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Chiral Hypervalent Iodine Mediated Enantioselective Phenol and Naphthol Dearomatisation: A Rapid Access to Oxazoline Based Spirocycles

Muhammad Umair Tariq

Department of Chemical Sciences

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

January 2020

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"And We have certainly honoured the children of Adam and carried them on the land and sea and provided for them of the good things and preferred them over much of what We have created, with [definite] preference."

Al-Quran 17:70

To my lovely son, Musa Muhammad

Publication(s)

This following publication(s) is/are based on the work presented in this thesis:

Spirooxazoline Synthesis by an Oxidative Dearomatizing Cyclization

Tariq, M.U. and Moran, W.J. *Eur. J. Org. Chem.*, **2020**, 5153-5160.

DOI:10.1002/ejoc.202000840

Design and Synthesis of Chiral Urea-Derived Iodoarenes and Their Assessment in the Enantioselective Dearomatizing Cyclization of a Naphthyl Amide

M. Umair Tariq, Wesley, J. Moran

Accepted in Tetrahedron

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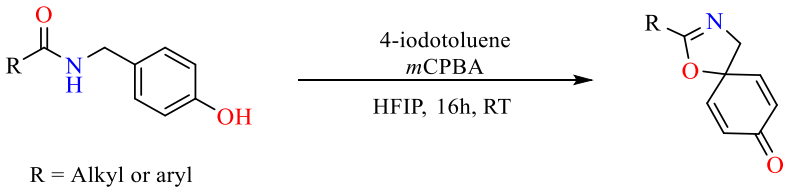
Last but not the least, my heartfelt gratitude to my beautiful wife for her love, confidence in my ability and continued support over the past two years. You are amazing and a huge blessing! I love and thank you so much.

Abstract

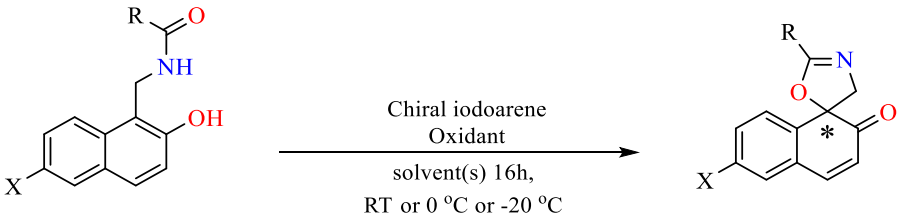
This thesis describes an investigation into the dearomatisation reactions of phenols and naphthols catalysed by in situ generated hypervalent iodine(III) species, thereby producing a range of spiro-oxazoline based compounds in achiral and enantio-enriched forms.

The first part of this dissertation illustrates the synthesis of spiro-oxazolines *via* oxidative dearomatisation of phenol and naphthol amides mediated by 4-iodotoluene as catalyst and *m*CPBA as terminal oxidant. Different iodoarenes, catalysts, and solvents were scanned, however, 4-iodotoluene and *m*CPBA provided the best results in hexafluoroisopropanol (HFIP). It was observed that altering the oxidant, iodoarene and solvent led to diminished yields in most cases. The stoichiometric and catalytic versions of the cyclisation were also successfully developed.



R = Alkyl or aryl

The second part of this thesis details the synthesis of novel chiral iodoarenes bearing chiral appendages. A range of novel iodoarenes possessing chiral ureas, lactates, amides and carbamates were synthesised in good to excellent yields. The newly synthesised chiral iodoarenes were then employed and studied in the intramolecular oxidative dearomatisation reactions of naphthol amides to obtain racemic and chiral oxazoline based spirocycles. A significant increase in the enantioselectivities was observed when alcoholic solvents were used as additives in dichloromethane or chloroform at –20 °C. In the presence of excess alcoholic solvent like ethanol, methanol and HFIP, poor selectivities were observed.



R = Alkyl or aryl
X = H or Br

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Abbreviations

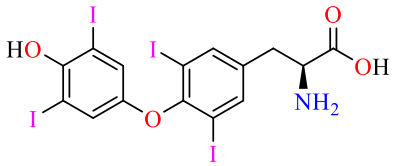
(aq.)	Aqueous solution
Brine	Saturated sodium chloride solution
CTAB	Cetyltrimethylammonium bromide
DCM	Dichloromethane
DPPA	Diphenylphosphoryl azide
EtOAc	Ethyl acetate
Hex	Hexane
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
IR	Infrared
Me	Methyl-
MeCN	Acetonitrile
Mes	Mesitylene group
MeOH	Methanol
m-CPBA	3-Chloroperbenzoic acid
MP	Melting point
ND	No developement
NMR	Nuclear magnetic resonance
OAc	Acetate
OTf	Trifluoromethanesulfonate
PIDA	(Diacetoxyiodo)benzene
PIFA	[Bis(trifluoroacetoxy)iodo]benzene

PTSA	*p*-Toluenesulfonic acid monohydrate
RT	Room temperature
Sat.	Saturated
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
UV	Ultraviolet

Chapter 1 Introduction

1.1. Iodine

Iodine belongs to the halogen family (group 17). It is represented by symbol **I** and has atomic number 53. Iodine is a bluish black solid with lustrous properties. Iodine is a non-metal, least electronegative and highly polarizable, non-radioactive halogen.[1] Compounds of iodine exist in various oxidation states. It can be found in -1, 0, +1, +3, +5, +7 oxidation states in organic and inorganic compounds. The reactivities of the hypervalent iodine compounds are somewhat similar to the properties of heavy metal reagents but without the toxicity issue. Iodine is also found in the human body as it is required for the normal functioning of the thyroid glands and production of thyroxin 1.[1]



Thyroxin **1**

Figure 1.1: Structure of thyroxin 1.

Due to the environmentally benign nature and inexpensiveness of iodine compounds, they have found huge applications in research and industry. In the past ten years, bulk prices of iodine were within the range of $20-100 per kilogram. Annually about 30,000 tons of iodine are produced from the estimated World's total reservoirs of 15 million metric tonnes found mostly in Japan and Chile.[2]

Industrial catalysis consumes about 16% of the world's production of iodine. Synthesis of acetic acid by Monsanto and Cativa processes involves hydroiodic acid as a co-catalyst. Iodine is used in LCD polarisers in the polymer industry and also finds vast applications in the food, medicine and pharmaceutical industries.[3]

1.2. Hypervalency

In 1969, J. I. Musher used the term 'hypervalent' for the ions or molecules of elements of group 15-18 having more than 8 electrons in their outermost shell.[4] The first hypervalent iodine compound iodobenzene dichloride ($PhICl_2$) was synthesised by a German chemist named C. Willgerodt in 1886 though it was known for its oxidising properties since 1893.[5, 6] General features of hypervalent compounds were summarised by K. Akiba[7] in the book *"Hypervalent Compounds"*. The formation of a hypervalent bond and possession of more than eight electrons in the valence shell by main group elements can be categorised into two classes:

- Involvement of d-orbitals responsible for dsp^3 or d^2sp^3 hybridisation.
- Generation of a new highly polarised three-centre four-electron ($3c\text{-}4e^-$) bond.

The organic derivatives of polyvalent iodine commonly known as hypervalent iodine compounds have gained significant research activity in the past three decades. Due to their versatile and environmentally benign nature, they are widely used in organic synthesis as reagents.[8, 9]

Compounds of iodine have the ability to form stable polycoordinate, multivalent compounds called hypervalent compounds when complexed with monodentate electronegative ligands like chloride. Factors responsible for widespread use of organoiodines in organic synthesis include, mild reaction conditions, low toxicity, easy handling and commercial availability of precursors as the key features of hypervalent iodine compounds.

Iodine exists in +3, +5, +7 oxidation states in its hypervalent compounds. Structures **1.1-1.7** represent the most common types of polyvalent iodine species. While the structures **1.2-1.7** are classified by using the Martin-Arduengo *N-X-L* nomenclature rules for hypervalent molecules. *N* shows the number of valence electrons, *X* being the central atom while *L* represents the number of ligands attached.[10, 11]

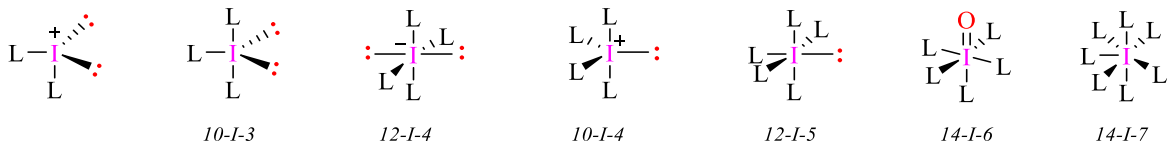
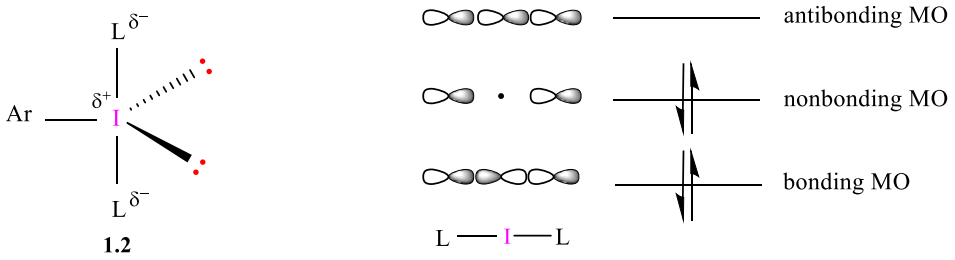


Figure 1.2: Typical structural types of polyvalent iodine compounds.

In the earlier literature, compounds of iodine(III) were called iodinanes whilst derivatives of iodine(V) were known as periodinanes. However in the modern literature, lambda nomenclature is used whilst dealing with variable valence in organic compounds. The symbol λ^n represents a heteroatom in its nonstandard valence state (*n*) in a chemically neutral compound. The lambda convention is particularly more useful for naming iodonium salts like Ph_2ICl as it reflects the true structure of the compounds having tricoordinated iodine atom.[12]

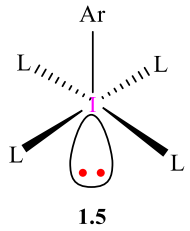
Hypervalent bonding in organoiodine compounds can be best explained by molecular orbital description which involves a $4e^-$−3c bond. In 1951, G. C. Pimentel and R. E. Rundle proposed the idea of three-centre four-electron ($4e^-$−3c) bond independently.[13, 14] The charge distribution on each of the ligands attached to the central atom in $4e^-$−3c bond is −0.5 whilst on that of central atom +1.0. In case of organoiodines(III), three molecular orbitals i.e. bonding, anti-bonding and non-bonding are produced as a result of interaction of filled 5p orbital of iodine atom and partially filled atomic orbitals of two ligands L attached to the central iodine atom but linear to each other. The high polarisability of the hypervalent bond is due to the node in the highest occupied molecular orbital (HOMO) at central iodine atom. As a result, more electronegative groups tend to occupy apical positions whilst least electronegative substituent R bound by normal covalent bond and both electron pairs occupy equatorial positions giving distorted trigonal bipyramidal shape to the molecule.



1.2

Figure 1.3: Pseudotrigonal bipyramidal structure and molecule orbital of the 3c-$4e^-$ bond

On the contrary, bonding in organoiodine(V) compounds, RIL_4, having bipyramidal structure, the normal covalent bond between organic R substituent and iodine are at apical position whilst four ligands L are being accommodated by two orthogonal hypervalent 3c-$4e^-$ bonds. Electronegative ligands reside at equatorial position while unshared electron pair and organic R substituent take apical positions as shown in figure 1.4.



1.5

Figure 1.4: Square pyramidal structure of $ArIL_4$

1.3. Classification of organoiodine(III) compounds

Depending upon the number of carbon ligands attached to the central iodine atom, organoiodines can be classified into three classes.

- Single C-Bond: Iodosyl/iodoso compounds and their derivatives (RIL_2, where L represents the non-carbon ligands and R can be an aryl/ alkyl/ or CF_3.
- Two C-Bonds: Iodonium salts fall into this category ($R_2I^+L^-$).
- Three C-bonds: (Iodanes having three C-I bonds are generally unstable).

Apart from the aforementioned categories, some cyclic hypervalent iodine(III) compounds also exist derived from *o*-iodobenzoic acid and are known as benziodoxazole **1.14** and benziodazoles **1.15**.[15] All these classes of iodine(III) compounds have found broad applications in organic synthesis: (difluoroiodo)arenes **1.8**, (dichloroiodo)arenes **1.9**, iodosylarenes **1.10**, [bis(acyloxy)iodo]arenes **1.11a, b**, aryliodine(III) organosulfonates **1.13** of which the most common example is Koser's reagent **1.12**, iodonium salts **1.16**, iodonium ylides **1.17** and iodonium imines **1.18**.

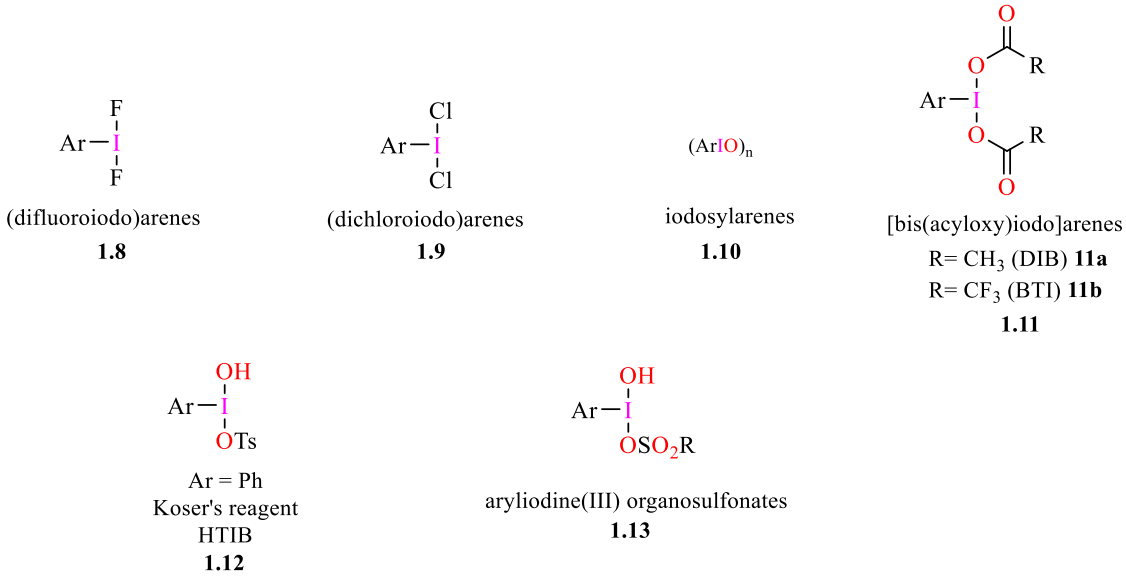


Figure 1.5: Common classes of organoiodine(III) compounds.

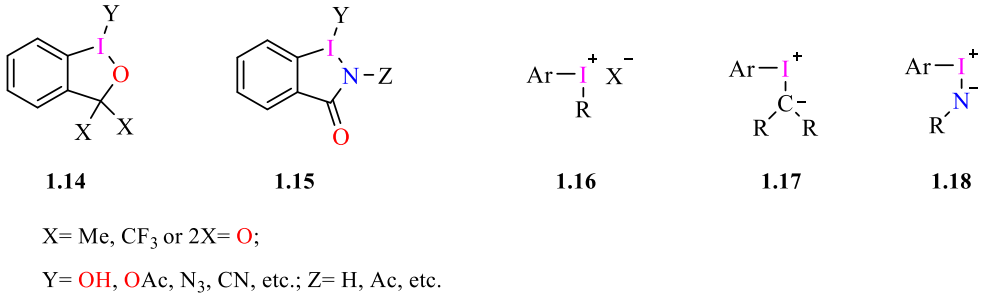
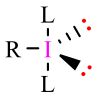


Figure 1.6: Cyclic organoiodine(III) compounds.

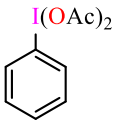
1.4. Hypervalent iodine compounds and their reactivity

Hypervalent iodine based compounds have received huge interest in the past few decades in organic synthesis as versatile and environmentally friendly reagents. One of the fascinating developments in this area is the discovery of the catalytic role of iodine in various transformations resulting in the formation of carbon-oxygen, carbon-nitrogen and carbon-carbon bonds in organic compounds. These transformations having iodine as a catalyst resembles heavy metal catalysed reactions but is advantageous due to environmental sustainability and efficient utilisation of natural resources. Some common λ^3-iodanes are mentioned in figure 1.7.



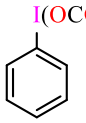
I(III): λ^3-iodanes

1.2



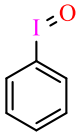
di(acetoxyiodo)benzene
DIB

1.11a



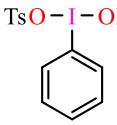
[(Bis(trifluoroacetoxy)iodo)benzene]
BTI

1.11b



Iodosylbenzene
IOB

1.10



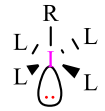
[Hydroxy(tosyloxy)iodo]benzene
HTIB

1.12

Figure 1.7: General structure and examples of λ^3-iodanes.

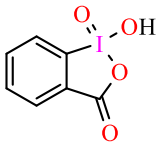
The aforementioned λ^3-iodanes are generally utilised in a wide range of chemical transformations such as alkene functionalisation, oxidative dearomatisation of electron rich aromatics, arylation reactions, oxidation of sulfides and α-functionalisation of ketones. A detailed explanation of these transformations is mentioned in section 1.5.

Hypervalent iodine(V) reagents, like DMP and IBX are employed in the oxidation of alcohols to obtain the corresponding carbonyl compounds. A fluorinated version of IBX has been developed by Wirth *et al.*[16] which exhibits greater solubility in common organic solvents and is used in oxidative synthetic transformations. Some common λ^5-iodanes are mentioned in figure 1.8.

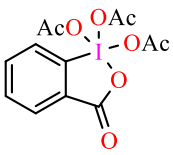


I(V): λ^5-iodanes

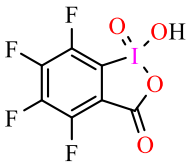
1.5



1.19
iodoxybenzoic acid
IBX



1.20
Dess-Martin periodinane
DMP

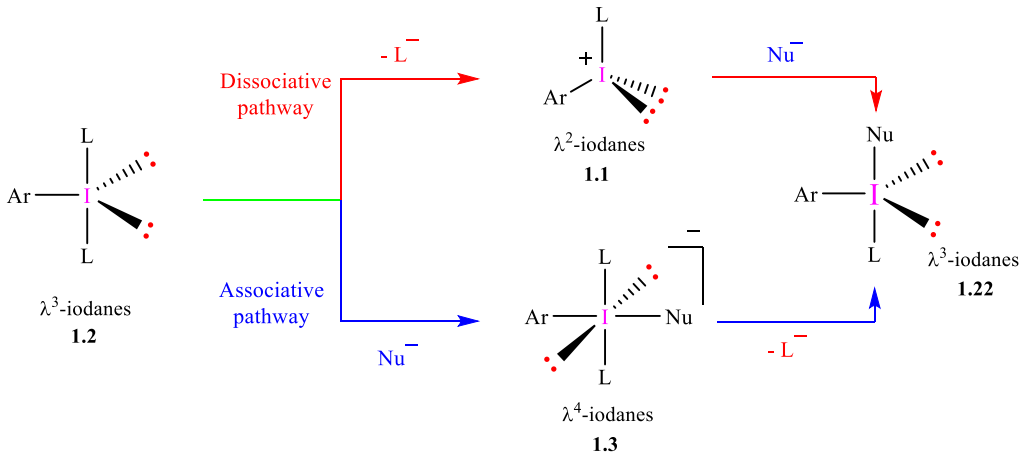


1.21
FIBX

Organo-λ^7-iodanes have not been reported yet however, inorganic iodine(VII) reagents exist in the form of IF_7, H_5IO_6, and HIO_4 (Periodic acids). This dissertation is aimed at λ^3-iodanes mediated transformations hence iodine(V) and (VII) compounds will not be discussed further.

The reactivity of trivalent iodine depends upon the number of carbon atoms and ligands attached to the central iodine atom. Common reactions of trivalent iodine compounds occur with RIL_2 class. The two ligands present at apical positions on the central iodine play a pivotal role in performing oxidation of several functional groups. These two ligands can act as good leaving groups when the highly electrophilic iodine(III) atom is attacked by nucleophiles. This process is called ligand exchange. In this process, λ^3 iodanyl group leaves with energetically favourable reduction of the hypervalent iodide I(III) to normal valence I(I).

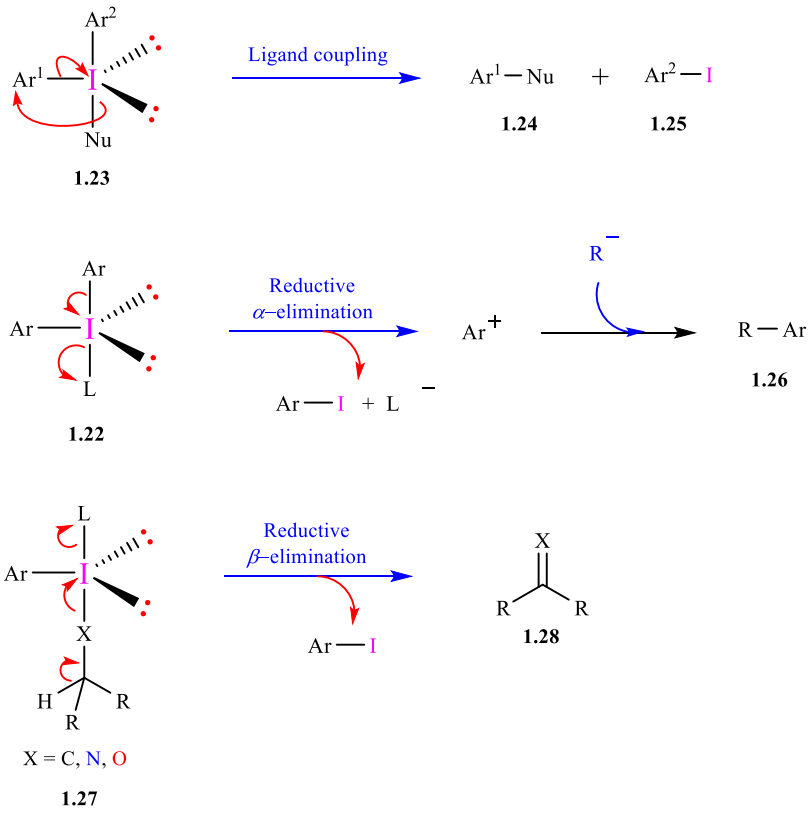
The ligand exchange in λ^3-iodanes can follow either associative or dissociative pathway.[1, 17] In dissociative pathway, one of the two ligands departs from iodane atom to generate dicoordinated λ^2-iodane **1.1** which is then attacked by appropriate nucleophile to give **1.22**. However, associative pathway involves the addition of the nucleophile to the iodane first hence generating square planar λ^4-iodane **1.3** then a ligand is dissociated to form **1.22** from **1.3**. (Scheme 1.1)



Scheme 1.1: Possible ligand exchange pathways of λ^3-iodanes with nucleophiles Nu^-

In the ligand exchange, energetically favourable reductive elimination of Ar-I happens because of the tremendous leaving aptitude of the Ar-I group (millions time better than a triflate ion. ^-OTf).[18] However, Ar-I can undergo reductive elimination essentially with or without ligand coupling. This mode of ligand coupling results in the arylation of the incoming nucleophile. The nucleophile and

the aryl group must be present at apical and equatorial position as shown in scheme 1.2.[19] The λ^3-iodanes undergo two different kind of reductive eliminations depending upon the fragmentation of the hypervalent iodine complex.[19-21] This is illustrated in scheme 1.2.



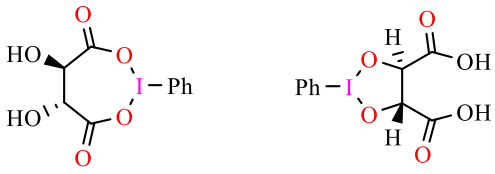
Scheme 1.2: Types of reductive elimination of iodane(III) species.

1.5. Chiral hypervalent iodine(III) reagents in asymmetric catalysis

1.5.1. Historic perspective

Pribram reported the first chiral hypervalent iodine compound in 1907, obtained from the mixture of *L*-tartaric acid and iodosobenzene.[22] However structures were not reported at that time. The suspected cyclic structures **1.29**, **1.30** are shown in the figure 1.9 below. The optical study of these two compounds demonstrated their chirality.

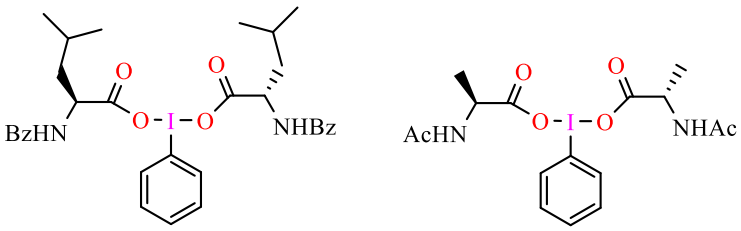
Structure of the first λ^3–iodanes by Pribram, ***1907***



1.29 **1.30**

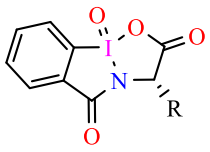
Figure 1.9: First chiral hypervalent iodine by Pribram.

In 1975, Merkushev reported the first chiral amino acid hypervalent iodine(III) derivatives however these were not used in any asymmetric reactions until in 1990s. The first chiral hypervalent iodine(V) reagents were reported by Zhdankin in 2000. They used chiral amino acids to provide chiral environment for better reactivity and stereocontrol in the oxidation of sulfides to sulfoxides.[23, 24]



1.31 **1.32**

Merkushev, **1975**



1.33

R = Me, $CH_2{}^iPr$, ^iPr

Zhdankin. **2000**

Figure 1.10: Chiral hypervalent iodine(III) and (V) reagents by Merkushev and Zhdankin respectively.

1.5.2. Developed strategies to control stereoselectivity and general reactivity patterns

The strong electrophilic nature of the hypervalent iodine and the leaving groups tendency to leave governs the reactivity of hypervalent iodine compounds. Other factors, like nature and number of the ligands attached to the central iodine atom also affect and determine its reactivity and stereoinduction of the process. In this context, two classes of hypervalent iodine(III) reagents are highlighted in figure 1.11.[25, 26] The general reactivity mechanism of λ^3-iodanes has been explained in great detail in scheme 1.1.

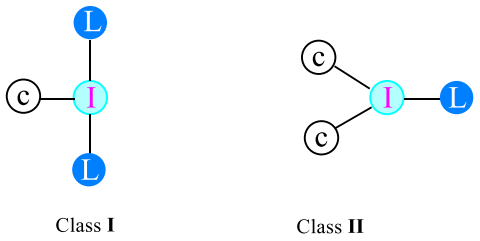


Figure 1.11: Structure classes of hypervalent iodine(III) compounds.

The reagents of class I are excellent oxidising agents due to the presence of heteroatom ligands and effectively permit this reactivity via ligand exchange hence they are extensively employed in oxidation reactions. The class II reagents are used in the transfer of one of the carbon substituents. The induction of chirality is determined by the chiral environment present around the iodine atom generated by heteroatom ligands or non-heteroatom ligands.

In enantioselective transformations, the design and development of the catalyst is extremely important for greater reactivity and higher stereoinduction. Depending upon the type of chirality installed on the structures of iodine(III)/(V) reagents, the hypervalent iodine catalysts are divided into four families. (Figure 1.12)

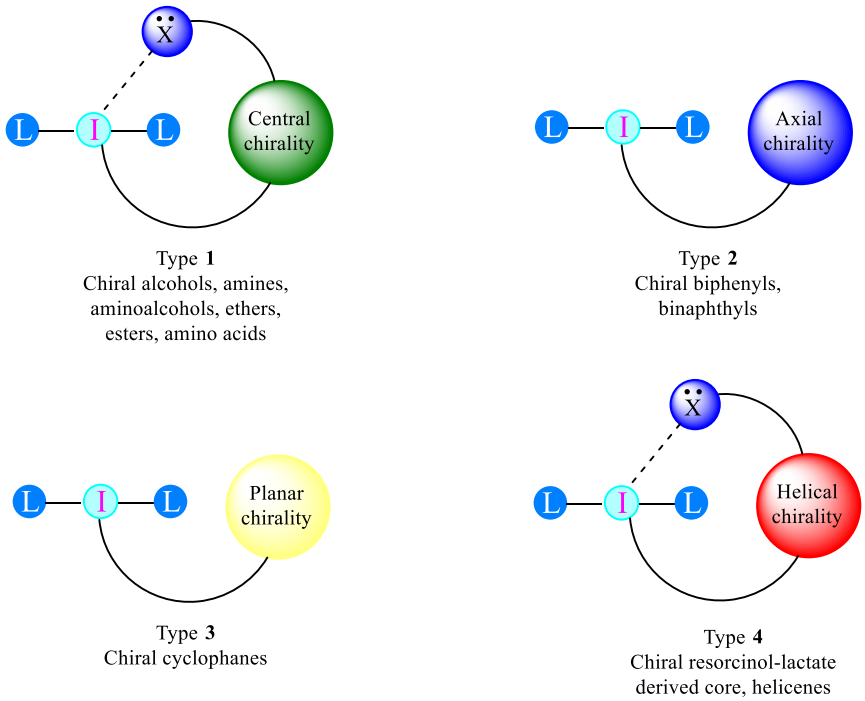


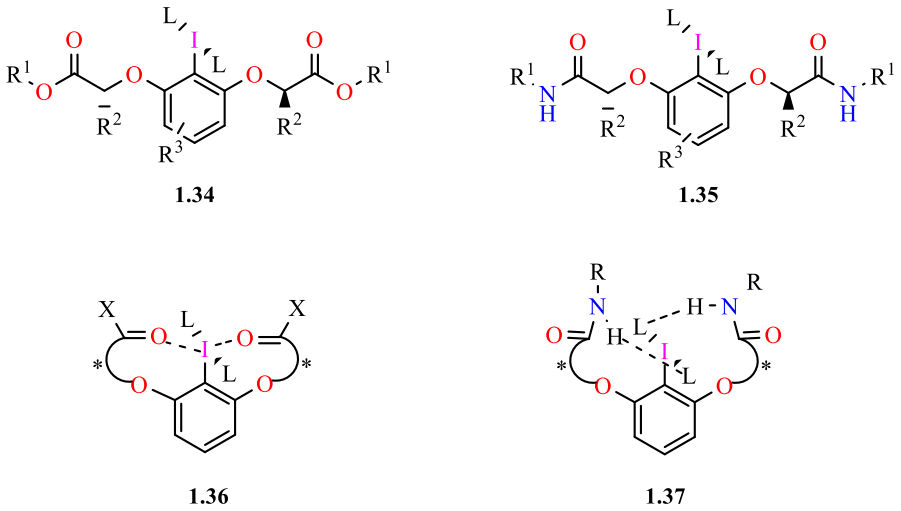
Figure 1.12: Strategies to control stereoselectivity

The type 1 chiral reagents are oxidised in situ to generate chiral hypervalent iodine(III) reagents. The chirality is generally present on one or multiple carbon atoms of the catalyst. Chiral alcohols, amines, amino alcohols etc. fall under this category. These heteroatom containing functionalities possess a coordinative tendency which helps in stabilising intramolecularly the hypervalent iodine intermediate. Many enantioselective transformations employ type I catalysts, however, the induction achieved is very limited thus producing desired products in less enantiomeric excess.

The type II and III structures incorporate axial and planar chirality. These classes involve chiral cyclophanes, chiral binaphthyls and chiral biphenyls. Despite reasonable success in terms of enantiocontrol using such catalysts, the need for improvement is still present.

In asymmetric hypervalent iodine mediated oxidations, the most successful and promising strategy for enantioselective induction is by using helicity possessing catalysts. In 2010, Fujita[27] and Ishihara.[28, 29] reported C_2-symmetric iodine catalysts **1.34, 1.35** bearing conformationally flexible chiral lactate and lactamide arms which provided greater enantiocontrol due to the formation of a peculiar helical fold **1.36** and **1.37** due to different noncovalent interactions around the iodine atom. (Figure 1.13)

Chiral resorcinol-lactate derived core

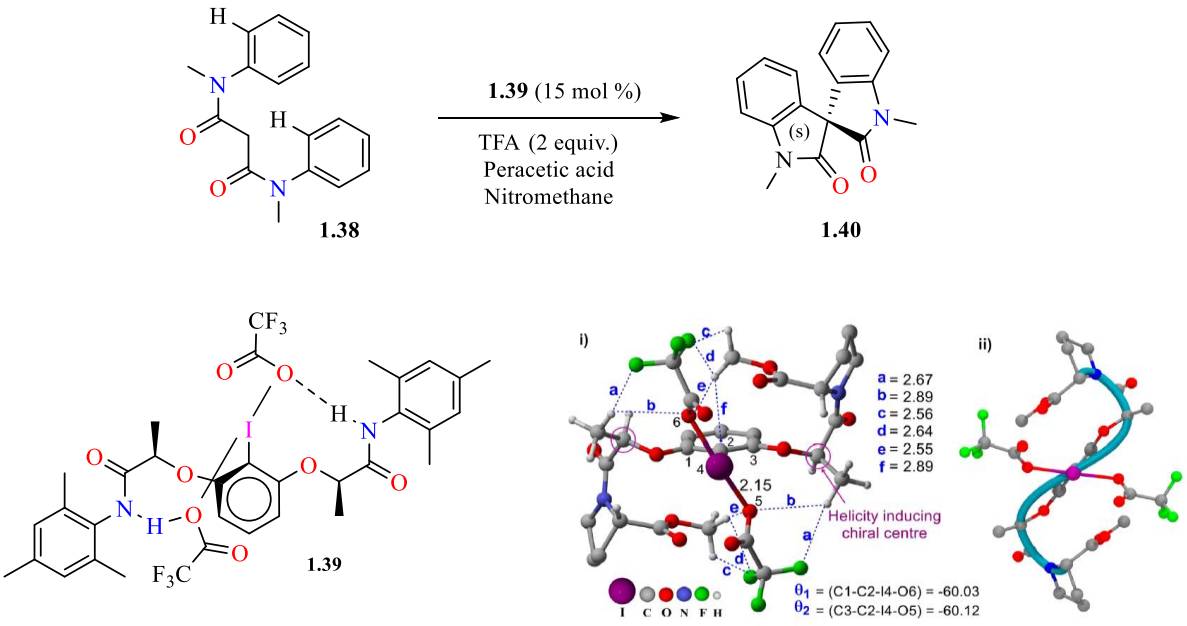


1.34 **1.35**

1.36 **1.37**

Figure 1.13: Helical chiral catalysts presenting chirality.

Sunoj *et al.*[30] reported the role of a resorcinol helical catalyst in the enantioselective spirocyclisation of an amide. The formation of the helical fold by the catalyst bearing chiral attachments is assisted by a number of non-covalent interactions. The chiral environment provided by the formation of helical fold helps to induce enantioselectivity in the products. (Scheme 1.3).

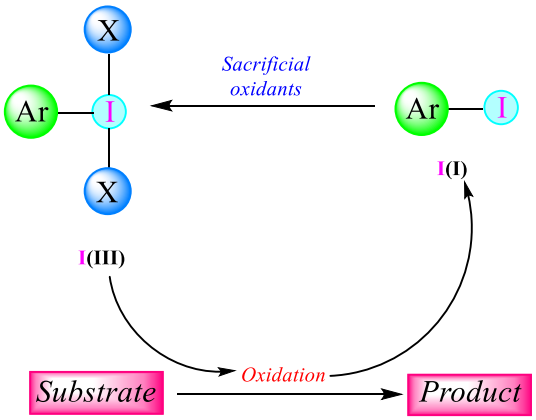


Scheme 1.3: Enantioselective cyclisation of amide by helical chiral iodoarene catalyst.[30]

1.6. Applications of chiral hypervalent iodines (CHIs)

Recently, huge efforts have been made for the employability of enantiomerically pure hypervalent iodine reagents in various oxidative transformations generating new C—O, C—N and C—C bonds in organic compounds. The catalytic role of hypervalent iodine reagents in transformations like oxidation of sulfides to sulfoxides, α-functionalisation of carbonyl compounds, dearomatisation of phenols, functionalisation of alkenes, rearrangement reactions and heterocyclisations has been extensively studied over the past few decades. In these manipulations, hypervalent iodine(III) species are generated in situ by oxidation using stoichiometric amounts of co-oxidant i.e. (*m*-CPBA, oxone, selectfluor etc.).[31, 32] Interestingly, these catalytic transformations are very similar to the transition metal-catalysed reactions, however, possess the advantage of environmental sustainability and efficient utilisation of natural resources.

In 2005, Ochiai and Kita reported independently the first synthesis of hypervalent iodine catalysts in situ by using catalytic amounts of iodoarene and stoichiometric amounts of terminal oxidants.[32, 33] The advantages and significance associated with using catalytic amounts of chiral hypervalent iodine in different transformations led to the formation of many more catalysts and has opened a whole new horizon for researchers. The general catalytic cycle for the formation of iodine(III) species in situ is illustrated below (scheme 1.4).



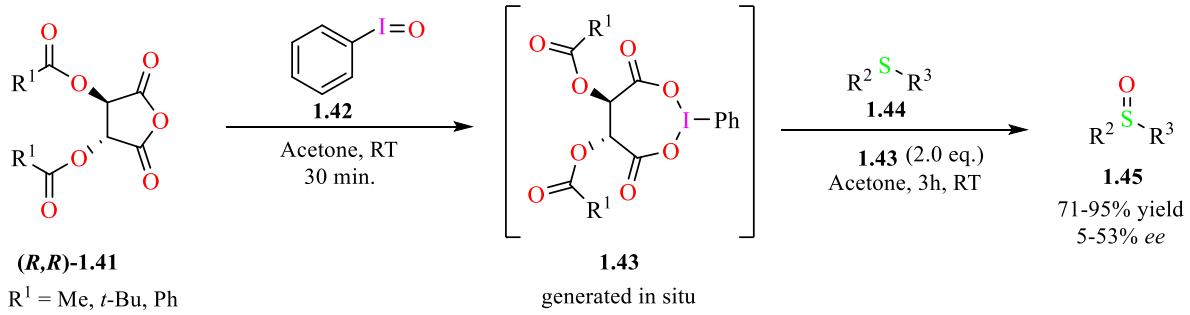
Scheme 1.4: Representation of general catalytic cycle to obtain hypervalent iodine(III) species.

Asymmetric transformations promoted by chiral hypervalent iodine complexes has gained considerable importance in the recent years. A few enantioselective reactions mediated by these reagents are mentioned below.

1.6.1. Asymmetric oxidation of sulfides

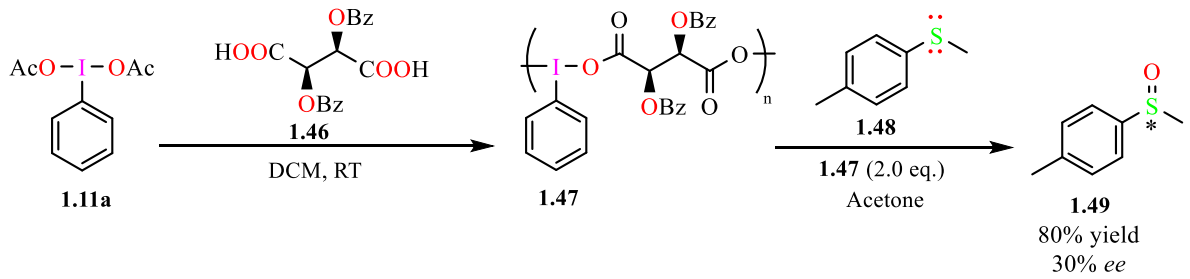
Enantiopure sulfoxides are important chiral auxiliaries and useful compounds in their own right. Chiral sulfoxides are utilised in a vast number of reactions such as Diels-Alder, Michael addition, *C-C* and *C-O* bond formation reactions.[34]

Imamoto[35] and Koser[36] demonstrated the first synthetic application of chiral I(III) reagents in the oxidation of sulfides **1.44** to sulfoxides **1.45** mediated by **1.43**. Corresponding sulfoxides were obtained in good yields with selectivities up to 53% *ee*. (Scheme 1.5)



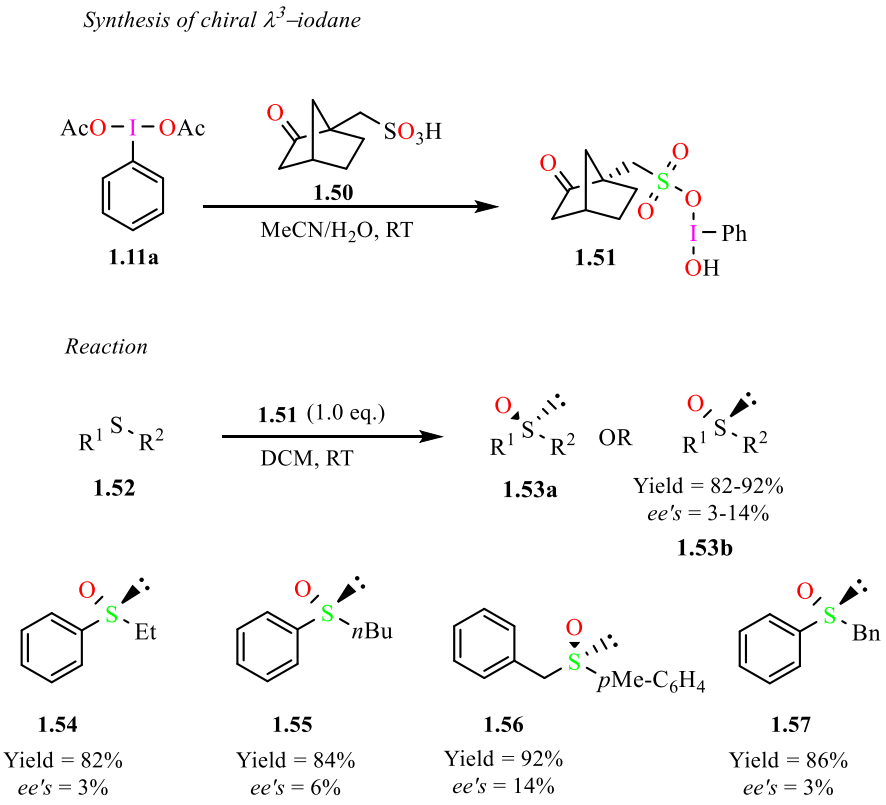
Scheme 1.5: Oxidation of sulfides to sulfoxides.

Koser and colleagues[36] synthesised iodine(III) dibenzoyl tartrates by reacting (diacetoxyiodo)benzene DIB **1.11a** with dibenzoyl-L-tartaric acid **1.46**. NMR studies proved that the chiral iodine compound **1.47** exists in polymeric form. (Scheme 1.6)



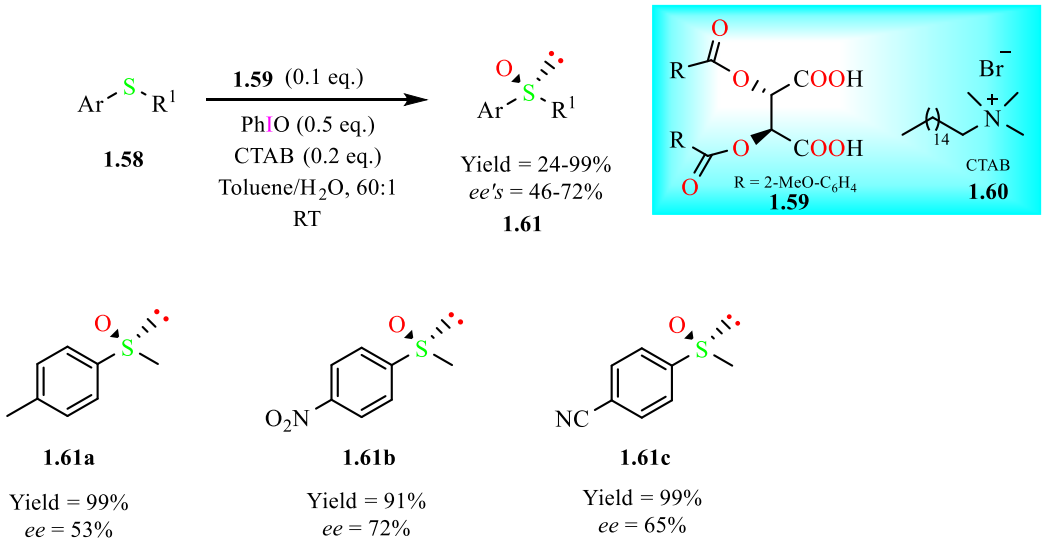
Scheme 1.6: CHI promoted oxidation of sulfides to sulfoxides.

Varvoglis *et al.*[37] synthesised a new chiral iodine catalyst by reacting (diacetoxyiodo)benzene (DIB) **1.11a** with (+)-10-camphorsulfonic acid **1.50** in 80% yield which was then tested by Chen and workers[38] in the enantioselective oxidation of sulfides. Gratifyingly sulfoxides were obtained in good yields but with poor selectivities.



Scheme 1.7: Synthesis of λ^3-iodoane by Chen et al.

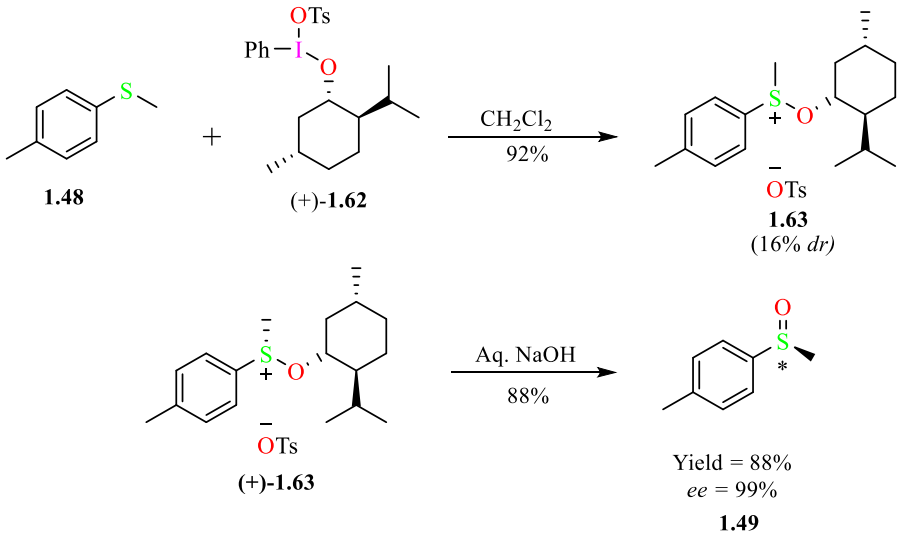
Kita *et al*. reported the first example of asymmetric oxidation of sulfides to sulfoxides mediated by hypervalent iodine(V) reagents.[39] The best catalytic activity was achieved by using 10 mol% of a chiral tartaric acid derivative, 20 mol% cetyltrimethylammonium bromide (CTAB) in the presence of iodoxybenzene ($PhIO_2$) in a cationic reversed micellar system to give the sulfoxides in excellent yields with good selectivities (Scheme 1.8).



Scheme 1.8: λ^3-iodoane mediated oxidation of sulfides to sulfoxides.

Later on, the same research group reported the success of the aforementioned transformation by using only water as a solvent and $MgBr_2$ to increase the enantioselectivity.[40]

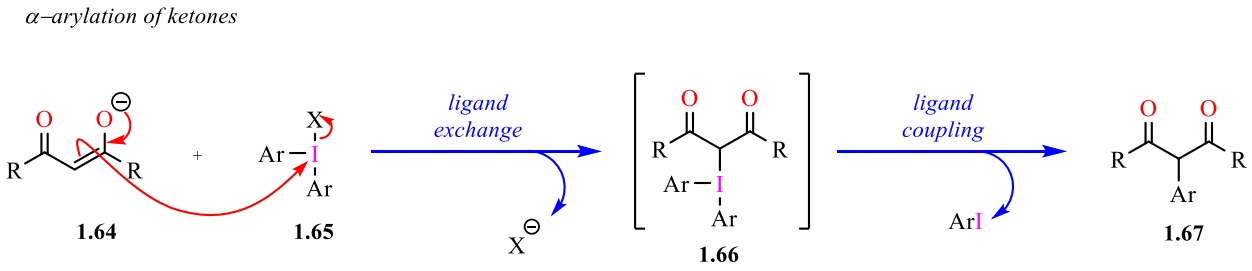
In 1990, Koser and Ray reported the enantioselective oxidation of sulfides **1.48** by using a chiral, non-racemic [menthyl-oxy(tosyloxy)iodo]benzenes derived from (1*S*,2*R*,5*S*)-(+)-menthol **1.62** and (1*R*,2*S*,5*R*)-(–)-menthol. Organic sulfides upon reacting with these reagents in DCM yielded optically active (menthyl-oxy)sulfonium tosylates. For instance, methyl *p*-tolyl sulfides **60** upon treatment with **1.62** gave (+)-menthyloxymethyl-*p*-tolylsulfonium tosylates **1.63** in 92% yield as a mixture of diastereomers (ca 58:42 dr). Recrystallisation of the mixture by DCM/Et_2O gave the major diastereomer (+)-**1.63** which upon hydrolysis by aq. NaOH yielded optically pure (*S*)-(–)-methyl *p*-tolyl sulfoxide (88% yield, >99% *ee*) **1.49** (scheme 1.9).[41]



Scheme 1.9: λ^3-idoane mediated oxidation of sulfides to sulfoxides reported by Koser et al.

1.6.2. Oxidative *α*-arylation and *α*-functionalisation of carbonyl compounds

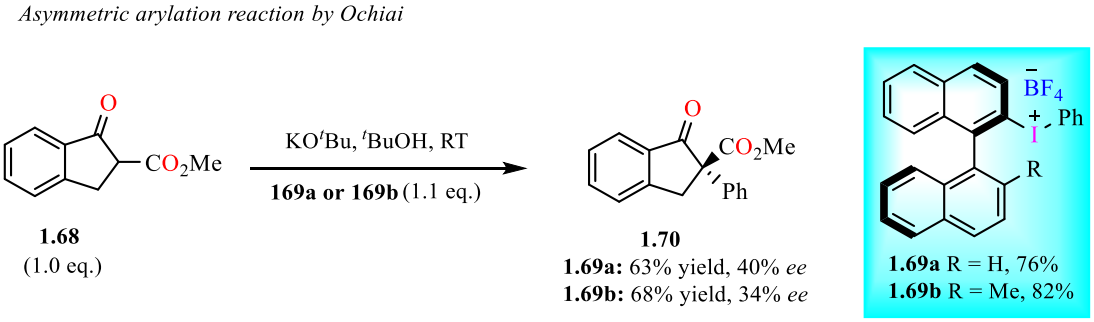
Ochiai and colleagues[42] reported the synthesis of chiral hypervalent iodine(III) reagents bearing axial chirality in 1990 which were then tested in the oxidative arylation reactions of 1,3-diketones. The general mechanism of oxidative arylation of the carbonyl compounds is outlined below.



