Iodo-2-(p-tolylsulfinyl) benzene 214a}\)

Following GP 25: Affording 214a as a yellow solid (96 mg, 18 %). \text{M.p.: 68 – 70 °C.} [\text{\(\alpha\)}\text{d}]^{20} = -80.5 (c= 0.82, \(\text{CHCl}_3\)). \(\text{\(^{1}H NMR (500 MHz, CDCl}_3\):} \delta= 8.00 \text{ (dd, } J = 7.9, 1.6 \text{ Hz, 1H)}, 7.81 – 7.77 \text{ (m, 1H)}, 7.67 – 6.64 \text{ (m, 2H), 7.62 – 7.56 \text{ (m, 1H)}, 7.25 – 7.21 \text{ (m, 2H), 7.17 \text{ (td, } J = 7.6, 1.6 \text{ Hz, 1H)}, 2.36 \text{ (s, 3H) ppm.}}\) \text{\(\text{\(^{13}C}\)
NMR (126 MHz, CDCl₃): δ = 147.9, 142.3, 141.5, 139.7, 132.5, 130.1, 130.0, 129.5, 126.9, 126.8, 125.0, 93.6, 21.6 ppm. HRMS (ESI): [M+H]⁺ calc. 342.9654, found. 342.9646 [C₁₃H₁₂IOS]⁺. IR (neat): ν = 3051, 1442, 1078, 1045, 1006, 814, 754 cm⁻¹.

Enantiomeric excess is determined by CHIRALPAK® ODH, (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: tᵣ = 8.12 min, minor isomer: tᵣ = 6.8 min, ee = 66 %.

6.5.2.3. LDA mediated iodination (GP 26)

Prepared according to a literature procedure. To a solution of diisopropylamine (5.4 mmol, 1.2 equiv.) in dry THF at –78 ºC and under argon atmosphere was added n-BuLi (2.5 M in hexane, 1.2 equiv.), and the mixture was stirred for 1 h at -78 ºC. A solution of (p-tolylsulfinyl) benzene derivatives 211b or 211c (4.5 mmol) in dry THF was added dropwise to the freshly prepared LDA solution at –78 ºC under argon atmosphere. After 2 h at –78 ºC, a solution of I₂ (5.4 mmol, 1.2 equiv.) dry in THF was added. The reaction mixture was then stirred overnight at room temperature. After the completing of the reaction, the reaction was quenched by adding a saturated aqueous solution of Na₂S₂O₈, and the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3x 10 mL). The combined organic layers were dried over...
MgSO$_4$, filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel ($n$-hexane/EtOAc 7:3).

2-Iodo-1-methoxy-3-(p-tolylsulfinyl) benzene 214b

Following GP 26: 1-Methoxy-3-(p-tolylsulfinyl) benzene 211b (1.10 g, 4.5 mmol), diisopropylamine (0.76 mL, 5.4 mmol), $n$-BuLi (2.2 mL, 5.4 mmol), and I$_2$ (1.37 g, 5.4 mmol) to afford 214b as a yellow oil (1.05 g, 63 %). $[\alpha]_D^{20} = -2.98$ (c=0.67, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.69 - 7.65$ (m, 2H), 7.65 - 7.62 (m, 1H), 7.56 - 7.51 (m, 1H), 7.23 - 7.19 (m, 2H), 6.92 - 6.89 (m, 1H), 3.90 (s, 3H), 2.34 (s, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 158.2, 149.8, 142.1, 141.7, 130.5, 130.0, 127.1, 118.9, 113.1, 85.9, 56.9, 21.6$ ppm. The spectroscopic data are in agreement with the literature.$^{30}$

Enantiomeric excess is determined by CHIRALPAK® ODH, (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R = 9.8$ min, minor isomer: $t_R = 11.8$ min, $ee = 7$ %.
2-Iodo-1,5-dimethoxy-3-(p-tolylsulfinyl) benzene 214c

Following GP 26: 1,3-Dimethoxy-5-(p-tolylsulfinyl) benzene 211c (1.24 g, 4.5 mmol), diisopropylamine (0.76 mL, 5.4 mmol), n-BuLi (2.2 mL, 5.4 mmol), and I$_2$ (1.37 g, 5.4 mmol) to afford 214c as a yellow solid (1.04 g, 58%).