Scheme 1.10: General mechanism of oxidative *α*-arylation of 1,3-diketones.

Interestingly, the same researchers in 1999 reported a novel asymmetric arylation reaction of *β*-ketoester enolates by employing chiral hypervalent iodine(III) catalysts such as **1.69a** and **1.69b**. (Scheme 1.11). It is believed that the higher reactivity of this salt is because of the nucleofugacity of the aryliodonio substituent. The arylation of the in situ produced enolate from **78** with chiral hypervalent iodine(III) reagents yielded *α*-phenylated **1.70** in moderate yields and

enantioselectivities. Despite the low induction achieved, it represented a historical landmark of this area.



Scheme 1.11: Chiral hypervalent iodine mediated arylation of cyclic β-ketoesters.

Another class of chiral iodonium salts has been synthesised by Olofsson and co-workers[43] in an attempt to provide alternative reagents for oxidative α-phenylation of ketones in higher optical yields, however, it appears succinct work has been done in this area as these catalysts were not evaluated in such reactions.

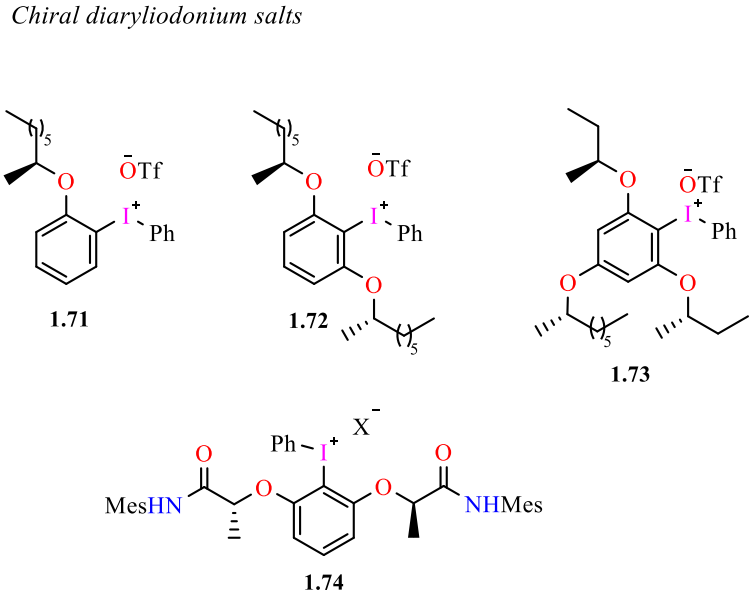
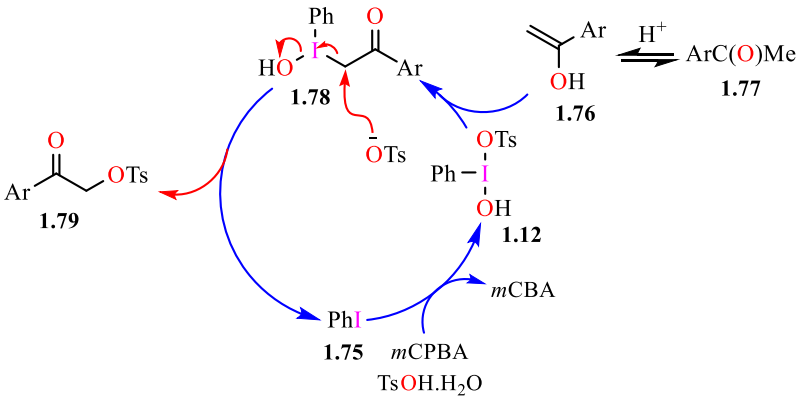


Figure 1.14: Chiral hypervalent iodonium salts by Olofsson et al.

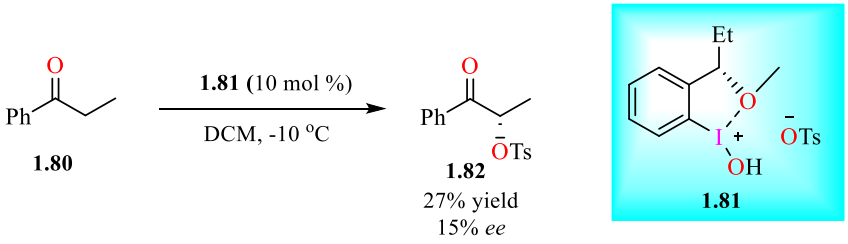
The α-functionalisation reactions of carbonyl compounds mediated by hypervalent iodine species have been much explored. Several groups such as alkoxy[44], hydroxyl, acetoxy[45], sulfonyloxy[46(a-c)]

and phosphoryloxy[44] are among others α-attached to a range of carbonyl compounds. This gives rapid access to α-oxygenated carbonyl compounds which could potentially be used in the synthesis of complex natural products. The general mechanism for this transformation is outlined below. (scheme 1.12). Mechanistically speaking, the process begins with the oxidation of iodobenzene **1.75** to produce Koser's reagent **1.12** in situ which is then attacked by the enol **1.76** formed by the starting ketone **1.77** to give rise to **1.78** which is followed by the tosylate ion attack to yield the corresponding α-tosylated ketone.



Scheme 1.12: General mechanism of Koser's reagent mediated α-oxytosylation of ketones.

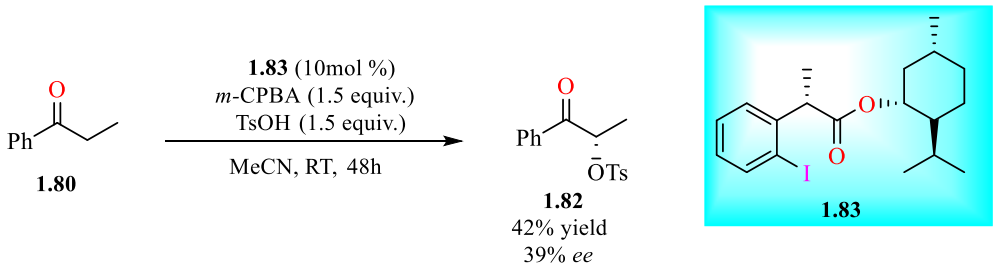
Wirth and colleagues[47] in 2005, reported the first enantioselective α-oxytosylation of propiophenone **1.80** mediated by chiral I(III) species **1.81** as stoichiometric reagents. Desired products **1.82** were achieved in low yields with 15% *ee* showing it to be a feasible protocol for the synthesis of non-racemic chiral compounds. (Scheme 1.13).



Scheme 1.13: Enantioselective α-oxytosylation of propiophenone.

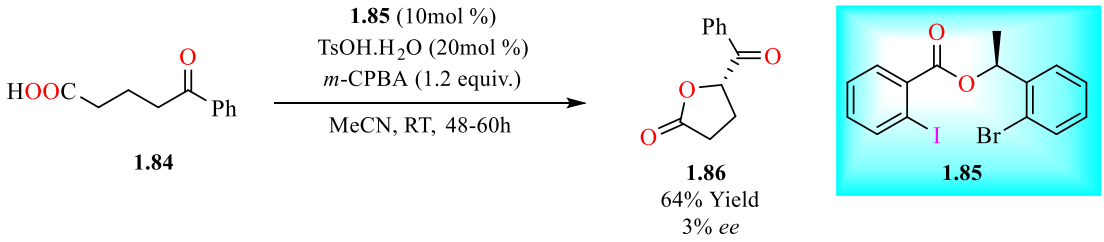
Later on, in 2007, Wirth and colleagues[48] prepared several chiral iodoarenes catalysts and tested them in enantioselective α-oxytosylation of propiophenone derivatives. In particular, they used 10 mol % of the **1.83** in α-oxytosylation of propiophenone **1.80** in the presence of *m*-CPBA as

stoichiometric oxidant and PTSA (TsOH) to afford the corresponding product **1.82** with enantioselectivities up to 39%.



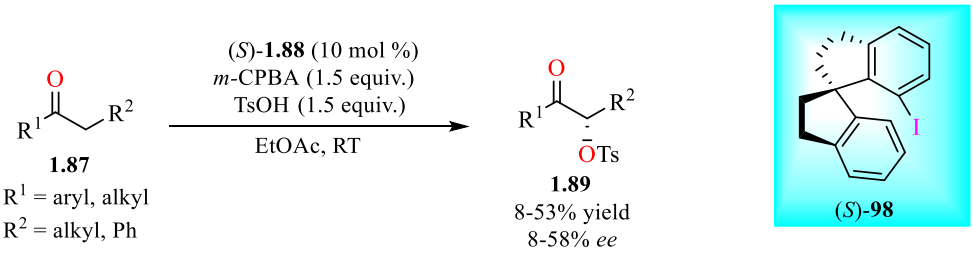
Scheme 1.14: Enantioselective α-oxytosylation of propiophenone

Wirth and workers[49], in 2010, reported the synthesis of a new family of chiral iodoarene catalysts and tested them in the enantioselective α-oxytosylation of propiophenone. However products were obtained in good yields but with relatively low enantioselectivities i.e. 26%. They decided to investigate the newly developed catalysts in the lactonisation reactions of 5-oxo-5-phenylpentanoic acid **1.84**. Unfortunately, the obtained products **1.86** showed extremely low or no enantioselectivity. (Scheme 1.15)



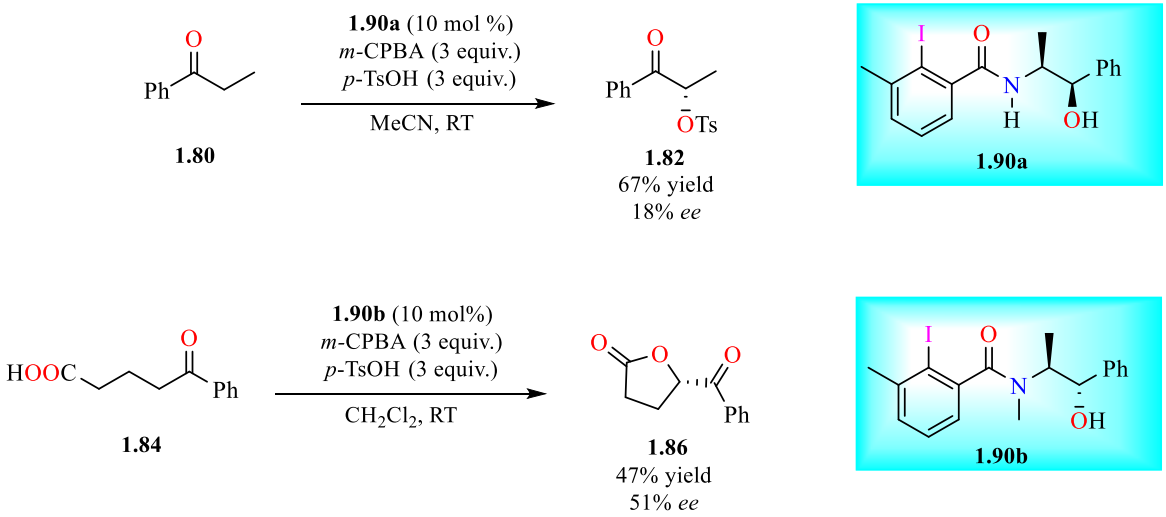
Scheme 1.15: Lactonisation reactions of 5-oxo-5-phenylpentanoic acid

A year later, Zhang *et al.*[50] synthesised a new family of chiral iodoarenes **1.88** possessing a spirobiindane scaffold and employed them in asymmetric α-oxytosylation of ketones **1.87** to test their chirality inducing ability. As an oxidant, *m*-CPBA was used along with PTSA (TsOH) to afford the desired products **1.89** with up to 58% *ee*. (Scheme 1.16).



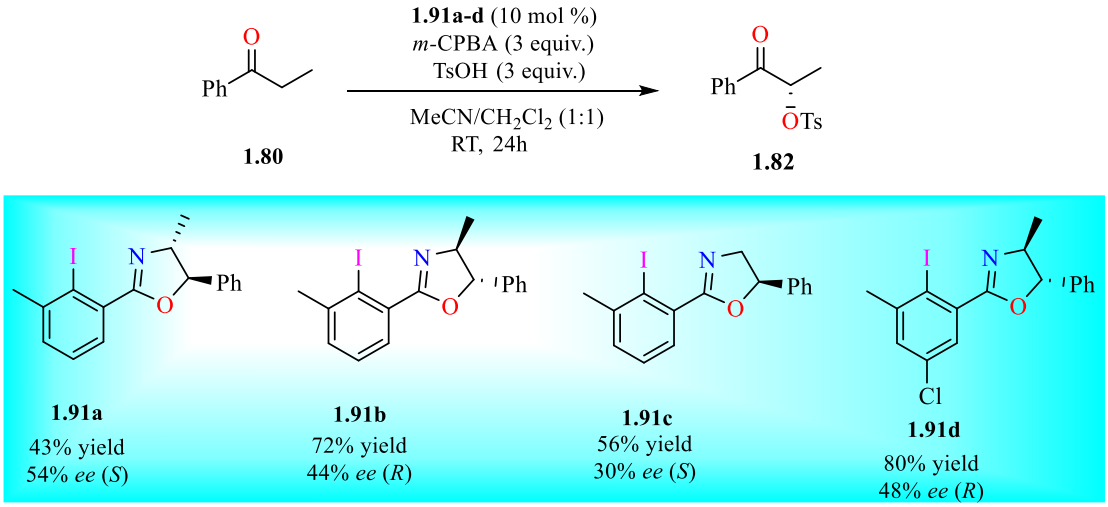
Scheme 1.16: Asymmetric α-oxytosylation of ketones by Zhang et al.

Moran and Rodriguez[51] in 2012 tested their newly developed chiral iodoarene catalysts **1.90a-b** along with *m*-CPBA as co-oxidant in the α-oxytosylation of propiophenone **1.80**. The product **1.82** were achieved in good yields and low *ee* i.e. 18%. The newly synthesised chiral iodoarene catalysts were then tried in lactonisation of 5-oxo-5-phenylpentanoic acid **1.84** in the presence of *m*-CPBA. The desired products **1.86** were obtained in good yields and improved enantioselectivities i.e. 51%. (Scheme 1.17)



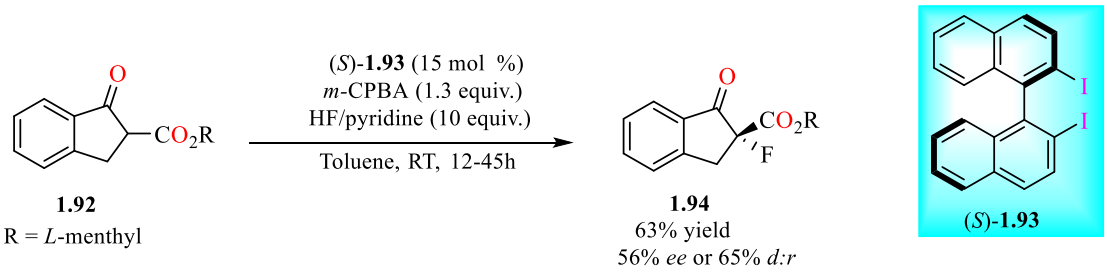
Scheme 1.17: Hypervalent iodine mediated α-oxytosylation of propiophenone and lactonisation of 5-oxo-5-phenylpentanoic acid.

Legault *et al.*[52] developed new iodooxazoline-based chiral iodoarenes **1.91a-d** which were tested in the α-oxytosylation of propiophenone **1.80**. An improvement in the enantioselectivities were noted in the obtained products **1.82**.



Scheme 1.18: Hypervalent iodine mediated α-oxytosylation of ketones

Kita *et al.*[53] reported the first example of enantioselective fluorination of β-ketoesters **1.92** mediated by catalytic system consisting of chiral iodoarene **1.93** as catalyst, HF/Pyridine as fluorinating source and *m*-CPBA as co-oxidant to give α-fluorinated β-ketoesters **1.94** in good yields and enantioselectivities. (Scheme 1.19)

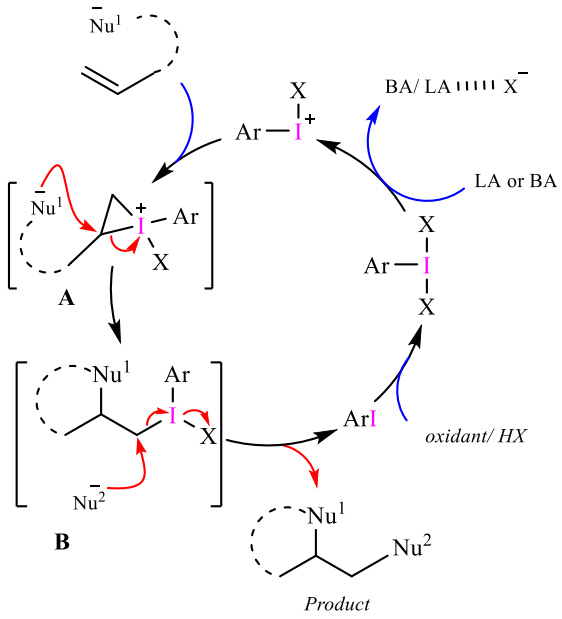


Scheme 1.19: Enantioselective fluorination of β-ketoesters catalysed by hypervalent I(III) reagents.

1.6.3. Functionalisation of alkenes

Asymmetric oxidation of alkenes to achieve multifunctional chiral compounds is considered an important transformation in organic chemistry.[54] In this regard, various attempts have been made to develop new reaction pathways using chiral hypervalent iodine reagents.[55-56] The alkenes can be activated by the strong electrophilic nature of hypervalent iodine(III) reagents thus enabling a vast range of functionalisation reactions. In the literature, diamination[57], dioxygenation[58], aminofluorination[59], *gem*-difluorination[60], 1,2-difluorination[61] and dicholorination[62] of alkenes has

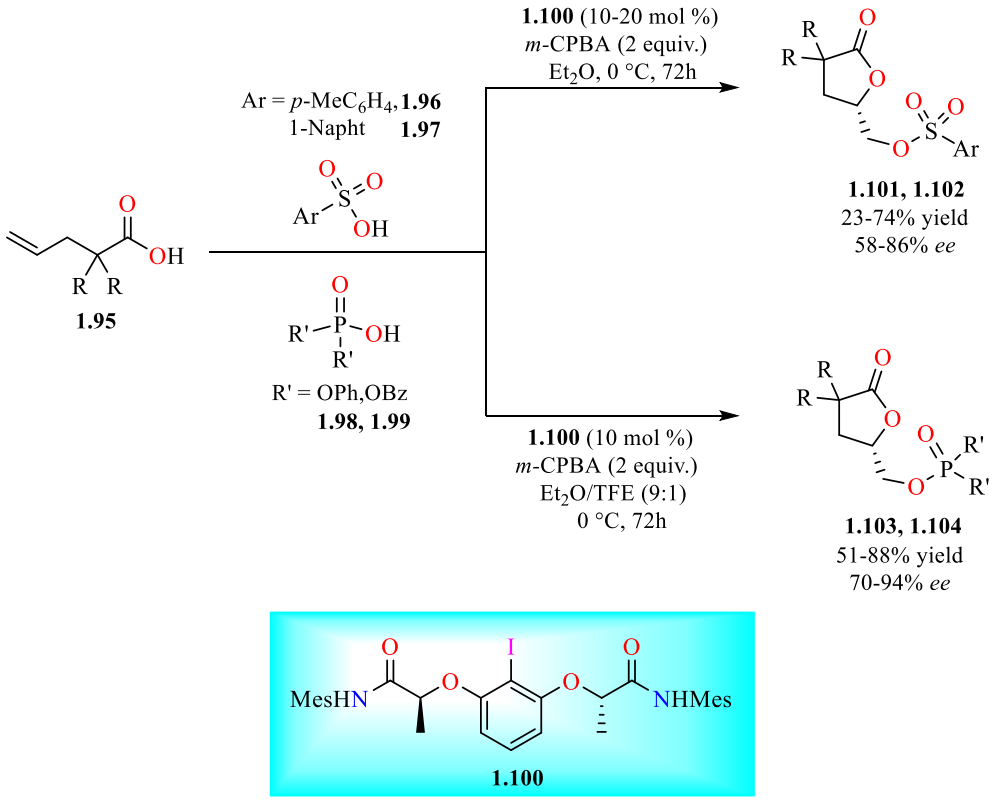
been reported. A general mechanism for alkene functionalisation and a few examples of alkene functionalisation are mentioned below. The process begins when the iodoarene(I) is converted to iodane(III) which upon interaction with Lewis acid or Brønsted acid allows the addition of iodine species to the alkene to generate presumed intermediate [A]. This intermediate undergoes subsequent S_N2 nucleophilic attack to afford the intermediate [B] which undergoes another nucleophilic attack to afford the desired product.



Scheme 1.20: Pathway of hypervalent iodine(III) mediated alkene functionalisation reaction.

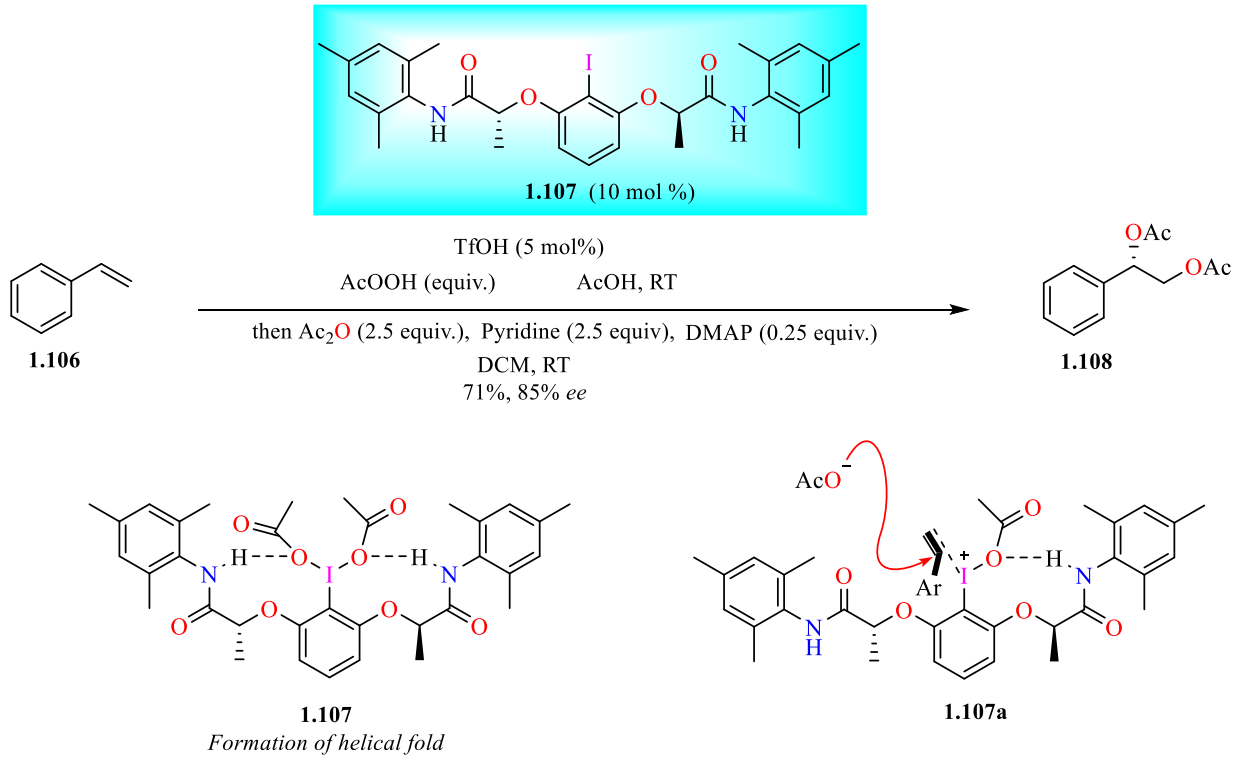
1.6.3.1. Dioxygenation of alkenes

Masson and colleagues[63] reported the very first example of enantioselective phosphoryl- and sulfonyl- oxylactonisation of 4-pentenoic acid derivatives **1.95** catalysed by chiral iodine(III) reagents **1.100**. Targeted compounds i.e. phosphoryloxy- **1.103, 1.104** and sulfonyloxy-γ-butyrolactones **1.101, 1.102** were obtained with good to excellent enantioselectivities in moderate yields. They used stoichiometric or catalytic amounts of chiral iodoarene **1.100**.



Scheme 1.21: Enantioselective phosphoryl- and sulfonyl- oxylactonisation of 4-pentenoic acid derivatives.

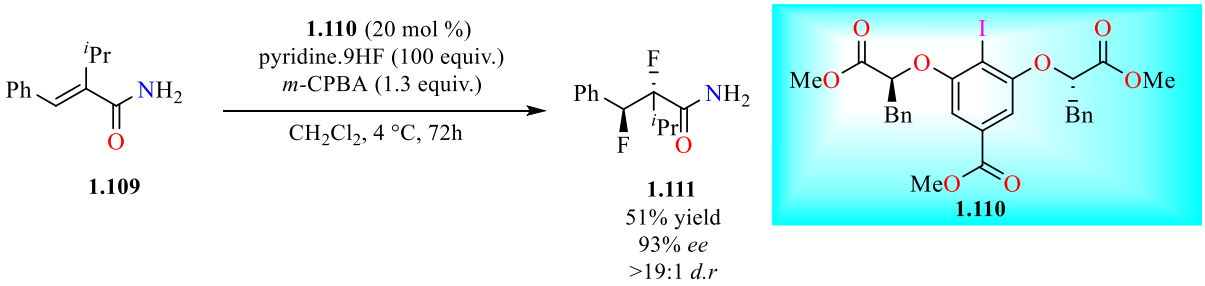
Muñiz and co-workers[64] reported an asymmetric dioxygenation reaction of styrenes. They used chiral catalyst **1.107** bearing an amide group. The NH groups of the chiral arm engage in the hydrogen bonding with the acetoxy groups present at the central iodine atom thus resulting in the formation of two nine membered rings. As a consequence of hydrogen bonding, a supramolecular helical chirality is created around the central iodine iodine atom as shown in scheme 1.22.



Scheme 1.22: Enantioselective intermolecular asymmetric diacetoxylation of styrenes.

1.6.3.2. Difluorination of alkenes

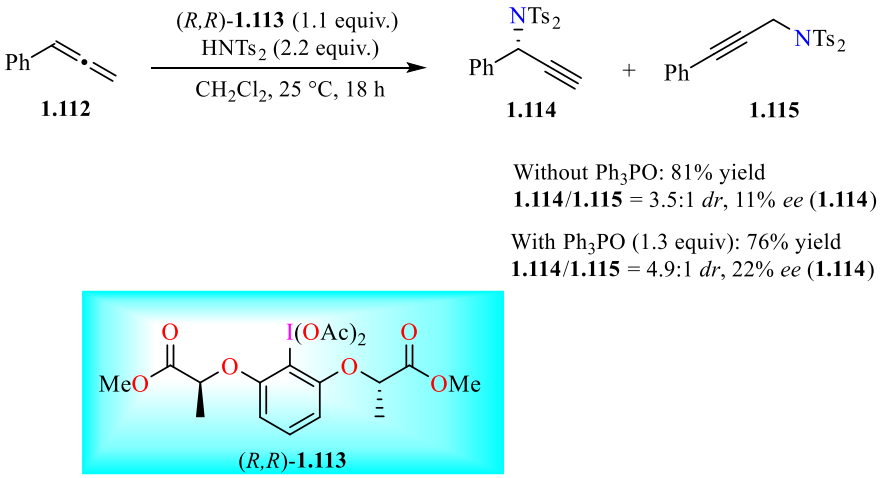
Recently, Jacobsen and co-workers[65] developed a protocol for the enantioselective catalytic difluorination of alkenes **1.109** catalysed by newly prepared chiral iodoarene **1.110** in the presence of a fluoride nucleophile and *m*-CPBA as stoichiometric oxidant. In particular, they prepared *α,β*-fluorinated cinnamide **1.111** in good yields with high enantioselectivities. (Scheme 1.23)



Scheme 1.23: Enantioselective catalytic difluorination of alkenes mediated by chiral iodoarenes.

1.6.3.3. Oxidative amination of alkenes

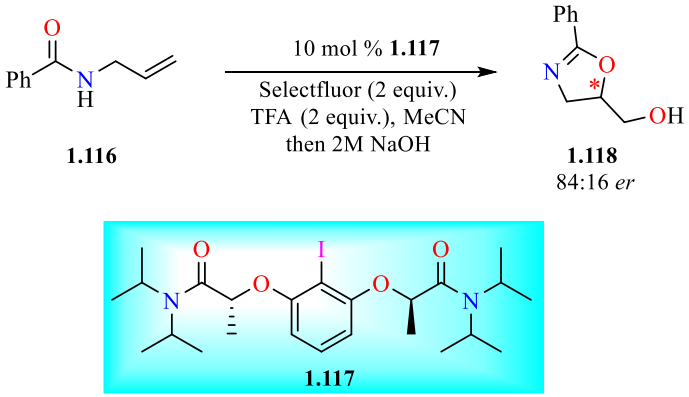
Muñiz and co-workers[66] reported the oxidative amination of 1-phenyl allene **1.112** catalysed by hypervalent iodine(III) reagents. The obtained propargylic amines **1.114, 1.115** were formed with poor enantioselectivity and moderate regioselectivity. Upon coupling iodoarene catalysts with triphenylphosphine oxide, the internal regioisomer was obtained with improvement in regioselectivity and enantioselectivity. (Scheme 1.24)



Scheme 1.24: Oxidative amination of 1-phenyl allene catalysed by hypervalent iodine(III) reagents

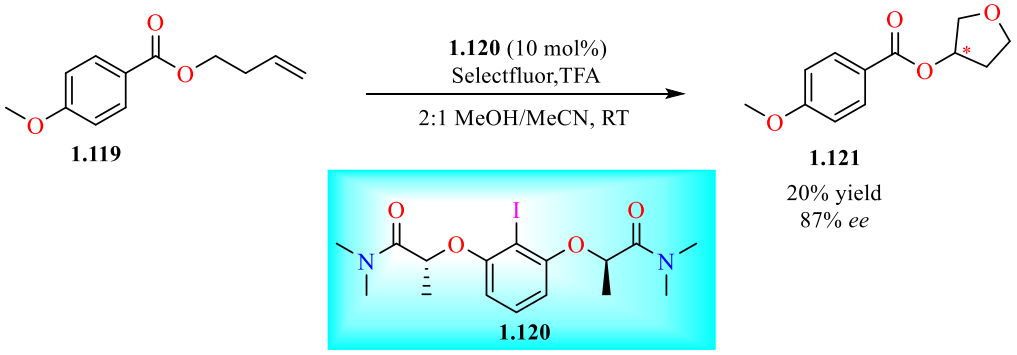
1.6.3.4. Other functionalisations of alkenes

In 2015, Moran and workers[67] reported the cyclisation of *N*-alkenylamides **1.116** catalysed by iodoarenes under oxidative conditions. Five, six and seven-membered rings with a range of substitutions were synthesised through this protocol. Preliminary data from the use of chiral iodoarenes as pre-catalysts show that enantiocontrol is feasible. A cyclisation forming five membered enantioenriched isoxazoline ring is mentioned below.



Scheme 1.25: Oxidative cyclization of *N*-alkenylamides **1.116** catalysed by chiral iodoarene **1.117**.

Previous work within our group[68] involved the synthesis of a variety of amide catalysts which were then employed in the cyclisations of ester analogues **1.119** to give the corresponding products **1.121** in moderate to good yields with excellent enantioselectivity. Catalyst **1.120** provided the highest enantioselectivity, i.e. 87% but in low yield.

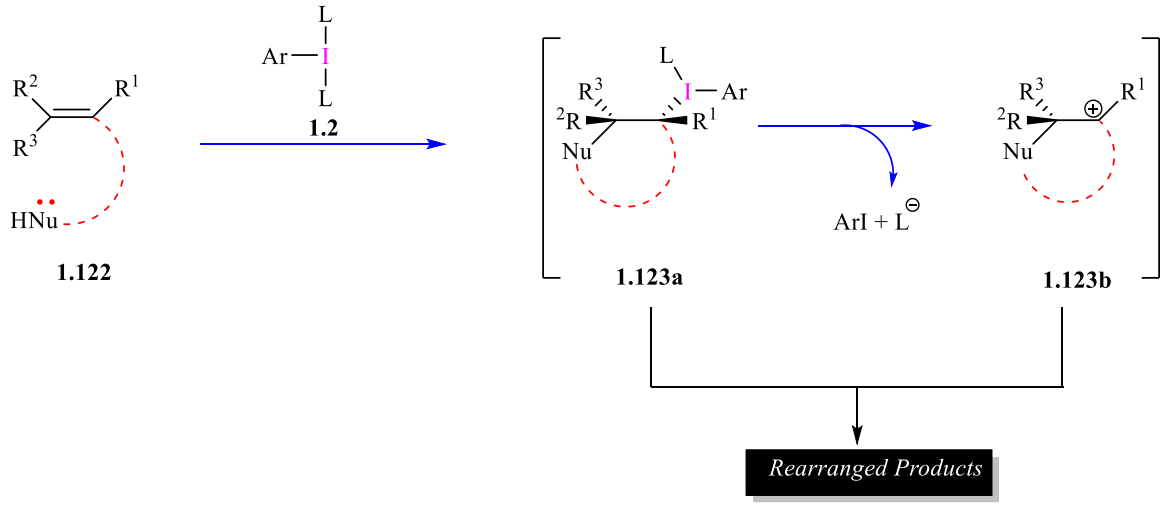


Scheme 1.26: Cyclisations of ester analogues **1.119** with amide catalysts **1.120** previously developed in our group.

1.6.4. Rearrangements

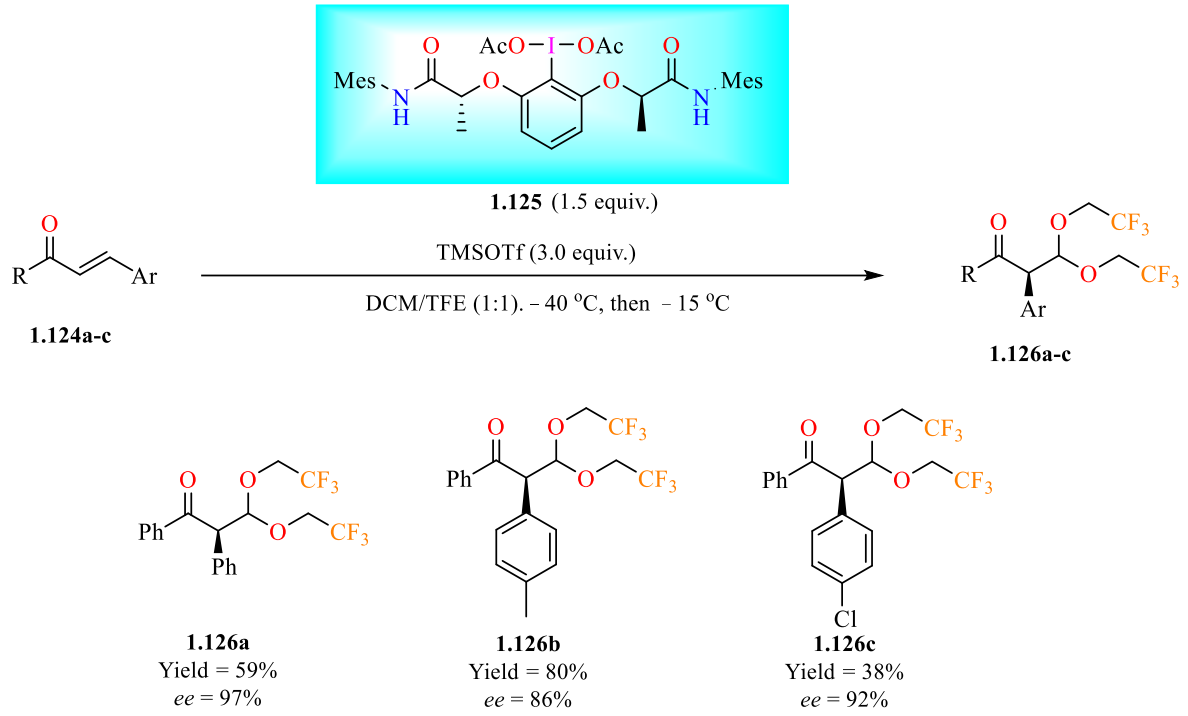
Hypervalent iodine reagents find their use in many rearrangement reactions. Numerous transformations have been reported in the literature such as ring expansions[69], ring contractions[70] and aryl migrations.[71] The general mechanism for hypervalent iodine(III) mediated rearrangements is illustrated below.

Mechanistically, iodane(III) species are added to the alkene resulting in the formation of intermediate **1.123a**. Loss of iodoarene and ligand gives rise to the carbocation intermediate **1.123b** which undergoes rearrangement to yield desired product.



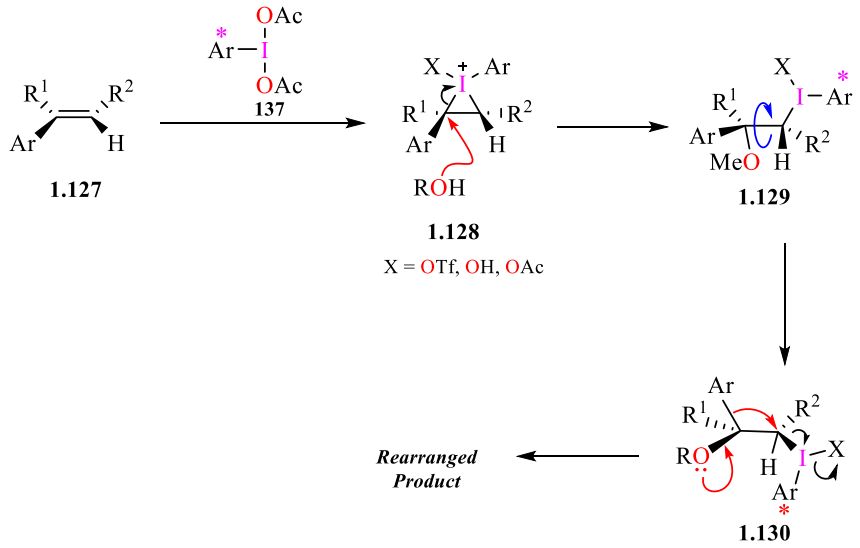
Scheme 1.27: General mechanism of hypervalent iodine mediated rearrangements.

The first oxidative rearrangement of α-β unsaturated ketones catalysed by hypervalent iodine(III) species was reported by Wirth and workers[72] in 2013. They achieved high enantioenriched α-arylated ketones via enantioselective rearrangement of ketones mediated by chiral iodoarenes. The activation of the hypervalent iodine reagent was achieved by the addition of the Lewis acid TMSOTf in order to achieve good conversion (instead of a Brønsted acid utilised first in these kind of reactions).



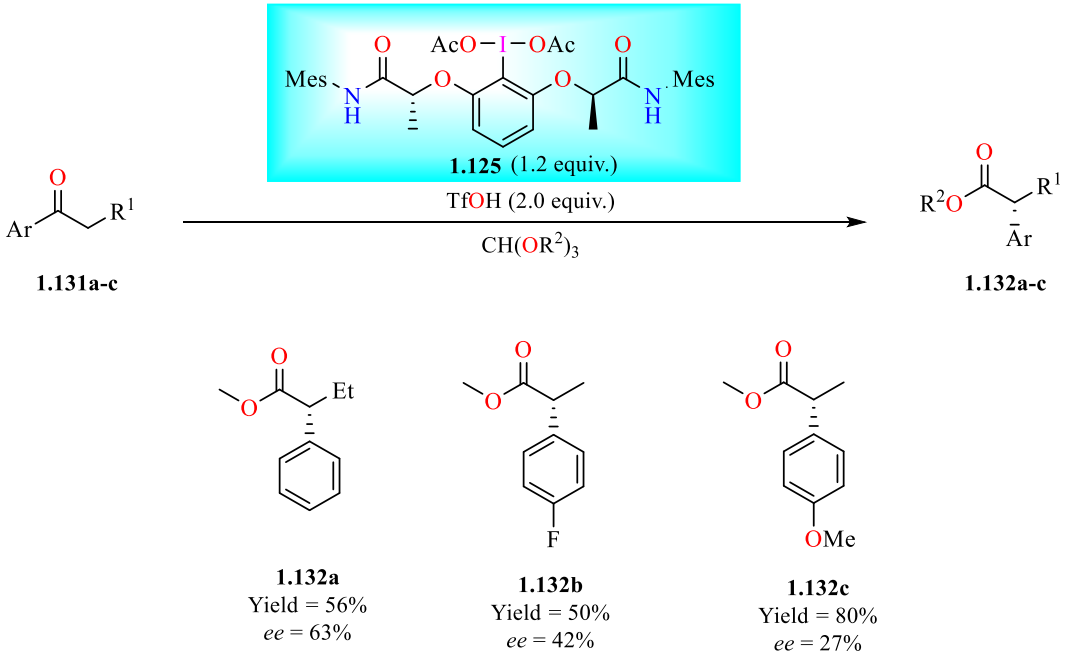
Scheme 1.28: Oxidative asymmetric rearrangement by Wirth and workers.

Intermediate **1.128** is formed when iodane(III) species are added to the alkene. This intermediate is then opened up by a molecule of alcohol (ROH) to give **1.129** which after rotation around a single bond undergoes 1,2-aryl migration with inversion of configuration to yield the final product.



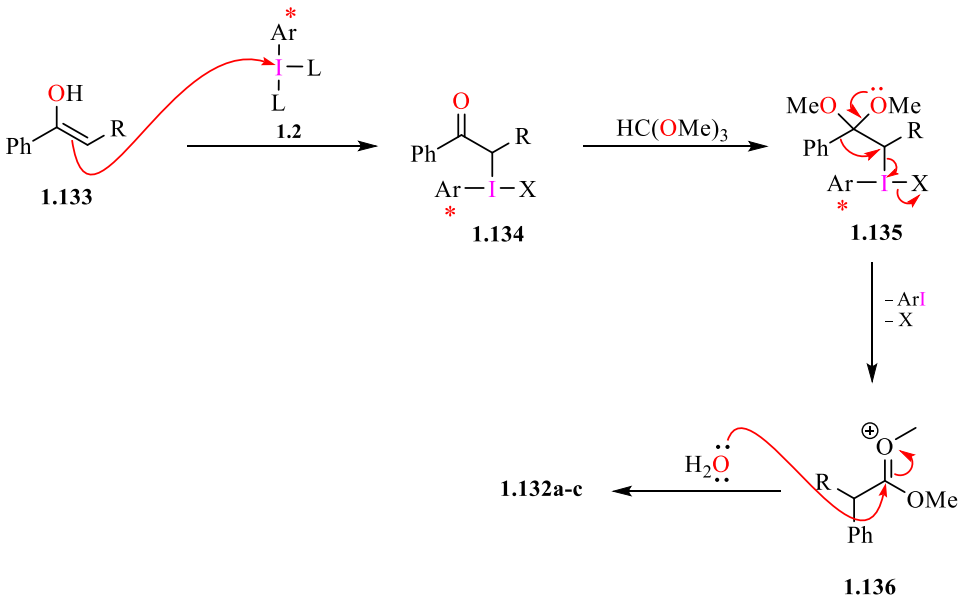
Scheme 1.29: Plausible rearrangement mechanism proposed by Wirth and workers.

Aryl ketone rearrangements catalysed by chiral iodine(III) reagents were reported by Wirth and co-workers in 2016.[73] They observed that the use of orthoesters(s) promoted the transformation and the ketones were converted into aryl ester first and then subsequently afforded desired products in reasonably moderate yields and selectivities.



Scheme 1.30: Chiral iodine(III) reagent mediated aryl ketone rearrangement by Wirth et al.

Enolate **1.133** attacks iodane(III) species and forms **1.134**. Addition of trimethyl orthoformate takes place to **1.134** and forms intermediate **1.135**. Intermediate **1.135** undergoes 1,2-phenyl migration resulting in the loss of iodoarene and the formation of **1.136** which ultimately yields the desired products **1.132a-c**.



Scheme 1.31: Mechanism of aryl ketone rearrangement catalysed by chiral iodine(III) reagents.

1.6.5. Oxidative dearomatisation reactions

Phenol dearomatisation is a powerful strategy in organic synthesis. Phenol and indoles are typical (hetero)aromatic test substances which have often been subjected to dearomatisation reactions. Numerous methodologies such as oxygenation, dehydrogenation, halogenation, arylation, allylation, alkynylation, alkylation and cycloaddition reactions have been developed for this purpose.[74-81] The advantage associated with dearomatising the (hetero)aromatic substrates is that some of their constituent planar carbon atoms can be transformed into stereogenic centres. Asymmetric protocols such as using chiral reagents, substrates with chiral appendages and catalysts can be used to control the three dimensional configuration of these stereogenic centres.[75-81]

Unarguably, phenols are the most extensively used aromatic species for the dearomatisation due to their mildly acidic electron rich aromatic nucleophilic nature. Depending upon the substitution patterns and functionalities, phenols can be dearomatised into different reactive species such as quinones, quinone methides, cyclohexadienones (possibly chiral) and key natural products.

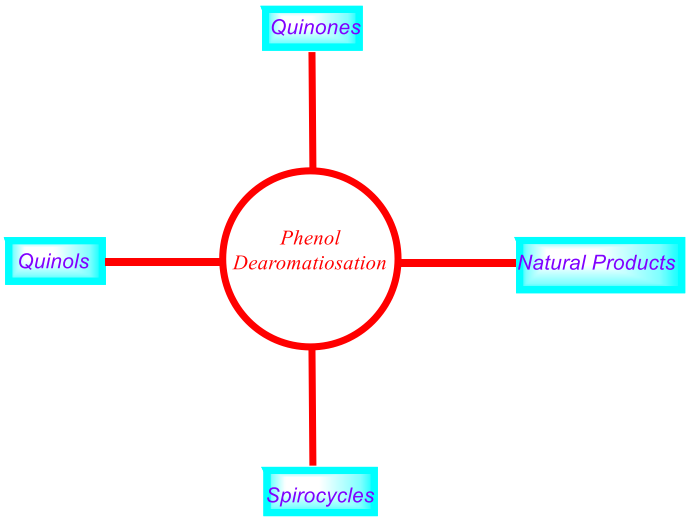
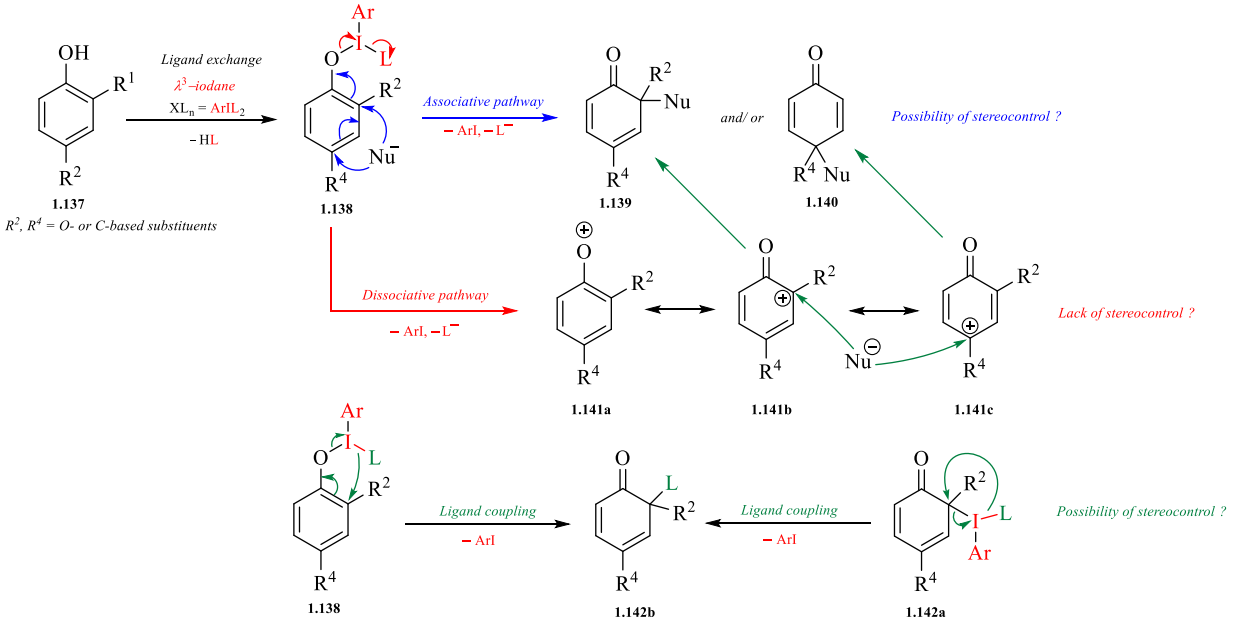


Figure 1.14: Synthesis of key intermediates via phenol dearomatisation reactions.

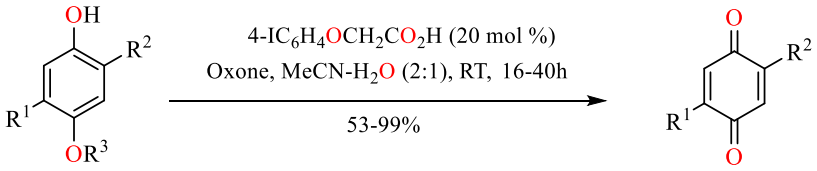
Dearomatisation reactions are greatly affected by the nature of the iodoarene used, reactivity of its ligands, nature of the starting phenol (substrate), nucleophilicity of the intervening species leading to dearomatisation and also on the reaction conditions like temperature and type of the solvent used. In the associative pathway, ArI and leaving group leaves after the nucleophilic attack happens hence providing the opportunity of stereocontrol. However, in the dissociative pathway phenoxinium ion **1.141a** is formed after the departure of ArI and leaving group which subsequently undergoes attack by the nucleophile at *ortho*- or *para*- position. The main disadvantage of this process is the lack of stereocontrol due to the early departure of ArI group. Moreover, the dearomatisation via ligand coupling can occur in two possible ways and of course with the advantage of stereocontrol. In the first mode of dearomatisation, intermediate **1.138** undergoes rearrangement and ligand is added to the *ortho*- position with the elimination of ArI group at the last stage thus providing the opportunity of stereocontrol. In the second case, the addition of the ArI group happens at the *ortho*- position of aromatic ring then the resulting intermediate **1.142a** undergoes rearrangement causing the addition of the ligand at the *ortho*- position and subsequent departure of ArI group after the dearomatisation has happened. A general explanation of possible ionic and ligand coupling pathways is outlined in scheme 1.32.



Scheme 1.32: Possible pathways of phenol dearomatisation catalysed by chiral iodine(III) reagents.

1.6.5.1 Oxidation of phenolic substrates to quinones and quinols

Yakura and Konishi, in 2007, reported the synthesis of *p*-quinones **1.144** from *p*-alkoxyphenols **1.143** in the presence of catalytic amounts of 4-iodophenoxyacetic acid and Oxone as terminal oxidant (Scheme 1.33).[82]

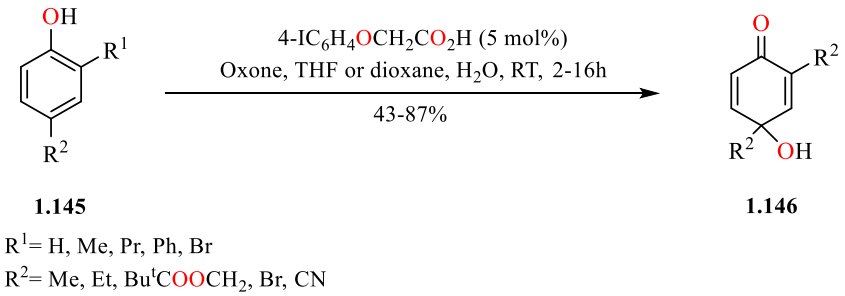


1.143 **1.144**

R^1= H or $MeCH_2CH_2CMe_2$
R^2= H, *t*-Bu, $MeCH_2CH_2CMe_2$, *t*-Bu Ph_2SiOCH_2, N_3CH_2, phthalimide
R^3= Me or Et

Scheme 1.33: Catalytic oxidation of *p*-alkoxyphenols to *p*-quinones

The reaction of *p*-substituted phenols **1.145** with catalytic amount of 4-iodophenoxyacetic acid and terminal oxidant Oxone afforded *p*-quinols **1.146** in excellent yields. (Scheme 1.34).[83, 84]



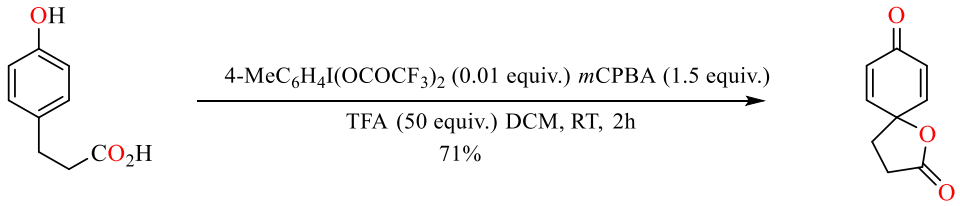
1.145 **1.146**

R^1= H, Me, Pr, Ph, Br
R^2= Me, Et, Bu^tCOOCH_2, Br, CN

Scheme 1.34: Catalytic oxidation of *p*-substituted phenols having an alkyl or aryl group at para position.

1.6.5.2. Oxidative spirocyclisation of aromatic substrates

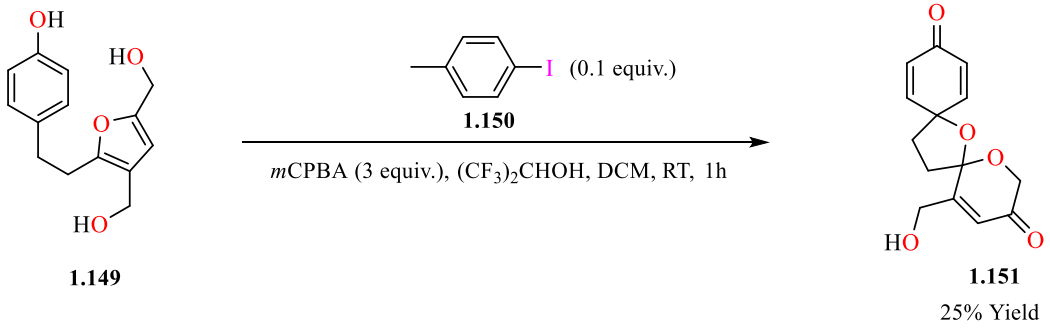
Kita and co-workers reported the first example of oxidative spirocyclisation reaction based upon the *in situ* generation of iodine(III) species and *m*-CPBA as terminal oxidant. The oxidation of phenolic substrates **1.147** with *m*-CPBA in DCM in the presence of 1 mol% *p*-[bis(trifluoroacetoxy)iodo]toluene and TFA at room temperature gave desired spirolactones **1.148** in good yields.[85]



1.147 **1.148**

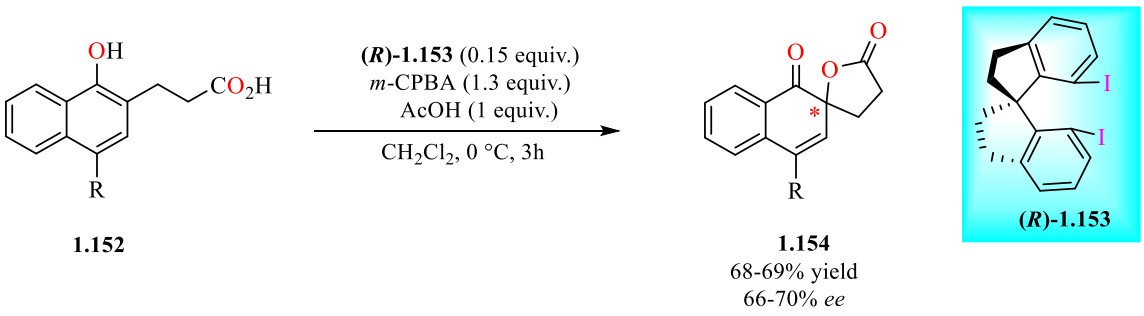
Scheme 1.35: Catalytic oxidative spirocyclisation reaction of substituted phenol.

In 2010, Kita *et al*. reported the catalytic synthesis of biologically active polyspirocyclohexa-2,5-dienones. The desired product **1.151** was isolated in low yields perhaps due to the oxidation of the starting material **1.149** by *m*-CPBA to afford unwanted products.[86]



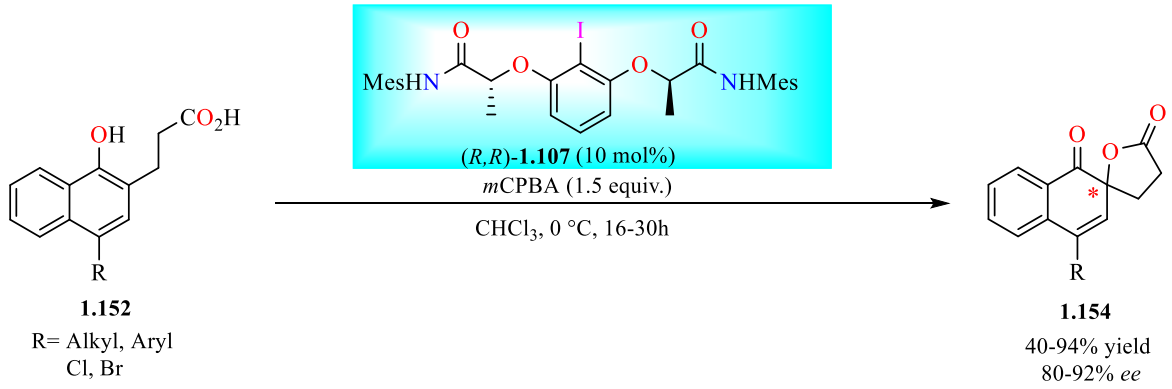
Scheme 1.36: Synthesis of bioactive polyspirocyclohexa-2,5-dienones via catalytic spirocyclisation.

Ishihara and co-workers reported the enantioselective catalytic spirocyclisation of phenolic substrates by employing achiral, non-racemic organic iodides as catalysts. Specifically, naphtholic substrates **1.152** underwent oxidative dearomatisation in the presence of chiral iodoarene **1.153** possessing a rigid spirobiindane backbone to give optically active products **1.154** with high enantioselectivities. (Scheme 1.37)[87-90]



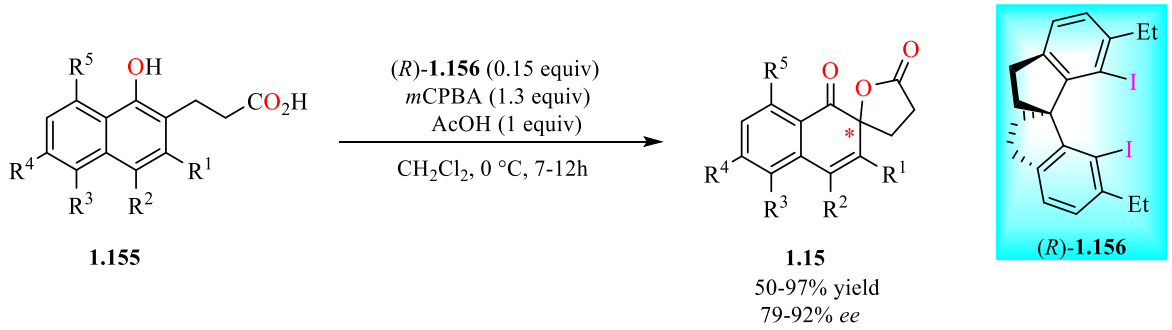
Scheme 1.37: Enantioselective catalytic oxidative spirocyclisation reactions using chiral iodoarenes as catalysts.

The same group reported the synthesis of conformationally flexible C_2-symmetric iodoarene catalysts and employed them in the aforementioned cyclisation of **1.152** (Scheme 1.38). Commonly known as *1st generation Ishihara's precatalysts*, this class of chiral iodoarenes has proved to be the best in terms of applicability and enantioselectivity in numerous oxidation reactions. This is due to the peculiar structural features which creates an ideal environment around the iodine atom for better reactivity and enhanced enantiocontrol.[90]



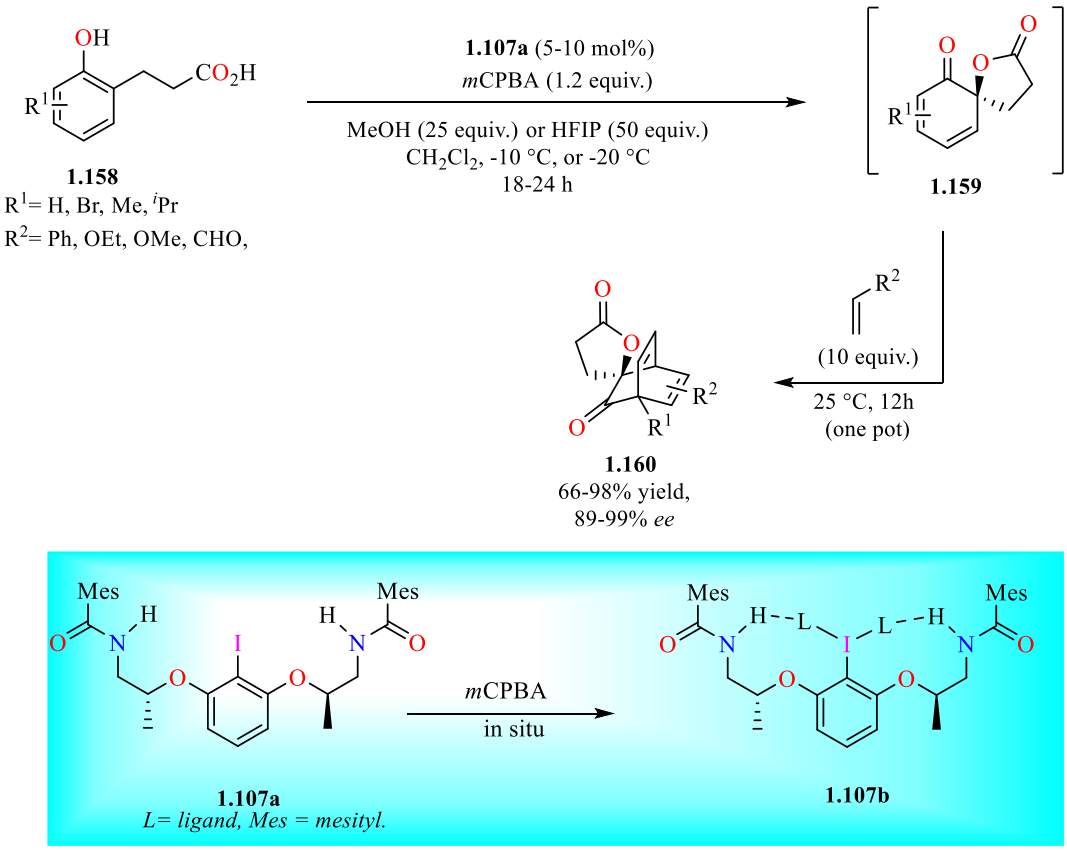
Scheme 1.38: Enantioselective catalytic oxidative spirocyclisation reactions using chiral iodoarenes as catalysts.

Kita and workers reported the synthesis of new chiral iodoarene catalyst (*R*)-**1.156** which was employed in the oxidative dearomatisation of various phenolic substances **1.155** in the presence of *m*CPBA as terminal oxidant and acetic acid to afford the desired spirolactones **1.157** in excellent yields and high enantioselectivities.[91] (Scheme 1.39)



Scheme 1.39: Enantioselective catalytic oxidative spirocyclisation reactions using chiral iodoarenes as catalysts.

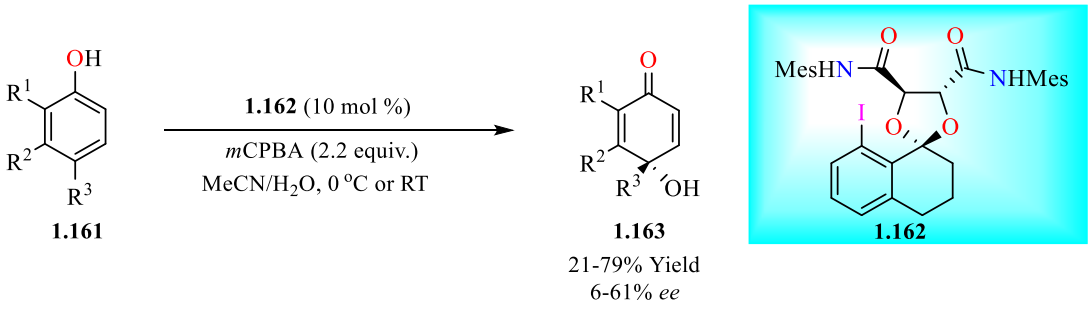
Ishihara and colleagues[92] developed C_2-symmetric chiral iodoarenes **1.107a** and tested it in the tandem enantioselective catalytic dearomatisation of phenolic substrates **1.158** and Diels-Alder reaction. The terminal oxidant *m*CPBA oxidised the chiral iodine(I) **1.107a** to chiral iodine(III) **1.107b** in situ which catalysed the reaction to produce cyclohexadienone spirolactones **1.159** enantioselectively and the corresponding Diels-Alder adducts **1.160**. (Scheme 1.40)



Scheme 1.40: Synthesis of enantiomerically pure cyclohexadienone spirolactones.

They observed that the use of alcoholic solvents such as HFIP or methanol as additives preferentially pushes the reaction towards an associative pathway to yield enantioenriched spirocycles. The use of alcoholic additives not only provided better yields of the products but also better selectivities. A dramatic increase in the enantioselectivities of the electron deficient naphthols was also noted and attributed to use of HFIP.

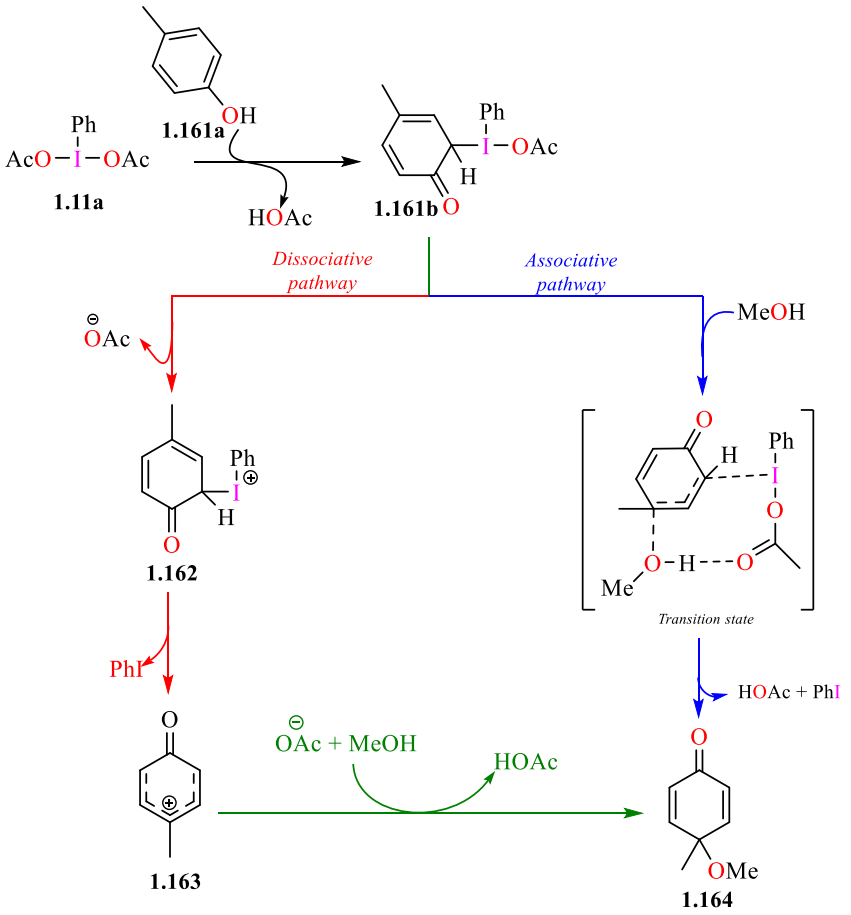
Harned and workers in 2013 subjected phenolic substrates **1.161** to asymmetric oxidation in the presence of newly developed chiral iodoarene catalyst **1.162** to afford different *p*-quinols **1.163** with moderate to good yields and enantioselectivities.[93] (Scheme 1.41)



Scheme 1.41: Synthesis of enantiomerically pure quinols

Ariafard *et al.*[94] investigated the mechanism of a PIDA mediated oxidative phenol dearomatisation in 2019 by employing DFT calculations. They found that the formation of the key intermediate i.e. dearomatised phenolate iodine(III) **1.161b** species is essential for the reaction to proceed. Experimental calculations suggested the formation of such kind of intermediate is mandatory for the reaction to proceed via associative pathway. It was also observed that in a polar solvent, the associative and dissociative pathways can be extremely competitive. They found that by resorting to the conventional phenol dearomatisation mechanism, dearomatisation should preferentially take place via dissociative pathway only, which was inconsistent with the experiment. A schematic explanation is given below. (scheme 1.42)

The phenol attacks the electrophilic iodine of the PIDA thus forms a key intermediate **1.161b** which could either undergo associative or dissociative pathway to give the desired product. The formation of the hydrogen bonds between the acetoxy group present at the central iodine with the molecule of methanol activates the para position for the nucleophilic attack while in the case of dissociative pathway acetoxy group present at the iodine leaves resulting in the formation of **1.162** and ultimately **1.163** which is then attacked by the acetoxy group to furnish the desired product **1.164**.



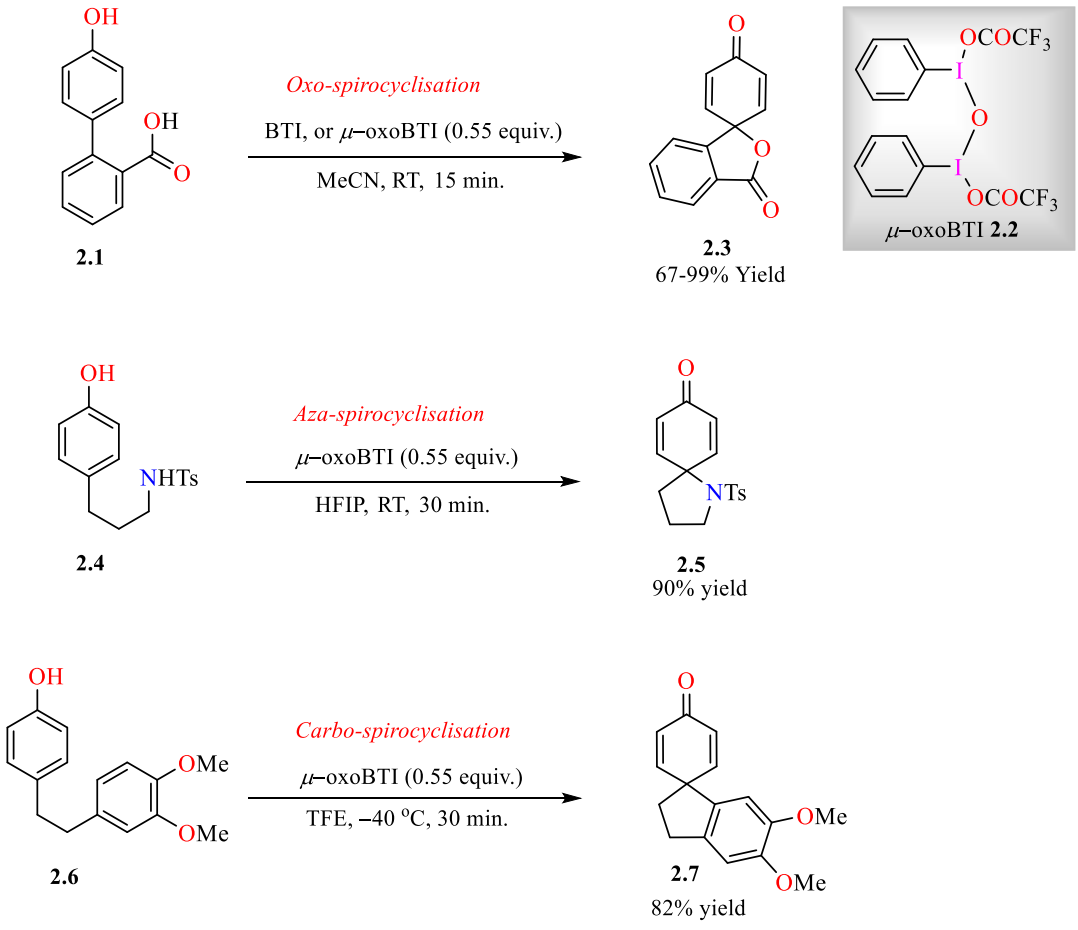
Scheme 1.42: Investigation of the oxidative phenol dearomatisation mechanism by Ariafard et al.

Chapter 2: Background

2.1. Genesis of the research project

2.1.1. Spirocyclisations

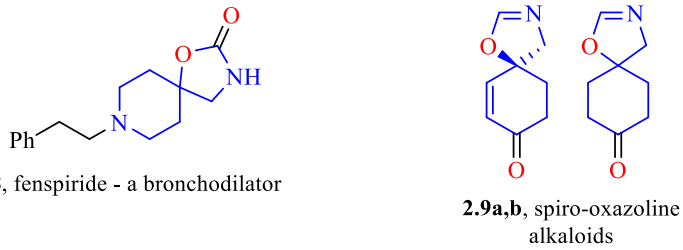
Spirocyclic cyclohexadienones and spirocyclic variants of quinols can be readily obtained by organoiodane catalysed oxidative dearomatisation of phenols tethered at their position 2 or 4 to form motifs which contain nucleophilic or pronucleophilic centres. Depending upon the nature of the nucleophile, spirocyclisations can generally be divided into three classes i.e. oxa-spirocyclisation, aza-spirocyclisation and carbo-spirocyclisation (scheme 2.1). From here onward only oxa- spirocyclisation will be discussed.



Scheme 2.1: Kita's μ-oxoBTI-mediated oxo-, aza-, and carbo-spirocyclisation.[95]

2.1.2. Oxo-spirocyclisations

In the field of synthetic and medicinal chemistry, the C-O bond is of utmost importance. Generally, the formation of a C-O bond involves the nucleophilic substitution or oxidative oxygenation. Spiroheterocycles containing C-O bonds are either important building blocks or extensively used in the pharmaceutical industry such as Fenspiride **2.8** which is an anti-inflammatory bronchodilator used in the treatment of respiratory disorders.[96] A variety of spiroheterocyclic derivatives such as **2.8** has been reported in the literature however only a few examples of natural products containing a spiro-oxazoline core such as **2.9a**, **2.9b** can be found in the literature.[97]

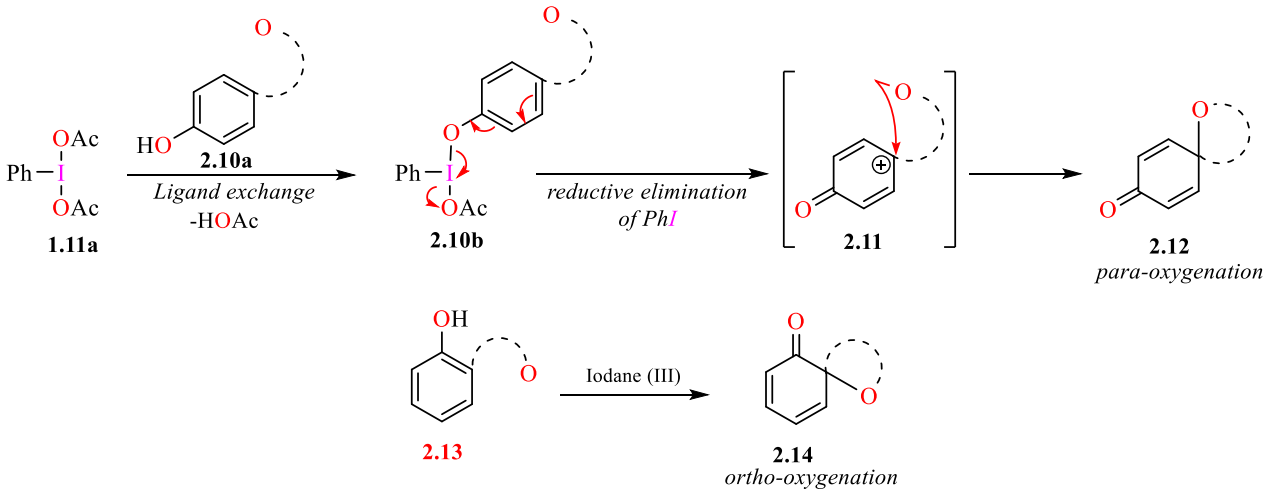


2.8, fenspiride - a bronchodilator

2.9a,b, spiro-oxazoline alkaloids

Figure 2.1: Examples of oxazaspirocycles.

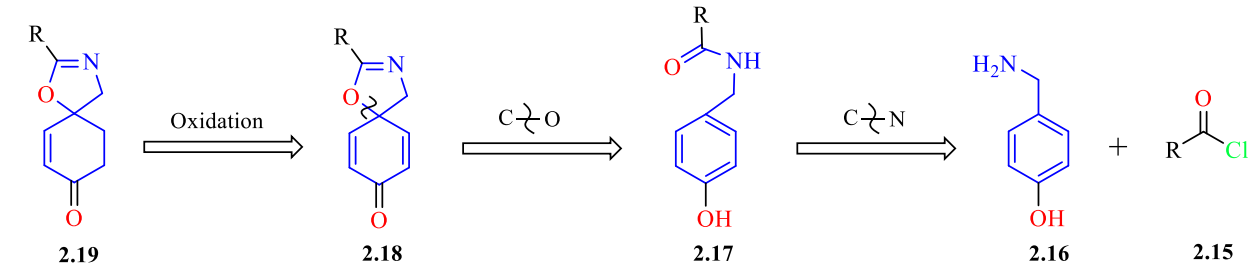
Our group has developed a novel protocol for the formation of C-O bond via iodane(III) mediated oxidative oxygenation of phenols and naphthols to obtain aesthetically pleasing oxazoline based spirocyclic cyclohexaenones and cyclohexadienones (may or may not be chiral). Depending upon whether nucleophile "oxygen" connects at phenolic/ naphtholic *ortho*- or *para*-, the reaction can be further categorised as *ortho*- or *para*- oxidative oxygenation as shown in scheme 2.2.



Scheme 2.2: Presumed mechanism of *para*- and *ortho*- oxygenation of phenols.

The process starts with the ligand exchange at hypervalent iodine atom forming intermediate **2.10b** which them undergoes reductive elimination to give cationic derivative of starting phenol **2.11**. Nucleophilic oxygen attacks the intermediate **2.11** to furnish the dienone **2.12** or **2.14**. The technique forces the generally nucleophilic phenol to express electrophilic character by the reversal of polarity i.e. umpolung.

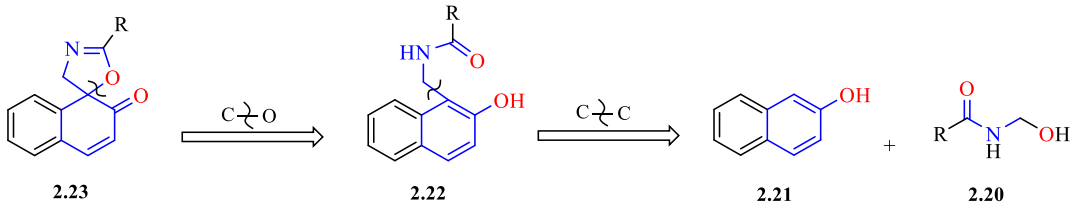
We envisaged that spirocyclic frameworks of the type **2.19a,b** could be prepared *via* oxidative oxygenation of phenols mediated by iodane(III) species via the aforementioned protocol. Accordingly, the first aim of this study was to synthesise oxazoline containing spirocycles similar to reported in literature **2.9a,b**. We envisaged that a pendant amide would cyclise on to the ring after activation by λ^3-iodane. A retrosynthetic analysis of this protocol is shown below.



Scheme 2.3: Retrosynthetic analysis of spiro-oxazoline based spirocycles.

We envisaged that the oxidation of the natural product **2.9a** should produce spiro-oxazoline **2.18**. The cleavage of C-O bond would give the starting amide **2.17** and upon breaking C-N bond would generate the synthons **2.16** and **2.15**.

The same strategy can be applied to access the substituted naphthol amides and to obtain the complex spiro-oxazoline based compounds which could be racemic or enantiopure. The spirocycle **2.23** would form the corresponding amide after C-O bond breakage. We envisaged that the amide **2.22** upon cleaving the C-C bond would give the desired synthons **2.21** and **2.20**.



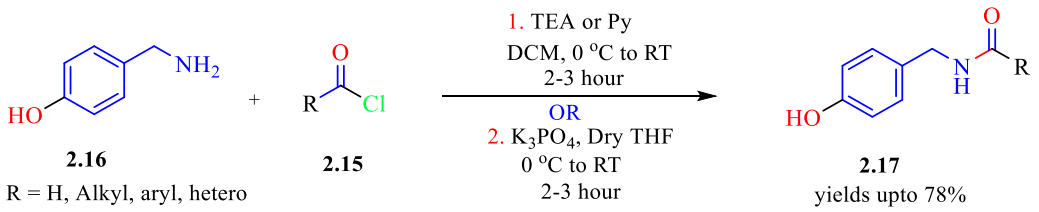
Scheme 2.4: Retrosynthetic analysis of naphthol based spiro-oxazoline.

The third aim was to develop chiral hypervalent iodine precatalysts bearing mono- or di-, carbamate, urea, lactate, and amide appendages which could be converted into the corresponding I(III) catalysts *in situ* for the dearomatisation reactions of naphthol amides to yield enantiopure spirocycles. It was hypothesised that the formation of the helical fold by the catalyst bearing chiral attachments due to a number of non-covalent interactions would generate a chiral environment due to the formation of helical fold which would help to induce enantioselectivity in the products.

Chapter 3: Results and discussions

3.1. Synthesis of phenolic amide substrates

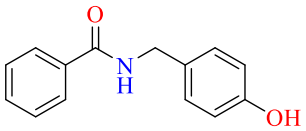
A range of substituted amides containing electron withdrawing, electron donating, heteroaromatic ring and neutral groups were synthesised using two different literature procedures[98, 99] by reacting 4-hydroxybenzylamine **2.16** with commercially available acyl chlorides to afford substituted amides in moderate to good yields. Amide **3.30** was synthesised using a reported literature procedure.[100]



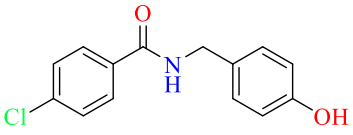
Scheme 3.1: Synthesis of substituted phenolic amides.

Amides **3.1** to **3.11** containing methoxy-, chloro-, bromo-, methyl- and nitro- groups were prepared in moderate to good yields according to the aforementioned procedures. Likewise, amides **3.12** to **3.16** containing fluoro- and trifluoromethyl groups were obtained in good to excellent yield. Next, we focused our attention on the preparation of amides containing heterocyclic functionalities like indole, pyrrole, furan, thiophene and pyridyl group **3.17** to **3.23**. Finally, amides **3.24** to **3.30** containing different alkyl substituents were prepared in good to excellent yield. The main aim to synthesise a wide range of substrates was to test the scope of the reaction.

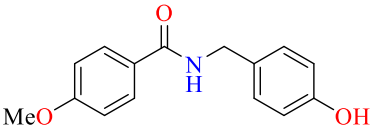
Amides containing substitution on aromatic ring



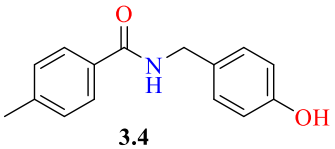
3.1
Yield = 55%



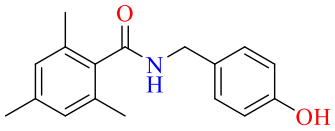
3.2
Yield = 49%



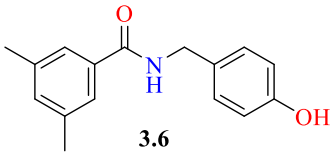
3.3
Yield = 61%



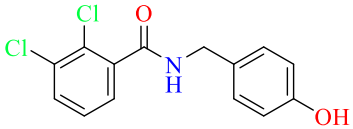
3.4
Yield = 59%



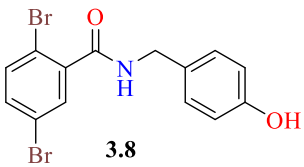
3.5
Yield = 46%



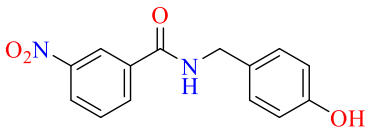
3.6
Yield =63%



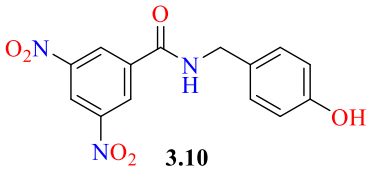
3.7
Yield = 68%



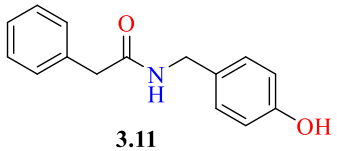
3.8
Yield = 34%



3.9
Yield = 51%

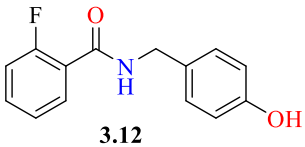


3.10
Yield = 45%

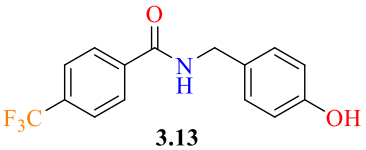


3.11
Yield = 61%

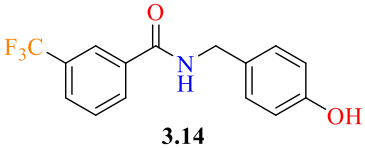
Amides containing Fluoro- and CF_3 on aromatic ring



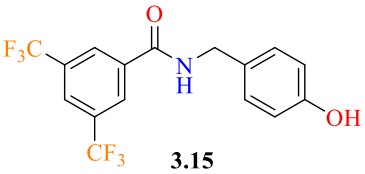
3.12
Yield = 54%



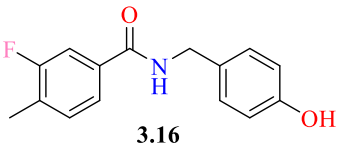
3.13
Yield = 78%



3.14
Yield = 63%



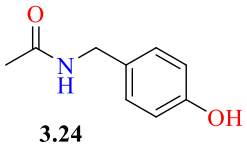
3.15
Yield = 68%



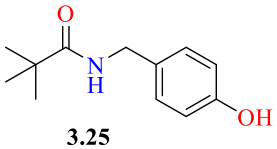
3.16
Yield = 53%

Amides **3.1-3.3** and **3.5** were prepared by method 1 while all the others were synthesised by method 2.

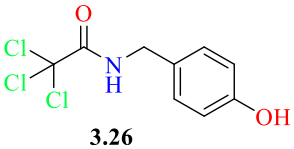
Amides containing aliphatic substitutions



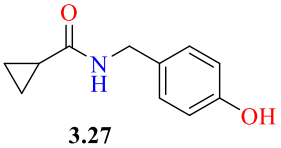
3.24
Yield =42%



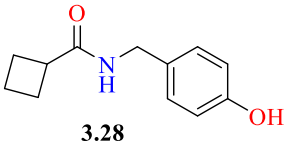
3.25
Yield = 48%



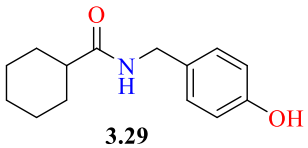
3.26
Yield = 44%



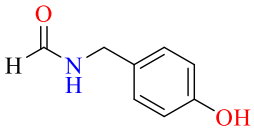
3.27
Yield = 30%



3.28
Yield = 31%

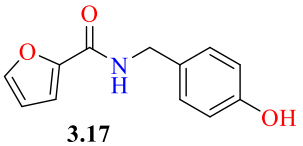


3.29
Yield = 53%

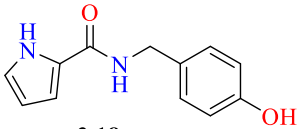


3.30
Yield = 75%

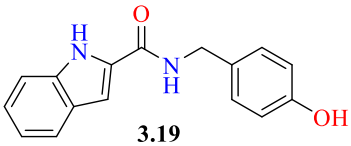
Amides bearing heterocyclic rings



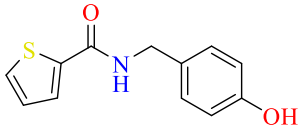
3.17
Yield = 65%



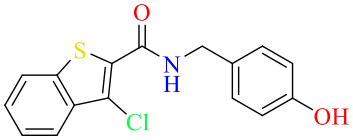
3.18
Yield = 39%



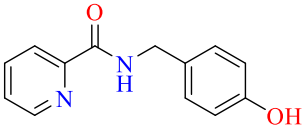
3.19
Yield = 43%



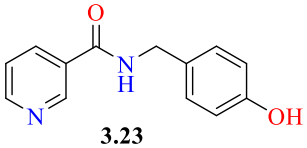
3.20
Yield = 51%



3.21
Yield = 78%



3.22
Yield = 61%

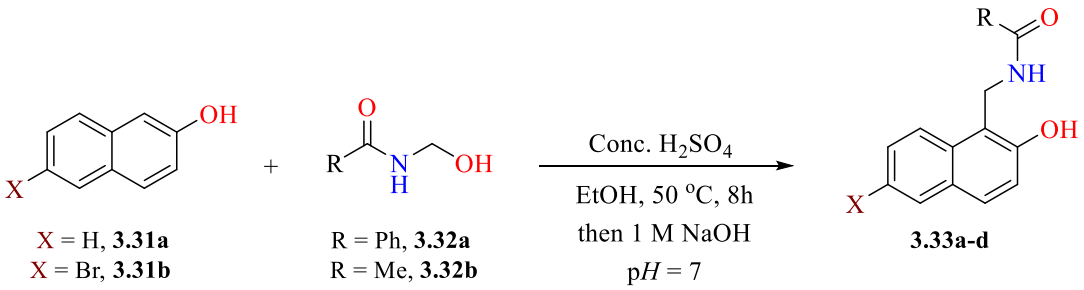


3.23
Yield = 57%

Figure 3.1: Synthesised phenolic amide.

3.2. Synthesis of naphtholic amide substrates

A range of naphtholic amides for dearomatisation reactions were synthesised in good to excellent yields using literature procedure.[101] In particular, naphthol or naphthol derivative **3.31a, b** were reacted with commercially available *N*-(hydroxymethyl)benzamide **3.32a** and *N*-(hydroxymethyl)acetamide **3.32b** in dry ethanol and concentrated sulfuric acid as catalyst to afford the corresponding naphthol amides **3.33a-d** in good to excellent yields.

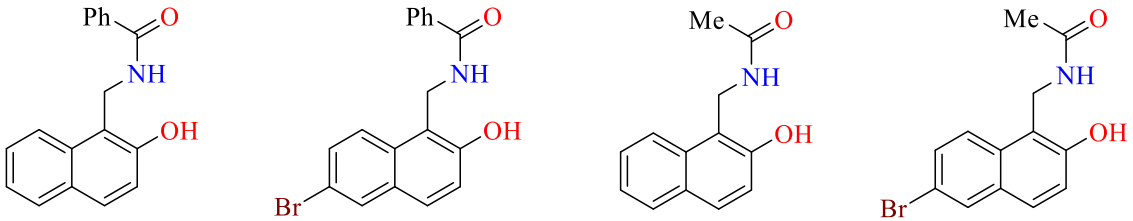


X = H, **3.31a**
X = Br, **3.31b**

R = Ph, **3.32a**
R = Me, **3.32b**

3.33a-d

Scheme 3.2: Synthesis of substituted naphthol amides.



71%
3.33a

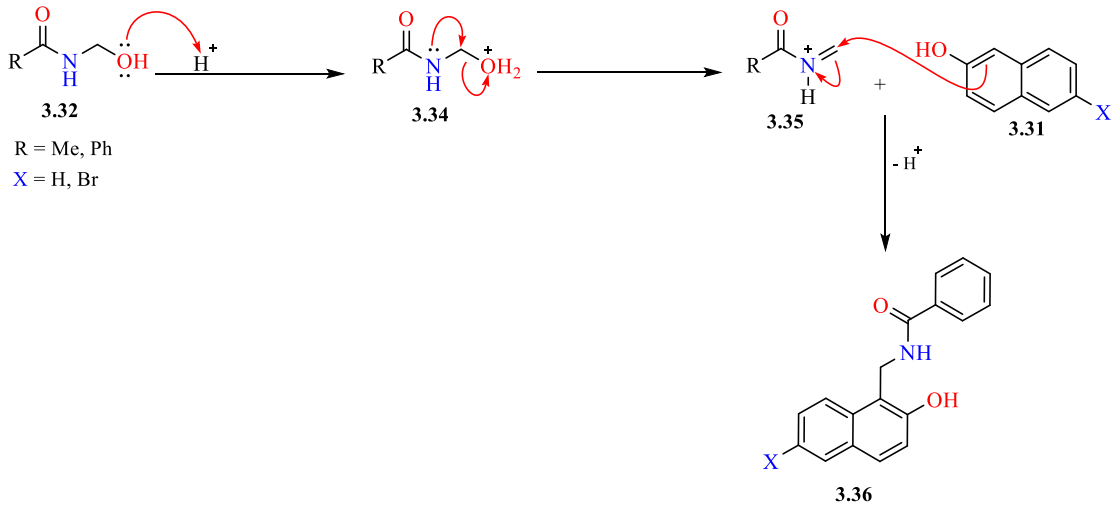
59%
3.33b

53%
3.33c

63%
3.33d

Figure 3.2: Synthesised naphtholic amides for dearomatisation reactions.

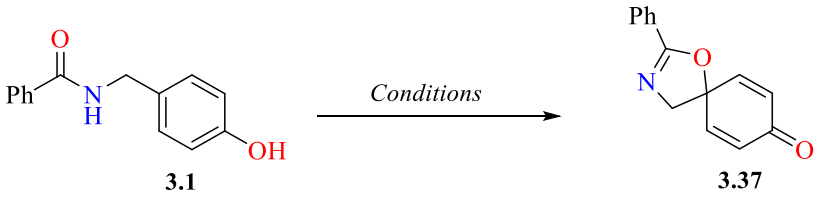
Mechanistically speaking, the unsaturated *N*-(hydroxymethyl)amide upon protonation by concentrated sulfuric acid loses a water molecule resultantly forming an iminium ion intermediate **A** which undergoes subsequent attack by the π-electrons of the naphthol and produces the desired naphthol amide. (scheme 3.3).



Scheme 3.3: Procedure for the synthesis of substituted naphthol amides.

3.3. Oxidative dearomatisation reactions of phenolic substrates

Newly synthesised phenolic amides were then tested in oxidative dearomatisation reactions. Initially, we started our investigation with the amide **3.1** and commercially available iodane(III) reagents in stoichiometric quantities. The reaction was carried out in fluorinated solvent i.e. TFE. The results of our investigation are summarised below.



Scheme 3.4: Oxidative dearomatisation reaction of amide **3.1**.

Entry	Reaction conditions	Yield
1	PIFA (1.5 equiv.), TFE, – 10 ^{o}C, 1hr	N.D.
2	PIFA (1.5 equiv.), TFE, 50 ^{o}C, 1hr	14 % Product Mostly SM
3	PIDA (1.5 equiv.), TFE, 50 ^{o}C, 1hr	31 % Product No SM
4	Koser's Reagent (1.5 equiv.), TFE, – 10 ^{o}C, 1hr	45 % Product No SM
5	Koser's Reagent (1.5 equiv.), TFE, 50 ^{o}C, 1hr	60 % Product No SM

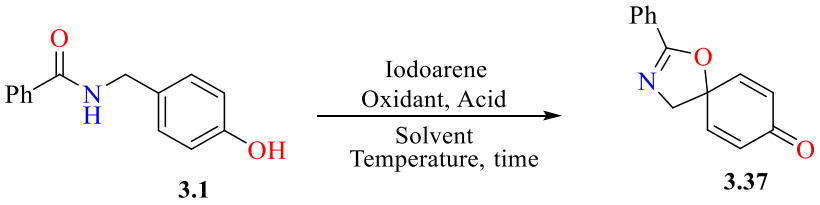
Yields were determined by adding 1,3,5-trimethoxybenzene as internal standard. N.D. = No development

Table 1: Optimisation of reaction conditions.

Amide **3.1** gave the desired spirocycle in 60% yield in the presence of freshly prepared Koser's reagent in TFE (table 1, entry 5) at 50 ^{o}C after one hour. However desired product was not obtained when the reaction was carried out using PIFA in TFE at – 10 ^{o}C (table 1, entry 1), only starting material was recovered. Repeating the same reaction at 50 ^{o}C gave only 14% product while the majority of the starting material was recovered (table 1, entry 2). Spirocycle **3.37** was obtained in 31% and 45% yields in the presence of PIDA and Koser's reagent when the reaction was carried out at 50 ^{o}C and – 10 ^{o}C respectively (table 1, entry 3 & 4).

Later on, we focused our attention to develop a catalytic version of this transformation. The aim of this was to generate hypervalent iodine(III) species *in situ* which would catalyse the reaction and give the desired spirocycle. The transformation was carried out at different temperatures, in the presence of different iodoarenes and solvents to obtain the corresponding spirocycle of amide **3.1**.

3.3.1. Screening of iodoarenes in MeCN



Scheme 3.5: Oxidative dearomatisation reaction of amide **3.1** in acetonitrile.

Entry	Oxidant	Iodoarene	Acid	Solvent	Temperature	Time	Yield (Crude)
1	*m*-CPBA 3 eq.	2-Iodoanisole 20 mol%	PTSA 3 eq.	MeCN	RT	16h	N.D.
2	*m*-CPBA 2.2 eq.	2-Iodoanisole 10 mol%	–	MeCN	RT	16h	N.D.
4	*m*-CPBA 2.2 eq.	Iodobenzene 10 mol%	–	MeCN	RT	16h	N.D.
5	*m*-CPBA 2.2 eq.	5-Iodo-m-xylene 10 mol%	–	MeCN	RT	16h	N.D.
6	*m*-CPBA 2.2 eq.	2-Iodotoluene 10 mol%	–	MeCN	RT	16h	N.D.
7	*m*-CPBA 2.2 eq.	3-Iodotoluene 10 mol%	–	MeCN	RT	16h	Traces
8	*m*-CPBA 2.2 eq.	4-Iodotoluene 10 mol%	–	MeCN	RT	16h	N.D.
9	*m*-CPBA 2.2 eq.	2-Iodotoluene 10 mol%	–	MeCN	60 °C	16h	Traces

Table 2: Optimisation of reaction conditions in MeCN mediated by a variety of iodoarenes. N.D. = No development

Earlier on we tried the conditions reported in the literature[90] to obtain the spirocycle **3.37** but no development was made (table 2, entry 1). So, we then attempted the same cyclisation without adding any acid as additive but again no reaction was evident. A range of commercially available

iodoarenes were tested as precatalysts in acetonitrile and terminal oxidant *m*CPBA (table 2, entries 1-9). Our experimentation revealed that only 3-iodotoluene and 2-iodotoluene yielded the targeted product in trace amounts. (Table 2, entries 7 & 9). However no significant development was noted in the case of other experiments.

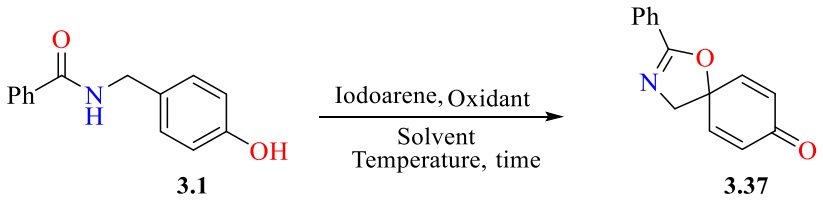
3.3.2. Screening of iodoarenes in DCM

Entry	Oxidant	Iodoarene	Solvent	Temperature	Time	Yield (Crude)
1	*m*-CPBA 2.2 eq.	5-iodo-m-xylene 10 mol%	DCM	RT	16h	<5%.
2	*m*-CPBA 2.2 eq.	4-iodotoluene 40 mol%	DCM	RT	16h	7%

Table 3: Optimisation of reaction conditions in dichloromethane.

We tested the amide **3.1** cyclisation reaction (scheme 3.5) in halogenated solvent i.e. dichloromethane. Iodoarene precatalysts like 5-iodo-m-xylene and 4-iodotoluene were employed in the presence of oxidant *m*CPBA in an attempt to obtain the desired spirocycle. Unfortunately, extremely low yields were observed in both cases (table 3, entry 1 & 2). It was also noted that the increase of catalyst loading (table 3, entry 2) did not help much.