M.p.: 175 – 177 °C. $[\alpha]_D^{20} = + 6.67$ (c=0.3, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.69 - 7.64$ (m, 2H), 7.27 (d, $J = 2.7$ Hz, 1H), 7.24 – 7.20 (m, 2H), 6.50 (d, $J = 2.7$ Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 2.35 (s, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 162.4$, 159.0, 149.8, 142.2, 141.6, 130.0, 127.2, 102.4, 101.9, 74.6, 56.8, 56.2, 21.6 ppm. HRMS (ESI): [M+H]$^+$ calc. 402.9865, found. 402.9871 [C$_{15}$H$_{16}$IO$_3$S]$^+$. IR (neat): $\nu = 2933$, 1579, 1423, 1155, 1033, 804 cm$^{-1}$.

6.5.3. Synthesis of NH- sulfoximines (GP 27)
Method A

Prepared according to a modified literature procedure. To a solution of chiral sulfoxides (1.30 mmol) in MeOH (2 mL), ammonium carbamate $\text{H}_2\text{NCO}_2\text{NH}_4$ (5.2 mmol, 4.0 equiv.) and (diacetoxyiodo)benzene PIDA (3.90 mmol, 3.0 equiv.) were added. The reaction mixture was stirred at room temperature for 16 h. After the completing of the reaction, the solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography on silica gel ($n$-hexane/EtOAc 1:1).

Method B

Prepared according to a modified literature procedure. To a solution of 2-iodothioanisole 220 (4.0 mmol) in MeOH (40 mL), ammonium carbonate $(\text{NH}_4)_2\text{CO}_3$ (6.0 mmol, 1.5 equiv.) was added. Then, (diacetoxyiodo)benzene PIDA (9.20 mmol, 2.3 equiv.) was added after dissolution of $(\text{NH}_4)_2\text{CO}_3$. The reaction mixture was stirred at room temperature for 16 h. After the completing of the reaction, the solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography on silica gel ($n$-hexane/EtOAc 1:1).
Imino(2-iodo-4-methylphenyl) (methyl)-λ⁶-sulfanone 219a

Following GP 27, Method A: 1-Methyl-4-(methylsulfinyl) benzene 215 (0.36 g, 1.30 mmol), H₂NCO₂NH₄ (0.40 g, 5.2 mmol), and PIDA (1.25 g, 3.90 mmol) to afford 219a as a yellow oil (0.19 g, 51%). [α]D20 = +5.56 (c= 0.72, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ= 8.19 – 8.12 (m, 1H), 7.97 – 7.92 (m, 1H), 7.35 – 7.29 (m, 1H), 3.27 (s, 3H), 2.37 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ= 177.4, 145.0, 143.6, 130.5, 129.7, 93.3, 42.7, 29.7 ppm. HRMS (ESI): [M+H]⁺ calc. 295.9606, found. 295.9609 [C₈H₁₁INOS]⁺. IR (neat): ν= 3255, 2358, 1701, 1217, 997, 815 cm⁻¹.

Enantiomeric excess is determined by YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: tR = 15.5 min, minor isomer: tR = 14.2 min, ee = 16 %.

Imino(2-iodophenyl) (p-tolyl)-λ⁶-sulfanone 219b

Following GP 27, Method A: 1-Iodo-2-(p-tolylsulfinyl) benzene 214a (0.44 g, 1.30 mmol), H₂NCO₂NH₄ (0.40 g, 5.2 mmol), and PIDA (1.25 g, 3.90 mmol) affording 219b as a yellow solid (0.12 g, 26 %). M.p.: 136 – 138 °C. [α]D20 = +10.5 (c=0.19, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ= 8.40 (dd, J = 8.0, 1.6 Hz, 1H), 8.02 (dd, J = 7.9, 1.6 Hz, 1H), 7.93 – 7.90 (m, 2H), 7.53 – 7.49 (m, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.17 – 7.11 (m, 1H), 2.42 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ= 145.3, 143.9, 143.4, 137.1, 133.4, 130.5, 129.5, 129.3, 128.8, 93.2, 21.7 ppm. HRMS (ESI): [M+H]⁺ calc. 238
357.9763, found. 357.9779 \([\text{C}_{13}\text{H}_{15}\text{IOS}]^+\). \textbf{IR} (neat): \nu= 3273, 2358, 1440, 1228, 1091, 964, 644, 559 cm\(^{-1}\).

Enantiomeric excess is determined by CHIRALPAK® ODH, (\(n\)-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 13.2\) min, minor isomer: \(t_R = 18.3\) min, \(ee = 70\) %.

**Imino(2-iodo-3-methoxyphenyl) (p-tolyl)-\(\lambda^6\)-sulfanone 219c**

Following \textbf{GP 27, Method A}: 2-Iodo-1-methoxy-3-(p-tolylsulfinyl) benzene 214b (0.48 g, 1.30 mmol), \(\text{H}_2\text{NCO}_2\text{NH}_4\) (0.40 g, 5.2 mmol), and PIDA (1.25 g, 3.90 mmol) to afford 219c as a yellow oil (0.23 g, 46 %). |\(\alpha|\)\(\text{D}_{20}\)\(^+\) = +1.41 (c=1.42, CHCl\(_3\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta= 7.94 – 7.88\) (m, 3H), 7.43 (t, \(J = 8.1\) Hz, 1H), 7.30 – 7.26 (m, 2H), 6.95 (dd, \(J = 8.2, 1.2\) Hz, 1H), 3.89 (s, 3H), 2.41 (s, 3H) ppm. \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta= 159.8, 147.4, 143.8, 137.0, 129.5, 129.4, 129.3, 122.7, 114.1, 86.8, 57.3, 21.7\) ppm. HRMS (ESI): [M+H] \(^+\) calc. 387.9868, found. 387.9870 \([\text{C}_{14}\text{H}_{15}\text{INO}_2\text{S}]^+\). \textbf{IR} (neat): \nu= 3273, 1456, 1226, 974, 781 cm\(^{-1}\).

Enantiomeric excess is determined by CHIRALPAK® ODH, (\(n\)-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 20.9\) min, minor isomer: \(t_R = 31.5\) min, \(ee = 7\)%.
**Imino(2-iodo-3,5-dimethoxyphenyl) (p-tolyl)-λ⁶-sulfanone 219d**

Following **GP 27, Method A**: (S)-2-Iodo-1,5-dimethoxy-3-(p-tolylsulfinyl) benzene 214c (0.52 g, 1.30 mmol), H$_2$NCO$_2$NH$_4$ (0.40 g, 5.2 mmol), and PIDA (1.25 g, 3.90 mmol) to afford 219d as a yellow oil (0.19 g, 36 %). $[\alpha]_{D}^{20} = -9.1$ (c=0.22, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta=$ 7.93 – 7.89 (m, 2H), 7.63 (d, $J=2.7$ Hz, 1H), 7.29 – 7.26 (m, 2H), 6.54 (d, $J=2.7$ Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.41 (s, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta=$ 161.0, 160.2, 147.4, 143.8, 136.9, 129.4, 129.1, 107.4, 102.0, 76.0, 57.2, 56.1, 21.8 ppm. HRMS (ESI): [M+H]$^+$ calc. 417.9974, found. 417.9974 [C$_{15}$H$_{17}$INO$_3$S]$^+$. IR (neat): $\nu=$ 3265, 1581, 1456, 1224, 1155, 977, 812 cm$^{-1}$.

Enantiomeric excess is determined by CHIRALPAK® ODH, ($n$-Hexane/$i$-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R =$ 10.1 min, minor isomer: $t_R =$ 11.9 min, ee= 7 %.