3.3.3. Screening of iodoarenes and oxidants in fluorinated solvents



Scheme 3.6: Oxidative dearomatisation reaction of amide **3.1** in fluorinated solvents.

In the light of above experimental observations, we concluded that a polar protic solvent such as TFE or HFIP is needed for the aforementioned transformation to give the desired spirocycle in reasonable yields. We began testing different iodoarenes as precatalysts in the presence of oxidant *m*CPBA in order to obtain the desired product. Gratifyingly, we obtained the desired spirocycle in low to moderate yields using fluorinated solvent TFE (table 4, entries 1-3 & 5). We also observed

that elevated temperature proved detrimental for the reaction and gave the desired product in extremely low yield (table 4, entry 4). Increase in catalyst load significantly increased the rate of reaction and resulted in enhanced yield (table 4, entry 5).

Entry	Oxidant	Iodoarene	Solvent	Temperature	Time	Yield (Crude)
1	*m*-CPBA 2.2 eq.	2-Iodoanisole 10 mol%	TFE	RT	16h	13%
2	*m*-CPBA 2.2 eq.	Iodobenzene 10 mol%	TFE	RT	16h	25%
3	*m*-CPBA 2.2 eq.	2-Iodotoluene 40 mol%	TFE	RT	16h	28%
4	*m*-CPBA 2.2 eq.	5-Iodo-m-xylene 10 mol%	TFE	60 ^{o}C	16h	<10%
5	*m*-CPBA 2.2 eq.	4-Iodotoluene 40 mol%	TFE	RT	16h	53%
6	*m*-CPBA 2.2 eq.	5-Iodo-m-xylene 10 mol%	HFIP	RT	16h	22%
7	*m*-CPBA 2.2 eq.	4-Iodotoluene 10 mol%	HFIP	RT	16h	33%
8	*m*-CPBA 2.2 eq.	4-Iodotoluene 10 mol%	HFIP	RT	48h	45%
9	*m*-CPBA 2.2 eq.	4-Iodotoluene 40 mol%	HFIP	RT	16h	75%
10	Oxone 2.2 eq.	4-Iodotoluene 20 mol%	HFIP	RT	24h	19%
11	Selectfluor 2.2 eq.	4-Iodotoluene 20 mol%	HFIP	RT	24h	15%
12	Peracetic Acid 2.2 eq.	4-Iodotoluene 20 mol%	HFIP	RT	24h	33%

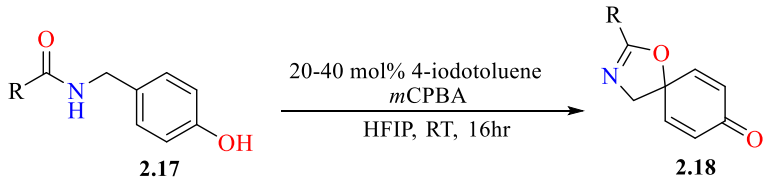
13	*m*-CPBA 2.2 eq.	4-Iodotoluene 20 mol%	HFIP	RT	16h	48%
14	*m*-CPBA 2.2 eq.	4-Iodotoluene 20 mol%	HFIP	RT	16h	67%
15	*m*-CPBA 2.2 eq.	PhI 20 mol%	HFIP	RT	16h	70%
16	*m*-CPBA 2.2 eq.	2-Iodoanisole 20 mol%	HFIP	RT	16h	32%

Table 4: Optimisation of reaction conditions in fluorinated solvents.

Spirocycle **3.37** was formed in low to moderate yields in the presence of trifluoroethanol (TFE) mediated by different iodoarene precatalysts. So we decided to test our reaction in hexafluoroisopropanol (HFIP). Due to its unique features, HFIP is usually described as a polar, low-nucleophilic solvent with high ability to stabilize aromatic radical cations. Pioneering work from Kita showed the powerful oxidising ability of hypervalent iodine compounds in combination with HFIP.[102]

Gratifyingly, smooth dearomatisation cyclisation occurred in the presence of 4-iodotoluene precatalyst and *m*CPBA as oxidant and gave the spirocycle in 75% yield (table 4 entry 9). Changing the oxidant from *m*CPBA to Oxone, Selectfluor or Peracetic acid led to lower yields (table 4 entries 10-12). Substituting iodoarene for other iodoarenes also proved detrimental to the reaction (table 3 entry 6 & 16). However using 20 mol % of iodobenzene surprisingly gave the product in elevated yield (table 4 entry 15). The use of 4-iodotoluene was preferred over iodobenzene as it exists in solid form making the measuring and handling easy. Based upon the optimised conditions, oxidative dearomatisation cyclisation of phenolic amide **3.1** was best achieved when 4-iodotoluene and *m*CPBA were used as precatalyst and oxidant respectively in HFIP which turned out to be the best solvent for this transformation.

Having optimised the reaction conditions, a range of substituted phenolic amides were subjected to oxidative dearomatisation spirocyclisation reactions mediated by 4-iodotoluene (20-40 mol %) and *m*CPBA as oxidant in HFIP. The obtained novel spirocycles are mentioned below.



Scheme 3.7: Phenol dearomatisation mediated by 4-iodotoluene.

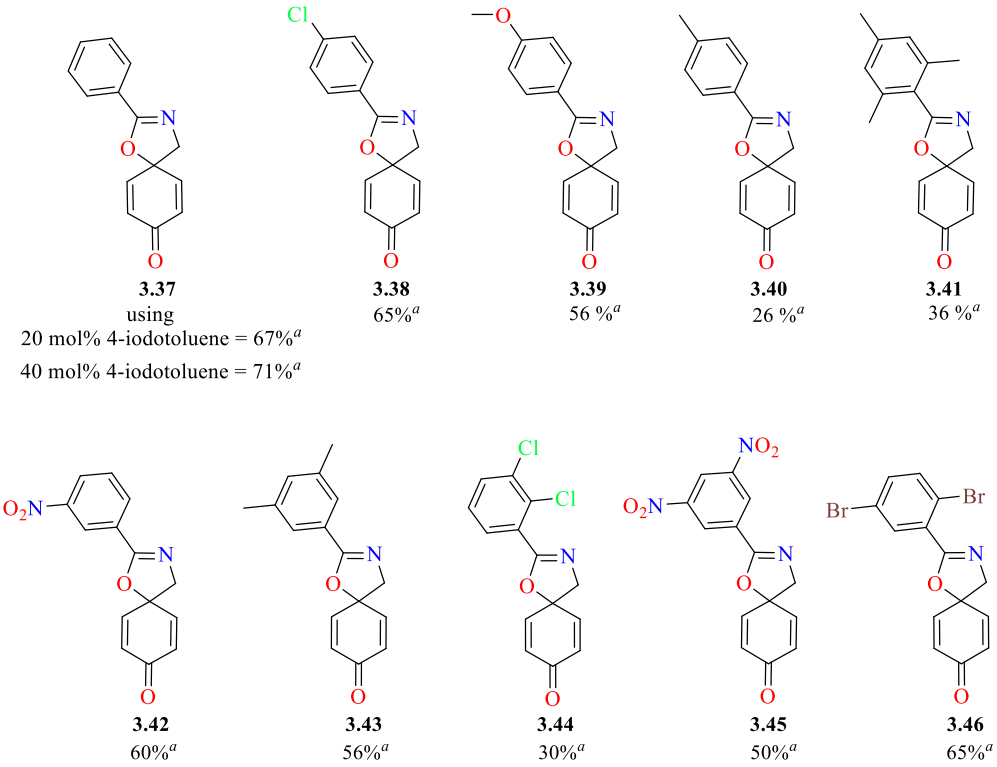


Figure 3.3: Synthesised substituted spirocycles containing neutral, electron donating and electron withdrawing groups.

A range of substituted spirocycles containing phenyl-, tolyl-, nitro-, dinitro-, bromo-, chloro-, and methoxy- groups were prepared from corresponding amides in moderate to good yields. It was observed that all the starting material was consumed after 16hr and no amount of starting material was noticed in the crude NMR of the reaction mixture. Compound **3.37** was obtained using 20 and 40 mol% 4-iodotoluene in 67% and 71% isolated yields. However, poor purification techniques led to the loss of the product and hence decrease in the yield of compounds **3.40**, **3.41** and **3.44**. Amides containing fluoro- and trifluoromethyl- groups underwent smooth oxidative dearomatisation reaction to produce corresponding spirocycles in excellent yield.

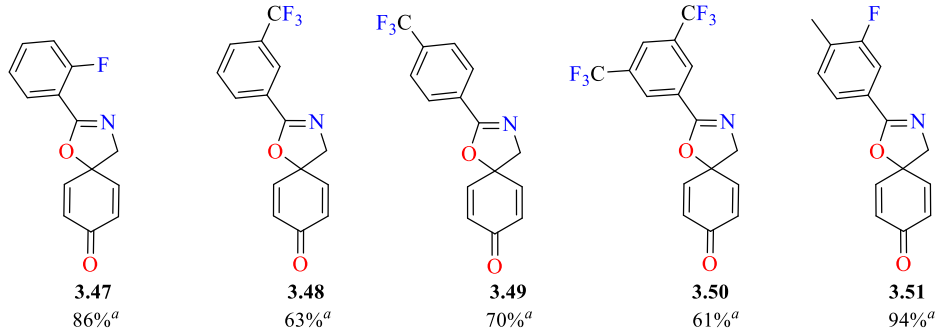


Figure 3.4: Synthesised oxazoline spirocycles containing fluoro- and trifluoromethyl- groups.

We next planned to test heterocyclic amides in the dearomatisation reactions. Gratifyingly, smooth dearomatisation was observed. It was noted that the simultaneous addition of the oxidant i.e. *m*CPBA led to the lower yields in case of spirocycles. However adding *m*CPBA in portions over 4 hours gave augmented yields in case of spirocycles **3.53**, **3.54** and **3.57**. Full consumption of the starting material was observed in case of spirocycles **3.54** and **3.58** however a pure sample of the product could not be obtained due to the highly unstable nature of the spirocycle.

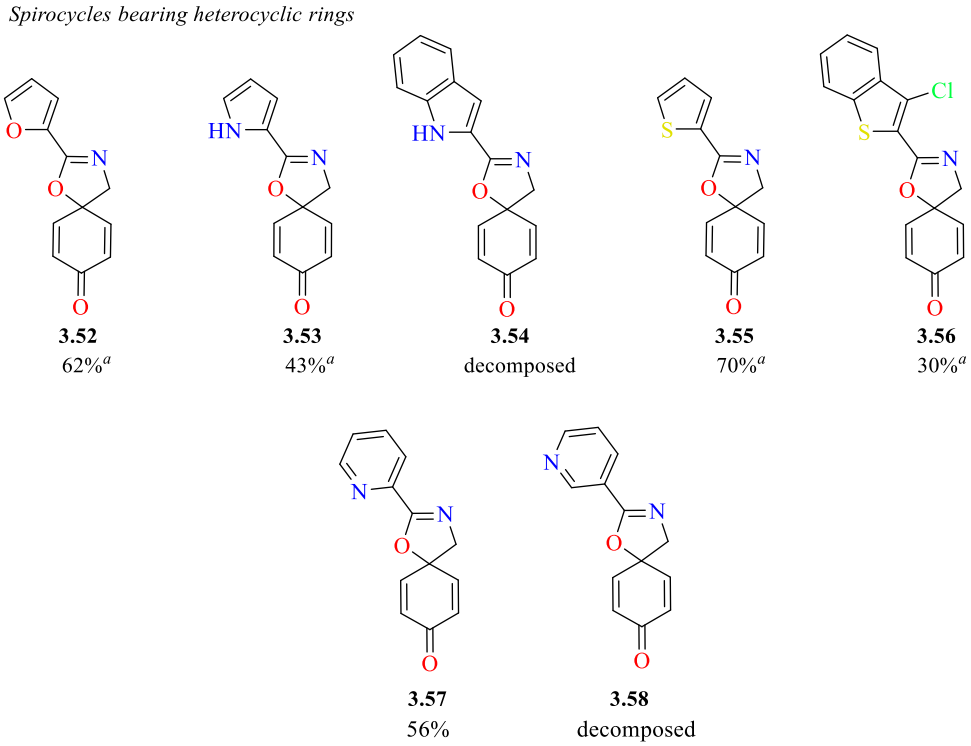


Figure 3.5: Synthesised oxazoline spirocycles containing heterocyclic rings.

Newly developed dearomatisation conditions were then applied to amides possessing alkyl and cyclic alkyl substituents. Spirocycle **3.59** was achieved quantitatively however a pure sample of it could not be obtained due to the stability issues. Spirocycle **3.60** was obtained in 41% isolated yield without the detection of any starting material in the crude NMR of the reaction mixture. Spirocycle **3.61** was not formed however only starting material was observed in the reaction mixture. It is believed that the presence of three chloride substituents affected the nucleophilicity of carbonyl oxygen due to their strong electron withdrawing ability thus making the nucleophile less reactive for intramolecular attack to furnish the desired spirocycle. It was also noted that the amides possessing cyclic alkyl substituents were not the ideal substrates for this transformation as **3.62** was obtained in extremely low yield while spirocycle **3.63** was not observed in the crude NMR of the reaction mixture at all. A complex proton NMR of the reaction mixture was obtained pointing towards the potential instability of the product or change in the reactivity of the amide. Further attempts to optimise the reactions conditions for the cyclic alkyl substituents were deemed unnecessary at this point.

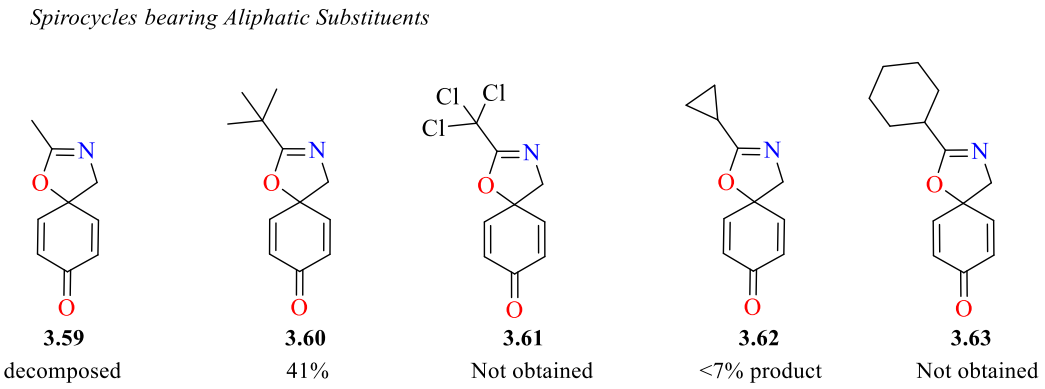
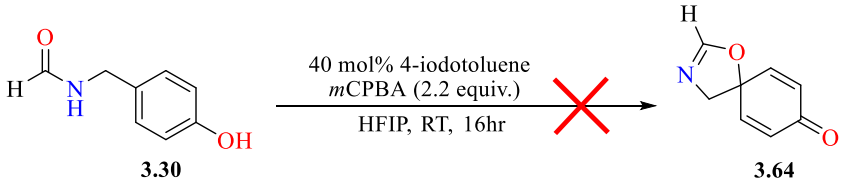


Figure 3.6: Oxazoline spirocycles containing aliphatic substituents.

3.3.4. Attempted synthesis of natural product precursor

We subjected the amide **3.30** to the conditions required for the spirocyclisations of phenolic amides to obtain the desired natural product precursor **2.18**. Sadly, only a trace amount of the expected product was noticed in the crude ^{1}H-NMR. The reaction was not further optimised.

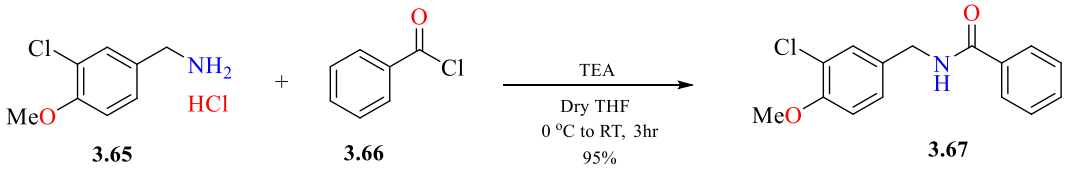


3.30 **3.64**

Scheme 3.8: Attempted synthesis of natural product precursor.

3.3.5. Effect of substituent on the reaction

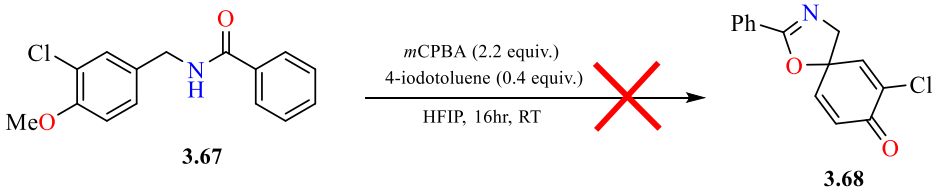
In order to investigate the effects of the substituent on the reaction, we decided to structurally amend the model substrate **3.1**. For this purpose, we synthesised amide **3.67** from the commercially available amine **3.65** and benzoyl chloride **3.66** (scheme 3.9) in order to have a substituent on the cyclohexadienone ring.[98] We also envisaged that the presence of the proton of the hydroxyl group may or may not be necessary for the reaction to proceed.



3.65 **3.66** **3.67**

Scheme 3.9: Synthesis of substituted amide **3.67**.

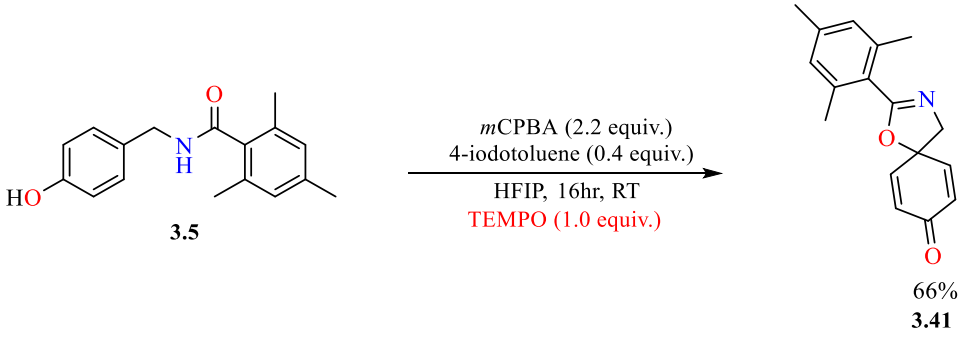
To test this hypothesis, we subjected the newly synthesised amide **3.67** to the conditions required for the dearomatisation (scheme 3.10). Ungratifying, the reaction failed to produce the expected product and almost all the starting amide was recovered. Our investigation proved that for the dearomatisation to happen smoothly, the presence of the proton of the phenolic group is mandatory and the presence of the *chloro*- substituent may also have impacted the reaction.



3.67 **3.68**

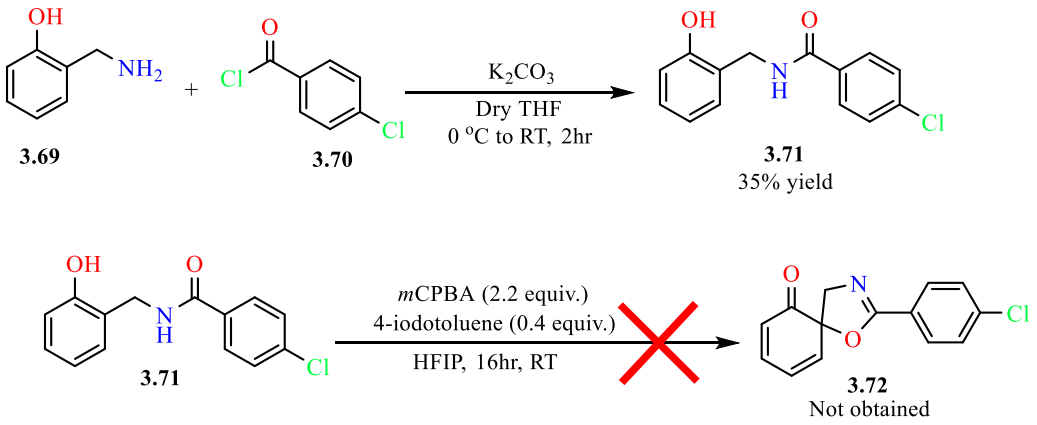
Scheme 3.10: Attempted dearomatisation of amide **3.67**.

We turned our attention to investigate whether the reaction proceeds via radical pathway or associative/dissociative pathway. For this purpose, we subjected amide **3.5** to the typical dearomatisation conditions and added free radical inhibitor TEMPO (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (scheme 3.11). Our investigation revealed that the reaction did not follow a radical pathway and proceeded as usual to form the desired spirocycle in 66% yield without forming any side product or the remaining starting material.



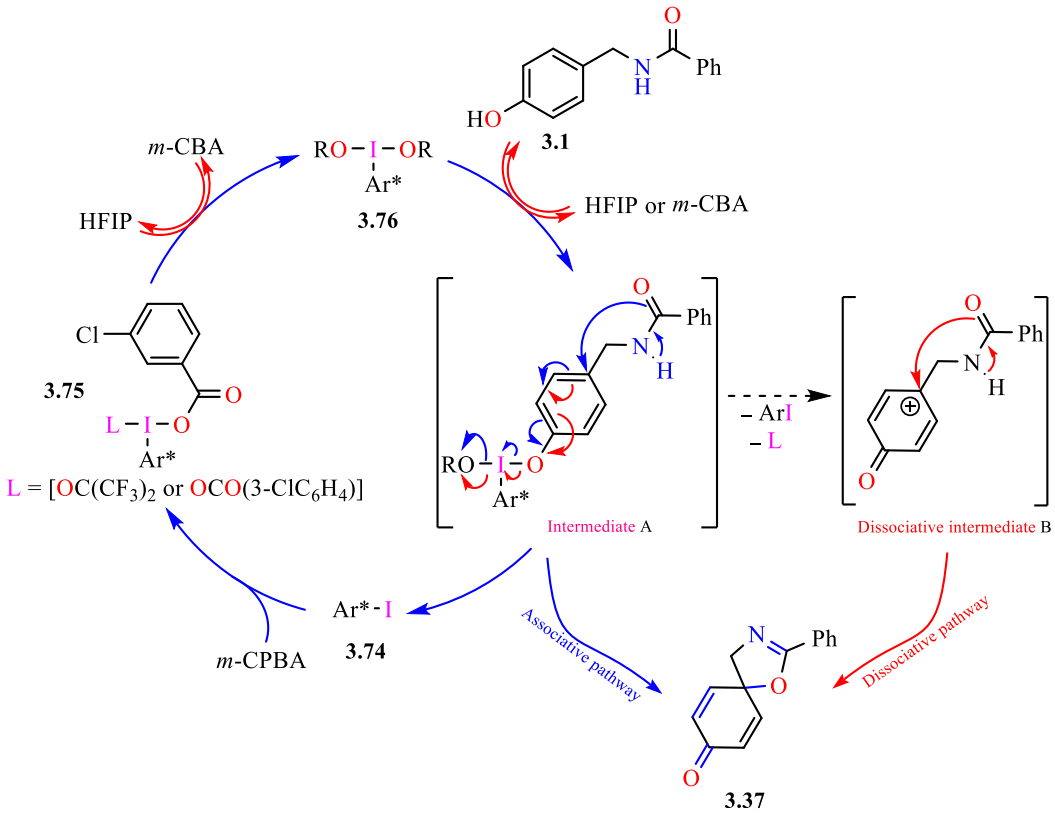
Scheme 3.11: Dearomatisation of amide **3.5** in the presence of TEMPO.

Having known that the *para*- oxidative dearomatisation of the phenols is indeed feasible, we decided to apply the developed protocol for the dearomatisation of substituted 2-hydroxybenzamides. In order to do so, we prepared the requisite amide according to the aforementioned conditions and subjected it to the dearomatisation reaction mediated by 4-iodotoluene and *m*CPBA as terminal oxidant (scheme 3.12). Sadly, the targeted spirocycle could not be obtained whilst a complicated mixture was obtained. We tried the same reaction again but instead of using HFIP we resorted to use dichloromethane as solvent. However, no noticeable development could be made. Further attempts to develop the conditions for this transformation were deemed unnecessary. (Scheme 3.12)



Scheme 3.12: Dearomatisation of amide **3.71** in the presence of TEMPO.

We hypothesised that the iodoarene(I) **3.74** undergoes oxidation by the terminal oxidant *m*CPBA to generate iodane(III) **3.76** species in situ which is then attacked by the nucleophilic hydroxyl group of the phenol **3.1** to produce intermediate A (scheme 3.13). The intermediate A is capable of following either dissociative or associative pathway to form the desired spirocycle. In the associative pathway, intramolecular attack of the nucleophile happens after which ArI group and ligand depart to produce the spirocycle. However, in the dissociative pathway the ArI group has already left forming the cationic intermediate B which after the nucleophilic attack generates the corresponding spirocycle **3.37**. The plausible mechanism of the phenol dearomatisation is discussed in scheme 3.13.

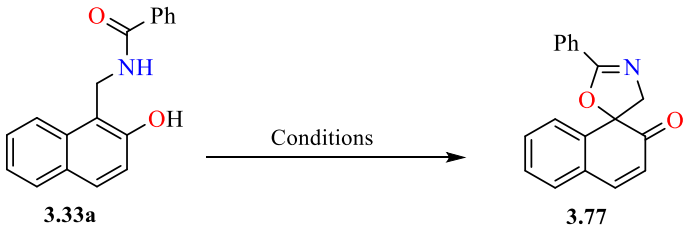


Scheme 3.13: Plausible mechanism of phenol dearomatisation.

3.4. Oxidative dearomatisation reactions of naphtholic substrates

The newly developed dearomatisation strategy could be applied to the substituted naphthol amides to obtain oxazoline based spirocycles. We started our investigation with the amide **3.33a** and subjected it to the conditions which would produce spirocycle. A range of solvents, iodoarenes and oxidants were tested during this process. The results of our investigation are summarised below. (Table 5)

3.4.1. Optimisations in MeCN



Scheme 3.14: Dearomatisation of amide **3.33a** in acetonitrile.

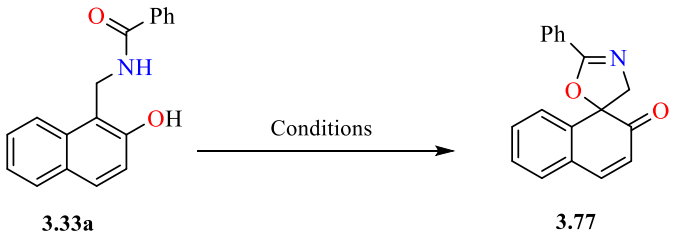
Entry	Oxidant	Iodoarene	Acid	Solvent	Time	Yield (Crude)
1	*m*-CPBA (2.2 eq.)	2-Iodoanisole 20 mol%	—	MeCN	16h	35%
2	*m*-CPBA (2.2 eq.)	2-Iodoanisole 20 mol%	PTSA	MeCN	16h	28%
3	Selectfluor (3 eq.)	2-Iodoanisole 20 mol%	—	MeCN	16h	N.D.
4	*m*-CPBA (3 eq.)	2-Iodoanisole 20 mol%	—	MeCN/H_2O 2:1	16h	10%
5	*m*-CPBA (2.2 eq.)	2-Iodoanisole 40 mol%	—	MeCN	16h	48%

Crude yields were determined by adding 1,3,5-trimethoxybenzene as internal standard. N.D. = No development

Table 5: Optimisation of the reaction in acetonitrile.

We initiated our experimentation with amide **3.33a**, 2-iodoanisole as the standard iodoarene in acetonitrile as the standard solvent. It was noted that the use of acids such as AcOH, PTSA as additives led to diminished yields (table 5, entry 2). The utilisation of dual solvent system also led to diminshed yields (table 5, entry 4). Moreover, no noticeable development was made by changing the oxidant to Selectfluor (table 5, entry 3). Increasing the catalyst loading from 20 mol% to 40 mol% had a favourable influence on the rate of the reaction and gave augmented yield (table 5, entry 5). Keeping in view the results, we decided to change the iodoarene to 4-iodotoluene and the solvent to HFIP or TFE.

3.4.2. Optimisations in fluorinated solvents



Scheme 3.15: Dearomatisation of amide **3.33a** in fluorinated solvents.

Entry	Oxidant	Iodoarene	Solvent	Time	Yield (Crude)
1	*m*-CPBA (3 eq.)	2-Iodoanisole 20 mol%	TFE	16h	39%
2	*m*-CPBA (2.2 eq.)	4-Iodotoluene 20 mol%	HFIP	16h	46%
3	*m*-CPBA (2.2 eq.)	4-Iodotoluene 40 mol%	HFIP	16h	75%
4	Selectfluor (2.2 eq.)	4-Iodotoluene 20 mol%	HFIP	48h	32%
5	Oxone (2.2 eq.)	4-Iodotoluene 20 mol%	HFIP	48h	N.D.
6	Peracetic acid (2.2 eq.)	4-Iodotoluene 20 mol%	HFIP	6 days	52%
7	Selectfluor (2.2 eq.)	4-Iodotoluene 20 mol%	HFIP:H_2O 1:2	6 days	N.D.
8	Oxone (2.2 eq.)	4-Iodotoluene 20 mol%	HFIP:H_2O 1:2	6 days	28%.
9	H_2O_2 (2.2 eq.)	4-Iodotoluene 20 mol%	HFIP	6 days	Traces
10	*m*-CPBA (2.2 eq.)	4-Iodotoluene 20 mol%	HFIP:H_2O 2:1	6 days	3%

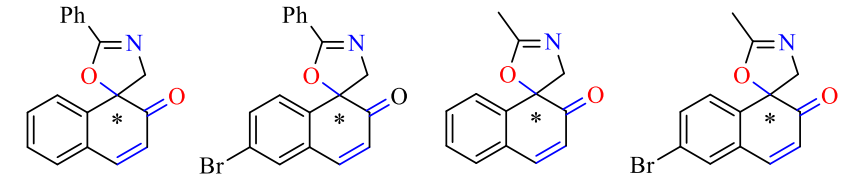
11	Koser's reagent (1 equiv.), HFIP, 16hr, RT	N.D.
12	Koser's reagent (1 equiv.), HFIP, 8hr, reflux	<5%

Crude yields were determined by adding 1,3,5-trimethoxybenzene as internal standard. N.D. = No development

Table 6: Optimisation of the reaction in acetonitrile.

It was observed that changing the solvent to TFE led to an increase in the product yield when the reaction was mediated by 2-iodoanisole and *m*CPBA (table 6, entry 1). Replacing 2-iodoanisole with 4-iodoanisole in HFIP provided a significant increase in the product yield while an increase in the catalyst loading (from 20 mol% to 40 mol%) gave the product in the highest yield (table 6, entries 2-3). It was also noted that changing the oxidant from *m*CPBA to Selectfluor, Oxone, Peracetic acid and H_2O_2 proved detrimental for the reaction (table 6, entries 4-10). It was also found that the use of commercially available iodane(III) species such as Koser's reagent in HFIP failed to provide the desired results (table 6, entries 11-12).

Having optimised the reaction conditions, different substituted naphtholic amides were subjected to oxidative dearomatisation spirocyclisation reactions mediated by 4-iodotoluene (20 mol %) and *m*CPBA as oxidant in HFIP. The obtained novel spirocycles are mentioned below.



3.77 Pure yield = 54 %

3.78 Pure yield = 51 %

3.79 Crude yield = 25 %

3.80 Traces

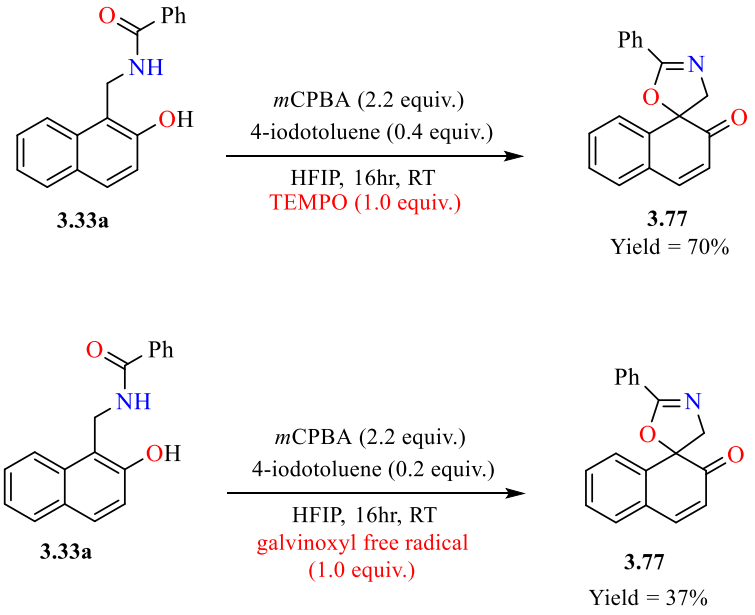
Figure 3.7: Naphthol amide derived spirocycles.

A pure sample of the spirocycle **3.79** could not be obtained due to the instability of the product.

3.4.3. Investigation of the reaction mechanism

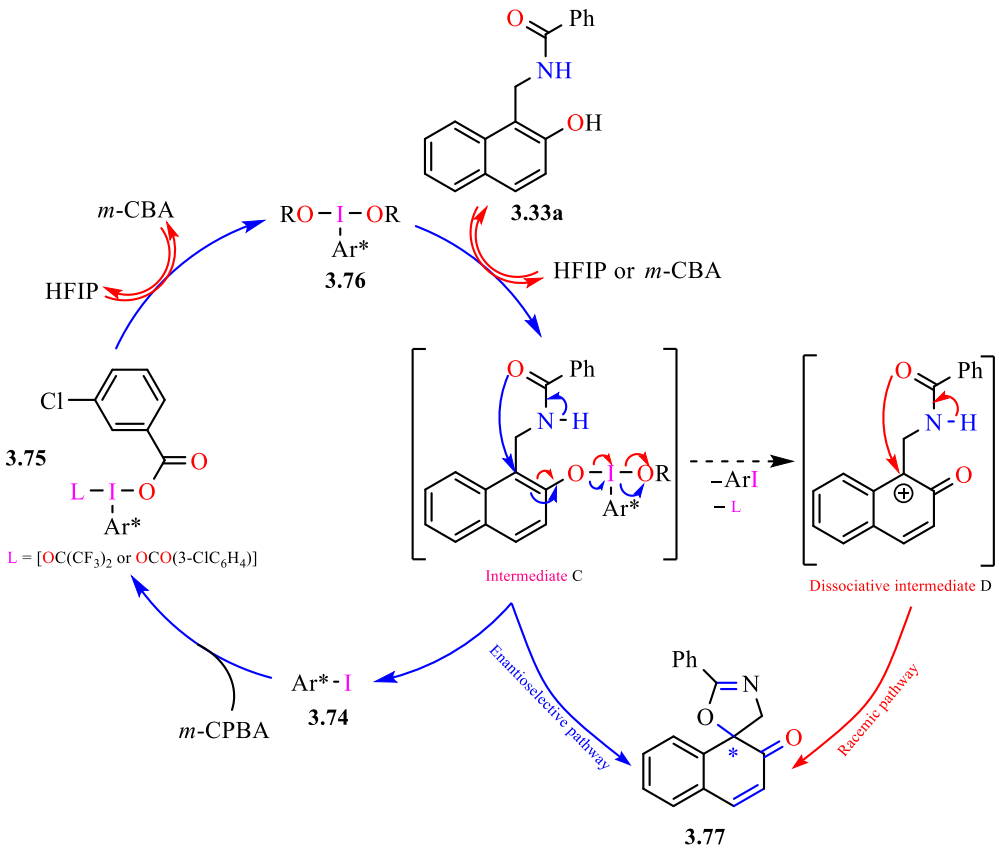
We focused our attention to investigate whether the reaction proceeds via radical pathway or associative/dissociative pathway. For this purpose, we subjected amide **3.33a** to the typical dearomatisation conditions and added free radical inhibitor TEMPO (2,2,6,6-

Tetramethylpiperidin-1-yl)oxyl and galvinoxyl, free radical. Our investigation revealed that the reaction did not follow a radical pathway and proceeded as usual to form the desired spirocycle in 70% (with 40 mol% 4-iodotoluene) and 37% (with 20 mol% 4-iodotoluene) yield respectively without forming any side product.



Scheme 3.16: Dearomatisation of amide **192a** in the presence of free radical inhibitors.

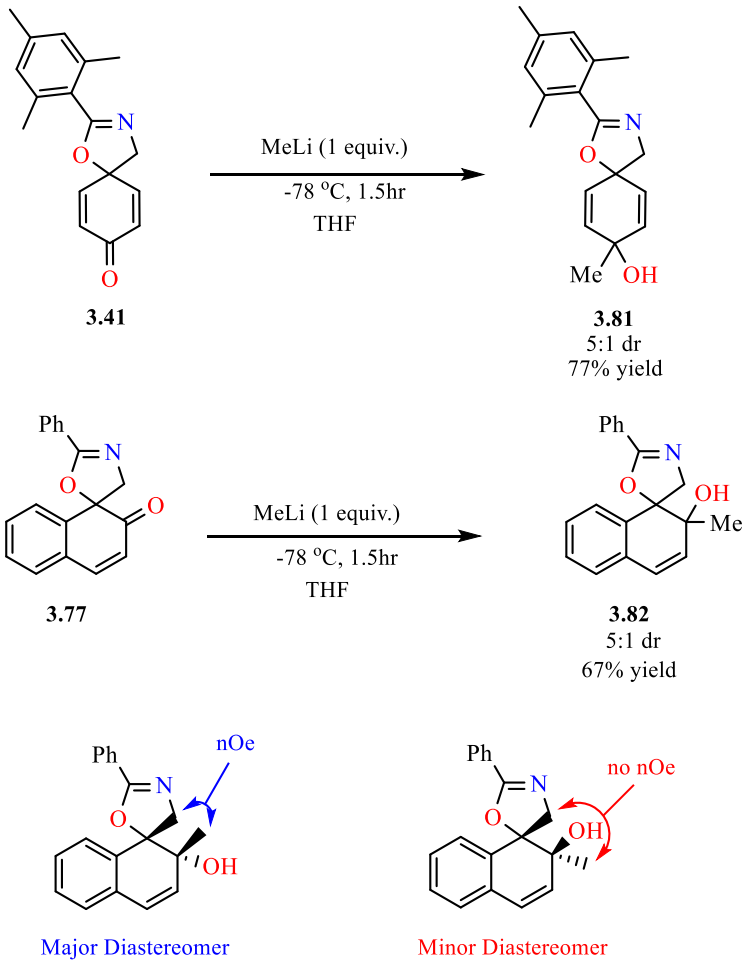
Mechanistically speaking, the iodoarene(I) undergoes oxidation by the terminal oxidant *m*CPBA to generate iodane(III) species *in situ* which is then attacked by the nucleophilic hydroxyl group of the naphthol to produce intermediate C. The intermediate C could either follow dissociative or associative pathway to give the targeted spirocycle. In the associative pathway, intramolecular attack of the nucleophile happens after which ArI group and ligand depart to produce the spirocycle with the advantage of stereocontrol. However, in the dissociative pathway the ArI group has already left forming the cationic intermediate D which after the nucleophilic attack generates the corresponding spirocycle **3.77** in a racemic manner. The plausible mechanism of the naphthol dearomatisation is discussed in scheme 3.17.



Scheme 3.17: Plausible mechanism of naphthol amide cyclisation.

3.5. Functionalisation of the spirocycles

The synthesised amides were subjected to the functionalisation reactions. Freshly synthesised spirocycles **3.41** and **3.77** were reacted with a (1.6 M) solution of methyllithium in hexanes (MeLi) in anhydrous tetrahydrofuran at −78 °C. Gratifyingly, the corresponding spiro-alcohols were obtained in good to excellent yields with 5:1 dr in both cases. (Scheme 3.18) In the case of compound **3.82**, the major diastereomer showed the interaction (nOe) between the protons of the methyl group and methylene group of the oxazoline ring however no such interaction was observed in case of the minor stereoisomer. (see experimental section, page 153)

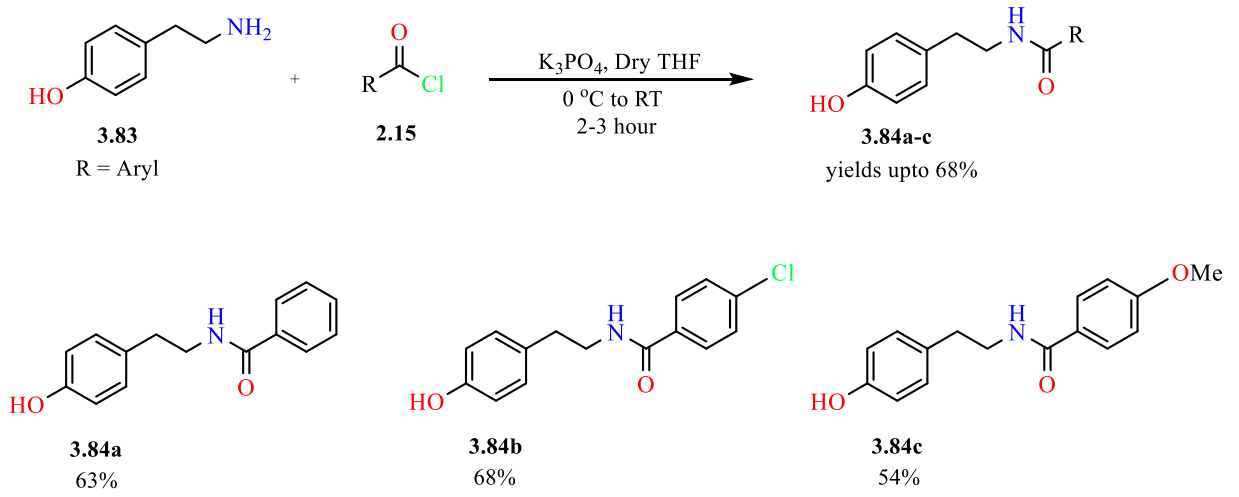


Scheme 3.18: Reaction of spirocycle **3.41** and **3.77** with methyl lithium.

We tried to reduce the spirocycle **3.41** using Pd/C in an admixture of ethyl acetate and methanol in the presence of hydrogen gas using a balloon but sadly the reaction did not work and almost all the starting material was recovered. Next, we carried out a conjugate addition to the spirocycle **3.41** by using cuprous iodide and methyllithium but sadly this reaction also did not work.

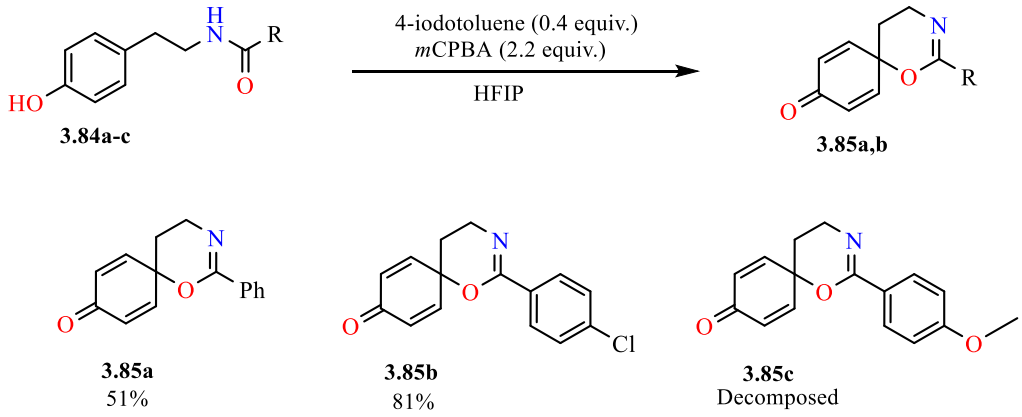
3.6. Synthesis of six membered spirocycles

Having confirmed that the dearomatisation of phenols and naphthols *via* hypervalent iodine species is feasible to construct five membered spirocycles, we decided to prepare another class of amides by reacting tyramine **3.83** with commercially available acyl chlorides using the aforementioned procedure.[99] Amides **3.84a-c** were obtained in good to excellent yield when appropriate acyl chlorides were reacted with tyramine **3.83**. These amides would generate six membered spirocycles upon subjecting to the dearomatisation conditions. (Scheme 3.19)



Scheme 3.19: Synthesis of substituted amides **3.84a-c**.

Gratifyingly, newly prepared amides underwent smooth dearomatisation to produce the corresponding six membered spirocycles when subjected to the already developed dearomatisation conditions. Spirocycle **3.85a** was isolated in 51% yield and spirocycle **3.85b** was achieved in 81% isolated yield. However, it was noted that the starting amide **3.84c** was fully converted to **3.85c** but a pure sample could not be obtained as the compound decomposed during the purification. (Scheme 3.20)



Scheme 3.20: Synthesis of substituted amides **3.84a-c**.

Compound **3.85a** has previously been reported. See *J. Org. Chem.*, **1991**, 56, 435.

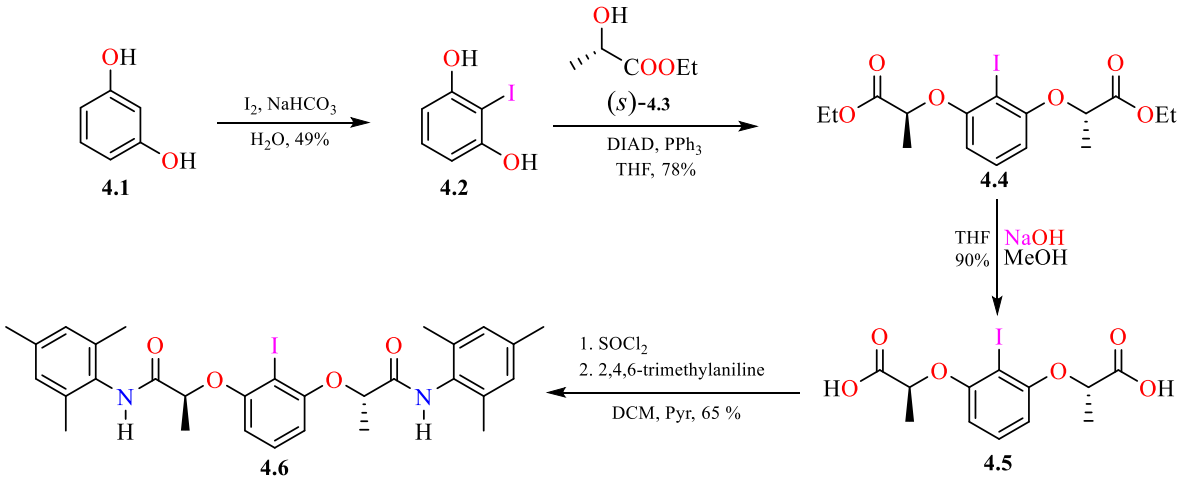
3.7. Summary

In conclusion, the synthesis of five membered spiro-oxazolines and six membered spirocycles *via* oxidative dearomatisation of phenol and naphthol amides mediated by 4-iodotoluene as catalyst and *m*CPBA as terminal oxidant. Different iodoarenes, catalysts, and solvents were scanned, however, 4-iodotoluene and *m*CPBA provided the best results in hexafluoroisopropanol (HFIP). It was observed that altering the oxidant, iodoarene and solvent led to diminished yields in most cases. The stoichiometric and catalytic versions of the cyclisation were also successfully developed.

Chapter 4: Enantioselective oxidative cyclisation of naphthol amides

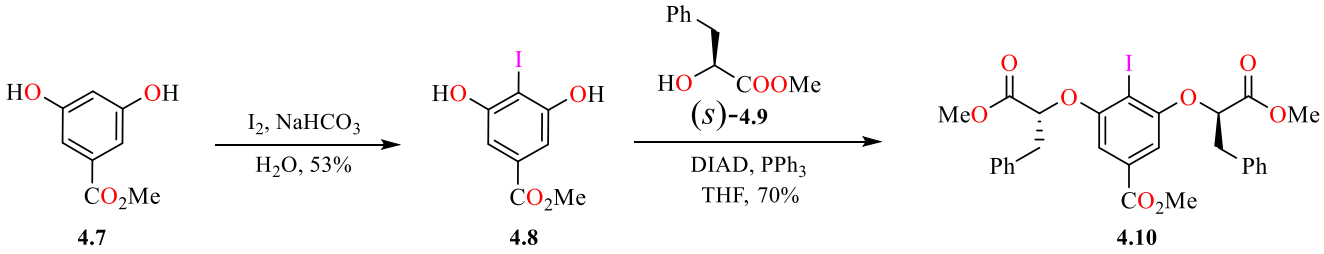
Having confirmed that the oxidative dearomatisation of naphthols with hypervalent iodine compounds is indeed feasible, our attention refocused upon the development of an enantioselective variant of the reaction. To the best of our knowledge, no such protocol has been reported before in the literature.

Initial experiments aiming to achieve the transformation of interest focused upon the utilisation of Ishihara type C_2-symmetric chiral iodoarenes in the presence of *m*CPBA as terminal oxidant. These kind of iodoarenes had already been used for the enantioselective cyclisation of carboxylic acids and can readily be synthesised.[90] The preparation of C_2-symmetric chiral iodoarenes started with the iodination of the resorcinol[103] **4.1** followed by Mitsunobu reaction of **4.2** with (-)-(*S*)-ethyl lactate, **4.3**. The obtained ester **4.4** was then subjected to base hydrolysis to furnish the diacid **4.5** which was elaborated to **4.6** *via* the acid chloride.



Scheme 4.1: Synthesis of C_2-symmetric iodoarene **4.6**

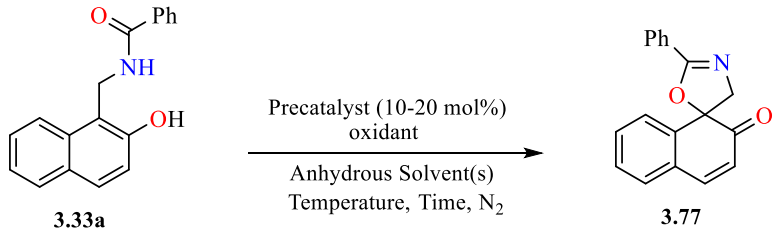
Similarly, iodination of **4.7** formed **4.8** [104] which after reaction with (*S*)-methyl-2-hydroxy-3-phenylpropanoate **4.9** under Mitsunobu conditions gave the desired iodoarene **4.10** in good yield.



Scheme 4.2: Synthesis of C_2-symmetric iodoarene **4.10**.