**Imino(methyl)(p-tolyl)-λ⁶-sulfanone 219e**

Following **GP 27, Method A**: (R$_S$)-1-Methyl-4-(methylsulfinyl) benzene 213 (0.20 g, 1.30 mmol), H$_2$NCO$_2$NH$_4$ (0.40 g, 5.2 mmol), and PIDA (1.25 g, 3.90 mmol) to afford 219e as a colorless oil (0.22 g, 85%). $[\alpha]_{D}^{20} = -12.9$ (c= 0.62, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta=$ 7.89 – 7.83 (m, 2H), 7.35 – 7.29 (m, 2H), 7.17 – 7.06 (m, 2H), 4.11 – 4.00 (m, 2H), 3.83 (s, 3H), 2.41 (s, 3H), 2.17 (s, 3H), 2.05 (s, 3H), 1.38 (s, 3H), 1.28 (s, 3H), 0.91 (t, $J=8.8$ Hz, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta=$ 161.2, 159.9, 147.5, 143.8, 136.9, 129.4, 129.1, 107.4, 102.0, 76.0, 57.2, 56.1, 21.8 ppm. HRMS (ESI): [M+H]$^+$ calc. 417.9974, found. 417.9974 [C$_{15}$H$_{17}$INO$_3$S]$^+$. IR (neat): $\nu=$ 3265, 1581, 1456, 1224, 1155, 977, 812 cm$^{-1}$.
3.10 (s, 3H), 2.42 (s, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$= 144.1, 140.3, 129.9, 127.8, 46.0, 21.5 ppm. The spectroscopic data are in agreement with the literature.$^{35}$

Enantiomeric excess is determined by YMC Chiral Amylose-C S-5μm (25 cm), ($n$-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R$ = 8.9 min, minor isomer: $t_R$ = 8.1 min, $ee$= 88%.

**Imino(2-iodophenyl) (methyl)-$\lambda^6$-sulfanone 221**

Following GP 27, Method B: 2-Iodothioanisole 220 (1.0 g, 4.0 mmol), (NH$_4$)$_2$CO$_3$ (0.57g, 6.0 mmol), PIDA (2.96 g, 9.20 mmol) affording racemic 221 as a yellow oil (0.76 g, 68%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$= 8.30 (d, $J$ = 7.9 Hz, 1 H), 8.12 (d, $J$ = 7.8 Hz, 1 H), 7.54 (t, $J$ = 7.6 Hz, 1 H), 7.21 (t, $J$ = 7.6 Hz, 1 H), 3.28 (s, 3 H), 2.75 (s, 1 H).$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$= 145.6, 143.1, 133.9, 130.6, 129.0, 93.3, 42.6. The spectroscopic data are in agreement with the literature.$^{37}$

### 6.5.4. Kinetic Resolution of Chiral Iodine based on Sulfoximine (GP 28)

Prepared according to a modified literature procedure.$^{38}$ To a solution of racemic imino(2-iodophenyl)(methyl)-$\lambda^6$-sulfanone 221 (2.4 g, 8.52 mmol) in dry acetone (15.0 mL), a solution of (+)-camphorsulfonic acid (1.0 g, 4.24 mmol, 0.5 equiv.) in dry acetone (5.0 mL) was added.
The reaction mixture was stirred at room temperature for 16 h. After the completing of the reaction, the crude was filtrated, and the salt was washed thoroughly with dry acetone. The salt was then recrystallized many times with warm MeCN to increase the enantiomeric excess of the desired product. After achieving high enantiomeric excess, the obtained salt was dissolved in DCM (10.0 ml), and saturated aqueous K$_2$CO$_3$ was added. The reaction mixture was stirred at room temperature for 1 h. After completion hydrolysis reaction, the mixture was washed water and extracted with DCM (3x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, concentrated under reduced pressure to afford the desired chiral product.

**Preparation of the salt of (+)-camphorsulfonic acid with (+) -(S)-S-methyl-S-2-iodophenylsulfoximine 222**

Following GP 28: Affording 222 as a white solid. **M.p.:** 141 – 143 ℃. [α]$^\text{D}_{20}$ = +7.7 (c= 0.26, MeOH). **$^1$H NMR** (500 MHz, CD$_3$OD_SPE): δ= 8.41 – 8.35 (m, 2H), 7.83 – 7.77 (m, 1H), 7.55 (td, J = 7.7, 1.6 Hz, 1H), 3.92 (s, 3H), 3.30 – 3.28 (m, 1H), 2.80 – 2.64 (m, 2H), 2.39 – 2.24 (m, 1H), 2.10 – 1.95 (m, 2H), 1.89 (d, J = 18.3 Hz, 1H), 1.64 – 1.57 (m, 1H), 1.46 – 1.38 (m, 1H), 1.13 (s, 3H), 0.86 (s, 3H) ppm. **$^{13}$C NMR** (126 MHz, CD$_3$OD_SPE): δ= 218.3, 145.6, 138.0, 137.7, 133.3, 130.8, 94.8, 94.9, 49.4, 49.3, 44.1, 43.6, 40.9, 27.8, 25.7, 20.5, 20.1 ppm. **HRMS (ESI):** [M+H]$^+$ found. 282.95 [C$_7$H$_{10}$INOS+]$^+$; [M+Na]$^+$ found. 255.07 [C$_{10}$H$_{15}$O$_4$SNa]$^+$. **IR** (neat): ν= 3332, 2958, 1726, 1187, 1169, 1024, 749 cm$^{-1}$. 