4.1. Screening of conditions

At the outset of the project only iodoarene **4.6** and **4.10** were known. So we decided to develop the conditions for the enantioselective dearomatisation of naphthol amide **3.33a** using these iodoarenes and oxidants.



Scheme 4.3: Enantioselective dearomatisation of naphthol amide **3.33a** by different C_2-symmetric iodoarenes.

Entry	Oxidant	Precatalyst	Solvent(s)	Temp.	Time	Pure yield (%)[a]	*ee*[b] (%)
1	*m*-CPBA (2.4 eq.)	**4.10** 20 mol%	MeCN:EtOH 2:1	RT	24h	55% product 30% SM	4
2	*m*-CPBA (2.4 eq.)	**4.10** 20 mol%	MeCN	RT	24h	42% Product 40% SM	3
3	*m*-CPBA (2.2 eq.)	**4.6** 20 mol%	DCM	RT	18h	31%	5
4	Peracetic acid (3.0 eq.)	**4.6** 20 mol%	DCM	RT	18h	-[c]	–
5	*m*-CPBA (1.2 eq.)	**4.6** 10 mol%	DCM:MeOH 3:1	− 20 °C	18h	36%	14

[a] Isolated yields after column chromatography. [b] Enantiomeric excess were determined by using chiralpak IB column (Petroleum ether:Isopropanol 80:20, Flow rate 1 mL/ min). [c] Complex reaction mixture was obtained.

Table 7: Optimisation of the dearomatisation reaction conditions.

Our experimentation showed that the increase in the catalyst load improved the overall yield of the reaction however a significant decline was observed in the selectivities. It was also noted that the use of alcoholic solvents like MeOH and EtOH had favourable influence on the rate of reaction significantly (table 7, entries 1-2 and 5). Keeping in view these results, we decided to decrease the catalyst load to 10 mol%, oxidant to 1.2 equiv. and replaced acetonitrile with a mixture of solvents i.e. DCM:Methanol (3:1) while leaving the reaction mixture to stir at −20 °C for 18 hours. To our delight, enantioselectivity considerably improved but at the expense of the rate of the reaction. (table 7, entry 5).

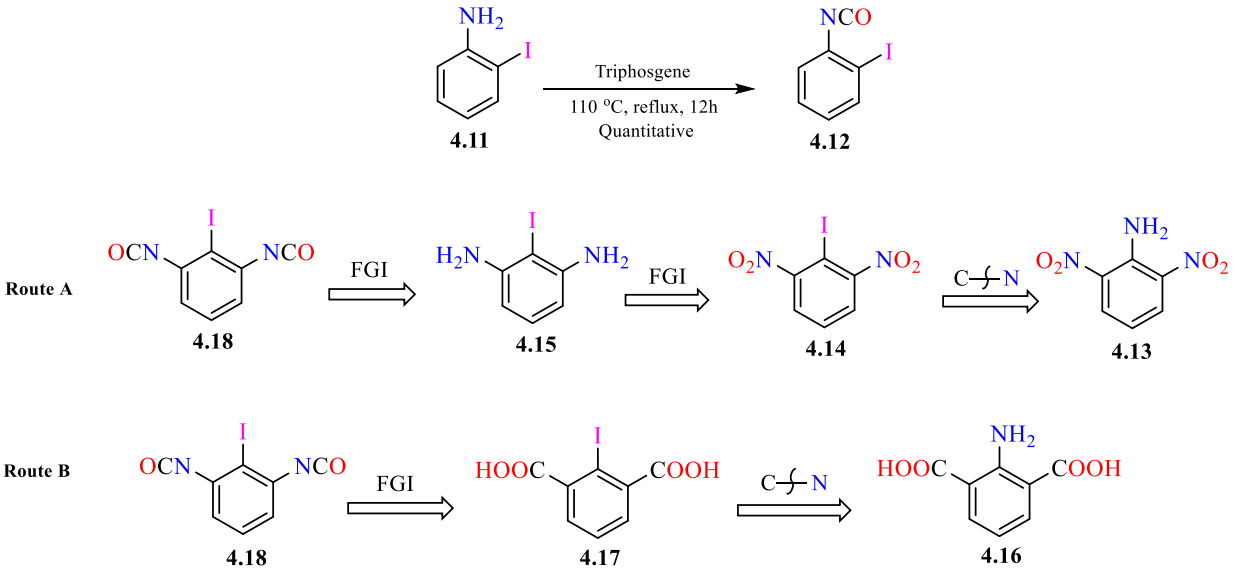
Having confirmed that the enantioselective oxidative dearomatisation of the naphthols is indeed feasible we decided to prepare our own novel iodoarene precatalysts. The aim to develop these iodoarenes was to test their oxidising potential in the oxidative dearomatisation reactions under various conditions.

4.2. Synthesis of novel iodoarenes

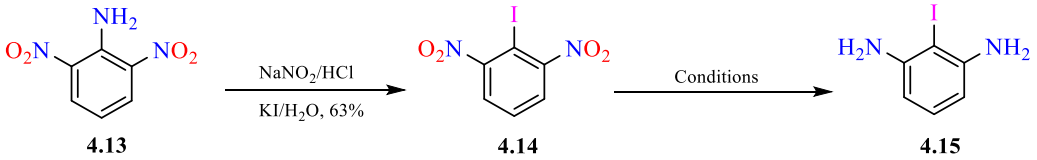
4.2.1. Synthesis of C_1 & C_2 symmetric iodoarenes bearing chiral carbamate appendages

With a view to develop novel chiral iodoarene precatalysts, the focus was shifted on the preparation of C_2-symmetrical chiral iodoarenes possessing optically active lactate motifs. Initially, we synthesised C_1-symmetrical chiral iodoarenes bearing carbamate appendages. These were synthesised by coupling 2-iodoisocyanatobenzene **4.12** with commercially available optical lactates **4.19**. 2-Iodoisocyanatobenzene **4.12** was prepared from 2-iodoaniline **4.11** following literature procedure.[105] The same methodology was used to prepare C_2-symmetrical chiral iodoarenes. For this purpose, diisocyanatoiodobenzene **4.18** prepared from 2-iodoisophthalic acid **4.17** following the literature procedure and was subsequently coupled with different lactates in the presence of CuI in DMF. However, the synthesis of diisocyanatoiodobenzene **4.18** came with challenges. The synthesis of **4.18** can be achieved through two different routes as explained in scheme 4.4.

At the outset of the research, we tried to access the diisocyanatoiodobenzene **4.18** via route A**.** 2,6-Dinitroiodobenzene **4.18** was obtained in good yield by iodination of commercially available 2,6-dinitroaniline **4.13**.[106] Several methods were tried for the reduction of **4.13** to obtain **4.14**, however, sadly none worked or partially worked.[107-113] The results are summarised in table 8.



Scheme 4.4: Synthesis and retrosynthetic pathways to access **4.12** and **4.18**.



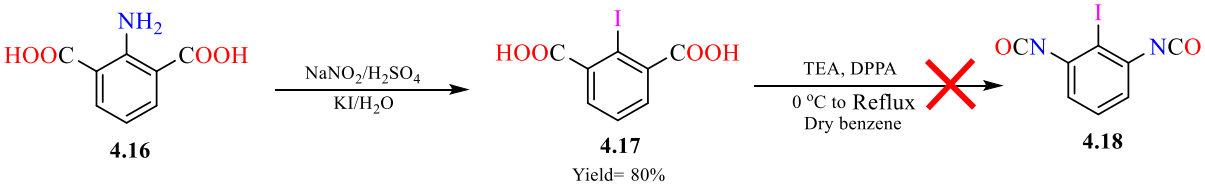
Scheme 4.5: Preparation and reduction of **4.14**.

Entry No.	Reactant	Conditions	Product
1	**4.14**	Fe Powder/$CaCl_2$, EtOH/H_2O, 60 °C, 1h	N.D.
2		Fe Powder/NH_4Cl, EtOH/H_2O, 85 °C, 4h	N.D.
3		$NaBH_4$/Charcoal H_2O-THF (1: 0.5ml), reflux, 50-60 °C, 2h	N.D.
4		10% Pd/C, H_2 gas Dry methanol, overnight, RT	N.D.
5		10% Pd/C, $N_2H_4.H_2O$ (20 equiv.), Dry methanol, Reflux, 90 °C, 1h	N.D.
6		$HSiCl_3$, DIPEA, Dry MeCN, 0 °C to RT.	N.D.
7		Iron Powder, AcOH, 60 °C, 2h.	Traces

Table 8: Reaction conditions for the reduction of **4.14** to **4.15**.

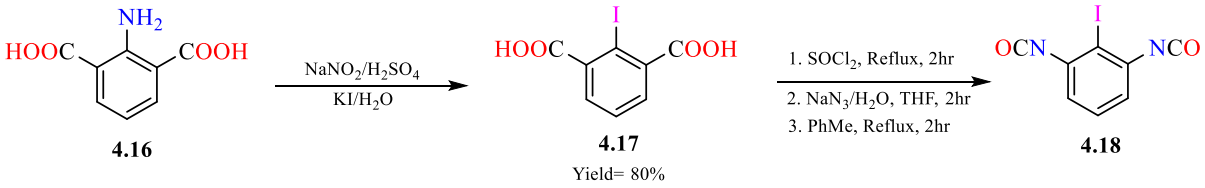
Partial reduction along with dehalogenation was observed upon using iron powder in acetic acid (table 8, entry 7,). However no product was observed in all other cases, whatsoever.

In order to obtain diisocyanatoiodobenzene **4.18**, route B was adopted. Commercially available 2-aminoisophthalic acid **4.16** was used to obtain **4.18** directly. In particular, 2-aminoisophthalic acid was converted into **4.17** which was then used in the presence of triethylamine and diphenylphosphory azide (DPPA) in dry benzene to produce **4.18**.[114] Unfortunately, the desired product could not obtained.



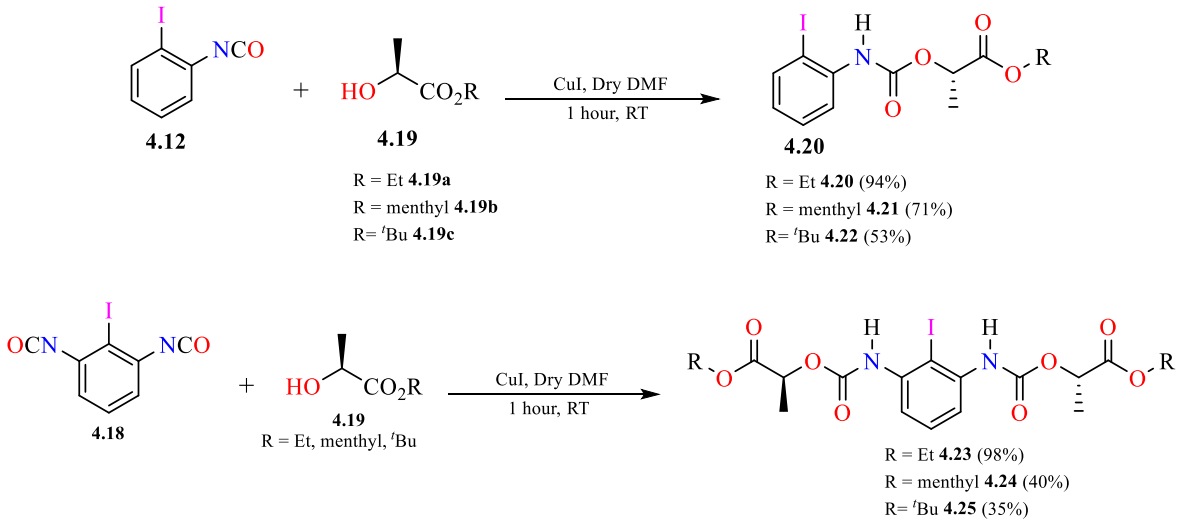
Scheme 4.6: Attempted synthesis of **4.18**.

Instead of obtaining **4.18** directly, an indirect route was followed as shown in scheme 4.7. For this purpose, 2-aminoisophthalic acid **4.16** was iodinated to obtain 2-iodoisophthalic acid **4.17** in 80% yield.[115] Upon refluxing **4.17** in $SOCl_2$ for 2 hours the corresponding acid chloride was generated which upon azidation and subsequent refluxing in toluene for 3 hours afforded **4.18** almost quantitatively. IR analysis confirmed the presence of isocyanate peak confirming the formation of **4.18**.



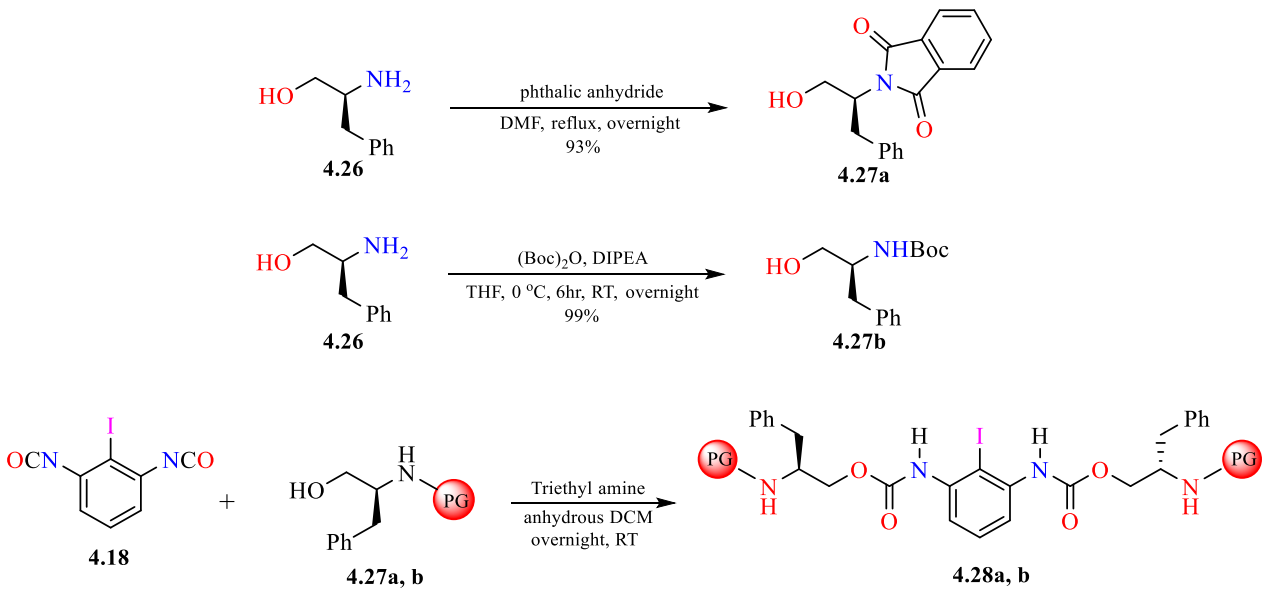
Scheme 4.7: Indirect synthesis of **4.18**.

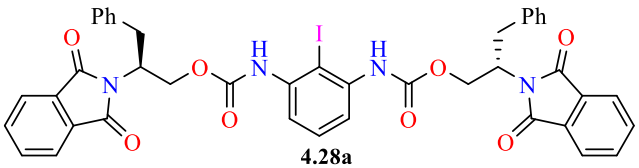
After successfully synthesising **4.12** and **4.18**, we then synthesised different C_1 and C_2-symmetric iodoarene precatalysts by reacting them with appropriate lactates.



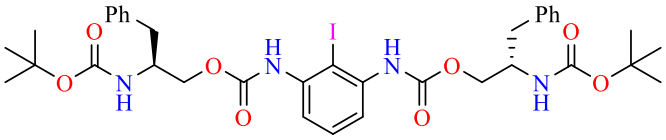
Scheme 4.8: Synthesis of C_1 and C_2-symmetric iodoarene precatalysts possessing chiral carbamate appendage.

It was noted during the purification of these carbamates that they were intolerant of silica and started disintegrating during the purification process. We also synthesised other carbamates following a different procedure.[116, 139] For this purpose, (*S*)-2-amino-3-phenylpropan-1-ol **4.26** was converted to **4.27a** and **4.27b** and then coupled with **4.18** to give corresponding carbamates **4.28a, b** in excellent yields.





4.28a
78%

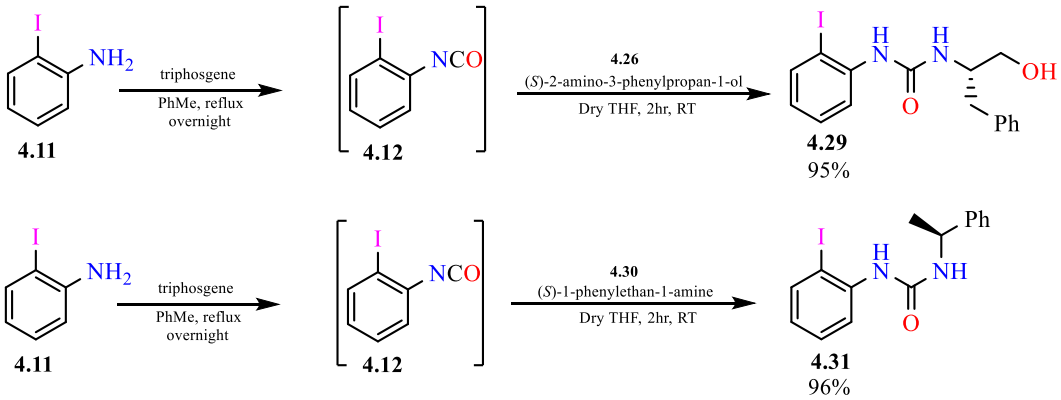


4.28b
69%

Scheme 4.9: Synthesis of C_2-symmetric iodoarene precatalysts possessing chiral carbamate appendage.

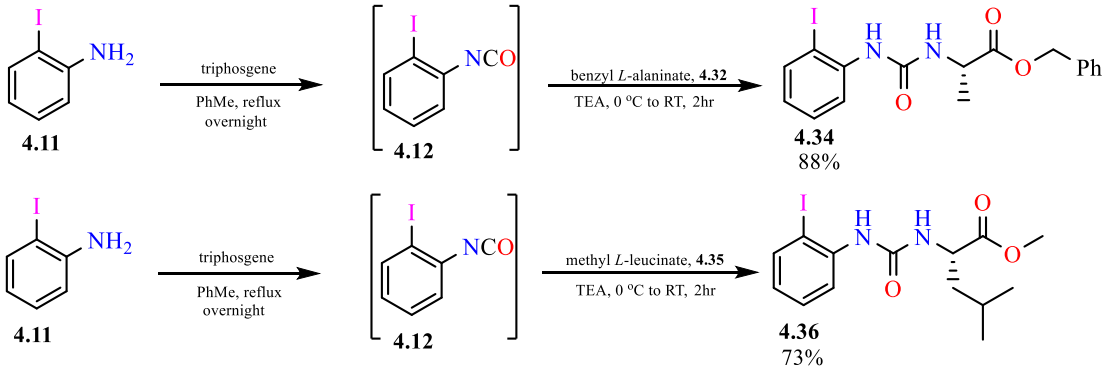
4.2.2. Synthesis of C_1 & C_2-symmetric iodoarenes bearing chiral urea appendages

Keeping in view the instability of the carbamates, we decided to prepare another class of iodoarene precatalysts possessing an oligourea foldamer. Oligoureas are well known for their helicity.[117] The main idea for the synthesis of iodourea based catalysts was that the weak interactions between the chiral arms with either the electrophilic I(III) centre or with the ligands on I(III) would supply a suitable chiral environment by forming a helical supramolecular fold for chiral induction. At the outset of the project we prepared C_1-symmetric iodoarenes **4.29** and **4.31** (scheme 4.10) having chiral urea arm but later we decided to synthesise C_2-symmetric iodoarenes as well (scheme 4.13).[118]



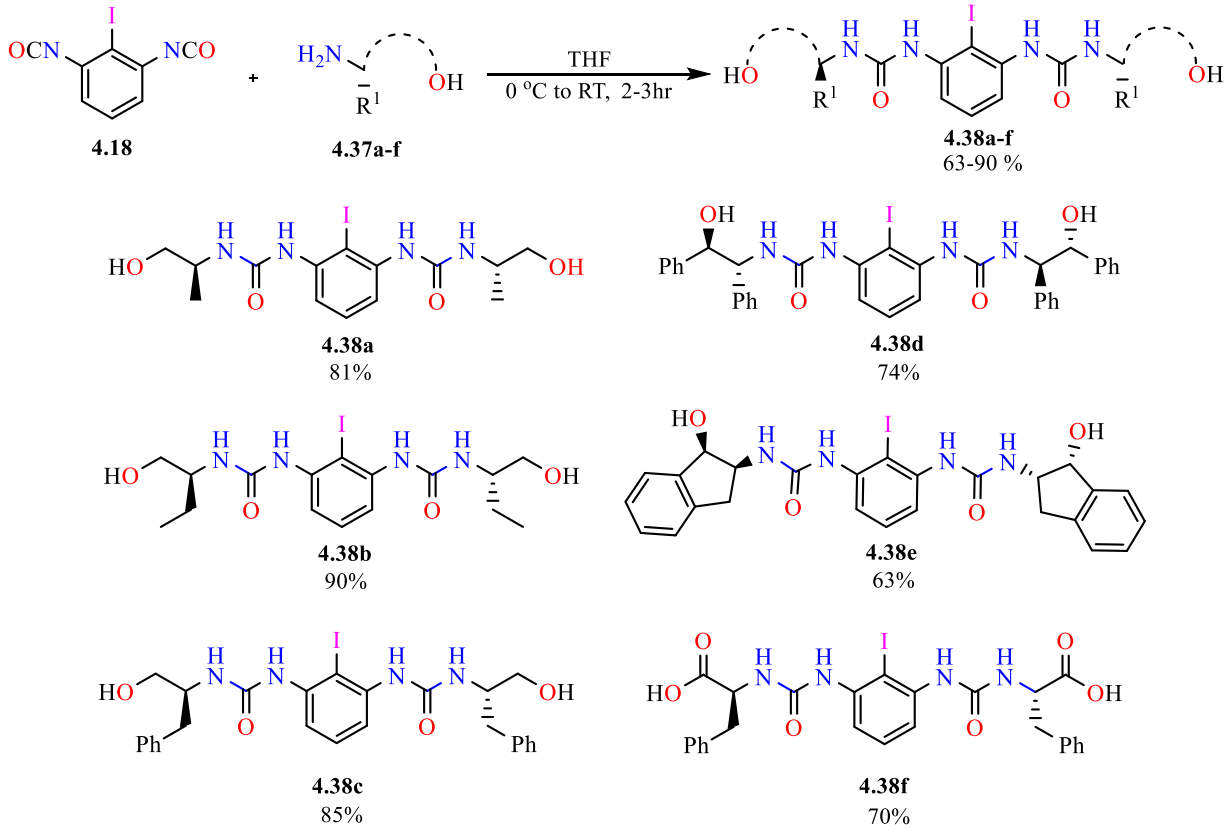
Scheme 4.10: Preparation of C_1-symmetric iodoarenes having chiral urea appendages.

The reaction of **4.12** with different chiral amine **4.26** and **4.30** in anhydrous THF produced various C_1-symmetric urea-iodoarenes **4.29** and **4.31**. Specifically speaking, (*S*)-2-amino-3-phenylpropan-1-ol **4.26** upon reaction with **4.12** produced **4.29** in 95% yield. Likewise, (*S*)-1-phenylethan-1-amine **4.30** reacted with **4.12** in THF to afford **4.31** in 96% yield. We also made two other marginally structurally different iodoarenes (**4.34** and **4.36**) bearing a chiral urea arm. Benzyl-*L*-alaninate **4.32** and methyl-*L*-leucinate upon reaction with **4.12** gave **4.34** and **4.36** in 88% and 73% yield respectively. [118]



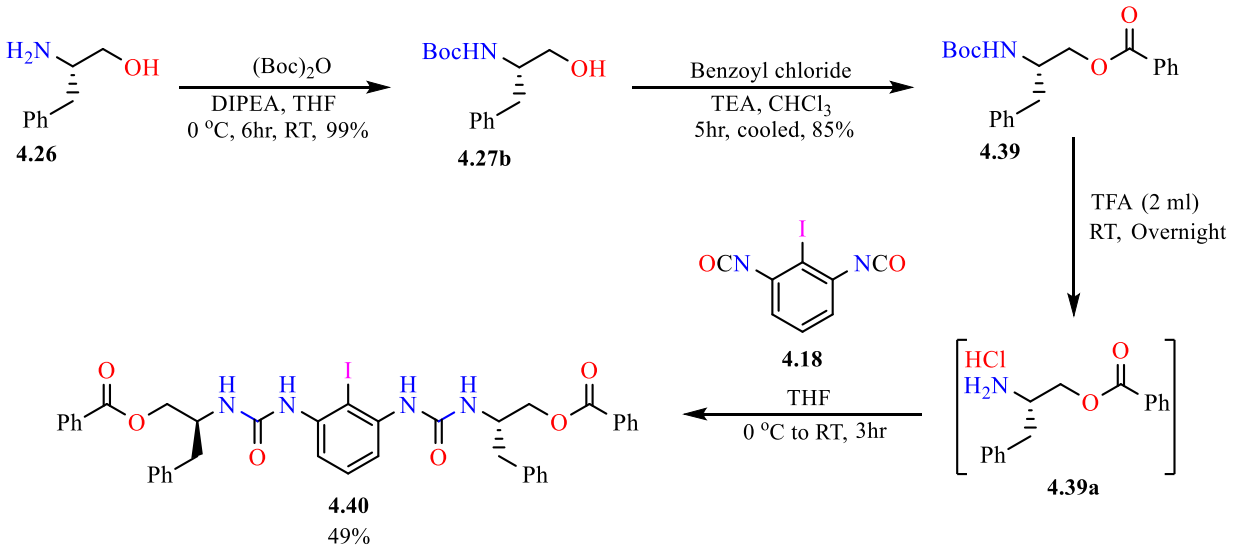
Scheme 4.11: Preparation of C_1-symmetric iodoarenes having chiral urea appendages.

After successfully preparing different C_1-symmetric urea based iodoarenes we refocused our attention to develop C_2-symmetric urea based iodoarenes. Different commercially available amino acid or aminoalcohols were reacted with diisocyanatoiodobenzene **4.18** to achieve the desired ureas. Specifically speaking, bis-urea **438a** and **438b** were synthesised by the reaction of diisocyanatoiodobenzene **4.18** with (*S*)-2-aminopropan-1-ol and (*S*)-2-aminobutan-1-ol in 81% and 90% yields respectively. [118]



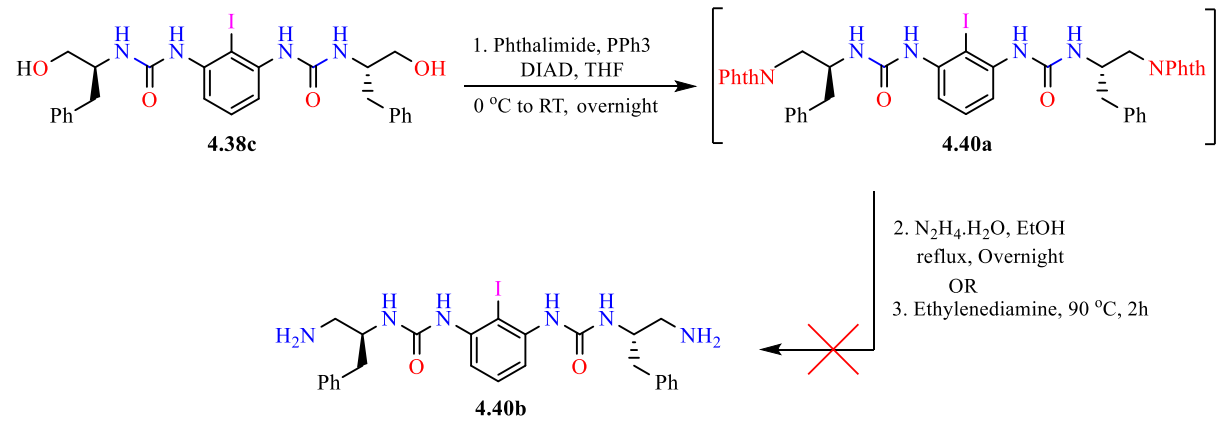
Scheme 4.11: Preparation of C_2-symmetric iodoarenes possessing chiral urea appendages.

Similarly, bis-ureas **4.38c** and **4.38d** were synthesised by the reaction of diisocyanatoiodobenzene **4.18** with (*S*)-2-amino-3-phenylpropan-1-ol and (1*R*,2*R*)-2-amino-1,2-diphenylethan-1-ol in good yields. The reaction of (1*R*,2*S*)-2-amino-2,3-dihydro-1H-inden-1-ol and *L*-phenylalanine with diisocyanatoiodobenzene **4.18** produced bis-ureas **4.38e** and **4.38f** in good yields. Bis-urea **4.40** was synthesised via a different method. We started with the protection of the amino group of (*S*)-2-amino-3-phenylpropan-1-ol **4.26** then subjected the obtained crude to the conditions which would allow *o*-acylation.[119, 120] Gratifyingly, we obtained the desired compound **4.39** in good yield. Next, the compound **4.39** was stirred in 2ml of TFA overnight to obtain the hydrochloride salt of the desired compound **4.39a** which upon coupling with **4.18** generated the targeted bis-urea in 49% yield. [121] (Scheme 4.12).



Scheme 4.12: Synthesis of C_2-symmetric iodoarenes **4.40**.

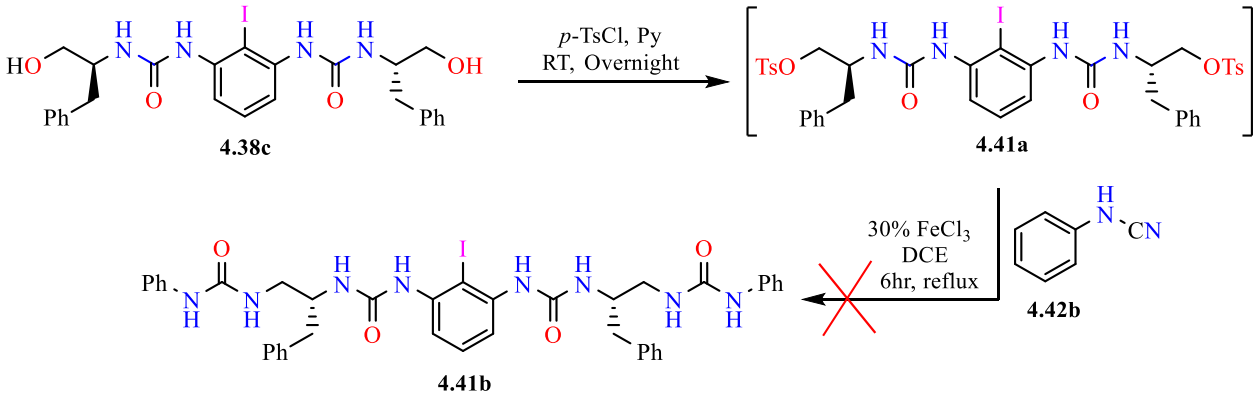
We refocused our attention on the incorporation of another urea moiety into the already synthesised bis-ureas. For this purpose, we started our investigation by choosing **4.38c** as the model substrate and subjected it to Mitsunobu conditions.[122] We tried different procedures[123, 124] to remove the phthalide group from **4.38** however none worked. In each case a complex mixture was obtained which did not contain either starting material or the product. Hence **4.40b** could not be obtained. (Scheme 4.13)



Scheme 4.13: Attempted synthesis of **4.40b**.

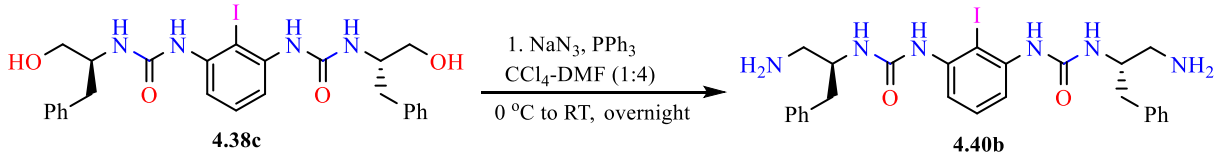
In order to add another urea moiety into **4.38**c directly the two hydroxyl groups on it need to be activated in order to do a Ritter-type reaction. Specifically speaking, the tosylated bis-urea **4.41a** upon reaction with phenyl cyanamide **4.42b** would produce the desired compound **4.41b**.

Unfortunately, all attempts to tosylate the free hydroxyl groups were unsuccessful and hence the Ritter-type reaction could not be carried out.[125, 126] (Scheme 4.14)



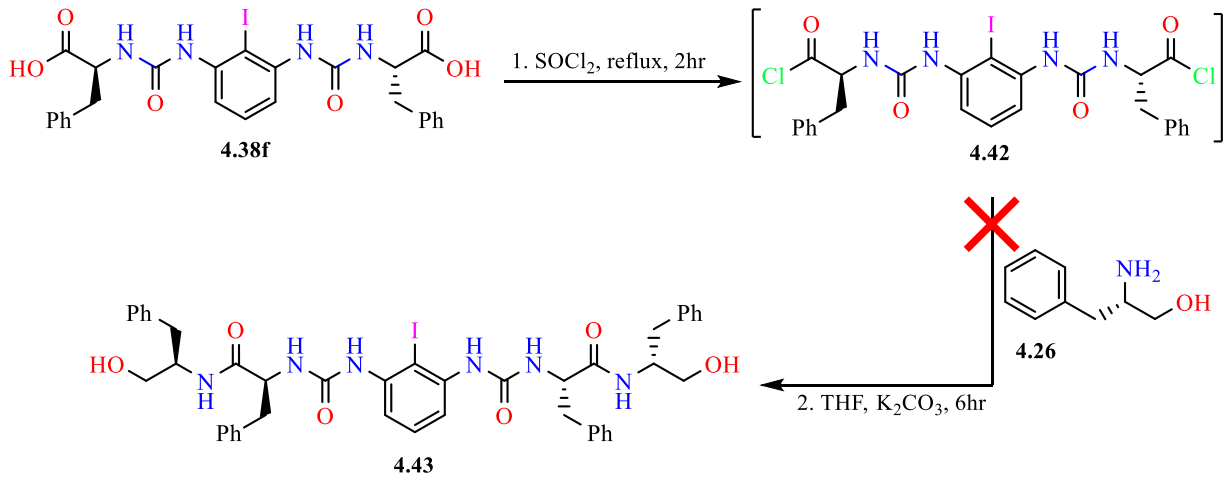
Scheme 4.14: Attempted synthesis of tetra-urea **4.41b**.

As a last resort we submitted **4.38c** to Appel reaction conditions. We added the bis-urea **4.38c** to a solution of carbon tetrachloride and DMF followed by the addition of triphenyl phosphine and sodium azide under inert conditions and left the reaction mixture to stir overnight.[127] Sadly, an unknown mixture of compounds was obtained which was discarded. (Scheme 4.15)



Scheme 4.15: Attempted synthesis of **4.40b**.

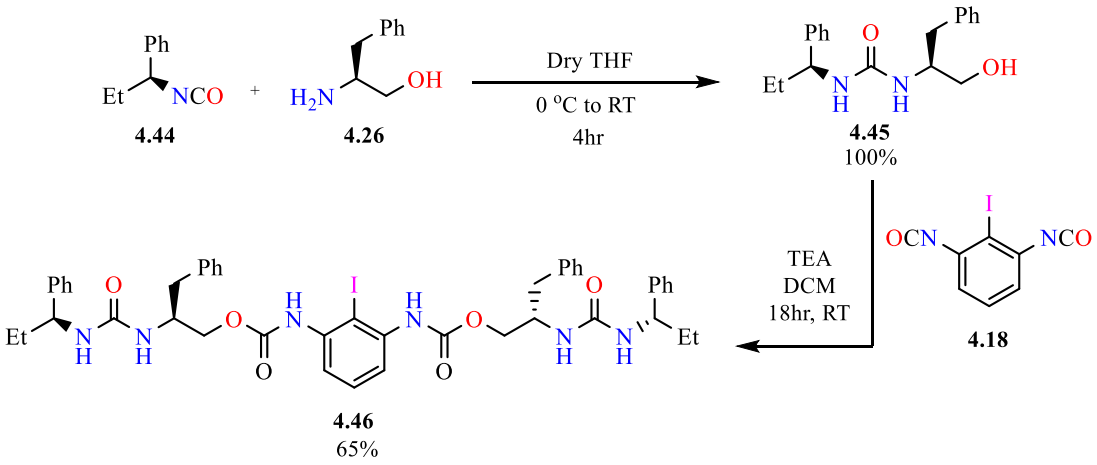
We also tried to make an iodoarene possessing chiral urea and amide arms. In order to achieve this, we took **4.38f** and refluxed it in thionyl chloride for two hours.[115] After such time, we treated it with *L*-phenylalaninol however the desired compound **4.43** could not be obtained. (Scheme 4.16)



Scheme 4.16: Attempted synthesis of chiral iodoarene having urea and amide arms.

4.2.3. Synthesis of C_2-symmetric iodoarenes bearing chiral urea-carbamate arm

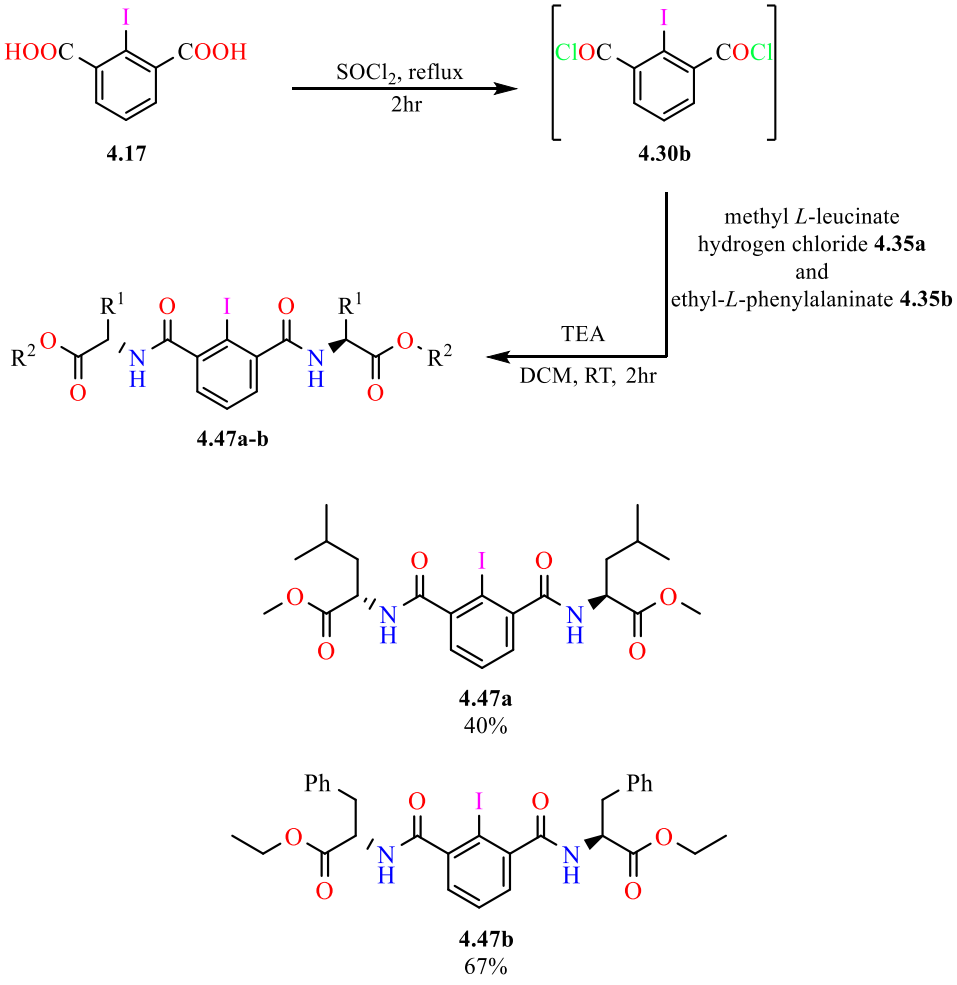
Next we synthesised another class of C_2-symmetric iodoarenes containing urea-carbamate functionalities on the chiral arm. We coupled commercially available isocyanate **4.44** with (*S*)-2-amino-3-phenylpropan-1-ol **4.26** in dry THF using aforementioned procedure and obtained **4.45** quantitatively. [118] Subsequently, we treated it with **4.18** in the presence of triethylamine in dichloromethane and left it to stir for 18 hours. Gratifyingly, iodoarene **4.46** was obtained in 65% yield. (Scheme 4.17)



Scheme 4.17: Synthesis of chiral iodoarene having urea-carbamate arm.

4.2.4. Synthesis of C_2-symmetric iodoarenes bearing chiral amide arm

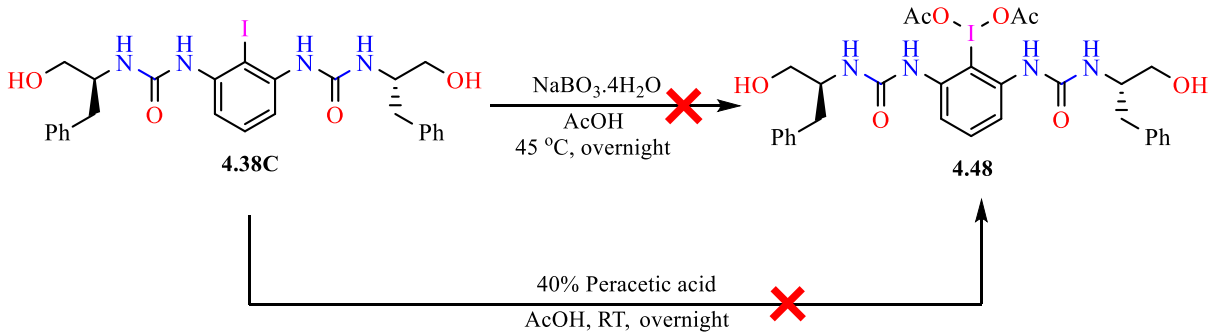
Iodoarenes bearing an amide arm had been previously synthesised and tested in enantioselective α-oxidation of ketones in our group.[128] So it would be worthwhile to prepare this kind of catalyst and to explore their reactivity in enantioselective spirocyclisation reactions. We refluxed 2-iodoisophthalic acid **4.17** in $SOCl_2$ for two hours and then coupled it with the hydrochloride salt of methyl-*L*-leucinate **4.35a** and ethyl *L*-phenylalaninate **4.35b** to obtain the desired bis-amide **4.47a-b** in 40% and 67% yields respectively.



Scheme 4.18: Synthesis of C_2-symmetric iodoarene **4.47a-b** bearing chiral amide arms.

4.2.5. Synthesis of C_2-symmetric λ^3-iodanes

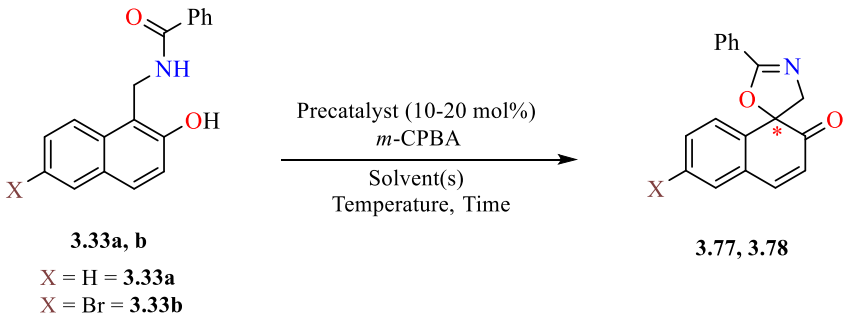
We envisaged that it would be advantageous to convert a few novel iodoarenes to λ^3-iodanes to evaluate them later in the enantioselective spirocyclisation reactions. For this purpose, we chose iodoarene **4.38c** as a model substrate and subjected it to two different conditions that would generate I(III) species.[129, 130] Unfortunately, analysis showed the decomposition of the starting iodoarene therefore the corresponding iodoarene(III) could not be obtained. (Scheme 4.19)



Scheme 4.19: Attempted synthesis of C_2-symmetric iodane(III).

4.2.6. Enantioselective oxidative cyclisation of naphthol amides

Having synthesised novel C_1 and C_2-symmetric iodoarenes containing chiral urea, chiral carbamate, chiral amide and chiral urea-carbamate arms we decided to explore their oxidising potential in the enantioselective naphthol amide spirocyclisation. At the beginning, most of the reactions were carried out in polar aprotic solvents like acetonitrile or acetonitrile in combination with alcoholic solvents however extremely poor enantioselectivities or no enantioselectivities were obtained.



Scheme 4.20: Enantioselective dearomatisation of naphthol amide **3.33a, b** by different C_1 and C_2-symmetric iodoarenes.

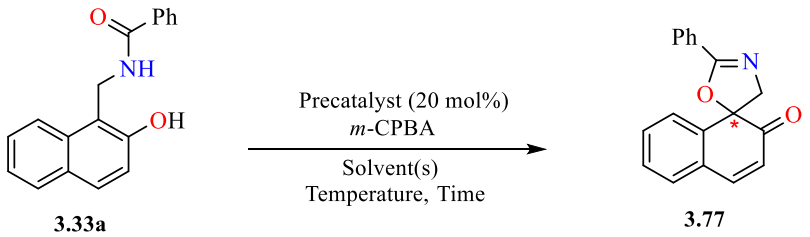
Entry	Reactant	Precatalyst	Solvent(s)	Temp.	Time	Yield (%)[a, b]	*ee*[c] (%)
1	**3.33a**	**4.46** 20 mol%	MeCN	RT	18h	56%[a] 46%[b]	2
2	**3.33a**	**4.28a** 20 mol%	MeCN	RT	18h	23%[a]	–[d]
3	**3.33a**	**4.28b** 20 mol%	MeCN	RT	18h	20%[a]	–[d]
4	**3.33a**	**4.38c** 20 mol%	MeCN	RT	18h	<5%[a]	–[d]
5	**3.33a**	**4.38f** 20 mol%	MeCN	RT	18h	N.R.	–[d]
6	**3.33a**	**4.23** 20 mol%	MeCN	RT	18h	30%[a]	–[d]
7	**3.33a**	**4.38c** 20 mol%	MeCN:EtOH 2:1	RT	18h	68%[a] 41%[b]	1
8	**3.33a**	**4.38c** 20 mol%	HFIP	40 °C	18h	44%[a] 19%[b]	3
9	**3.33b**	**4.38c** 20 mol%	HFIP	40 °C	18h	25%[a] 14%[b]	4
10	**3.33a**	**4.40** 20 mol%	HFIP	40 °C	18h	36%[a]	–[d]
11	**3.33a**	**4.23** 20 mol%	Dry EtOAc	RT	18h	N.R.	N.D.

Table 9: Optimisation of the dearomatisation reaction conditions.

[a] Crude yields were determined by adding 1,3,5-Trimethoxybenzene as internal standard [b] Isolated yields after column chromatography. [c] Enantiomeric excess were determined by using chiralpak IB column (Petroleum ether:Isopropanol 80:20). [d] Pure sample could not be obtained. N.R. = No reaction. N.D. No development

Based upon the obtained results, we concluded that the solvents that performed the best in the racemic series were completely unsuitable for the enantioselective reaction (table 9, entries 1-6 and 8-10). Substituting solvent to ethyl acetate lead to diminished yield while the addition of ethanol as additive along with acetonitrile increased the rate of reaction but at the cost of enantioselectivity. (table 9, entries 7, 11).

Next, we subjected amide **3.33a** to dearomatisation conditions in the presence of C_1 and C_2-symmetric urea based iodoarenes. The results of our investigation are summarised below. (table 10).



3.33a **3.77**

Scheme 4.21: Enantioselective dearomatisation of naphthol amide **3.33a** mediated by different C_1 and C_2-symmetric iodoarenes.

Entry	Reactant	Precatalyst	Solvent(s)	Temp.	Time	Yield (%)[a]	*ee* (%)
1	**3.33a**	**4.38a** 20 mol%	MeCN	– 20 °C (4hr) then RT	18h	30% [a]	_ [b]
2	**3.33a**	**4.38b** 20 mol%	MeCN	– 20 °C (4hr) then RT	18h	<10% [a]	_ [b]
3	**3.33a**	**4.38d** 20 mol%	MeCN	– 20 °C (4hr) then RT	18h	<10% [a]	_ [b]
4	**3.33a**	**4.36** 20 mol%	MeCN	RT	18h	<5% [a]	_ [b]
5	**3.33a**	**4.34** 20 mol%	MeCN	RT	18h	20% [a]	_ [b]
6	**3.33a**	**4.36** 20 mol%	Peracetic acid, DCM, – 10 °C (6hr) then RT			N.R.	N.D.

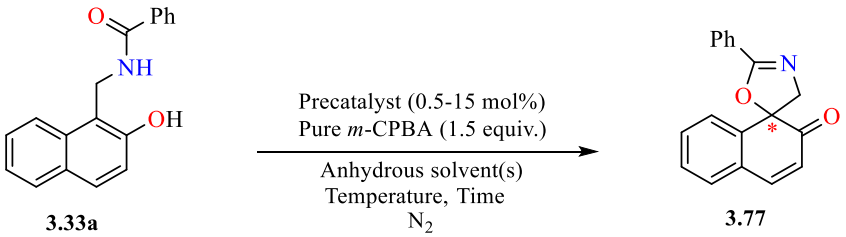
7	**3.33a**	**4.38f** 20 mol%	Selectfluor, TFA, DCM, – 10 ºC (6hr) then RT	N.R.	N.D.

[a] Crude yields were determined by adding 1,3,5-Trimethoxybenzene as internal standard. [b] Pure sample could not be obtained. N.R. = No reaction. N.D. No development

Table 10: Optimisation of the dearomatisation reaction conditions.

Lowering the temperature to -20 °C had a disfavourable effect upon the reaction as it led to lower yields (table 10, entries 1-3). The use of iodoarenes **4.36** and **4.34** also provided poorer yields (table 10, entries 4-5). Trying oxidants other than *m*CPBA failed to produce the desired product and led to complex reaction mixtures (table 10, entries 6-7).

Ishihara *et al*.[92] showed that the addition of alcoholic solvents like HFIP or MeOH to the reaction mixture improved the yield and the *ee* of products of oxidative *ortho*-lactonisation. Accordingly, we decided to carry out further experiments employing similar modifications.



Scheme 4.22: Enantioselective dearomatisation of naphthol amide **3.33a** mediated by different C_1 and C_2-symmetric iodoarenes.

Entry	Reactant	Precatalyst	Solvent(s)	Temp. and Time	Yield (%)[a]	*ee* [c] (%)
1	**3.33a**	**4.23** 10 mol%	DCM	– 78 °C (6hr) then RT 16hr	Traces	N.D.
2	**3.33a**	**4.40** 10 mol%	DCM	– 78 °C (6hr) then RT 16hr	<10%[a]	N.D.
3	**3.33a**	**4.38c** 5 mol%	DCM:MeOH 3:1	– 78 °C (6hr) then RT 16hr	30%[b]	3
4	**3.33a**	**4.46** 10 mol%	DCM:MeOH 3:1	– 78 °C (6hr) then RT 16hr	37%[b]	2
5	**3.33a**	**4.28a** 15 mol%	DCM:MeOH 3:1	– 78 °C (6hr) then RT 16hr	66%[b]	2
6	**3.33a**	**4.28b** 15 mol%	DCM:MeOH 3:1	– 78 °C (6hr) then RT 16hr	66%[b]	1
7	**3.33a**	**4.38b** 15 mol%	DCM:MeOH 3:1	– 78 °C (6hr) then RT 16hr	<10%[a]	N.D.
8	**3.33a**	**4.38e** 15 mol%	DCM:MeOH 3:1	– 78 °C (6hr) then RT 16hr	<5% [a]	N.D.
9	**3.33a**	**4.47** 15 mol%	DCM	RT, 18hr	N.R.	N.D.
10	**3.33a**	**4.38e** 15 mol%	MeOH	RT, 18hr	<5% [a]	N.D.
11	**3.33b**	**4.6** 15 mol%	DCM:MeOH 3:1	– 78 °C (6hr) then RT 16hr	32%[b]	10
12	**3.33b**	**4.38e** 15 mol%	DCM:MeOH 3:1	– 78 °C (6hr) then RT 16hr	21%[b]	7

[a] Crude yields were determined by adding 1,3,5-Trimethoxybenzene as internal standard [b] Isolated yields after column chromatography. [c] Enantiomeric excess were determined by using chiralpak IB column (Petroleum ether:Isopropanol 80:20). N.R. = No reaction. N.D. No development

Table 11: Optimisation of the dearomatisation reaction conditions of amide **3.33a, b**.

It was noted the rate of reaction was slightly faster when anhydrous methanol was added as additive along with dichloromethane however it failed to improve the enantioselectivities (table 11, entries 3-6, 11-12). In some other cases, the use of dichloromethane and methanol were not found to be useful as it led to lower yields (table 11, entries 7-8). It was also observed that the reaction did not proceed as expected upon using iodoarene 4.47, 4.40 and 4.38e. Our analysis of the crude mixture showed the presence of unreacted starting material in all these cases (table 11, entries 2, 8-10).

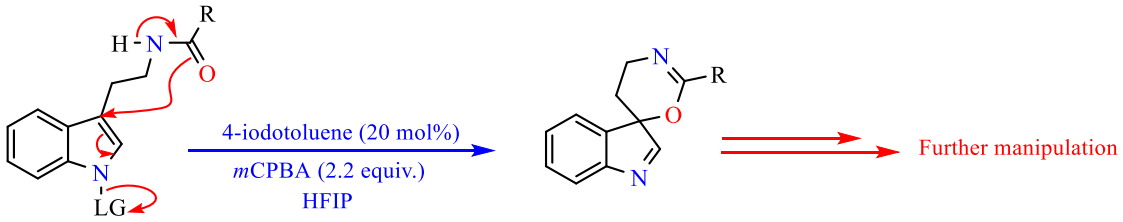
4.2.7. Summary

New chiral C_1 and C_2-symmetric iodoarenes were successfully designed and evaluated in oxidative spirocyclisation of naphthol amides as an attempt to improve the overall yield of the reaction and enantioselectivity. Yet, it remains rather elusive to attain high enantioselectivities and high yields simultaneously. As a matter of fact, the solvents which gave augmented yields resulted in the formation of racemic product whilst the solvents which promote asymmetric induction afforded low yields. The future work will be the continuation of our investigation into developing enantioselective conditions for the cyclisation of naphthol amides by designing and evaluating new chiral iodoarenes.

4.2.8. Future work

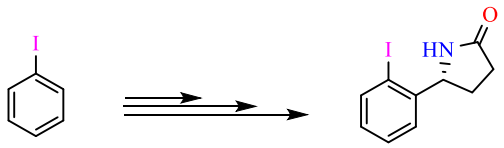
We have described hypervalent iodine(III) promoted dearomatisation of phenol and naphthol amides leading to the formation of a library of novel functionalised spirocycles. Although we have shown a wide reaction scope by altering the aryl/ alkyl substituent attached to the amide moiety to access more than 35 novel oxazoline based spirocycles however research into hypervalent iodine(III) mediated dearomatisation of phenols, naphthols and indoles remains under investigated.

Moreover, the developed strategy for the dearomatisation of phenols and naphthols can be extended to the indoles to access complex oxazoline based spirocycles containing indole derived core. (Scheme 4.23).



Scheme 4.23: Hypervalent iodine(III) mediated dearomatisation of indoles.

Additionally, further investigation into enantioselective dearomatisation of naphthols remains a major challenge. For this purpose, new iodoarene precatalyst(s) containing optically active lactam moiety shall be synthesised and evaluated in order to get enantioenriched naphthol based spirocycles. (scheme 4.24).



Scheme 4.24: Iodoarene precatalyst(s) containing chiral lactam moiety.

Chapter 5 Experimental

Unless otherwise stated, proton (^{1}H NMR, 300, 400 MHz) and carbon (^{13}C NMR, 100, 75 MHz) spectra were recorded in deuterated chloroform ($CDCl_3$) solution at room temperature. Chemical shifts are reported in parts per million (ppm) while the coupling constants, *J*, are in hertz (Hz). Multiplicities are provided as "s" (singlet), "d" (doublet), "t" (triplet), "q" (quartet), "p" (pentet), "dd" (doublet of doublets), "dt" (doublet of triplets), "ddd" (doublet of doublet of doublets), "m" (multiplet), "td" (triplet of doublets). Infrared (IR) spectra (cm–1) were recorded on Nicolet 380 spectrum spotlight system, equipped with a diamond probe ATR attachment. Low and high-resolution mass spectra (m/z) were obtained in the electrospray (ESI) mode. Melting points (uncorrected) were measured on a Stuart SMP10 apparatus.

All reagents and solvents were purchased from commercial sources and used without further purification except THF (freshly distilled from Na/benzophenone under argon). The reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F_{254} pre-coated plates. Spots were visualized with a UV lamp, KMnO4 stain or vanillin stain. Flash chromatographic separations were performed on Aldrich, 35-70μ, 60A silica gel as per literature conditions. Enantiomeric excesses were determined with analytical chiral columns Chiralpak IA and Chiralpak IB with UV detector at 254 nm or 286.16nm.

Synthesis of Benzamides

General Procedure A

To a solution of the amine (2.44 mmol, 1 equiv.) and base (1 equiv.) in DCM (12 mL) at 0 ^{o}C was added an acid chloride (1 equiv.) which was left to stir at room temperature for 1-2 hours. The reaction mixture was diluted with DCM (50 mL), quenched with $NaHCO_3$ (25 mL) and the organic layer was separated and concentrated under vacuum. The obtained residue was diluted with MeOH (25 mL) and DCM (5 mL) and NaOH (1 M, 18 mL) was added. After stirring for 10 minutes at room temperature, TLC analysis showed any bis-acylated product was cleaved to give the desired mono-acylated product. The reaction mixture was acidified with glacial acetic acid until neutral and then concentrated under vacuum. The product was extracted with DCM (50 mL) and washed with brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under

reduced pressure. Organic residues were purified by recrystallisation (MeOH/Petroleum) to give the desired product as a solid. (50-60% yield).

General Procedure B

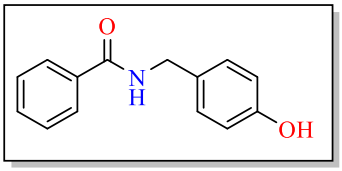
A solution of acyl chloride (2 mmol) in THF (4 mL) was cooled to 0 ^{o}C under nitrogen. Potassium phosphate tribasic (2.5 mmol) was added in one portion followed by the amine (2 mmol). The mixture was stirred for 1-2 hour at room temperature then the reaction mixture was concentrated under reduced pressure. Water (6 mL) and EtOAc (2 mL) were added, the organic layer separated and then washed with 0.5 N HCl (5 mL) followed by water (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by recrystallisation in EtOAc-Hexanes.

General Procedure C

Synthesis of Substituted Naphthol Amides

To the appropriate naphthol or substituted naphthol (1.0 g, 6.94 mmol) and unsaturated hydrocarbon amide (1.05 g, 6.94 mmol) were dissolved in anhydrous ethanol (100 mL). Concentrated sulfuric acid (10 mL) was added dropwise and the reaction mixture was stirred for 7 hours at 50 ^{o}C. After such time, the reaction mixture was cooled down and washed with 1 M NaOH (50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was recrystallised from Hexane-Ethyl acetate to afford the desired product.

Synthesis of *N*-(4-hydroxybenzyl)benzamide 3.1



Procedure A was used to obtain *N*-(4-hydroxybenzyl)benzamide as colourless solid. Yield (1.03 g, 55%).

FT-IR (cm^{-1}): ν = 3397, 3073, 2820, 1614.

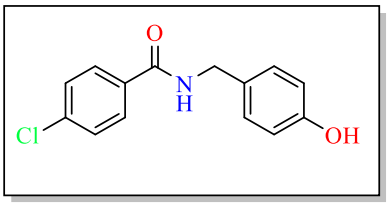
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.31 (br, s, 1H), 8.96 (br, s, 1H), 7.90 (d, *J* = 7.1 Hz, 2H), 7.54-7.44 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.38 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 166.5, 156.7, 134.9, 131.6, 130.3, 129.0, 128.7, 127.7, 115.4, 42.6.

HRMS: m/z calc'd for $C_{14}H_{13}NO_2$ $[M+Na]^+$ 250.0838, found 250.0840.

Melting Point: 151-153 °C.

Synthesis of 4-chloro-*N*-(4-hydroxybenzyl)benzamide 3.2



Compound was prepared using general procedures A as off-white solid (Yield 1.03 g, 49%).

FT-IR (cm^{-1}): ν = 3353, 3176, 2921, 1630.

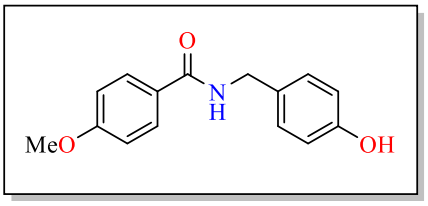
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.29 (s, 1H), 9.02 (br, 1H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 4.35 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 165.3, 156.7, 136.4, 133.6, 130.1, 129.6, 129.1, 128.8, 115.4, 42.7.

HRMS: m/z calc'd for $C_{14}H_{12}ClNO_2$ $[M+H]^+$ 262.0629, found 262.0631.

Melting Point: Literature M.P.[131]: 196-197 °C, **Experimental M.P.** 195-196 °C.

Synthesis of *N*-(4-hydroxybenzyl)-4-methoxybenzamide 3.3



Compound was obtained as off-white crystalline solid through general method B (1.29 g, 61%).

FT-IR (cm^{-1}): ν = 3257, 3009, 2971, 2936, 2836, 1604.

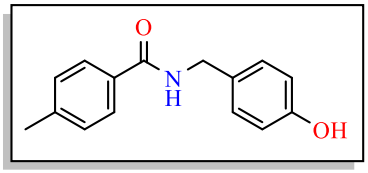
^{1}H NMR: (DMSO-d$_6$, 400 MHz) δ: 9.26 (s, 1H), 8.78 (br, 1H), 7.86 (d, *J* = 8.9 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 4.34 (d, *J* = 6.0 Hz, 2H), 3.80 (s, 3H).

^{13}C NMR: (DMSO-d$_6$, 75 MHz) δ: 165.9, 161.9, 156.6, 131.8, 130.5, 129.5, 127.1, 115.4, 113.9, 55.8, 42.5.

HRMS: m/z calc'd for $C_{15}H_{15}NO_3$ $[M+H]^+$ 258.1125, found 258.1126.

Melting Point: 155-156 ℃.

Synthesis of *N*-(4-hydroxybenzyl)-4-methylbenzamide 3.4



Compound was obtained as light yellow crystalline solid through general method A (Yield 0.35 g, 59%).

FT-IR (cm^{-1}): ν = 3017, 2922, 1628, 1508, 1237, 745.

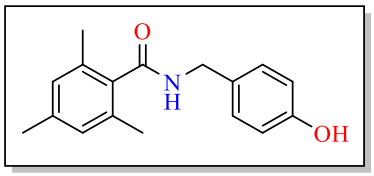
^{1}H NMR: (CDCl3, 400 MHz) δ: 7.67 (d, *J* = 8.1 Hz, 2H), 7.23-7.19 (m, 4H), 6.80 (d, *J* = 8.3 Hz, 2H), 6.33 (t, *J* = 5.7 Hz, 1H), 5.57 (s, 1H), 4.35 (d, *J* = 5.7 Hz, 2H), 2.38 (s, 3H).

^{13}C NMR: (DMSO-d$_6$, 75 MHz) δ: 167.5, 155.5, 142.1, 131.4, 130.0, 129.4, 129.3, 127.0, 115.7, 43.7, 21.5.

HRMS: m/z calc'd for $C_{15}H_{15}NO_2$ $[M+H]^+$ 242.1176, found 242.1180.

Melting Point: 133-134 ℃.

Synthesis of *N*-(4-hydroxybenzyl)-2,4,6-trimethylbenzamide 3.5



Compound was prepared by general method B as pale yellow solid (Yield 0.81 g, 46%).

FT-IR (cm^{-1}): ν = 3373, 3163, 2917, 1620.

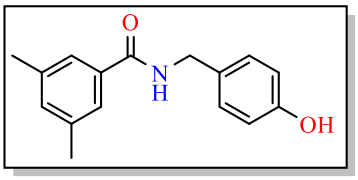
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.29 (s, 1H), 8.61 (br, 1H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.83 (s, 2H), 6.71 (m, 2H), 4.30 (d, *J* = 6.0 Hz, 2H), 2.23 (s, 3H), 2.13 (s, 6H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 169.5, 156.7, 137.5, 136.3, 134.0, 130.0, 129.3, 128.0, 115.4, 42.2, 21.1, 19.3.

HRMS: m/z calc'd for $C_{17}H_{19}NO_2$ $[M+H]^+$ 270.1489, found 270.1496.

Melting Point: 150-151 °C.

Synthesis of *N*-(4-hydroxybenzyl)-3,5-dimethylbenzamide 3.6



Compound was prepared by general method B as beige colour solid (Yield 3.4 g, 63%).

FT-IR (cm^{-1}): ν = 3260, 2914, 1621, 1515.

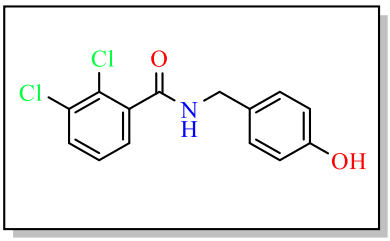
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.28 (s, 1H), 8.83 (t, *J* = 5.9 Hz, 1H), 7.50 (s, 2H), 7.14 (s, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 4.34 (d, *J* = 5.9 Hz, 2H), 2.31 (s, 6H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 166.7, 156.7, 138.0, 135.0, 132.8, 130.4, 129.1, 125.8, 115.4, 42.6, 21.3.

HRMS: m/z calc'd for $C_{16}H_{17}NO_2$ $[M+H]^+$ 256.1332, found 256.1339.

Melting Point: 165-166 °C.

Synthesis of 2,3-dichloro-*N*-(4-hydroxybenzyl)benzamide 3.7



Compound was prepared by general method B as white solid (Yield 1.3 g, 68%).

FT-IR (cm^{-1}): ν = 3331, 3066, 1624, 772.

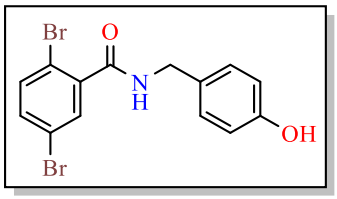
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.33 (s, 1H), 8.96 (t, *J* = 5.6 Hz, 1H), 7.70 (d, *J* = 7.3 Hz, 1H), 7.42-7.34 (m, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 6.74 (d, *J* = 8.2 Hz, 2H), 4.34 (d, *J* = 5.8 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 166.0, 156.8, 139.9, 132.5, 131.4, 129.5, 129.1, 128.9, 128.6, 127.8, 115.5, 42.5.

HRMS: m/z calc'd for $C_{14}H_{11}Cl_2NO_2$ $[M+H]^+$ 296.0240, found 296.0250.

Melting Point: 161-163 °C.

Synthesis of 2,5-dibromo-*N*-(4-hydroxybenzyl)benzamide 3.8



Compound was prepared by general method B as dark brown solid (Yield 1.93 g, 34%).

FT-IR (cm^{-1}): ν = 3290, 3076, 1628, 1580, 1510, 1310, 1225.

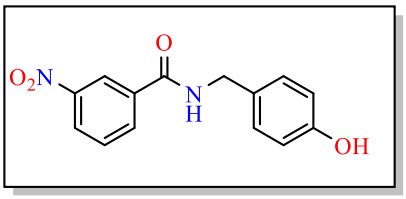
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.32 (s, 1H), 8.94 (t, *J* = 5.7 Hz, 1H), 7.62-7.54 (m, 3H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 2H), 4.32 (d, *J* = 5.8 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 166.1, 156.9, 141.4, 135.2, 134.0, 131.7, 129.4, 129.2, 121.0, 118.6, 115.5, 42.6.

HRMS: m/z calc'd for $C_{14}H_{11}Br_2NO_2$ $[M+H]^+$ 383.9229, found 385.9231.

Melting Point: 187-188 °C.

Synthesis of *N*-(4-hydroxybenzyl)-3-nitrobenzamide 3.9



Compound was prepared by general method A as beige powder (Yield 2 g, 45%).

FT-IR (cm^{-1}): ν = 3080, 3022, 1634, 1530, 1344, 1223.

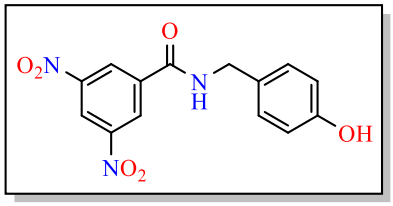
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.50 (s, 1H), 9.35 (t, *J* = 5.7 Hz, 1H), 8.72 (t, *J* = 1.7 Hz, 1H), 8.39-8.32 (m, 2H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.40 (d, *J* = 5.7 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 164.3, 157.0, 148.3, 136.3, 134.2, 130.6, 129.7, 129.3, 126.3, 122.5, 115.5, 43.0.

HRMS: m/z calc'd for $C_{14}H_{12}N_2O_4$ $[M+H]^+$ 273.0870, found 273.0874.

Melting Point: 168-169 °C.

Synthesis of *N*-(4-hydroxybenzyl)-3,5-dinitrobenzamide 3.10



Compound was prepared by general method B as yellow solid (Yield 2.1 g, 45%).

FT-IR (cm^{-1}): ν = 3435, 3107, 1644, 1530, 1350.

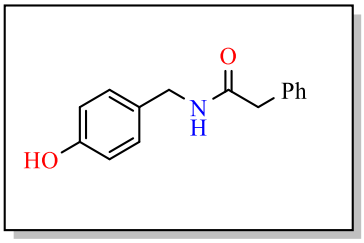
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.64 (t, *J* = 9.3 Hz, 1H), 9.35 (s, 1H), 9.10 (d, *J* = 1.8 Hz, 2H), 9.00 (t, *J* = 1.8 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 2H), 4.44 (d, *J* = 5.5 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 162.3, 157.0, 148.7, 137.4, 129.5, 129.3, 128.1, 121.3, 115.6, 43.3.

HRMS: m/z calc'd for $C_{14}H_{11}N_3O_6$ $[M+H]^+$ 318.0721, found 318.0717.

Melting Point: 204-205 °C.

Synthesis of *N*-(4-hydroxybenzyl)-2-phenylacetamide 3.11



Compound was obtained as white solid through general method B (0.91g, 46%).

FT-IR (cm^{-1}): ν = 3218, 3060, 1612, 1588, 1482.

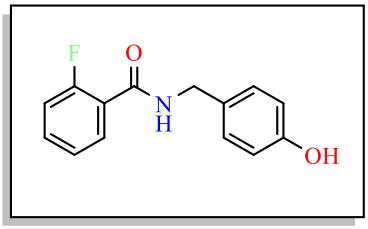
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.29 (s, 1H), 8.43 (br, 1H), 7.32-7.22 (m, 5H), 7.03 (d, J= 8.5 Hz, 2H), 6.69 (d, J= 8.5 Hz, 2H), 4.41 (d, J= 6.0 Hz, 2H), 3.44 (s, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 170.3, 156.7, 136.9, 130.0, 129.4, 129.0, 128.6, 126.7, 115.4, 42.8, 42.3.

HRMS: m/z calc'd for $C_{15}H_{15}NO_2$ $[M+H]^+$ 241.1103, found 241.1110.

Melting Point: 173-175 °C.

Synthesis of 2-fluoro-*N*-(4-hydroxybenzyl)benzamide 3.12



Compound was prepared by general method B as beige coloured solid (Yield 1.40 g, 54%).

FT-IR (cm^{-1}): ν = 3400, 3224, 3078, 1614.

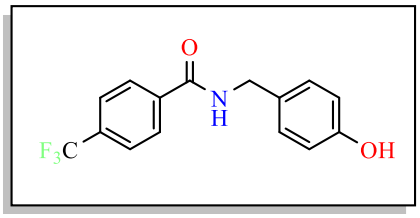
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.30 (s, 1H), 8.74 (t, *J* = 6.0 Hz, 1H), 7.63-7.57 (m, 1H), 7.52-7.47 (m, 1H), 7.30-7.24 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 4.33 (d, *J* = 5.9 Hz, 2H)

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 164.0, 159.6 (d, *J* = 248.6 Hz), 156.7, 132.7 (d, *J* = 8.4 Hz), 130.5 (d, *J* = 3.3 Hz), 129.8, 128.9, 124.9 (d, *J* = 3.3 Hz), 124.7 (d, *J* = 14.6 Hz), 116.5 (d, *J* = 22.3 Hz), 115.5, 42.6.

HRMS: m/z calc'd for $C_{14}H_{12}FNO_2$ $[M+H]^+$ 246.0925, found 246.0928.

Melting Point: 129-130 ℃.

Synthesis of *N*-(4-hydroxybenzyl)-4-(trifluoromethyl)benzamide 3.13



Compound was prepared by general method A as white solid (Yield 1.5 g, 78%).

FT-IR (cm^{-1}): ν = 3355, 3193, 1635, 1190.

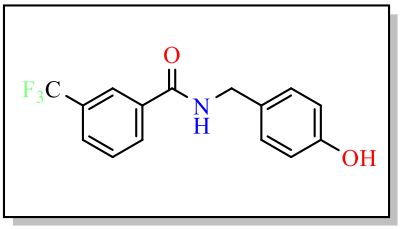
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.30 (s, 1H), 9.18 (t, *J* = 5.6 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.14-7.12 (m, 2H), 6.73-6.70 (m, 2H), 4.38 (d, *J* = 5.7 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 165.2, 156.7, 138.6, 131.7, 131.3, 129.9, 129.1, 128.6, 125.8 (q, *J* = 272 Hz), 115.5, 42.8.

HRMS: m/z calc'd for $C_{15}H_{12}F_3NO_2$ $[M+H]^+$ 296.0893, found 296.0896.

Melting Point: 155-156 ℃.

Synthesis of *N*-(4-hydroxybenzyl)-3-(trifluoromethyl)benzamide 3.14



Compound was prepared by general method A as light pink solid (Yield 1.2 g, 63%).

FT-IR (cm^{-1}): ν = 3307, 3139, 1632, 1441.

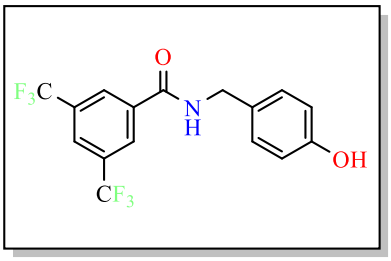
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.34 (s, 1H), 9.21 (t, *J* = 5.7 Hz, 1H), 8.23 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J*= 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 4.39 (d, *J* = 5.8 Hz, 2H),

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 165.01, 156.8, 135.7, 131.8, 130.1, 129.8, 129.7, 129.4, 129.2, 128.2 (q, *J* = 32.0 Hz), 124.2 (q, *J* = 272.2 Hz), 115.5, 42.8.

HRMS: m/z calc'd for $C_{15}H_{12}F_3NO_2$ $[M+H]^+$ 296.0893, found 296.0898.

Melting Point: 154-155 °C.

Synthesis of *N*-(4-hydroxybenzyl)-3,5-bis(trifluoromethyl)benzamide 3.15



Compound was prepared by general method A as pink solid (Yield 2.4 g, 68%).

FT-IR (cm^{-1}): ν = 3272, 3140, 1642, 1286, 1142.

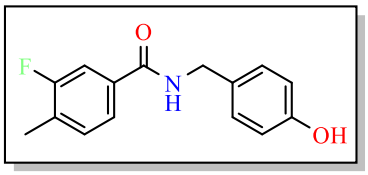
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.42 (t, *J* = 5.6 Hz, 1H), 9.34 (s, 1H), 8.54 (s, 2H), 8.31 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.42 (d, *J* = 5.7 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 163.4, 156.9, 137.0, 131.0 (q, *J* = 33.1 Hz), 129.5, 129.4, 128.6 (q, *J* = 2.8 Hz), 125.3 (q, *J* = 3.5 Hz), 123.7 (q, *J* = 273.1 Hz), 115.5, 43.1.

HRMS: m/z calc'd for $C_{16}H_{11}F_6NO_2$ $[M+H]^+$ 364.0772, found 364.0770.

Melting Point: 176-177 °C.

Synthesis of 3-fluoro-*N*-(4-hydroxybenzyl)-4-methylbenzamide 3.16



Compound was prepared by general method B as pink solid (Yield 1.78 g, 53%).

FT-IR (cm^{-1}): ν = 3314, 3012, 1630.

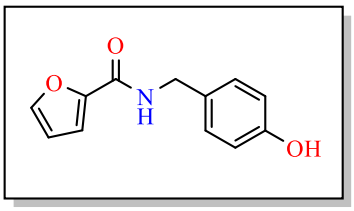
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.30 (s, 1H), 8.96 (t, *J* = 5.8 Hz, 1H), 7.64 (m, 2H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J*= 8.4 Hz, 2H), 4.40 (d, *J* = 5.9 Hz, 2H), 2.30 (s, 3H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 165.1 (d, *J* = 2.3 Hz), 162.0, 159.6, 156.7, 134.6 (d, *J* = 7.0 Hz), 132.0 (d, *J* = 5.1 Hz), 130.1, 129.1, 128.2 (d, *J* = 17.5 Hz), 123.5 (d, *J* = 3.4 Hz), 115.5, 114.1 (d, *J* = 23.6 Hz), 42.7, 14.6 (d, *J* = 3.3 Hz).

HRMS: m/z calc'd for $C_{15}H_{14}FNO_2$ $[M+H]^+$ 260.1081, found 260.1086.

Melting Point: 131-132 °C.

Synthesis of *N*-(4-hydroxybenzyl)furan-2-carboxamide 3.17



Compound was prepared by general method B as pink solid (Yield 1.15 g, 65%).

FT-IR (cm^{-1}): ν = 3119, 2815, 1633, 1591, 1513, 1221, 1184, 1038.

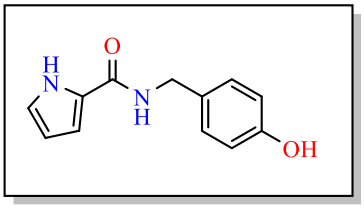
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.29 (s, 1H), 8.81 (t, *J* = 6.0 Hz, 1H), 7.83 (s, 1H), 7.12-7.10 (m, 3H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.62-6.61 (m, 1H), 4.31 (d, *J* = 6.1 Hz, 2H).

^{13}C NMR: (DMSO-d$_6$, 75MHz) δ: 158.1, 156.7, 148.4, 145.4, 130.1, 129.1, 115.4, 113.8, 112.3, 41.9.

HRMS: m/z calc'd for $C_{12}H_{11}NO_3$ $[M+H]^+$ 218.0812, found 218.0815.

Melting Point: 162-163 °C.

Synthesis of *N*-(4-hydroxybenzyl)-1*H*-pyrrole-2-carboxamide 3.18



Compound was prepared by general method B as brick red powder (Yield 1.37, 39%).

FT-IR (cm^{-1}): ν = 3417, 3115, 2838, 1650, 1526, 1513, 1334, 1188.

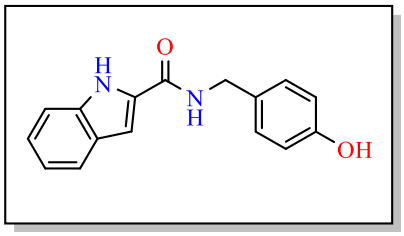
^{1}H NMR: (DMSO-d$_6$, 400 MHz) δ: 11.44 (s, 1H), 9.30 (s, 1H), 8.41 (t, *J* = 6.0 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.86-6.84 (m, 1H), 6.81-6.80 (m, 1H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.10-6.06 (m, 1H), 4.31 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR: (DMSO-d$_6$, 75MHz) δ: 161.0, 156.6, 130.7, 129.0, 126.8, 121.7, 115.4, 110.3, 109.0, 41.8.

HRMS: m/z calc'd for $C_{12}H_{12}N_2O_2$ $[M+H]^+$ 217.0972, found 217.0976.

Melting Point: 175-176 °C.

Synthesis of *N*-(4-hydroxybenzyl)-1H-indole-2-carboxamide 3.19



Compound was prepared by general method A as red solid (Yield 1.37, 39%).

FT-IR (cm^{-1}): ν = 3407, 3248, 1631, 1613, 1596, 1574, 1446, 1233.

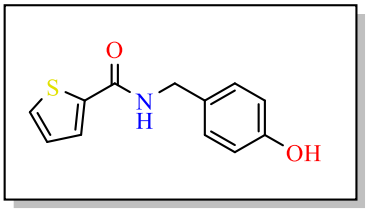
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 11.60 (s, 1H), 9.31 (s, 1H), 8.92 (t, *J* = 6.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.19-7.14 (m, 4H), 7.05-7.01 (m, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.40 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75MHz) δ: 161.4, 156.7, 136.9, 132.2, 130.2, 129.1, 127.6, 123.7, 122.0, 120.1, 115.5, 112.8, 103.0, 42.2.

HRMS: m/z calc'd for $C_{16}H_{15}N_2O_2^+$ $[M+H]^+$ 267.1128, found 267.1129.

Melting Point: 175-176 °C.

Synthesis of *N*-(4-hydroxybenzyl)thiophene-2-carboxamide 3.20



Compound was prepared by general method B as light brown solid (Yield 0.97 g, 51%).

FT-IR (cm^{-1}): ν = 3073, 2827, 1613, 1548, 1510, 1239.

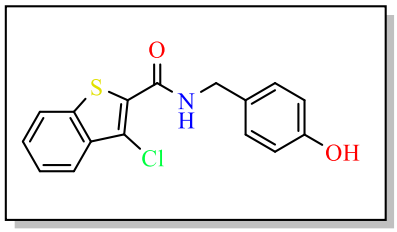
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.29 (s,1H), 8.93 (t, *J* = 5.8 Hz, 1H), 7.80 (d, *J* = 3.7 Hz, 1H), 7.74 (d, *J* = 5.0 Hz, 1H), 7.13 (m, 3H), 6.72 (d, *J* = 8.4 Hz, 2H), 4.34 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 161.4, 156.8, 140.6, 131.2, 130.1, 129.1, 128.4, 128.3, 115.6, 42.7.

HRMS: m/z calc'd for $C_{12}H_{11}NO_2S$ $[M+H]^+$ 234.0583, found 234.0587.

Melting Point: 191-192 °C.

Synthesis of 3-chloro-*N*-(4-hydroxybenzyl)benzo[*b*]thiophene-2-carboxamide 3.21



Compound was prepared by general method B as light brown crystalline solid (Yield 0.2 g, 78%).

FT-IR (cm^{-1}): ν = 3242, 3062, 2357, 1606, 1519, 1268, 1239.

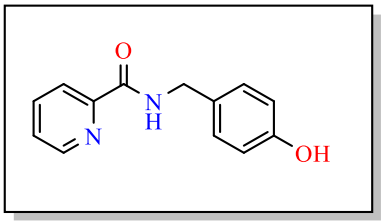
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.34 (s, 1H), 8.90 (t, *J* = 5.8 Hz, 1H), 8.12 (m, 1H), 7.90 (m, 1H), 7.60 (m, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.74 (d, *J* = 8.3 Hz, 2H), 4.41 (d, *J* = 5.9 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 160.7, 156.9, 137.1, 136.5, 132.9, 129.5, 129.2, 128.0, 126.4, 124.0, 123.0, 119.2, 115.6, 43.1.

HRMS: m/z calc'd for $C_{16}H_{12}ClNO_2S$ $[M+H]^+$ 318.0350, found 318.0350.

Melting Point: 200-201 °C.

Synthesis of *N*-(4-hydroxybenzyl)picolinamide 3.22



Compound was prepared by general method B as brown solid (Yield 1.16 g, 61%).

FT-IR (cm^{-1}): ν = 3175, 2850, 1632, 1531, 1514, 1231.

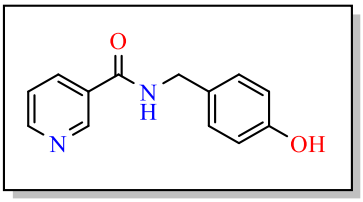
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.30 (s, 1H), 9.18 (t, *J* = 5.8 Hz, 1H), 8.62-8.61 (m, 1H), 8.05-7.95 (m, 2H), 7.59-7.56 (m, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.70 (d, *J* = 8.2 Hz, 2H), 4.40 (d, *J* = 6.2 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 164.2, 156.8, 150.6, 148.9, 138.2, 130.2, 129.3, 126.9, 122.4, 115.5, 42.5.

HRMS: m/z calc'd for m/z calc'd for $C_{13}H_{12}N_2O_2$ $[M+H]^+$ 229.0972, found 229.0975.

Melting Point: 182-184 °C.

Synthesis of *N*-(4-hydroxybenzyl)nicotinamide 3.23



Compound was prepared by general method B as pale yellow solid (Yield 0.96 g, 47%).

FT-IR (cm^{-1}): ν = 3173, 2847, 1638, 1542, 1525, 1236.

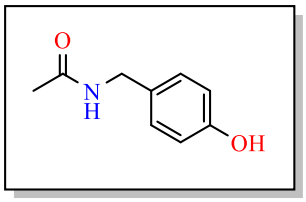
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.31 (s, 1H), 9.14 (t, *J* = 5.6 Hz, 1H), 9.04 (d, *J* = 1.7 Hz, 1H), 8.71-8.69 (m, 1H), 8.21 (d, *J* = 7.9 Hz, 1H), 7.51 (dd, J_1 = 7.9, J_2 = 4.8 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 6.72 (d, *J* = 8.3 Hz, 2H), 4.40 (d, *J* = 5.9 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 165.1, 156.8, 152.3, 148.9, 135.5, 130.4, 129.9, 129.1, 123.9, 122.4, 115.5, 42.5.

HRMS: m/z calc'd for m/z calc'd for $C_{13}H_{12}N_2O_2$ $[M+H]^+$ 229.0972, found 229.0980.

Melting Point: 183-186 °C.

Synthesis of *N*-(4-hydroxybenzyl)acetamide 3.24



Compound was prepared by general method A as pale yellow sticky solid (Yield 0.28 g, 42%).

FT-IR (cm^{-1}): ν = 3017, 2812, 2690, 1626, 1593, 1514, 1222.

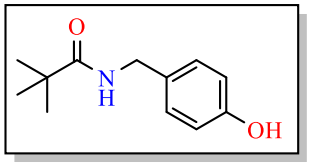
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.28 (s, 1H), 8.21 (t, *J* = 5.8 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.70 (d, *J* = 8.3 Hz, 2H), 4.11 (d, *J* = 5.8 Hz, 2H), 1.84 (s, 3H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 169.4, 156.7, 130.2, 129.1, 115.5, 42.4, 23.2.

HRMS: m/z calc'd for $C_9H_{11}NO_2$ $[M+H]^+$ 166.0863, found 166.0862.

Melting Point: 116-117 °C.

Synthesis of *N*-(4-hydroxybenzyl)pivalamide 3.25



Compound was prepared by general method B as brown solid (0.8 g, 48%).

FT-IR (cm^{-1}): ν = 3418, 3121, 2963, 2932, 1627.

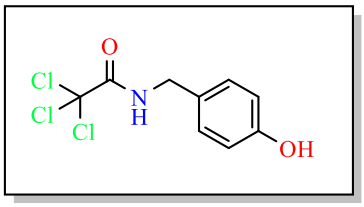
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.23 (s, 1H), 7.92 (br, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H), 4.14 (d, *J* = 6.0 Hz, 2H), 1.11 (s, 9H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 177.6, 156.5, 130.8, 128.5, 115.3, 42.0, 38.4, 27.9.

HRMS: m/z calc'd for $C_{12}H_{17}NO_2$ $[M+H]^+$ 208.1332, found 208.1337.

Melting Point: 135-136 °C.

Synthesis of 2,2,2-trichloro-*N*-(4-hydroxybenzyl)acetamide 3.26



Compound was prepared by general method B as pale yellow sticky solid (Yield 0.31 g, 49%).

FT-IR (cm^{-1}): ν = 3250, 3061, 2850, 1631, 1556, 1385, 1254.

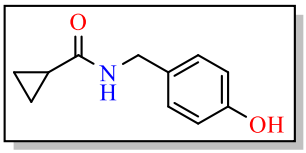
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.28 (s, 1H), 8.21 (t, *J* = 5.8 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.70 (d, *J* = 8.3 Hz, 2H), 4.11 (d, *J* = 5.8 Hz, 2H), 1.84 (s, 3H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 169.4, 156.7, 130.2, 129.1, 115.5, 42.4, 23.2.

HRMS: m/z calc'd for $C_9H_9Cl_3NO_2^+$ $[M+H]^+$ 267.9693, found 267.9698.

Melting Point: 141-142 °C.

Synthesis of *N*-(4-hydroxybenzyl)cyclopropanecarboxamide 3.27



Compound was prepared by general method B as pink solid (Yield 0.21 g, 30%).

FT-IR (cm^{-1}): ν = 3280, 3181, 2954, 1634, 1599, 1575, 1385, 1246.

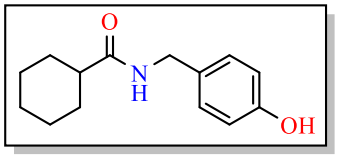
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.29 (s, 1H), 8.42 (t, *J* = 5.5 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.70 (d, *J* = 7.9 Hz, 2H), 4.15 (d, *J* = 6.0 Hz, 2H), 1.60-1.55 (m, 1H), 0.71-0.61 (m, 4H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 172.8, 156.7, 130.2, 129.1, 115.4, 42.3, 14.0, 6.6.

HRMS: m/z calc'd for $C_{11}H_{14}NO_2$ $[M+H]^+$ 192.1019, found 192.1022.

Melting Point: 115-118 °C.

Synthesis of *N*-(4-hydroxybenzyl)cyclohexanecarboxamide 3.29



Compound was prepared by general method B as beige coloured solid (Yield 0.53 g, 61%).

FT-IR (cm^{-1}): ν = 3277, 2929, 2853, 1625, 1592, 1541, 1515, 1366, 1207, 1169.

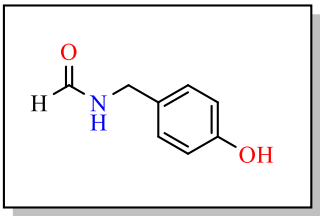
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.24 (s, 1H), 8.07 (t, *J* = 5.8 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.67 (d, *J* = 8.3 Hz, 2H), 4.10 (d, *J* = 5.9 Hz, 2H), 2.15-2.07 (m, 1H), 1.69-1.58 (m, 5H), 1.37-1.1 (m, 6H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 175.4, 156.6, 130.4, 128.7, 115.4, 44.5, 41.8, 29.7, 26.0, 25.7.

HRMS: m/z calc'd for $C_{14}H_{20}NO_2$ $[M+H]^+$ 234.1489, found 234.1488.

Melting Point: 119-120 °C.

Synthesis of *N*-(4-hydroxybenzyl)formamide 3.30



Compound was prepared by using known literature procedure as yellow solid.[132] (Yield 2.3 g, 95%).

FT-IR (cm^{-1}): ν = 3254, 3023, 2889, 2818, 2692, 1651, 1597, 1537, 1512, 1455, 1381, 1330, 1245, 1172, 1085, 828.

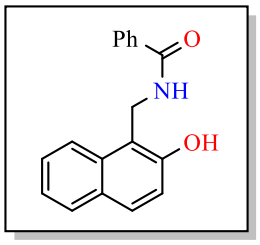
^{1}H NMR: ($CDCl_3$, 300 MHz) δ: 8.30 (s, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 5.80 (s, 1H), 5.10 (s, 1H), 4.43 (d, *J* = 5.8 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 161.3, 156.7, 129.5, 129.1, 115.5, 40.7.

HRMS: m/z calc'd for $C_8H_{10}NO_2$ $[M+H]^+$ 152.0706, found 152.0710.

Melting Point: Literature M.P.[132] 124-126 °C, **Experimental M.P.** 121-123 °C.

Synthesis of *N*-((2-hydroxynaphthalen-1-yl)methyl)benzamide 3.33a



Compound was prepared by general method C as light brown solid (Yield 2.74 g, 71%).

FT-IR (cm^{-1}): ν = 3265, 3130, 1660, 1650.

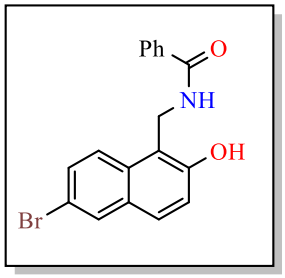
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 10.29 (s, 1H), 9.12 (t, *J* = 5.1 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.91-7.89 (m, 2H), 7.82-7.77 (m, 2H), 7.47 (m, 4H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 8.9 Hz, 1H), 4.88 (d, *J* = 5.2 Hz, 2H).

^{13}C NMR: (DMSO-d$_6$, 75 MHz) δ: 168.0, 154.4, 134.1, 133.8, 131.9, 129.8, 128.7, 127.9, 126.9, 123.3, 123.1, 119.4, 116.1, 34.9.

HRMS: m/z calc'd for $C_{18}H_{15}NO_2$ $[M+H]^+$ 278.1176, found 278.1181.

Melting Point: 177-178 °C.

Synthesis of *N*-((6-bromo-2-hydroxynaphthalen-1-yl)methyl)benzamide 3.33b



Compound was prepared by general method C as pale yellow solid (Yield 0.95 g, 59%).

FT-IR (cm^{-1}): ν = 3462, 3425, 3148, 1624, 1572, 1501, 1293.

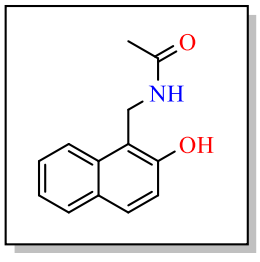
^{1}H NMR: (DMSO-d$_6$, 400 MHz) δ: 10.40 (s, 1H), 9.07 (t, *J* = 5.1 Hz, 1H), 8.09 (d, *J* = 2.1 Hz, 1H), 8.03 (d, *J* = 9.1 Hz, 1H), 7.88-7.86 (m, 2H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.59 (dd, J_1= 9.1 Hz, J_2 = 2.2 Hz, 1H), 7.54-7.52 (m, 1H), 7.46-7.42 (m, 2H), 7.25 (d, *J* = 9.0 Hz, 1H), 4.84 (d, *J* = 5.2 Hz, 2H).

^{13}C NMR: (DMSO-d$_6$, 75 MHz) δ: 167.8, 154.8, 134.1, 132.5, 131.9, 130.4, 130.0, 129.7, 129.0, 128.7, 127.9, 125.8, 120.5, 116.5, 115.9, 34.7.

HRMS: m/z calc'd for $C_{18}H_{14}BrNO_2$ $[M+H]^+$ 356.0281, found 356.0282.

Melting Point: 211-212 °C.

Synthesis of *N*-((2-hydroxynaphthalen-1-yl)methyl)acetamide 3.33c



Compound was prepared by general method C as beige solid (Yield 0.8 g, 53%).

FT-IR (cm^{-1}): ν = 3243, 3097, 2357, 2340, 1622, 1555, 1225.

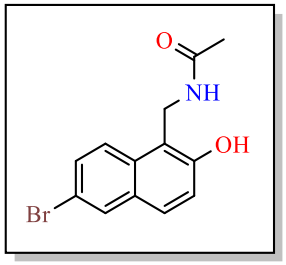
^{1}H NMR: (DMSO-d$_6$, 400 MHz) δ: 10.16 (s, 1H), 8.46 (t, *J* = 5.0 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.50-7.45 (m, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 4.62 (d, *J* = 5.4 Hz, 2H), 1.84 (s, 3H).

^{13}C NMR: (DMSO-d$_6$, 75 MHz) δ: 170.7, 154.2, 133.7, 129.7, 128.7, 128.6, 127.0, 123.2, 123.1, 119.3, 116.3, 34.0, 22.7.

HRMS: m/z calc'd for $C_{13}H_{13}NO_2$ $[M+H]^+$ 216.1019, found 216.1022.

Melting Point: 163-164 ℃.

Synthesis of *N*-((6-bromo-2-hydroxynaphthalen-1-yl)methyl)acetamide 3.33d



Compound was prepared by general method C as pale yellow solid (Yield 1.67 g, 63%).

FT-IR (cm^{-1}): ν = 3316, 3163, 1620, 1551, 1255, 1158, 1075.

^{1}H NMR: (DMSO-d$_6$, 400 MHz) δ: 10.32 (s, 1H), 8.42 (t, *J* = 5.0 Hz, 1H), 8.10 (d, *J* = 2.1 Hz, 1H), 7.90 (d, *J* = 9.1 Hz, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.55 (dd, J_1 = 9.1 Hz, J_2 = 2.1 Hz, 1H), 7.22 (d, *J* = 8.9 Hz, 1H), 4.60 (d, *J* = 5.4 Hz, 2H), 1.81 (s, 3H).

^{13}C NMR: (DMSO-d$_6$, 75 MHz) δ: 170.9, 154.7, 132.3, 130.4, 129.9, 129.7, 128.9, 125.7, 120.4, 116.7, 115.4, 34.0, 22.7.

HRMS: m/z calc'd for $C_{13}H_{12}BrNO_2$ $[M+H]^+$ 294.0124, found 294.0128.

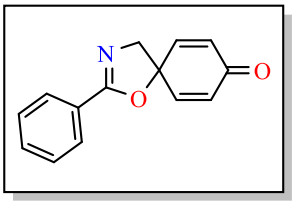
Melting Point: 197-198 ℃.

Synthesis of Spirocycles

General Procedure D for Cyclisation of Benzamide and Naphthol Amide Analogues

To a stirred solution of amide (1 equiv.) in solvent (6 mL) was added *m*-CPBA (2.2 equiv.) and 4-iodotoluene (40 mol %). The resulting mixture was stirred overnight at room temperature. After such time, saturated solution of $NaHCO_3$ (6 mL) was added to the reaction mixture followed by the addition of water (6 mL). The organic layer was extracted by using ethyl acetate (10 mL x 3), dried over $MgSO_4$, filtered and concentrated to afford the corresponding spirocycles.

Synthesis of 2-phenyl-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.37



Compound was synthesised according to the aforementioned general procedure D as brown oil (158 mg, 67%).

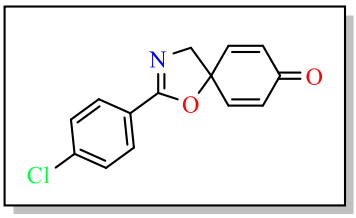
FT-IR (cm^{-1}): ν = 3160, 2991, 1668, 1650, 1630, 1251.

^{1}H NMR: (DMSO, 400 MHz) δ: 7.90 (d, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 9.9 Hz, 2H), 6.27 (d, *J* = 9.9 Hz, 2H), 4.13 (s, 2H).

^{13}C NMR: (DMSO, 75 MHz) δ: 185.0, 162.1, 147.7, 132.1, 129.2, 128.5, 128.4, 127.1, 79.5, 64.1.

HRMS: m/z calc'd for $C_{14}H_{12}NO_2$ $[M+H]^+$ 227.0946, found 227.0945.

Synthesis of 2-(4-chlorophenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.38



Compound was obtained as brown solid (33 mg, 65 %) using the general procedure D.

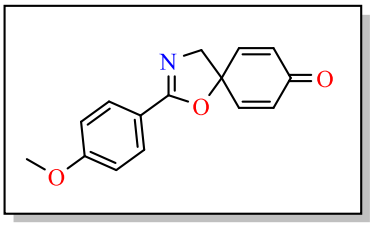
FT-IR (cm^{-1}): ν = 3052, 2920, 2870, 1714, 1672, 1653, 1635, 1596, 1490, 1337, 1261.

^{1}H NMR: [$CDCl_3$, 400 MHz)] δ: 7.88 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 10.0 Hz, 2H), 6.30 (d, *J* = 10.0 Hz, 2H), 4.12 (s, 2H).

^{13}C NMR: [$(CD_3)_2CO$, 75 MHz) δ: 184.3, 164.3, 155.6, 136.6, 130.0, 129.1, 129.0, 128.9, 79.5, 64.4.

HRMS: m/z calc'd for $C_{14}H_{10}ClNO_2$ $[M+H]^+$ 260.0473, found 260.0477.

Synthesis of 2-(4-methoxyphenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.39



Compound was synthesised using general procedure D as colourless oil (28 mg, 56 %).

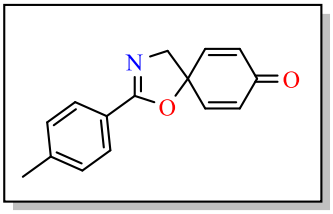
FT-IR (cm^{-1}): ν = 3080, 2925, 1666, 1648, 1632, 1608, 1253.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.87 (d, *J* = 8.8 Hz, 2H), 6.95-6.91 (m, 4H), 6.27 (d, *J* = 9.9 Hz, 2H), 4.08 (s, 2H), 3.84 (s, 3H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.8, 163.3, 162.6, 146.3, 130.2, 128.8, 119.1, 114.0, 79.1, 64.5, 55.5.