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(+)-(S)-S-Methyl-S-2-iodophenyl sulfoximine 223

Following GP 22: Affording chiral 223 as a colorless oil. \([\alpha]_D^{20} = +23.1 \text{ (c}=0.26, \text{CHCl}_3)\). Enantiomeric excess is determined by YMC Chiral Amylose-C S-5 μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 14.7\) min, minor isomer: \(t_R = 17.1\) min, \(ee = 57\%\).

6.5.5. N-acylated sulfoximines (GP 29)

Prepared according to a literature procedure.\(^{39}\) To a solution of NH-sulfoximines (2.69 mmol) in dry DCM, acyl chloride (2.69 mmol) was added at 0 °C followed by dropwise addition of pyridine (4.0 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature overnight. After the completing of the reaction, the mixture was washed with 1M HCl (2x 5 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (2x 10 mL). The combined organic layers were dried over MgSO\(_4\), filtered, concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (n-hexane/EtOAc 8:2).
2-Iodo-\(N\)-(methyl(oxo)(p-tolyl)-\(\lambda^6\)-sulfaneylidene) benzamide 225

Following GP 29: \(R\)-Imino(methyl)(p-tolyl)-\(\lambda^6\)-sulfanone 219e (0.46 g, 2.69 mmol), pyridine (0.32 mL, 4.0 mmol), and 2-iodobenzoyl chloride 224b (0.72 g, 2.69 mmol) to afford 225 as a light yellow oil (0.91 g, 85\%). \(\alpha\) \(\text{D}^{20} = +1.82\) (c= 1.1, CHCl\(_3\)). \(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)): \(\delta= 8.01 – 7.96\) (m, 2H), 7.93 – 7.89 (m, 1H), 7.83 – 7.79 (m, 1H), 7.43 – 7.38 (m, 2H), 7.38 – 7.33 (m, 1H), 7.09 – 7.03 (m, 1H), 3.48 (s, 3H), 2.45 (s, 3H) ppm. \(^{13}\text{C NMR}\) (126 MHz, CDCl\(_3\)): \(\delta= 175.6, 145.2, 141.5, 140.6, 135.3, 131.3, 130.3, 130.2, 127.9, 127.4, 93.1, 44.3, 21.7\) ppm. HRMS (ESI): [M+H]\(^+\) calc. 399.9868, found. 399.9870 \([\text{C}_{15}\text{H}_{15}\text{INO}_{2}\text{S}]^+\). IR (neat): \(\nu= 2922, 1624, 1288, 1215, 1141, 974, 742\) cm\(^{-1}\).

Enantiomeric excess is determined by CHIRALPAK® ODH, (\(n\)-Hexane/\(i\)-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 24.3\) min, minor isomer: \(t_R = 19.1\) min, \(ee= 57\) %.
N-((2-Iodophenyl) (oxo)(p-tolyl)-λ⁶-sulfaneylidene) benzamide 226

Following GP 29: Imino(2-iodophenyl) (p-tolyl)-λ⁶-sulfanone 219b (0.96 g, 2.69 mmol), pyridine (0.32 mL, 4.0 mmol), and benzoyl chloride 224a (0.31 mL, 2.69 mmol) to afford 226 as a white solid (1.18 g, 95 %). M.p.: 155 – 157 °C. [α]D²⁰ = + 21.0 (c=0.19, CHCl₃).