HRMS: m/z calc'd for $C_{15}H_{13}NO_3$ $[M]^+$ 256.0968, found 256.0970.

Synthesis of 2-(*p*-tolyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.40



Compound was synthesised using general procedure D as light brown oil (13 mg, 26 %).s

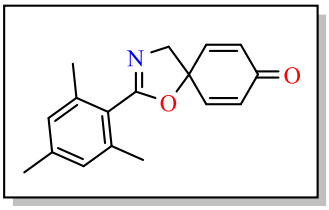
FT-IR (cm^{-1}): ν = 3110, 2935, 1664, 1646, 1532, 1083, 973.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.86 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 9.7 Hz, 2H), 6.97 (d, *J* = 9.9 Hz, 2H), 6.32 (d, *J* = 9.9 Hz, 2H), 4.14 (s, 2H), 2.43 (s, 3H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.7, 163.5, 146.2, 142.6, 129.3, 128.8, 128.4, 124.0, 79.1, 64.6, 21.6.

HRMS: m/z calc'd for $C_{15}H_{14}O_2$ $[M+H]^+$ 240.1019, found 240.1022.

Synthesis of 2-mesityl-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.41



Compound was obtained through general procedure D as pale yellow oil (36 mg, 36 %).

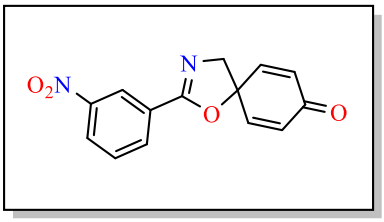
FT-IR (cm^{-1}): ν = 3040, 2921, 2830, 1716, 1671, 1635, 1611, 1574, 1429, 1248.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 6.94 (d, *J* = 10.0 Hz, 2H), 6.86 (s, 2H), 6.25 (d, *J* = 10.0 Hz, 2H), 4.12 (s, 2H), 2.34 (s, 6H), 2.25 (s, 3H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.7, 163.9, 146.1, 140.1, 137.0, 128.7, 128.5, 124.6, 78.8, 64.6, 21.2, 19.9.

HRMS: m/z calc'd for $C_{17}H_{17}NO_2$ $[M+H]^+$ 268.1332, found 268.1341.

Synthesis of 2-(3-nitrophenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.42



Compound was synthesised using general procedure D as pale yellow oil (30 mg, 60 %).

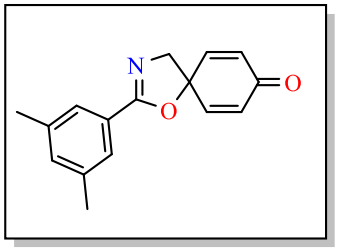
FT-IR (cm^{-1}): ν = 3059, 2976, 2871, 1695, 1645, 1635, 1579, 1449, 1347, 1265, 1212.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 8.79 (t, *J* = 1.93 Hz, 1H), 8.41-8.37 (m, 1H), 8.31-8.28 (m, 1H), 7.66 (t, *J* = 8.20 Hz, 1H), 6.95 (d, *J* = 10.1 Hz, 2H), 6.33 (d, *J* = 10.1 Hz, 2H), 4.19 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.4, 161.4, 145.2, 134.1, 129.8, 129.2, 128.5, 126.4, 123.5, 79.9, 64.7.

HRMS: m/z calc'd for $C_{14}H_{10}N_2O_4$ $[M+H]^+$ 271.0713, found 271.0719.

Synthesis of 2-(3,5-dimethylphenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.43



Compound was synthesised using general procedure D as yellow oil (56 mg, 56 %).

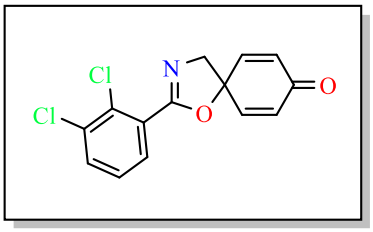
FT-IR (cm^{-1}): ν = 3102, 1672, 1652, 1634, 1601, 1209.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.60 (s, 2H), 7.20 (s, 1H), 6.94 (d, *J* = 10.0 Hz, 2H), 6.29 (d, *J* = 10.0 Hz, 2H), 4.14 (s, 2H), 2.40 (s, 6H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.8, 163.9, 146.2, 138.4, 135.9, 134.0, 129.0, 126.3, 79.2, 64.6, 21.3.

HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{15}NO_2$ 254.1176, found 254.1180.

Synthesis of 2-(2,3-dichlorophenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.44



Compound was synthesised using general procedure D as colourless oil (30 mg, 30 %).

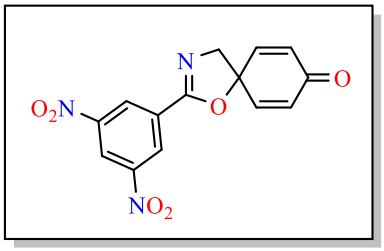
FT-IR (cm^{-1}): ν = 3060, 2991, 1667, 1634, 1414, 1195.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.69-7.67 (m, 1H), 7.63-7.60 (m, 1H), 7.31-7.27 (m, 1H), 7.00 (d, *J* = 10.0 Hz, 2H), 6.32 (d, *J* = 10.0 Hz, 2H), 4.20 (s, 2H),

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.6, 161.7, 145.6, 134.7, 133.1, 132.1, 129.6, 129.1, 128.4, 127.3, 79.6, 64.8.

HRMS: m/z calc'd for $C_{14}H_9Cl_2NO_2$ $[M+H]^+$ 294.0083, found 294.0080.

Synthesis of 2-(3,5-dinitrophenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.45



Compound was synthesised using general procedure D as yellow oil (50 mg, 50 %).

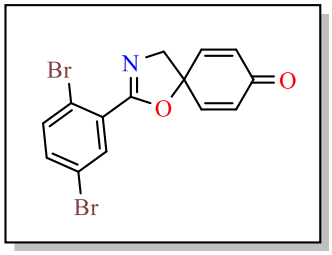
FT-IR (cm^{-1}): ν = 3069, 1664, 1632, 1538, 1342, 1281, 1251.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 9.19-9.18 (m, 1H), 9.10-9.09 (m, 2H), 6.94 (d, *J* = 9.9 Hz, 2H), 6.36 (d, *J* = 9.9 Hz, 2H), 4.24 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.2, 159.7, 148.7, 144.6, 141.3, 129.5, 128.3, 121.4, 80.8, 65.0.

HRMS: m/z calc'd for $C_{14}H_9N_3O_6$ $[M+H]^+$ 316.0564, found 316.0564.

Synthesis of 2-(2,5-dibromophenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.46



Compound was synthesised using general procedure D as light brown oil (32.5 mg, 65 %).

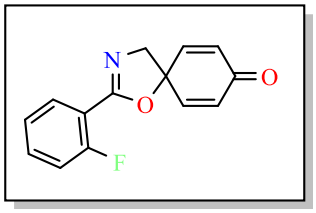
FT-IR (cm^{-1}): ν = 3063, 2920, 2841, 1718, 1670, 1634, 1576, 1455, 1238.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.90 (d, *J* = 2.5 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.45 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 6.99 (d, *J* = 10.0 Hz, 2H), 6.32 (d, *J* = 10.0 Hz, 2H), 4.20 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.6, 161.5, 145.4, 135.6, 135.3, 134.8, 129.8, 129.1, 121.2, 120.8, 79.9, 64.8.

HRMS: m/z calc'd for $C_{14}H_9Br_2NO_2$ $[M+H]^+$ 381.9073, found 381.9070.

Synthesis of 2-(2-fluorophenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.47



Compound was synthesised using general procedure as D light brown oil (51 mg, 86 %).

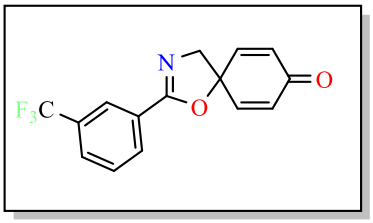
FT-IR (cm^{-1}): ν = 3115, 2936, 2856, 1654, 1641, 1536, 1066, 978, 756, 695.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.90-7.84 (m, 1H), 7.54-7.46 (m, 1H), 7.23-7.14 (m, 2H), 6.95 (d, *J* = 10.1 Hz, 2H), 6.30 (d, *J* = 10.1 Hz, 2H), 4.17 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.6, 161.5 (d, *J* = 259 Hz), 145.8, 133.6 (d, *J* = 8.9 Hz), 131.1, 129.0, 124.2 (d, *J* = 3.7 Hz), 116.9 (d, *J* = 21.7 Hz), 115.0 (d, *J* = 10.1 Hz), 78.7, 65.0.

HRMS: m/z calc'd for $C1_4H_{10}FNO_2$ $[M+H]^+$ 244.0768, found 244.0770.

Synthesis of 2-(3-(trifluoromethyl)phenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.48



Compound was synthesised using general procedure D as yellow oil (50 mg, 63 %).

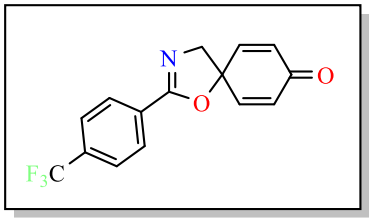
FT-IR (cm^{-1}): ν = 3046, 2936, 2836, 1714, 1670, 1635, 1626, 1571, 1409, 1320, 1250.

^{1}H NMR: ($CDCl_3$, 300 MHz) δ: 8.22 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 10.1 Hz, 2H), 6.31 (d, *J* = 10.1 Hz, 2H), 4.15 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.6, 162.2, 145.6, 131.6, 131.2 (q, *J* = 33 Hz), 129.2, 129.0, 128.6 (q, *J* = 3.8 Hz), 127.5, 125.4 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 273.3 Hz), 79.7, 64.7.

HRMS: m/z calc'd for $C_{15}H_{10}F_3NO_2$ $[M+H]^+$ 294.0736, found 294.0741.

Synthesis of 2-(4-(trifluoromethyl)phenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.49



Compound was synthesised using general procedure D as pale yellow oil (70 mg, 70 %).

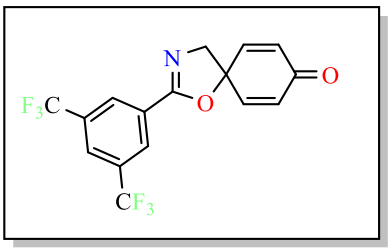
FT-IR (cm^{-1}): ν = 3048, 2934, 2850, 1715, 1673, 1635, 1620, 1575, 1412, 1320, 1249.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 8.08 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 10.0 Hz, 2H), 6.32 (d, *J* = 10.0 Hz, 2H), 4.20 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.7, 162.2, 145.7, 133.6 (q, *J* = 32.7 Hz), 130.1, 129.0, 128.8, 125.5 (q, *J* = 3.69 Hz), 123.8 (q, *J* = 272.5 Hz), 79.7, 64.7.

HRMS: m/z calc'd for $C_{15}H_{10}F_3NO_2$ $[M+H]^+$ 294.0736, found 294.0741.

Synthesis of 2-(3,5-bis(trifluoromethyl)phenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.50



Compound was synthesised using general procedure D as blood red oil (61 mg, 61 %).

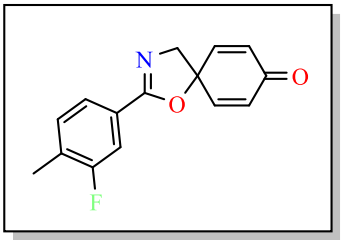
FT-IR (cm^{-1}): ν = 3078, 2980, 1674, 1636, 1602, 1396, 1280, 1250.

^{1}H NMR: ($CDCl_3$, 300 MHz) δ: 8.42 (s, 2H), 8.03 (s, 1H), 6.95 (d, *J* = 10.0 Hz, 2H), 6.34 (d, *J* = 10.0 Hz, 2H), 4.20 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.3, 161.0, 145.1, 132.3 (q, *J* = 34.4 Hz), 129.3, 128.9, 128.6 (q, *J* = 3.8 Hz), 125.3 (q, *J* = 3.7 Hz), 123.0 (q, *J* = 272.8 Hz), 80.1, 64.7.

HRMS: m/z calc'd for $C_{16}H_9F_6NO_2$ $[M+H]^+$ 361.0537, found 361.0540.

Synthesis of 2-(3-fluoro-4-methylphenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.51



Compound was synthesised using general procedure D as light brown oil (75 mg, 94 %).

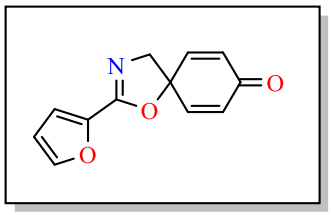
FT-IR (cm^{-1}): ν = 3056, 2961, 1678, 1632, 1602, 1389, 1283, 1252.

^{1}H NMR: ($CDCl_3$, 300 MHz) δ: 7.64-7.56 (m, 2H), 7.28-7.22 (m, 1H), 6.93 (d, *J* = 10.1 Hz, 2H), 6.30 (d, *J* = 10.1 Hz, 2H), 4.11 (s, 2H), 2.33 (d, *J* = 1.6 Hz, 3H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.7, 161.0 (d, *J* = 245 Hz), 146.0, 131.6 (d, *J* = 5.3 Hz), 129.5 (d, *J* = 17.5 Hz), 128.9, 126.1 (d, *J* = 9.0 Hz), 124.0 (d, *J* = 3.8 Hz), 115.0 (d, *J* = 25 Hz), 79.4, 64.6.

HRMS: m/z calc'd for $C_{15}H_{13}FNO_2$ $[M+H]^+$ 258.0925, found 258.0929.

Synthesis of 2-(furan-2-yl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.52



Compound was synthesised using general procedure D as colourless oil (31 mg, 62 %).

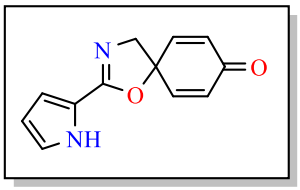
FT-IR (cm^{-1}): ν = 3128, 2872, 2779, 1715, 1672, 1635, 1560, 1479, 1399, 1266.

^{1}H NMR: ($CDCl_3$, 300 MHz) δ: 7.65-7.92 (m, 1H), 7.84-7.82 (m, 1H), 7.50 (t, *J* = 3.7 Hz, 1H), 6.99 (d, *J* = 10.1 Hz, 2H), 6.32 (d, *J* = 10.1 Hz, 2H), 4.20 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.5, 155.6, 146.1, 145.4, 141.8, 129.1, 115.7, 111.8, 79.5, 64.3.

HRMS: m/z calc'd for $C_{12}H_9NO_3$ $[M+H]^+$ 216.0655, found 216.0655.

Synthesis of 2-(1*H*-pyrrol-2-yl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.53



Compound was synthesised using general procedure D as reddish oil (43 mg, 43 %).

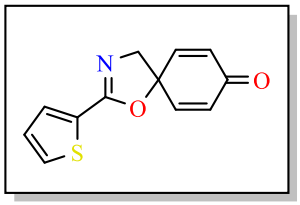
FT-IR (cm^{-1}): ν = 3100, 2942, 2830, 1671, 1635, 1620, 1448, 1270.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 10.70 (s, 1H), 6.95-6.90 (m, 3H), 6.81-6.79 (m, 1H), 6.29-6.25 (m, 3H), 4.10 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.8, 158.6, 145.9, 129.1, 123.3, 118.8, 114.4, 110.3, 79.2, 63.7.

HRMS: m/z calc'd for $C_{12}H_{11}N_2O_2$ $[M+H]^+$ 215.0815, found 215.0821.

Synthesis of 2-(thiophen-2-yl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.55



Compound was synthesised using general procedure D as pale yellow oil (35 mg, 70 %).

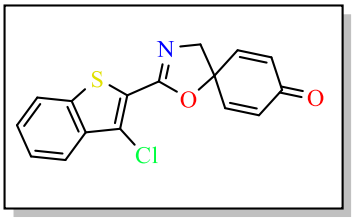
FT-IR (cm^{-1}): ν = 3090, 2861, 2760, 1667, 1648, 1633, 1428, 1250.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.62 (dd, J_1 = 3.7 Hz, J_2 = 1.1 Hz, 1H), 7.53 (dd, J_1 = 3.7 Hz, J_2 = 1.1 Hz, 1H), 7.13 (dd, J_1 = 5.0 Hz, J_2 = 3.7 Hz, 1H), 6.95 (d, J = 10.1 Hz, 2H), 6.30 (d, J = 10.1 Hz, 2H), 4.11 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.7, 159.2, 146.0, 131.7, 131.0, 129.0, 128.9, 127.9, 79.9, 64.6.

HRMS: m/z calc'd for $C_{12}H_9NO_2S$ $[M+H]^+$ 232.0427, found 232.0429.

Synthesis of 2-(3-chlorobenzo[b]thiophen-2-yl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.56



Compound was synthesised using general procedure D as pale yellow oil (15 mg, 30 %).

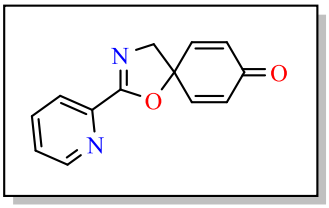
FT-IR (cm^{-1}): ν = 3148, 3051, 2838, 2741, 1671, 1643, 1633, 1517, 1228.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.96-7.94 (m, 1H), 7.84-7.82 (m, 1H), 7.53-7.50 (m, 2H), 6.99 (dt, J_1 = 10.1 Hz, J_2 = 3.1 Hz, 2H), 6.32 (dt, J_1 = 10.1 Hz, J_2 = 3.1 Hz, 2H), 4.20 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.7, 158.5, 145.5, 138.1, 137.0, 129.2, 127.8, 125.6, 125.2, 123.5, 122.7, 122.1, 79.9, 64.6.

HRMS: m/z calc'd for $C_{16}H_{10}ClNO_2S$ $[M+H]^+$ 316.0194, found 316.0195.

Synthesis of 2-(pyridin-2-yl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.57



Compound was synthesised using general procedure D as pale yellow oil (28 mg, 56 %).

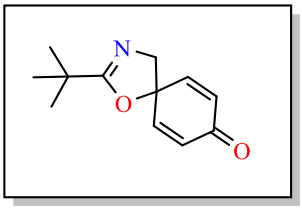
FT-IR (cm^{-1}): ν = 3054, 2851, 2760, 1671, 1633, 1522, 1483, 1345, 1265.

^{1}H NMR: ($CDCl_3$, 300 MHz) δ: 8.76-8.74 (m, 1H), 8.07-8.04 (m, 1H), 7.83 (td, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.48-7.43 (m, 1H), 6.98 (d, J = 10.2 Hz, 2H), 6.30 (d, J = 10.2 Hz, 2H), 4.20 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.6, 150.1, 145.7, 136.9, 129.0, 126.2, 124.2, 80.0, 64.7.

HRMS: m/z calc'd for $C_{13}H_{10}N_2O_2$ $[M+H]^+$ 227.0815, found 227.0818.

Synthesis of 2-(*tert*-butyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 3.60



Compound was synthesised using general procedure D as colourless oil (196 mg, 41 %).

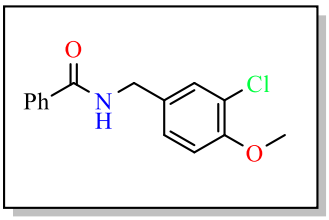
FT-IR (cm^{-1}): ν = 2972, 2872, m1663, 1633, 1609, 1480, 1395, 1267, 1129.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 6.82 (d, *J* = 10.1 Hz, 2H), 6.24 (d, *J* = 10.1 Hz, 2H), 3.87 (s, 2H), 1.26 (s, 9H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.4, 161.4, 145.2, 134.1, 129.8, 128.5, 126.4, 123.5, 79.9, 64.7.

HRMS: m/z calc'd for $C_{12}H_{15}NO_2$ $[M+H]^+$ 205.1103, found 205.1110.

Synthesis of *N*-(4-hydroxybenzyl)formamide 3.67



Compound was prepared by general method A as white powder (Yield 2 g, 45%).

FT-IR (cm^{-1}): ν = 3248, 3076, 3000, 2929, 2853, 1632, 1574, 1546, 1462, 1427, 1354, 1282, 1182, 1063, 1094, 974, 937, 872, 814, 756, 698, 654.

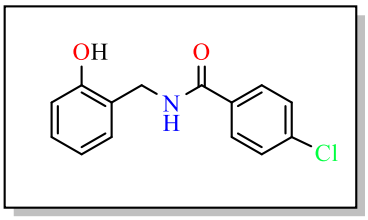
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.06 (t, *J* = 6.3 Hz, 1H), 7.90-7.88 (m, 2H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.56-7.46 (m, 3H), 7.38 (d, *J* = 2.2 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 4.41 (d, *J* = 6.3 Hz, 2H), 3.82 (s, 3H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 166.6, 153.8, 134.7, 133.4, 131.7, 129.3, 128.8, 127.8, 129.7, 121.1, 113.1, 56.5, 42.1.

HRMS: m/z calc'd for $C_{15}H_{15}ClNO_2$ $[M+H]^+$ 276.0786, found 276.0795.

Melting Point: Literature:[133] 117−118 °C, Experimental: 119-120 °C.

Synthesis of 4-chloro-*N*-(2-hydroxymethyl)benzamide 3.71



Compound was prepared by general method A as yellow solid (Yield 0.22 g, 35%).

FT-IR (cm^{-1}): ν = 3351, 3184, 2934, 1635, 1565, 1440.

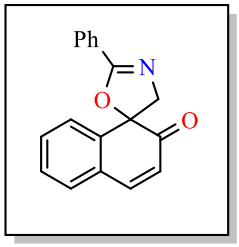
^{1}H NMR: (DMSO-d$_6$, 400 MHz) δ: 9.60 (s, 1H), 9.02 (t, *J* = 5.5 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.10-7.08 (m, 2H), 6.80-6.78 (m, 2H), 4.43 (d, *J* = 5.7 Hz, 2H).

^{13}C NMR: (DMSO-d$_6$, 75 MHz) δ: 166.0, 155.3, 136.6, 133.5, 129.7, 128.9, 128.6, 128.3, 125.6, 119.3, 115.5, 38.6.

HRMS: m/z calc'd for $C_{14}H_{13}ClNO_2$ $[M+H]^+$ 262.0629, found 262.0628.

Melting Point: 190-194 °C.

Synthesis of 2'-phenyl-2*H*,4'*H*-spiro[naphthalene-1,5'-oxazol]-2-one 3.77



The compound was prepared by general procedure D to give the pure product as a pale yellow oil. (26 mg, 52%).

FT-IR (cm^{-1}): ν = 3160, 3053, 2869, 1715, 1673, 1652, 1603, 1569, 1547, 1367, 1338, 1283, 770.

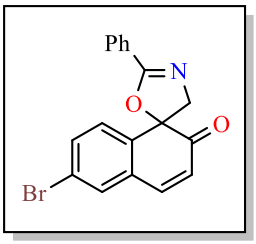
^{1}H NMR: (CDCl$_3$, 400 MHz) δ: 8.08-8.06 (m, 2H), 7.56-7.35 (m, 8H), 6.21 (d, *J* = 10.0 Hz, 1H), 4.48 (d, *J* = 15.4 Hz, 1H), 4.01 (d, *J* = 15.4 Hz, 1H).

^{13}C NMR: ($CDCl_3$ 75 MHz) δ: 197.7, 164.2, 145.8, 142.3, 131.8, 130.9, 129.6, 129.0, 128.9, 128.7, 128.5, 126.9, 125.5, 123.6, 86.5, 69.7.

HRMS: m/z calc'd for $C_{18}H_{13}NO_2$ $[M+H]^+$ 276.1019, found 276.1019.

HPLC: Chiralpak IB, 254 nm, hexane/IPA gradient (100:0 to 90:10 over 35 min), 1 mL/min, retention time (12.948, 15.064).

Synthesis of 6-bromo-2'-phenyl-2*H*,4'*H*-spiro[naphthalene-1,5'-oxazol]-2-one 3.78



This compound was obtained using the general procedure D. (Yield, 25.5 mg, 51%).

FT-IR (cm^{-1}): ν = 3273, 3060, 2922, 2869, 1718, 1679, 1655, 1602, 1579, 1556, 1483, 1367, 1338, 1283, 1246.

^{1}H NMR: ($CDCl_3$, 300 MHz) δ: 8.08-8.05 (m, 2H), 7.57-7.42 (m, 6H), 7.34-7.31 (m, 1H), 6.28 (d, *J* = 10.0 Hz, 1H), 4.51 (d, *J* = 15.0 Hz, 1H), 4.02 (d, *J* = 15.0 Hz, 1H),

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 196.8, 164.2, 144.0, 140.9, 133.6, 132.1, 131.89, 130.9, 128.7, 128.5, 127.3, 126.7, 124.8, 122.8, 86.1, 69.6.

HRMS: m/z calc'd for $C_{18}H_{12}BrNO_2$ $[M+H]^+$ 354.0124, found 356.0111+

HPLC: Chiralpak IB, 254 nm, hexane/IPA gradient (100:0 to 80:20 over 35 min), 1 mL/min, retention time (21.175, 23.621).

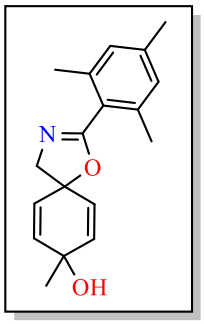
Functionalisation of Spirocycles

General Procedure E

To the solution of the corresponding spirocycle (1 equiv.) in dry THF (5 mL) under argon atmosphere was added MeLi (1.2 equiv., 1.6 M in hexane) dropwise at -78 °C over 5 minutes. The reaction mixture was stirred at the same temperature for 1 hour. The reaction was monitored with TLC. The reaction was quenched with saturated NH_4Cl solution (5 mL) at -78 °C. Aqueous layer

was extracted with ethyl acetate (2 x 5 mL), combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography using Pet. ether: Ethyl acetate (4:1 then 2:1) to yield the corresponding product. Experimental data for the major diastereomer is provided only.

Synthesis of 2-mesityl-8-methyl-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-ol 3.81



The compound was obtained as colourless oil using the general procedure E. (70 mg, 77%) Spectral data for major stereoisomer is given below.

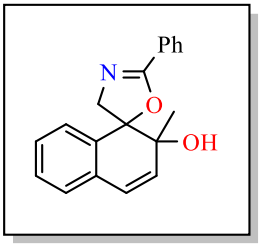
FT-IR (cm^{-1}): ν = 3268, 2969, 2720, 1602, 1542, 1506, 1458, 1378, 1268.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.05 (s, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.80 (s, 2H), 6.68 (d, *J* = 8.5 Hz, 1H), 6.30 (s, 1H), 5.90 (t, *J* = 5.5 Hz, 1H), 4.50 (d, *J* = 5.5 Hz, 2H), 2.30 (s, 9H), 2.20 (s, 3H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 170.8, 154.0, 138.6, 134.6, 134.2, 130.9, 129.3, 128.3, 126.8, 124.5, 115.2, 43.6, 21.1, 19.2, 15.9.

HRMS: m/z calc'd for $C_{18}H_{21}NO_2$ $[M+H]^+$ 284.1645, found 284.1645.

Synthesis of 2-methyl-2'-phenyl-2*H*,4'*H*-spiro[naphthalene-1,5'-oxazol]-2-ol 3.82



The compound was obtained as colourless oil using the general procedure E. (60 mg, 67%) Spectral data for major stereoisomer is given below.

FT-IR (cm^{-1}): ν = 3241, 2975, 2851, 2700, 1606, 1523, 1501, 1478, 1346, 1285, 1220.

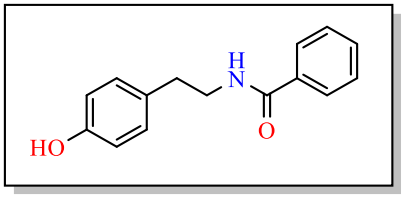
^{1}H NMR: ($CDCl_3$, 400 MHz) δ: (Major diastereomer) 7.97-7.95 (m, 2H), 7.48-7.45 (m, 1H), 7.39-7.34 (m, 3H), 7.29-7.25 (m, 1H), 7.23-7.19 (m, 1H), 7.16-7.14 (m, 1H), 6.51 (d, *J* = 9.8 Hz, 1H), 6.00 (d, *J* = 9.8 Hz, 1H), 4.44 (d, *J* = 15.4 Hz, 1H), 4.10 (d, *J* = 15.4 Hz, 1H), 2.67 (s, 1H), 1.32 (s, 3H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 163.2, 137.0, 134.5, 131.6, 131.4, 128.9, 128.6, 128.4, 128.3, 127.4, 127.3, 124.9, 91.0, 72.7, 60.5, 21.3.

HRMS: m/z calc'd for $C_{19}H_{17}NO_2$ $[M+H]^+$ 292.1332, found 292.1336.

Synthesis of Tyramine Based Amides

Synthesis of *N*-(4-hydroxyphenethyl)Benzamide 3.84a



Compound was prepared by general method B as off white solid (Yield 2 g, 63%).

FT-IR (cm^{-1}): ν = 3323, 3025, 1636, 1538, 1511, 1250.

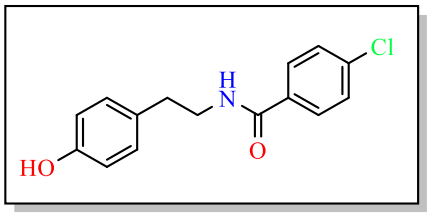
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.15 (s, 1H), 8.50 (t, *J* = 5.7 Hz, 1H), 7.80 (d, *J* = 7.3 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.67 (d, *J* = 8.3 Hz, 2H), 3.40 (q, J_1 = 14.1 Hz, J_2 = 6.6 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 166.6, 156.1, 135.2, 131.5, 130.0, 129.9, 128.7, 127.6, 115.5, 41.8, 34.8.

HRMS: m/z calc'd for $C_{15}H_{15}NO_2$ $[M+H]^+$ 242.1176, found 242.1180.

Melting Point: 158-159 °C.

Synthesis of 4-chloro-*N*-(4-hydroxyphenethyl)benzamide 3.84b



Compound was prepared by general method B as white solid (Yield 2.4 g, 68%).

FT-IR (cm^{-1}): ν = 3307, 2871, 2797, 1650, 1592, 1511, 1240.

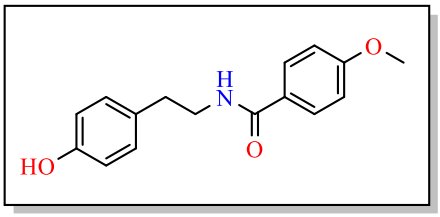
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.20 (s, 1H), 8.62 (t, *J* = 5.5 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 3.40 (q, J_1 = 14.1 Hz, J_2 = 6.6 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H).

^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 165.5, 156.2, 136.4, 133.9, 130.0, 129.9, 129.5, 128.8, 115.6, 41.8, 34.8.

HRMS: m/z calc'd for $C_{15}H_{14}ClNO_2$ $[M+H]^+$ 276.0786, found 276.0790.

Melting Point: 178-179 °C.

Synthesis of *N*-(4-hydroxyphenethyl)-4-methoxybenzamide 3.84c



Compound was prepared by general method B as white fluffy solid (Yield 1.6 g, 54%).

FT-IR (cm^{-1}): ν = 3315, 2890, 1645, 1427.

^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.20 (s, 1H), 8.40 (t, *J* = 5.5 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 2H), 7.00 (m, 4H), 6.68 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 3H), 3.39 (q, J_1 = 14.0 Hz, J_2 = 6.5 Hz, 2H), 2.70 (t, *J* = 7.5 Hz, 2H).

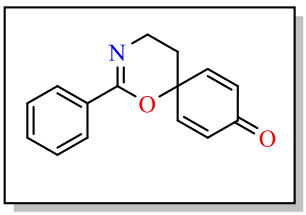
^{13}C NMR: (DMSO-d_6, 75 MHz) δ: 166.1, 162.0, 156.1, 130.1, 129.9, 129.4, 127.4, 115.6, 114.0, 55.8, 41.6, 34.9.

HRMS: m/z calc'd for $C_{16}H_{17}NO_3$ $[M+H]^+$ 272.1281, found 272.1286.

Melting Point: 170-171 °C.

Spirocyclisation of Tyramine Based Amides

Synthesis of 2-phenyl-1-oxa-3-azaspiro[5.5]undeca-2,7,10-trien-9-one 3.85a



Compound was synthesised using general procedure D as pale yellow oil (51 mg, 51 %).

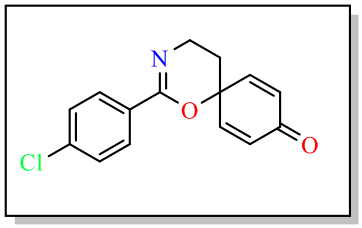
FT-IR (cm^{-1}): ν = 3067, 2925, 2867, 2761, 1672, 1655, 1653, 1536, 1346, 1279, 1219.

^{1}H NMR: ($CDCl_3$, 300 MHz) δ: 7.90 (d, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 2H), 6.97 (d, *J* = 10.2 Hz, 2H), 6.30 (d, *J* = 10.2 Hz, 2H), 3.80 (t, *J* = 6.1 Hz, 2H), 2.00 (t, *J* = 6.1 Hz, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.8, 154.4, 146.7, 133.2, 131.0, 129.0, 128.2, 127.1, 71.6, 40.2, 30.4.

HRMS: m/z calc'd for $C_{15}H_{13}NO_2$ $[M+H]^+$ 240.1019, found 240.1019.

Synthesis of 2-(4-chlorophenyl)-1-oxa-3-azaspiro[5.5]undeca-2,7,10-trien-9-one 3.85b



Compound was synthesised using general procedure D as pale yellow oil (81 mg, 81 %).

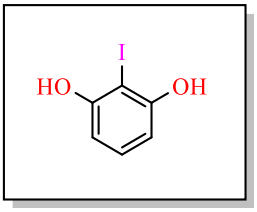
FT-IR (cm^{-1}): ν = 3053, 2867, 2740, 1673, 1656, 1638, 1596, 1536, 1486, 1398, 1346, 1278.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.83 (dt, J_1 = 8.6 Hz, J_2 = 2.5 Hz, 2H), 7.33 (dt, J_1 = 8.6 Hz, J_2 = 2.5 Hz, 2H), 6.94 (d, J = 10.2 Hz, 2H), 6.28 (d, J = 10.2 Hz, 2H), 3.73 (t, J = 6.2 Hz, 2H), 2.00 (t, J = 6.2 Hz, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 184.5, 153.3, 146.3, 137.0, 131.6, 129.1, 128.5, 128.4, 71.7, 40.2, 30.3.

HRMS: m/z calc'd for $C_{15}H_{12}ClNO_2$ $[M+H]^+$ 274.0629, found 274.0629.

Synthesis of 2-iodobenzene-1,3-diol 4.2



The compound **4.2** was synthesised following literature procedure reported by Tsujiyama and co-authors[103]. To a solution of resorcinol **4.1** (5.0 g, 45.41 mmol) in deionised water (45.45 mL) placed in an ice bath were added iodine (12.36 g, 48.72 mmol) and $NaHCO_3$ (4.30 g, 51.28 mmol) in one portion. The resulting mixture was stirred at room temperature for half an hour. The obtained precipitates were filtered, extracted twice with diethyl ether (2 × 50 mL), dried over MgSO4, and concentrated to give **4.2** as a white solid (9.01 g, 84% yield).

FT-IR (cm^{-1}): ν = 3456, 3363, 1593, 1582, 1491, 1458, 1304, 1278, 1250, 1185, 1159, 1022, 994, 784, 704.

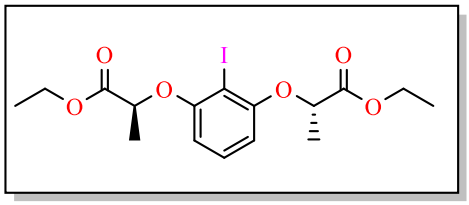
^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.10 (t, J = 8.0 Hz, 1H), 6.55 (d, J = 8.0 Hz, 2H), 5.45 (s, 2H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 155.9, 130.5, 107.5, 77.5.

HRMS: m/z calc'd for $C_6H_5IO_2^+$ $[M+H]^+$ 235.9334, found 235.9333.

Melting Point: Literature M.P.[134] 107-109 ºC. **Experimental M.P.** 108-109 ºC.

Synthesis of diethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*S*,2'*S*)-dipropionate 4.4



To a solution of **4.2** (0.50 g, 2.12 mmol) in THF (20 mL) under nitrogen at 0 °C were added triphenyl phosphine PPh_3 (1.4g, 5.3 mmol) and ethyl-*L*-lactate (0.6 mL, 5.3 mmol). To this mixture diisopropyl azodicarboxylate (DIAD, 1.9 M in toluene, 1.04 mL, 5.3 mmol) was added dropwise and the resulting mixture was stirred for an hour in an ice bath and then at room temperature overnight. The reaction mixture was concentrated under vacuum and purified by flash column chromatography on silica gel (eluent: 9:1 petroleum ether 40-60/EtOAc) which afforded **4.4** as a colourless oil (1.25 g, 72% yield).[90]

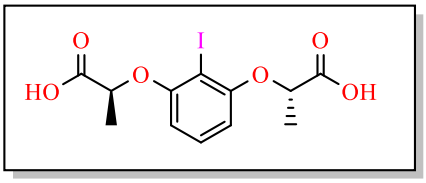
FT-IR (cm^{-1}): ν = 2986, 1751, 1583, 1452, 1246.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.10 (t, *J* = 8.3 Hz, 1H), 6.31 (d, *J* = 8.3 Hz, 2H), 4.70 (q, *J* = 6.9 Hz, 2H), 4.13–4.23 (m, 4H), 1.65 (d, *J* = 6.8 Hz, 6H), 1.20 (t, *J* = 7.3 Hz, 6H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 171.9, 158.3, 129.6, 107.3, 81.0, 74.4, 61.6, 18.8, 14.5.

HRMS: m/z calc'd for $C_{16}H_{22}IO_6^+$ $[M+H]^+$ 437.0456, found 437.0454.

Synthesis of ((2*R*,2'*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))dipropanoic acid 4.5



To a solution of **4.4** (1.3g, 2.7 mmol) in THF (10 mL), methanol (10 mL) and 2 M NaOH (10 mL) were added and the reaction was left to stir at room temperature overnight. The reaction mixture was cooled to 0 °C, quenched with HCl (1M, 20 mL) and extracted with EtOAc (3 × 30 mL). The organic layers were dried over anhydrous MgSO4 and the solvents were removed in vacuum to give analytically pure **4.5** as a white solid (3.5 g, 99% yield).[90]

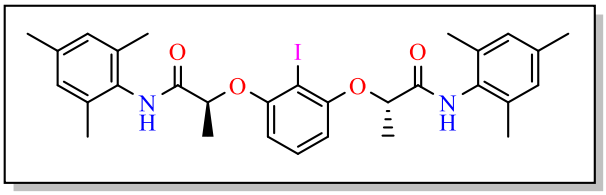
FT-IR (cm^{-1}): ν = 3600–2700, 2525, 1715, 1581, 1458, 1252.

^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.24 (t, *J* = 8.1 Hz, 1H), 6.42 (d, *J* = 8.8 Hz, 2H), 4.88 (q, *J* = 6.8 Hz, 2H), 1.58 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 173.6, 158.7, 130.7, 107.0, 81.0, 73.4, 19.4.

HRMS: m/z calc'd for $C_{16}H_{22}IO_6^+$ $[M+H]^+$ 380.9757, found 380.9755.

Synthesis of (2*S*,2'*S*)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))bis(*N*-mesitylpropanamide) 4.6



To a solution of **4.5** (0.50 g, 2.12 mmol) in THF (20 mL) under nitrogen at 0 °C were added triphenyl phosphine PPh_3 (1.4g, 5.3 mmol) and ethyl-*L*-lactate (0.6 mL, 5.3 mmol). To this mixture diisopropyl azodicarboxylate (DIAD, 1.9 M in toluene, 1.04 mL, 5.3 mmol) was added dropwise and the resulting mixture was stirred for an hour in an ice bath and then at room temperature overnight. The reaction mixture was concentrated under vacuum and purified by flash column chromatography on silica gel (eluent: 9:1 petroleum ether 40-60/EtOAc) which afforded **4.4** as a colourless oil (1.25 g, 72% yield).[90]

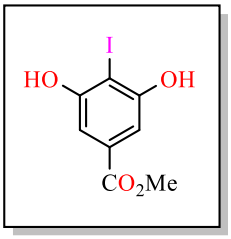
FT-IR (cm^{-1}): ν = 3251, 1670, 1532, 1469, 1256, 1131.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 8.03 (s, 2H), 7.36 (t, *J* = 8.3 Hz, 1H), 6.88 (s, 4H), 6.64 (d, *J* = 8.3 Hz, 2H), 5.00 (q, *J* = 6.8 Hz, 2H), 2.26 (s, 6H), 2.15 (s, 12H), 1.77 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR: ($CDCl_3$, 75 MHz) δ: 170.0, 156.6, 137.3, 135.2, 130.6, 130.1, 128.9, 107.0, 80.4, 76.4, 21.0, 18.8, 18.1.

HRMS: m/z calc'd for $C_{30}H_{36}IN_2O_4$ [M+H] 615.1720, found 615.1717.

Synthesis of methyl 3,5-dihydroxy-4-iodobenzoate 4.8



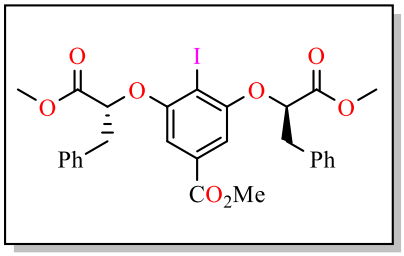
To a solution of **4.7** (1.80 g, 10.70 mmol) in MeOH (15 mL), a solution of NIS (2.20g, 9.77 mmol) in MeOH (15 mL) was added slowly at 0 ^{o}C. The reaction mixture was gradually brought to room temperature while stirring. After 16 h the reaction mixture was diluted with ice water and quenched by saturated Na_2SO_3, then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. Recrystallisation with ethyl acetate/ethanol gave the desired compound as white solid in a yield of 2.54 g (8.64 mmol, 81%) with the same spectroscopic data as those previously reported.[135]

^{1}H NMR: (DMSO-d$_6$, 400 MHz) δ: 10.53 (s, 2H), 6.95 (s, 2H), 3.80 (s, 3H)

^{13}C NMR: (DMSO-d$_6$, 100 MHz) δ: 166.0, 158.2. 130.6, 104.8, 81.9, 52.2.

HRMS: m/z calc'd for $C_8H_8IO_4^+$ $[M+H]^+$ 294.9462, found 294.9459.

Synthesis of dimethyl 2,2'-((2-iodo-5-(methoxycarbonyl)-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-bis(3-phenylpropanoate) 4.10



To a stirred suspension of methyl 3,5-dihydroxy-4-iodobenzoate **4.8** (0.5 g, 3.42 mmol), triphenylphosphine (PPh_3) (2.44 g, 9.30 mmol) and benzyl-(*S*)-methyl-2-hydroxy-3-phenylpropanoate **4.9** (1.29 g, 7.18 mmol) in tetrahydrofuran (32.0 mL) at 0 °C was added DIAD (1.55 mL, 7.90 mmol) dropwise over 30 minutes and the resulting mixture was warmed to room temperature. The reaction mixture was stirred overnight. After such time, the reaction mixture was

concentrated under reduced pressure. The residue was purified by flash column chromatography using petroleum ether/ ethyl acetate (9:1 and then 5:1) to give **4.10** as a white solid (1.38 g, 65%). Spectroscopic data is in accordance with the previously reported data.[136]

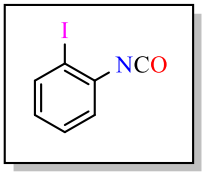
FT-IR (cm^{-1}): ν = 3028, 2952, 1753, 1721, 1577, 1434, 1417, 1325, 1243, 1197, 1113, 1011.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.44 (d, *J* = 7.5 Hz, 4H), 7.32 (t, *J* = 7.3 Hz, 4H), 7.28−7.25 (m, 2H), 6.89 (s, 2H), 4.95 (dd, J_1 = 7.6 Hz, J_2 = 4.7, 2H), 3.85 (s, 3H), 3.70 (s, 6H), 3.34-3.31 (m, 4H).

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 170.5, 166.0, 158.0, 136.0, 131.6, 130.0, 128.5, 127.2, 106.4, 86.2, 78.7, 52.5, 52.4, 39.0.

HRMS: m/z calc'd for $C_{28}H_{28}IO_8^+$ $[M+H]^+$ 619.0823, found 619.0817.

Synthesis of 1-iodo-2-isocyanatobenzene 4.12

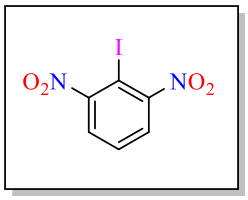


Triphosgene (1.08 g, 3.65 mmol) was added to a stirring solution of 2-iodoaniline **4.11** (2 g, 9.13 mmol) in toluene (50 mL) at room temperature and the resulting solution was refluxed for 12 h. After cooling the reaction to room temperature, the reaction mixture was concentrated under vacuum (in a fume hood!). The residue was redissolved in 50 mL of hexane and filtered. The filtrate was concentrated to afford the desired isocyanates **4.12** as pale yellow oil in quantitative yield which was used in the next step without further purification.[105]

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.82-7.80 (m, 1H), 7.34-7.30 (m, 1H), 7.16-7.14 (m, 1H), 6.95-6.90 (m, 1H).

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 139.5, 129.3, 129.1, 128.3, 127.2, 125.3, 95.4.

Synthesis of 2-iodo-1,3-dinitrobenzene 4.14



Sodium nitrite (0.83 g, 12 mmol) was added portion wise to sulfuric acid (9 mL) and the mixture was stirred and heated to 70 °C until the full dissolution of the solid. The resultant solution was cooled below 40 °C. 2,6-Dinitroaniline (2.0 g, 11 mmol) dissolved in AcOH (22 mL) was added dropwise to $NaNO_2$ solution while the temperature was maintained below 40 °C. The obtained solution was stirred for 30 minutes at room temperature. The reaction mixture was then poured in to a stirred solution of KI (2.0 g, 12 mmol) in water (20 mL) at 70 °C. The resultant mixture was stirred for 15 minutes then poured into 200 mL of H_2O. The solid material was filtered, washed with water, and dried to give pale yellow solid (2.41g, 75%).

FT-IR (cm^{-1}): ν = 3087, 1530, 1366, 590.

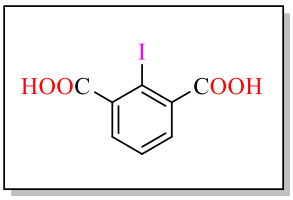
^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 8.15 (d, *J*= 8.1 Hz, 2H), 7.84 (t, *J*= 8.1 Hz, 1H).

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 156.5, 131.9, 127.3, 83.5.

HRMS: m/z calc'd for $C_{16}H_3IN_2O_4$ [M^+] 293.9132, found 293.9136.

Melting Point: Literature M.P. [137] = 113 °C, **Experimental M.P**. = 114-116 °C.

Synthesis of 2-Iodoisophthalic acid 4.17



To a solution of 2-Aminoisophthalic acid (2.0 g, 11.04 mmol) in conc. sulfuric acid (10 mL) at 0 °C was added a solution of $NaNO_2$ (1.15 g) in conc. H_2SO_4 (10 mL) at 0 °C. The resulting solution was stirred gently and 85% phosphoric acid (20 mL) was added at a rate designed to maintain the temperature below 10 °C. The mixture was left stirring for 2 hours at room temperature. After such

time, urea (1.2 g) was added. The solution was stirred for 5 minutes and then poured in to ice and filtered. A solution of KI (3.6 g) in water (4 mL) was added to the filtrate and mixture was heated for 30 minutes. The mixture was cooled to 5 ^{o}C before filtration. The obtained solid was washed with sodium bisulfite solution (30 mL), and water (30 mL) and the dried. Recrystallisation from hot water afforded beige coloured solid (2.55 g, 80%).

FT-IR (cm^{-1}): ν = 2783, 2620, 2511, 1678, 1573, 597.

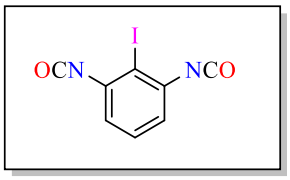
^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 13.36 (s, 2H), 7.59-7.57 (m, 2H), 7.53-7.49 (m, 1H).

^{13}C NMR: ($CDCl_3$, 100MHz) δ: 169.7, 141.6, 130.1, 128.7, 91.5.

HRMS: m/z calc'd for $C_8H_5IO_4$ $[M-H]^-$ 290.9158, found, 290.9161.

Melting Point: Literature M.P. [138] = 236-238 ^{o}C, **Experimental M.P.** = 237-238 ^{o}C.

Synthesis of 2-Iodo-1,3-diisocyanatobenzene 4.18



A solution of 2-Iodoisophthalic acid (1.5 g, 5.14 mmol) in thionyl chloride (40 mL) was refluxed for 2h and evaporated under reduced pressure to afford crude 2-Iodoisophthaloyl chloride quantitatively. To a solution of the crude mixture in THF (15 mL) was added NaN_3 (2.22 g in 8 mL water) and stirred in an ice bath for 2h. To the mixed solution was added saturated $NaHCO_3$ (10 mL) solution and extracted with toluene (30 mL), dried over $MgSO_4$ and evaporated to half under reduced pressure to give a toluene solution of 2-Iodoisophthaloyl diazide. Without purification, the crude mixture was refluxed for 2 hours in toluene to afford crude 2-Iodo-1,3-diisocyanatobenzene as light brown liquid (1.42 g, 96%). The progress of the reaction was monitored by IR.[115]

FT-IR (cm^{-1}): ν = 3370, 3024, 2251, 2141, 1723, 1573, 1494, 1396, 1214, 781, 728.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.91 (d, *J* = 7.8 Hz, 2H), 7.66 (t, *J*= 7.8 Hz, 1H).

^{13}C NMR: ($CDCl_3$, 100MHz) δ: 139.1, 129.7, 128.2, 122.2, 97.1.

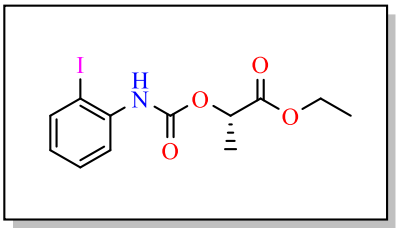
HRMS: m/z calc'd for $C_8H_3IN_2O_2$ $[M\text{-}CO+2H+H]^+$ (259.9446), found 260.9516.

The desired compound was observed as the $[M\text{-}CO+2H+H]^+$ and $[M\text{-}2CO+4H+H]^+$ adducts. This shows the degradation of the desired product to the amine and diamine.