$^1$H NMR (500 MHz, CDCl₃): δ= 8.68 (dd, $J$ = 8.1, 1.6 Hz, 1H), 8.29 – 8.25 (m, 2H), 8.08 – 8.02 (m, 2H), 7.98 (dd, $J$ = 7.8, 1.2 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.56 – 7.49 (m, 1H), 7.48 – 7.41 (m, 2H), 7.39 – 7.32 (m, 2H), 7.22 (td, $J$ = 7.6, 1.6 Hz, 1H), 2.45 (s, 3H) ppm.

$^{13}$C NMR (126 MHz, CDCl₃): δ= 173.3, 144.9, 143.4, 141.4, 135.8, 134.3, 134.1, 132.3, 132.1, 129.9, 129.8, 129.5, 129.1, 128.2, 92.4, 21.9 ppm.

HRMS (ESI): [M+H]$^+$ calc. 462.0025, found. 462.0036 [C$_{20}$H$_{17}$INO$_2$S]$^+$. IR (neat): ν= 2922, 2550, 1681, 1627, 1275, 1208, 941, 765 cm⁻¹.

Enantiomeric excess is determined by YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_R$ = 20.4 min, minor isomer: $t_R$ = 13.6 min, ee= 70 %.
Following GP 29: (+)-(S)-S-Methyl-S-2-iodophenylsulfoximine 223 (0.76 g, 2.69 mmol), pyridine (0.32 mL, 4.0 mmol), and benzoyl chloride (0.31 mL, 2.69 mmol) to afford 227 as a colorless oil (0.96 g, 93%). \([\alpha]_{D}^{20} = +30.0 \ (c= 0.2, \text{CHCl}_3)\). 1H NMR (500 MHz, CDCl3): \(\delta = 8.41 \ (d, J = 8.0, 1.6 \text{ Hz}, 1\text{H}), 8.21 – 8.08 \ (m, 3\text{H}), 7.68 – 7.61 \ (m, 1\text{H}), 7.55 – 7.47 \ (m, 1\text{H}), 7.44 – 7.35 \ (m, 2\text{H}), 7.29 \ (td, J = 7.6, 1.6 \text{ Hz}, 1\text{H}), 3.59 \ (s, 3\text{H}) \) ppm. 13C NMR (126 MHz, CDCl3): \(\delta = 173.8, 143.2, 141.0, 135.2, 134.5, 132.3, 131.4, 129.8, 129.4, 128.1, 91.8, 41.5 \) ppm. HRMS (ESI): [M+H]+ calc. 385.9712, found. 385.9719 [C14H13INO2S]+. The spectroscopic data are in agreement with the literature.40

Enantiomeric excess is determined by YMC Chiral Amylose-C S-5μm (25 cm), (n-Hexane/i-PrOH = 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: \(t_R = 15.4 \text{ min}\), minor isomer: \(t_R = 19.9 \text{ min}, ee = 46 \%\).
6.5.1.3. Oxidation of iodine reagent (GP 30)

Prepared according to a literature procedure. To a stirred solution of iodoarene 223 in acetic acid at 50 ºC, NaBO$_3$·4H$_2$O (30 equiv) was added portionwise over 15 minutes. The mixture was stirred at 50 ºC overnight till the reaction completed. The acetic acid was evaporated under reduced pressure, and the residue then was washed with water. The organic layer was separated, and the aqueous layer was extracted with DCM (2x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, concentrated under reduced pressure. The residue was washed with n-hexane to afford the pure product.

(S)-3-Methyl-3-oxido-1H-1λ^3,3λ^4-benzo[d] [1,3,2] iodathiazol-1-yl acetate 228

Following GP 30: (+)-(S)-Methyl-S-2-iodophenylsulfoximine 223 (0.11g, 0.40 mmol), NaBO$_3$·4H$_2$O (1.85 g, 12 mmol) affording 228 as a white solid. M.p.: 176 – 178 ºC. $\left[\alpha\right]_{D}^{20} = +2.6$ (c=1.54, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 8.37 – 8.33 (m, 1H), 7.92 – 7.78 (m, 3H), 3.40 (s, 3H), 2.11 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 178.1, 134.4, 133.9, 132.3, 131.3, 128.2, 117.5, 47.7, 22.2 ppm. IR (neat): $\nu$ = 3001, 2365, 1717, 1603, 1312, 1208, 991, 754 cm$^{-1}$. 

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References