General Procedure F for the synthesis of C_1 and C_2-symmteric carbamates 4.20-4.22 and 4.23-4.25

Crude Iodoisocyanatobenzene **4.12** or **4.18** (2.04 mmol) was added to a green heterogeneous mixture of corresponding *L*-lactate (2.04 mmol), reagent grade CuI (2.04 mmol) and dry DMF (25 mL). The solution was stirred for 2.5 hours at room temperature then diluted with DEE (40 mL), washed with water (40 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography using Pet-EtOAc (5:1 and then 4:1) to afford pure desired product.

Synthesis of ethyl (*S*)-2-(((2-iodophenyl)carbamoyl)oxy)propanoate 4.20



Compound **4.20** was synthesised using general procedure F in 94% (0.7 g) yield as light brown oil.

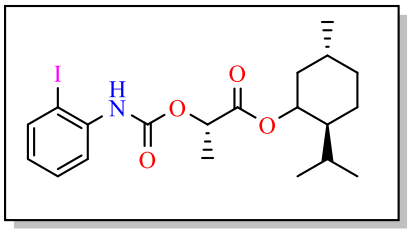
FT-IR (cm^{-1}): ν = 3240, 2992, 2910, 2850, 2730, 2253, 1739, 1630, 1587, 1532, 1434, 1299, 902, 715.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.95 (d, *J* = 8.2 Hz, 1H), 7.69-7.67 (m, 1H), 7.27-7.22 (m, 1H), 7.04 (s, 1H), 6.75-6.71 (m, 1H), 5.06 (q, *J* = 7.1 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 1.48 (q, *J* = 7.1 Hz, 2H), 1.22 (t, , *J* = 7.1 Hz, 3H).

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 171.1, 152.5, 139.0, 138.0, 129.3, 125.4, 125.1, 89.2, 69.6, 61.5, 17.1, 14.2.

HRMS: m/z calc'd for $C_{12}H_{15}INO_4$ $[M+H]^+$ 364.0040, found 364.0038.

Synthesis of (2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (2*S*)-2-(((2-iodophenyl)carbamoyl)oxy)propanoate 4.21



Compound **4.21** was synthesised using general procedure F in 71% (0.69 g) yield as pale yellow oil.

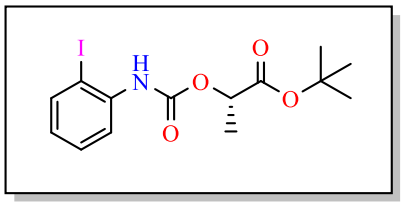
FT-IR (cm^{-1}): ν = 3310, 2950, 2890, 2253, 1738, 1690, 1575, 1524, 1434, 1213, 902, 720.

^{1}H NMR: (CDCl$_3$, 400 MHz) δ: 8.05 (d, J = 7.9 Hz, 1H), 7.78 (dd, J_1 = 7.9 Hz, J_2 = 1.1 Hz, 1H), 7.37-7.33 (m, 1H), 7.10 (s, 1H), 6.82 (td, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 1H), 5.15 (q, J = 7.0 Hz, 1H), 4.82-4.75 (m, 1H), 3.50 (q, J = 7.0 Hz, 1H), 2.02-1.92 (m, 2H), 1.74-1.69 (m, 3H), 1.57 (d, J = 7.1 Hz, 3H), 1.42 (d, J = 7.0 Hz, 1H), 1.23 (t, J = 7.1 Hz, 1H), 0.93-0.90 (7H), 0.81 (d, J = 6.9 Hz, 3H).

^{13}C NMR: (CDCl$_3$, 100 MHz) δ: 170.6, 152.4, 138.9, 138.1, 129.3, 125.3, 88.8, 75.5, 69.7, 47.0, 40.6, 34.2, 31.4, 26.3, 23.5, 22.0, 20.7, 17.1, 16.4.

HRMS: m/z calc'd for $C_{20}H_{28}INNaO_4$ $[M+Na]^+$ 496.0955, found 496.0934.

Synthesis of *tert*-butyl (*S*)-2-(((2-iodophenyl)carbamoyl)oxy)propanoate 4.22



Compound **4.22** was synthesised using general procedure F in 53% (0.42 g) yield as pale-yellow oil.

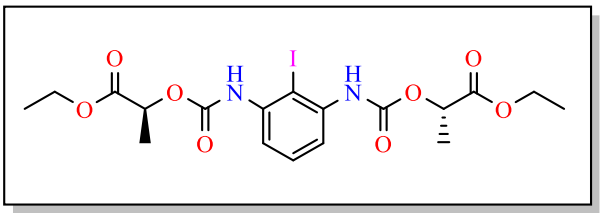
FT-IR (cm^{-1}): ν = 3310, 2950, 2890, 2253, 1738, 1690, 1575, 1524, 1434, 1213, 902, 720.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.93 (d, *J* = 8.2 Hz, 1H), 7.64 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.23-7.19 (m, 1H), 7.01 (s, 1H), 6.69 (td, J_1 = 7.6 Hz, J_2 = 1.3 Hz, 1H), 4.92 (q, *J* = 7.1 Hz, 1H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.39 (s, 9H).

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 170.1, 152.5, 138.9, 138.2, 129.3, 125.3, 120.5, 89.0, 82.1, 70.0, 28.0, 17.1,

HRMS: m/z calc'd for $C_{14}H_{18}INNaO_4$ $[M+Na]^+$ 414.0173, found 414.0173.

Synthesis of diethyl 2,2'-((((2-iodo-1,3-phenylene)bis(azanediyl))bis(carbonyl))bis(oxy))(2*S*,2'*S*)-dipropionate 4.23



Compound **4.22** was synthesised using general procedure F in 98% (1.8 g) yield as pale yellow oil.

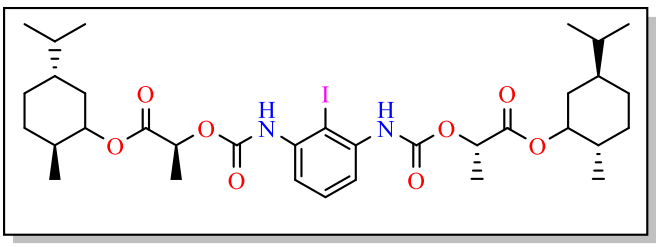
FT-IR (cm^{-1}): ν = 3310, 2950, 2890, 2253, 1738, 1690, 1575, 1524, 1434, 1213, 902, 720.

^{1}H NMR: (Acetone-d_6, 400 MHz) δ: 8.01 (s, 2H), 7.57 (d, *J* = 7.9 Hz, 2H), 7.39 (t, *J* = 8.1 Hz, 1H), 5.10 (q, *J* = 7.1 Hz, 2H), 4.24-4.16 (m, 4H), 1.51 (d, *J* = 7.1 Hz, 6H), 1.26 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR: (MeOD, 100 MHz) δ: 171.5, 154.1, 140.0, 128.6, 122.0, 97.1, 69.6, 61.0, 16.0, 13.1.

HRMS: m/z calc'd for $C_{18}H_{23}IN_2NaO_8$ $[M+Na]^+$ 545.0391, found 545.0388.

Synthesis of bis((2*S*,5*S*)-5-isopropyl-2-methylcyclohexyl) 2,2'-((((2-iodo-1,3-phenylene)bis(azanediyl))bis(carbonyl))bis(oxy))(2*S*,2'*S*)-dipropionate 4.24



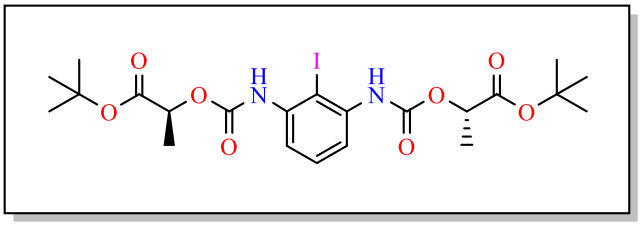
Compound **4.24** was synthesised using general procedure F in 40% (0.21 g) yield as colourless oil.

^{1}H NMR: (Acetone-d_6, 400 MHz) δ: 7.91 (s, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 8.1 Hz, 1H), 5.08 (q, *J* = 7.0 Hz, 2H), 4.76 (td, J_1 = 10.9 Hz, J_2 = 4.3 Hz, 2H), 2.02-1.95 (m, 5H), 1.70 (d, *J* = 11.7 Hz, 5H), 1.53-1.51 (m, 8H), 1.04 (t, *J* = 11.7 Hz, 2H), 0.93-0. 91 (m, 15H), 0.80 (d, *J* = 7.0 Hz, 7H).

^{13}C NMR: (Acetone-d_6, 100 MHz) δ: 170.2, 153.0, 140.0, 129.0, 119.5, 91.4, 74.6, 69.6, 40.6, 34.1, 31.2, 26.1, 23.5, 21.7, 20.3, 16.7, 16.1.

HRMS: m/z calc'd for $C_{34}H_{51}IN_2O_8Na$ $[M+Na]^+$ 765.2582, found 765.2573.

Synthesis of di-tert-butyl 2,2'-((((2-iodo-1,3-phenylene)bis(azanediyl))bis(carbonyl))bis(oxy))(2*S*,2'*S*)-dipropionate 4.25



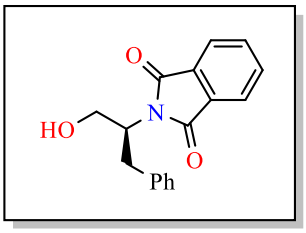
Compound **4.25** was synthesised using general procedure F in 35% (0.501 g) yield as colourless oil.

^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.67 (d, *J* = 8.2 Hz, 2H), 7.23 (t, *J* = 8.2 Hz, 1H), 6.99 (br, 2H), 4.95 (q, *J* = 7.1 Hz, 2H), 1.44 (d, *J* = 7.1 Hz, 6H), 1.41 (s, 18H).

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 170.1, 152.5, 138.6, 129.5, 116.7, 82.1, 69.9, 27.9, 17.1.

HRMS: m/z calc'd for $C_{22}H_{35}IN_3O_8$ $[M+NH_4]^+$ 596.1463, found 596.1461.

Synthesis of (*S*)-2-(1-hydroxy-3-phenylpropan-2-yl)isoindoline-1,3-dione 4.27a



Compound **4.27a** was prepared using known literature procedure[139]. A mixture of *L*-phenyl alaninol (1.0 g, 6.61 mmol) and phthalic anhydride (0.99 g, 6.61) in DMF (6 mL) was stirred

overnight under reflux. Distilled water (10 mL) was added to the reaction mixture and precipitates of the pure product were collected as off white solid. (1.5 g, 81%)

FT-IR (cm^{-1}): ν = 3462, 3089, 3062, 2938, 1772, 1705, 1611, 1497.

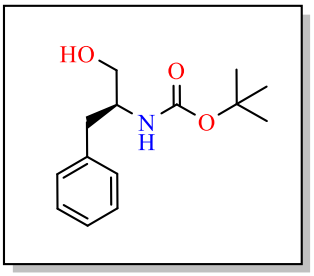
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.78 (s, 4H), 7.20-7.16 (m, 2H), 7.11-7.09 (m, 3H), 5.03 (t, *J* = 6.1 Hz, 1H), 4.49-4.41 (m 1H), 3.99-3.92 (m, 1H), 3.71-3.65 (m, 1H), 3.16-3.02 (m, 2H).

^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 168.6, 138.6, 134.8, 131.6, 129.1, 128.7, 126.8, 123.3, 61.1, 55.9, 34.3.

HRMS: m/z calc'd for $C_{17}H_{16}NO_3$ $[M+H]^+$ 282.1125, found 282.1124.

Melting Point: Literature M.P. [140] = 94-96 °C, **Experimental M.P.** = 93-95 °C.

Synthesis of *tert*-butyl (*S*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate 4.27b



Compound **4.27b** was prepared using known literature procedure[119]. Boc-anhydride (1.44 g, 6.61 mmol) was added to a solution of *L*(-)-2-amino-3-phenyl-1-propanol (1 g, 6.61 mmol) and DIPEA (1.15 mL, 6.61 mmol) in THF (50 mL) under nitrogen at 0 °C. The mixture was then allowed to stir for 6h at room temperature. Solvent was removed under reduced pressure and the resulting residue was dissolved in 100 mL of EtOAc, washed twice with 100 mL of water then with 100 mL of brine, dried over $MgSO_4$ and finally concentrated under reduced pressure to give desired compound as pale yellow solid. (Yield 1.59 g, 95%)

FT-IR (cm^{-1}): ν = 3373, 3277, 3075, 1660, 1541, 1367, 1283, 1174, 1058, 855, 830, 700.

^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.28-7.24 (m, 2H), 7.21-7.15 (m, 3H), 6.60 (d, *J* = 8.5 Hz, 1H), 4.70 (t, *J* = 5.4 Hz, 1H), 3.59-3.54 (m, 1H), 3.30-3.24 (m, 2H), 2.84-2.79 (m, 1H), 2.59-2.53 (m, 1H), 1.40 (s, 9H).

^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 155.6, 139.9, 129.6, 128.5, 126.2, 77.8, 63.4, 54.4, 37.2, 27.3.

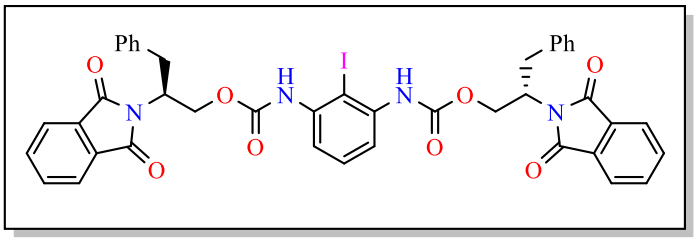
HRMS: m/z calc'd for $C_{14}H_{22}NO_3$ $[M+H]^+$ 252.1594, found 252.1596.

Melting Point: Literature M.P.[141] = 104-106 °C, **Experimental M.P.** = 96-98 °C.

General procedure G for the synthesis of C_2-symmetric iodoarenes 4.28a, b

Compounds **4.28a, b** were synthesised with the slight amendment to the known literature procedure.[116] To a stirred solution of the protected amino alcohol **4.27a, b** (0.40 g, 1.41 mmol) and triethyl amine (0.2 mL, 1.41 mmol) in anhydrous dichloromethane (6 mL) was added 2-Iodo-1,3-diisocyanatobenzene **4.18** (0.2 g, 0.70 mmol) dropwise and the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residues were loaded on a short silica pad and were purified using petroleum ether/ ethyl acetate (5:1) to give the corresponding carbamate.

Synthesis of bis((*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropyl) (2-iodo-1,3-phenylene)dicarbamate 4.28a



The compound was obtained using general procedure G as yellow oil. (Yield 0.33 g, 56%).

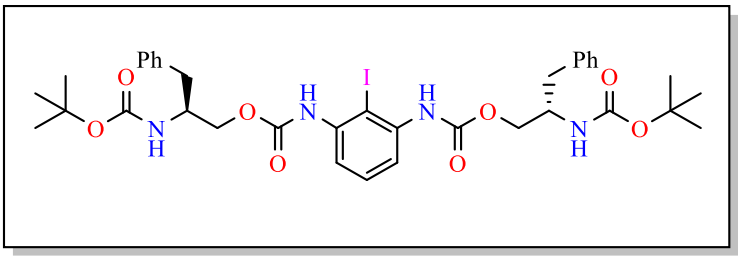
FT-IR (cm^{-1}): ν = 3344, 3027, 2955, 1772, 1715, 1700, 1620, 1586, 1495, 1466, 1364, 1277, 1201, 1087, 1013, 917, 785, 758, 698.

^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.71-7.56 (m, 8H), 7.42 (s, 1H), 7.19-7.10 (m, 11H), 6.93 (s, 2H), 4.89-4.50 (m, 5H), 4.17-4.08 (m, 1H), 3.95-3.90 (m, 1H), 3.39-3.14 (m, 4H).

^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 168.3, 153.0, 147.8, 138.7, 136.8, 134.0, 131.4, 128.9, 128.6, 126.9, 123.2, 90.4, 64.3, 52.0, 34.7.

HRMS: m/z calc'd for $C_{42}H_{33}IN_4NaO_8$ $[M+Na]^+$ 871.1235, found 871.1225.

Synthesis of bis((*S*)-2-((tert-butoxycarbonyl)amino)-3-phenylpropyl) (2-iodo-1,3-phenylene)dicarbamate 4.28b



The compound was obtained using general procedure G as colourless oil. (Yield 0.58 g, 64%).

FT-IR (cm^{-1}): ν = 3338, 2978, 1702, 1687, 1589, 1531, 1492, 1468, 1453, 1391, 1292, 1265, 1167, 1091, 1054, 854, 785, 753, 698.

^{1}H NMR: (DMSO-d$_6$, 400 MHz) δ: 7.35-7.15 (m, 13H), 6.89 (d, *J* = 8.3 Hz, 2H), 6.60 (d, *J* = 8.3 Hz, 1H), 4.04-3.87 (m, 5H), 3.61-3.53 (m, 1H), 3.30-3.25 (m, 1H), 2.84-2.64 (m, 4H), 1.33 (s, 18H).

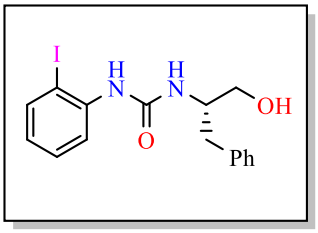
^{13}C NMR: (DMSO-d$_6$, 100 MHz) δ: 155.6, 154.5, 140.9, 138.8, 128.6, 128.5, 126.5, 126.2, 88.6, 78.1, 66.0, 54.4, 37.4, 28.7.

HRMS: m/z calc'd for $C_{36}H_{45}IN_4NaO_8$ $[M+Na]^+$ 811.2174, found 811.2138.

General procedure E for the synthesis of C_1 & C_2-symmetric iodoarenes bearing urea arm

To the solution of the corresponding isocyanate (0.7 mL, 4.34 mmol, 1 equiv.) in THF (60 mL) kept at 0 ^{o}C was added the solution of amine (0.73 g, 4.75 mmol, 1.1 equiv.) in THF (10 mL) dropwise. The ice bath was removed and the reaction mixture was brought to room temperature. The reaction mixture was stirred for 3-4 hours or until the TLC analysis showed the completion. The reaction mixture was concentrated under reduced pressure. The residue were washed hexane multiple times. Recrystallisation either with dichloromethane/ ethyl acetate or ethanol provided the desired compound.

Synthesis of (*S*)-1-(1-hydroxy-3-phenylpropan-2-yl)-3-(2-iodophenyl)urea 4.29



Compound **4.29** was prepared using general procedure E as pale yellow solid. (1.64 g, 95%)

FT-IR (cm^{-1}): ν = 3356, 3298, 3021, 2918, 2874, 2821, 1693, 1629, 1607, 1573, 1462, 1432, 1380, 1088.

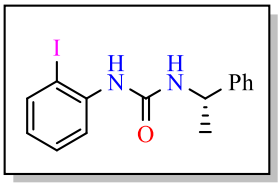
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.79-7.76 (m, 2H), 7.64 (s, 1H), 7.31-7.24 (m, 5H), 7.22-7.19 (m, 1H), 7.12 (d, J = 8.2 Hz, 1H), 6.74 (td, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 1H), 4.91 (s, 1H), 3.89-3.79 (m, 1H), 3.42-3.34 (m, 2H), 2.89-2.84 (m, 1H), 2.72-2.67 (m, 1H).

^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 155.0, 141.1, 139.6, 139.2, 129.7, 128.8, 128.6, 126.4, 124.5, 122.7, 90.4, 62.8, 53.3, 37.7.

HRMS: m/z calc'd for $C_{16}H_{18}IN_2O_2$ $[M+H]^+$ 397.0407, found 397.0405.

Melting Point: 156-157 °C.

Synthesis of (*S*)-1-(2-iodophenyl)-3-(1-phenylethyl)urea 4.31



Compound **4.31** was prepared using general procedure E as pale yellow solid. (0.71 g, 96%)

FT-IR (cm^{-1}): ν = 3278, 2974, 1731, 1636, 1576, 1525, 1494, 1463, 1433, 1276, 1016, 730, 695.

^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.85 (dd, J_1 = 8.3 Hz, J_2 = 1.4 Hz, 1H), 7.78 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H), 7.60-7.58 (m, 2H), 7.36-7.34 (m, 4H), 7.29-7.24 (m, 2H), 6.74 (td, J_1 = 7.7 Hz, J_2 = 1.4 Hz, 1H), 4.82 (app. quint, J = 7.3 Hz, 1H), 1.40 (d, J = 7.1 Hz, 3H).

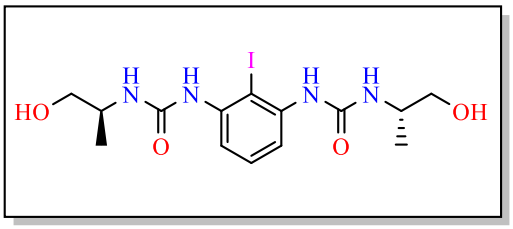
^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 154.6, 145.5, 140.9, 139.3, 128.9, 128.8, 127.2, 126.3, 124.5, 122.3, 90.3, 49.3, 23.6.

HRMS: m/z calc'd for $C_{15}H_{16}IN_2O$ $[M+H]^+$ 367.0302, found 367.0300.

Melting Point: 165-166 °C.

Synthesis of 1,1'-(2-iodo-1,3-phenylene)bis(3-((*S*)-1-hydroxypropan-2-yl)urea) 4.38a

Compound **4.31** was prepared using general procedure E as white solid. (0.501 g, 81%)



FT-IR (cm^{-1}): ν = 3284, 2980, 2851, 2359, 2341, 1632, 1162, 1035, 988, 741.

^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.60 (s, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.14 (t, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 2H), 4.78 (s, 2H), 3.70-3.65 (m, 2H), 3.42-3.28 (m, 4H), 1.08 (d, *J* = 6.8 Hz, 6H).

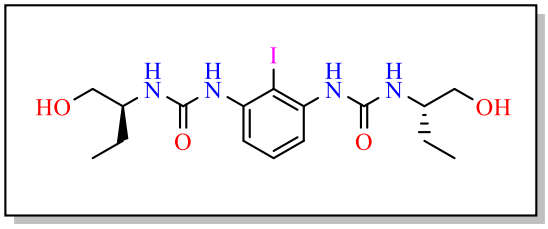
^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 155.1, 141.6, 128.2, 117.5, 89.7, 65.2, 47.4, 18.2.

HRMS: m/z calc'd for $C_{14}H_{22}IN_4O_4$ $[M+H]^+$ 437.0680, found 437.0698.

Melting Point: 249-250 °C.

Synthesis of 1,1'-(2-iodo-1,3-phenylene)bis(3-((*S*)-1-hydroxybutan-2-yl)urea) 4.38b

Compound **4.31** was prepared using general procedure E as pale yellow solid. (0.6 g, 90%)



FT-IR (cm^{-1}): ν = 3290, 2962, 2930, 2873, 2355, 1633, 1556, 1463, 1410, 1274, 1223, 1074, 1018, 784, 737, 639.

^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.62 (s, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.14 (t, *J* = 8.1 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 2H), 4.78 (s, 2H), 3.56-3.42 (m, 4H), 3.35-3.32 (m, 2H), 1.64-1.54 (m, 2H), 1.43-1.31 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 6H).

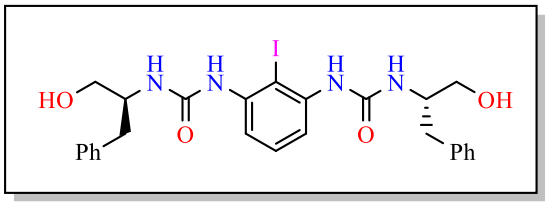
^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 155.4, 141.7, 128.2, 117.5, 89.7, 63.4, 53.0, 24.7, 10.9.

HRMS: m/z calc'd for $C_{16}H_{26}IN_4O_4$ $[M+H]^+$ 465.0993, found 465.0990.

Melting Point: 252-254 °C.

Synthesis of 1,1'-(2-iodo-1,3-phenylene)bis(3-((*S*)-1-hydroxy-3-phenylpropan-2-yl)urea) 4.38c

Compound **4.31** was prepared using general procedure E as yellow solid. (1.74 g, 85%)



FT-IR (cm^{-1}): ν = 3297, 3024, 2919, 1634, 1548, 1465, 1271, 725, 695.

^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.65 (s, 2H), 7.32-7.20 (m, 12H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 2H), 4.91 (s, 2H), 3.85-3.78 (m, 2H), 3.43-3.32 (m, 4H), 2.89-2.70 (m, 4H).

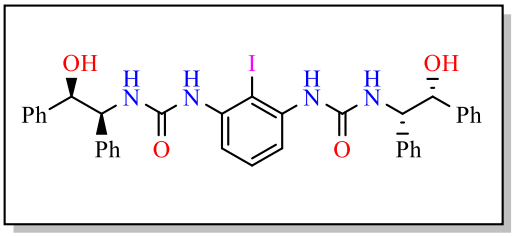
^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 155.2, 141.6, 139.6, 129.7, 128.6, 126.4, 117.7, 90.0, 62.8, 53.3, 37.7.

HRMS: m/z calc'd for $C_{26}H_{30}IN_4O_4$ $[M+H]^+$ 589.1306, found 589.1321.

Melting Point: 265-266 °C.

Synthesis of 1,1'-(2-iodo-1,3-phenylene)bis(3-((1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl)urea) 4.38d

Compound **4.31** was prepared using general procedure E as white solid. (0.37 g, 74%)



FT-IR (cm^{-1}): ν = 3343, 3213, 2981, 1647, 1587, 1556, 1503, 1465, 1396, 1276, 1231, 1068, 1047, 741.

^{1}H NMR: (DMSO-d$_6$, 400 MHz) δ: 7.98 (s, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 7.4 Hz, 4H), 7.42 (d, *J* = 7.4 Hz, 4H), 7.36-7.32 (m, 8H), 7.26-7.20 (m, 4H), 7.07-7.06 (m, 2H), 6.99-6.95 (m, 1H), 5.68 (d, *J* = 4.1 Hz, 2H), 4.90-4.85 (m, 4H).

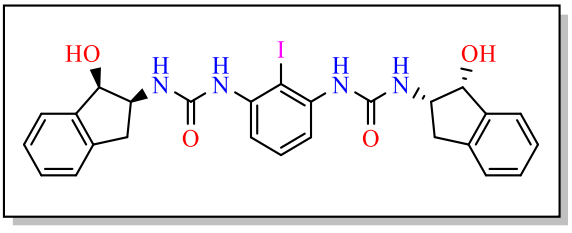
^{13}C NMR: (DMSO-d$_6$, 100 MHz) δ: 155.1, 144.1, 143.2, 141.5, 128.2, 128.1, 127.9, 127.6, 127.3, 127.0, 126.9, 118.1, 90.4, 76.0, 59.6.

HRMS: m/z calc'd for $C_{36}H_{33}IN_4O_4$ $[M+Na]^+$ 735.1439, found 735.1441.

Melting Point: 221-223°C.

Synthesis of 1,1'-(2-iodo-1,3-phenylene)bis(3-((1*R*,2*S*)-1-hydroxy-2,3-dihydro-1H-inden-2-yl)urea) 4.38e

Compound **4.31** was prepared using general procedure E as off-white solid. (0.52 g, 63%)



FT-IR (cm^{-1}): ν = 3318, 3240, 2912, 1682, 1632, 1550, 1465, 1400, 1359, 1231, 1142, 1047, 730.

^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 8.10 (s, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.29-7.20 (m, 11H), 5.23 (d, *J* = 4.1 Hz, 2H), 5.12 (dd, J_1 = 8.7 Hz, J_2 = 4.9 Hz, 2H), 4.48 (q, *J* = 4.5 Hz, 2H), 3.08 (dd, J_1 = 16.2 Hz, J_2 = 4.6 Hz, 2H), 2.82 (d, *J* = 16.1 Hz, 2H).

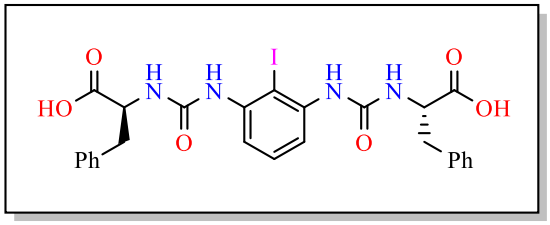
^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 155.9, 143.6, 141.9, 141.0, 128.2, 127.6, 126.7, 125.4, 124.5, 118.7, 91.3, 72.7, 58.1, 25.6.

HRMS: m/z calc'd for $C_{26}H_{25}IN_4O_4$ $[M+H]^+$ 585.0993, found 585.0989.

Melting Point: 247-248 °C

Synthesis of (2*S*,2'*S*)-2,2'-((((2-iodo-1,3-phenylene)bis(azanediyl))bis(carbonyl))bis(azanediyl))bis(3-phenylpropanoic acid) 4.38f

Compound **4.38f** was prepared using general procedure E as pale-yellow solid. (0.76 g, 70%)



FT-IR (cm^{-1}): ν = 3217, 3025, 2890, 1714, 1638, 1547, 1494, 1464, 1407, 1275, 1214, 1075, 745.

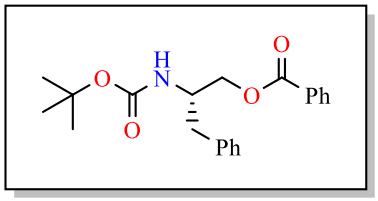
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.88 (s, 2H), 7.33-7.21 (m, 16H), 7.15-7.11 (m, 1H), 4.48-4.41 (m, 2H), 3.14-3.08 (m, 2H), 2.98-2.91 (m, 2H).

^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 173.9, 170.7, 155.0, 141.4, 137.8, 129.9, 128.7, 127.0, 118.2, 90.5, 54.5, 38.0.

HRMS: m/z calc'd for $C_{26}H_{26}IN_4O_6$ $[M+H]^+$ 617.0892, found 617.0898.

Melting Point: 227-229 °C

Synthesis of (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropyl benzoate 4.39



Compound **4.39** was synthesised by the known literature procedure[120]. To a solution of the **4.27b** (1.0 g, 3.98 mmol), triethyl amine (0.78 mL, 5.57 mmol) in chloroform (20 mL) kept at 0 ^{o}C was added benzoyl chloride (0.60 mL, 5.17 mmol) dropwise. The reaction was allowed to stir for 5 hours under continuous cooling. The reaction mixture was concentrated under reduced pressure and the residue were loaded on a short silica pad and were purified using petroleum ether: ethyl acetate (5:1) to afford **4.39** as colourless oil (yield: 1.21 g, 85%).

FT-IR (cm^{-1}): ν = 3365, 2978, 1712, 1695, 1601, 1520, 1453, 1389, 1365, 1284, 1246, 1158, 1059, 734.

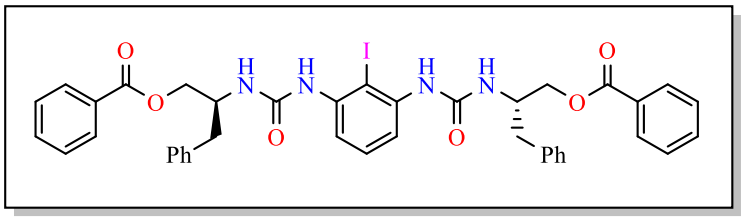
^{1}H NMR: (CDCl$_3$, 400 MHz) δ: 8.07 (d, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.34-7.31 (m, 2H), 7.27-7.24 (m, 3H), 4.75 (s, 1H), 4.33-4.25 (m, 3H), 2.99-2.90 (m, 2H), 1.43 (s, 9H).

^{13}C NMR: (CDCl$_3$, 100 MHz) δ: 166.4, 162.3, 135.4, 133.2, 130.6, 129.3, 129.0, 128.9, 128.7, 126.7, 79.8, 65.7, 50.8, 38.1, 28.3.

HRMS: m/z calc'd for $C_{21}H_{26}NO_4$ $[M+H]^+$ 355.1784, found 355.1780.

Melting Point: 118-119 °C

Synthesis of (2*S*,2'*S*)-((((2-iodo-1,3-phenylene)bis(azanediyl))bis(carbonyl))bis(azanediyl))bis(3-phenylpropane-2,1-diyl) dibenzoate 4.40



The compound **4.39** (0.2 g, 0.56 mmol) was placed in 15 mL round bottom flask under nitrogen atmosphere at 0 ^{o}C. TFA (2 mL) was added slowly and the reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The obtained residue **4.39a** were used as such for the next step. The residue of the compound **4.39a** were coupled with **4.18** according to the general procedure E to give **4.40** as yellow solid (0.12 g, 49%).

FT-IR (cm^{-1}): ν = 3288, 3064, 2923, 2852, 1716, 1641, 1538, 599.

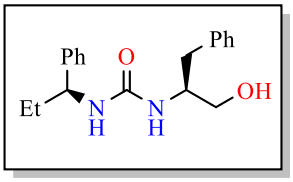
^{1}H NMR: (DMSO-d$_6$, 400 MHz) δ: 8.05-8.02 (m, 4H), 7.70-7.66 (m, 2H), 7.57-7.52 (m, 4H), 7.41-7.37 (m, 2H), 7.33-7.30 (m, 10H), 7.26-7.21 (m, 4H), 7.14-7.08 (m, 1H), 4.36-4.17 (m, 6H), 2.99-2.84 (m, 4H).

^{13}C NMR: (DMSO-d$_6$, 100 MHz) δ: 166.1, 155.1, 149.8, 138.6, 133.9, 130.1, 129.9, 129.7, 129.2, 128.8, 128.4, 126.7, 88.5, 66.6, 50.2, 37.8.

HRMS: m/z calc'd for $C_{40}H_{38}IN_4O_6$ $(M+H)^+$ 797.1831, found 797.1835.

Melting Point: 230-232 °C

Synthesis of 1-((*S*)-1-hydroxy-3-phenylpropan-2-yl)-3-((*S*)-1-phenylpropyl)urea 4.45



The compound **4.45** was synthesised according to the general procedure E as colourless oil (0.41 g, 100%).

FT-IR (cm^{-1}): ν = 3336, 3026, 2927, 2356, 2341, 1610, 1586, 1565, 1493, 1449, 1380, 1253, 1073, 1046, 740, 696.

^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.31-7.16 (m, 10H), 6.40 (d, *J* = 8.6 Hz, 1H), 5.80 (d, *J* = 8.6 Hz, 1H), 4.84 (s, 1H), 4.51 (q, *J* = 7.3 Hz, 1H), 3.71-3.67 (m, 1H), 3.35-3.25 (m, 2H), 2.80-2.75 (m, 1H), 2.62-2.57 (m, 1H), 1.67-1.53 (m, 2H), 0.79 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 157.7, 145.1, 139.6, 129.7, 128.5, 128.4, 126.6, 63.0, 54.8, 52.9, 37.7, 30.5, 11.1.

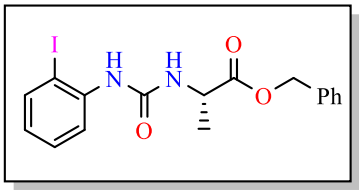
HRMS: m/z calc'd for $C_{19}H_{25}N_2O_2$ $(M+H)^+$ 313.1911, found 313.1909.

Melting Point: 130-131 °C

General procedure I for the synthesis of C_1 & C_2-symmetric iodoarenes bearing urea and carbamate arm

To the solution of the corresponding isocyanate (0.5 g, 2.04 mmol, 1 equiv.) in THF (30 mL) kept at 0 °C was added the solution of amine (0.48 g, 2.24 mmol, 1.1 equiv.) and triethylamine (0.57 mL, 4.08 mmol, 2.0 equiv.) in THF (10 mL) dropwise. The ice bath was removed and the reaction mixture was brought to room temperature. The reaction mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure. The residue was washed with hexane multiple times. Recrystallisation either with dichloromethane/ ethyl acetate or ethanol provided the desired compound.

Synthesis of benzyl ((2-iodophenyl)carbamoyl)-*L*-alaninate 4.34



The compound **4.34** was synthesised according to the general procedure I as pale yellow solid (0.37 g, 88%).

FT-IR (cm^{-1}): ν = 3299, 3060, 2979, 2605, 2498, 1720, 1633, 1556, 1512, 1463, 1452, 1432, 1318, 1291, 1221, 1164, 1097, 750.

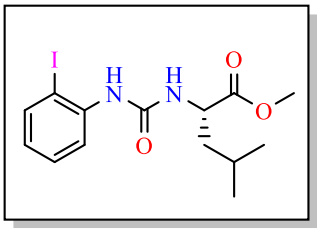
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.84-7.79 (m, 2H), 7.74 (s, 1H), 7.58 (d, *J* = 6.9 Hz, 1H), 7.39-7.27 (m, 6H), 6.77 (t, *J* = 7.4 Hz, 1H), 5.20-5.12 (m, 2H), 4.33-4.26 (m, 1H), 1.36 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 173.7, 154.9, 140.7, 139.3, 136.5, 129.0, 128.9, 128.4, 128.1, 124.9, 122.5, 90.5, 66.3, 48.9, 18.0.

HRMS: m/z calc'd for $C_{17}H_{18}IN_2O_3$ $(M+H)^+$ 425.0357, found 425.0359.

Melting Point: 161-163 °C

Synthesis of methyl ((2-iodophenyl)carbamoyl)-*L*-leucinate 4.36



The compound **4.36** was synthesised according to the general procedure I as yellow solid (0.58 g, 73%).

FT-IR (cm^{-1}): ν = 3301, 2951, 2868, 1737, 1641, 1573, 1557, 1519, 1463, 1433, 1367, 1273, 1255, 1205, 1155, 1016, 980, 762, 743, 653.

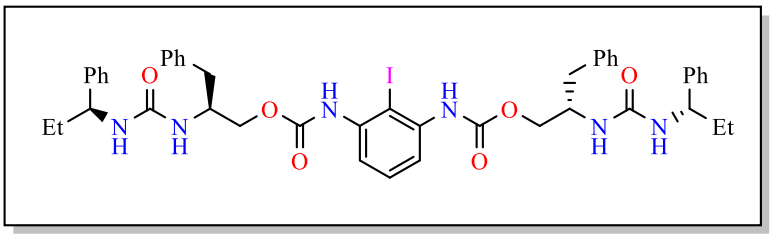
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 7.84-7.78 (m, 2H), 7.72 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.27 (t, *J* = 8.1 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 4.26-4.21 (m, 1H), 3.65 (s, 3H), 1.73-1.66 (m, 1H), 1.58 (t, *J* = 7.3 Hz, 2H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 174.2, 155.1, 140.7, 139.4, 128.9, 124.8, 122.5, 90.5, 52.3, 51.5, 41.0, 24.8, 23.2.

HRMS: m/z calc'd for $C_{14}H_{20}IN_2O_3$ $(M+H)^+$ 391.0513, found 391.0510.

Melting Point: 158-160 °C

Synthesis of bis((*S*)-3-phenyl-2-(3-((*S*)-1-phenylpropyl)ureido)propyl) (2-iodo-1,3-phenylene)dicarbamate 4.46



The compound **4.46** was synthesised according to the general procedure I as dark brown solid (0.73 g, 65%).

FT-IR (cm^{-1}): ν = 3270, 3026, 2961, 1702, 1633, 1584, 1519, 1461, 1398, 1202, 1109, 1109, 1018, 745, 696, 621.

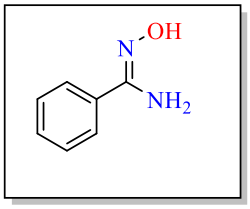
^{1}H NMR: (DMSO-d$_6$, 400 MHz) δ: 9.02 (s, 2H), 7.32-7.19 (m, 23H), 6.45 (d, *J* = 8.0 Hz, 2H), 5.87 (d, *J* = 8.0 Hz, 2H), 4.56-4.49 (m, 2H), 4.02-3.95 (m, 6H), 2.83-2.72 (m, 4H), 1.67-1.59 (m, 4H), 0.79 (t, *J* = 7.0 Hz, 6H).

^{13}C NMR: (DMSO-d$_6$, 100 MHz) δ: 157.4, 154.6, 144.9, 141.0, 138.7, 129.7, 128.7, 128.6, 126.6, 83.9, 66.2, 54.9, 50.2, 37.7, 30.4, 11.2.

HRMS: m/z calc'd for $C_{46}H_{52}IN_6O_6$ $(M+H)^+$ 933.2807, found 933.2813.

Melting Point: 249-251 °C

Synthesis of *(Z)-N'*-hydroxybenzimidamide 4.42a



Known literature procedure was used to synthesise this compound.[142] To a solution of benzonitrile (5 mL, 48.48 mmol) in dry ethanol (50 mL) was added 50% aq. hydroxylamine (2.25 mL, 72.73 mmol) dropwise. The resulting solution was refluxed for 3 hours and evaporated under reduced

pressure. Residues were purified by flash chromatography using petroleum ether and ethyl acetate Pet-EtOAc (1:1) as eluents to afford pure product as white crystals (3.66 g, 92%).

FT-IR (cm^{-1}): ν = 3590, 3525, 3419, 2920, 1644, 1594, 1576.

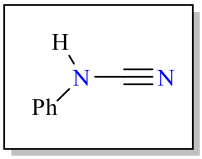
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 9.65 (s, 1H), 7.71-7.67 (m, 2H), 7.38-7.36 (m, 3H), 5.82 (s, 2H).

^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 151.3, 129.9, 129.3, 128.5, 125.8.

HRMS: m/z calc'd for $C_7H_9N_2O$ $(M+H)^+$ 137.0709, found 137.0707.

Melting Point: Literature M.P.[142] = 65-66 °C, **Experimental M.P.** = 65-67 °C.

Synthesis of *N*-Phenylcyanamide 4.42b



Known literature procedure was used to synthesise this compound.[142] To a stirred solution of benzamidoxime (2.45 g, 17.99 mmol), in pyridine (18 mL) at 0 °C was added tosyl chloride (3.6 g, 18.9 mmol) under nitrogen. The mixture was stirred at 0 °C for 10 minutes then at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. Residues were purified by flash chromatography using petroleum ether and ethyl acetate Pet-EtOAc (5:1 and then 4:1) as eluents to afford pure product as white powder (1.3 g, 61%).

FT-IR (cm^{-1}): ν = 3459, 3170, 2988, 2911, 2221, 1592.

^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 10.14 (s, 1H), 7.35-7.31 (m, 2H), 7.03-6.97 (m, 3H).

^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 139.0, 130.1, 122.9, 115.3, 112.4.

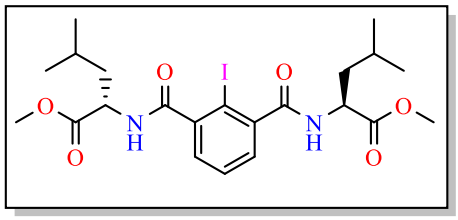
HRMS: m/z calc'd for $C_7H_7N_2$ $(M+H)^+$ 119.0604, found 119.0604.

Melting Point: Literature M.P.[142] = 35-36 °C, **Experimental M.P.** = 36-38 °C.

General procedure J for the synthesis of C_2-symmetric iodoarenes bearing chiral amide appendage

To the solution of the 2-iodoisophthaloyl dichloride (0.40 g, 1.22 mmol, 1 equiv.) in dichloromethane (40 mL) kept at 0 °C was added the solution of amine (0.49 g, 2.70 mmol, 2.2 equiv.) and triethylamine (0.74 mL, 7.32 mmol, 6.0 equiv.) in THF (10 mL) dropwise. The ice bath was removed and the reaction mixture was brought to room temperature. The reaction mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure. The residue was redissolved in ethyl acetate and washed with 2 M HCl (10 ml). The organic layers were separated, combined, dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallisation of the residue with dichloromethane/ ethyl acetate provided the desired compound.

Synthesis of dimethyl 2,2'-((2-iodoisophthaloyl)bis(azanediyl))(2*S*,2'*S*)-bis(4-methylpentanoate) 4.47a



The compound **4.47a** was synthesised according to the general procedure J as yellow solid (0.27 g, 40%).

FT-IR (cm^{-1}): ν = 3271, 2955, 2605, 1739, 1650, 1528, 1434, 1267, 1200, 693.

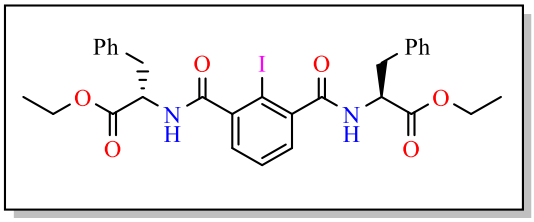
^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 7.43-7.34 (s, 3H), 6.30 (d, *J* = 8.5 Hz, 2H), 4.85-4.79 (m, 2H), 3.77 (m, 6H), 1.90-1.63 (m, 6H), 1.02-0.96 (m, 12H).

^{13}C NMR: ($CDCl_3$, 100 MHz) δ: 173.0, 169.0, 143.9, 128.8, 128.6, 90.4, 52.5, 51.2, 41.4, 24.9, 22.9.

HRMS: m/z calc'd for $C_{22}H_{32}IN_2O_6$ $(M+Na)^+$ 569.1119, found 569.1118.

Melting Point: 209-211 °C.

Synthesis of diethyl 2,2'-((2-iodoisophthaloyl)bis(azanediyl))(2*S*,2'*S*)-bis(3-phenylpropanoate) 4.47b



The compound **4.47b** was synthesised according to the general procedure J as yellow solid (0.38 g, 65%).

FT-IR (cm^{-1}): ν = 3278, 2978, 1731, 1650, 1525, 1368, 1209, 1117, 1031, 695.

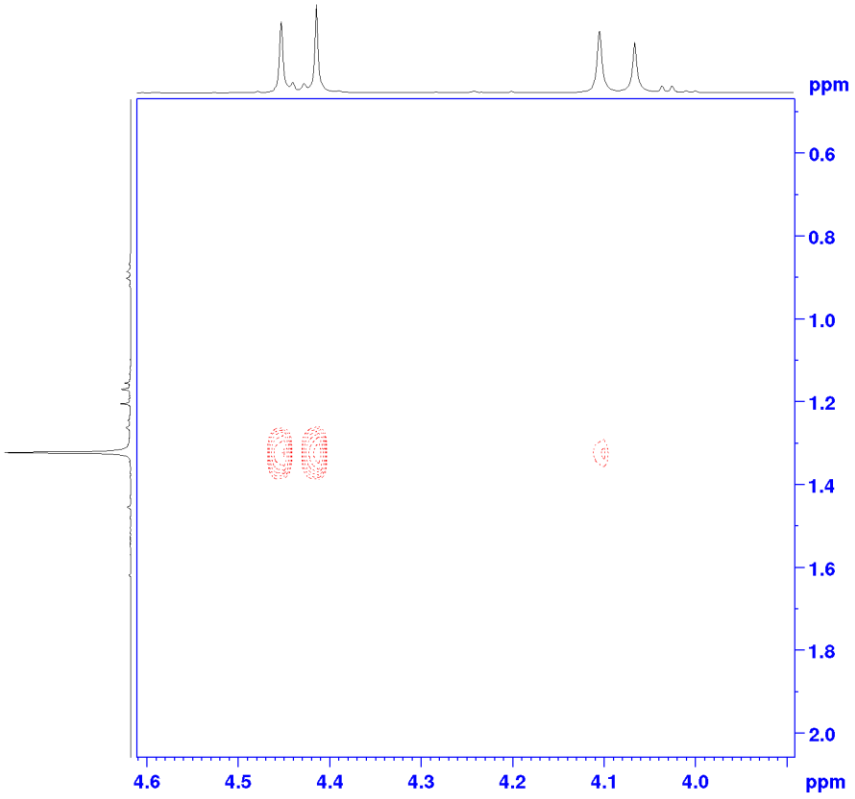
^{1}H NMR: (DMSO-d_6, 400 MHz) δ: 8.94 (d, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.34-7.29 (m, 8H), 7.26-7.21 (m, 2H), 7.05 (d, *J* = 7.6 Hz, 2H), 4.65-4.60 (m, 2H), 4.16-4.08 (m, 4H), 3.16-2.97 (m, 4H), 1.18 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR: (DMSO-d_6, 100 MHz) δ: 171.6, 169.3, 144.3, 137.8, 129.7, 128.7, 128.4, 127.0, 92.0, 61.1, 54.3, 36.9, 14.6.

HRMS: m/z calc'd for $C_{30}H_{32}IN_2O_6$ $(M+H)^+$ 643.1300, found 643.1306.

Melting Point: 184-186 °C.

NOESY measurements for major diastereomer of compound 3.82

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Current Data Parameters
NAME      UT-482 MAJOR CDCl3
EXPNO              14
PROCNO              1

F2 - Acquisition Parameters
Date_          20190322
Time              3.37 h
INSTRUM          spect
PROBHD   Z116098_0048 (
PULPROG     noesygpphpp
TD                2048
SOLVENT           CDCl3
NS                   2
DS                  32
SWH           3846.154 Hz
FIDRES        3.756010 Hz
AQ            0.2662400 sec
RG                20.45
DW              130.000 usec
DE               19.69 usec
TE               294.0 K
D0            0.00011822 sec
D1            1.96641195 sec
D8            0.50000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
D16           0.00020000 sec
IN0           0.00026000 sec
TDav                 1
SFO1         400.1317399 MHz
NUC1                1H
P1                9.25 usec
P2               18.50 usec
P17            2500.00 usec
PLW1        24.00000000 W
PLW10        2.28169990 W
GPNAM[1]     SMSQ10.100
GPZ1             40.00 %
P16            1000.00 usec

F1 - Acquisition parameters
TD                 256
SFO1         400.1317 MHz
FIDRES        30.048077 Hz
SW             9.612 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                1024
SF           400.1300087 MHz
WDW               QSINE
SSB                   2
LB        0 Hz
GB        0
PC                1.00

F1 - Processing parameters
SI                1024
MC2         States-TPPI
SF           400.1300087 MHz
WDW               QSINE
SSB                   2
LB        0 Hz
GB        0
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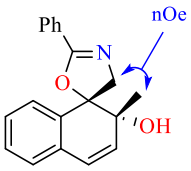
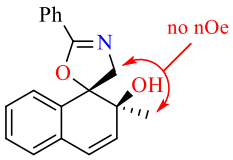


Major Diastereomer



Minor Diastereomer

References

1. Zhdankin, V. V.; *Hypervalent Iodine Chemistry*: *John Wiley & Sons Inc*: **2014**, UK.

2. Tremblay, J-F. *Chem. Eng. News*, **2011**, *49*, 89, 22-24.

3. Kaiho. T. Iodine Chemistry and applications, *John Wiley & Sons Inc*: **2014**, Chichester, UK.

4. Musher, J. I. *Angew. Chem. Int. Ed*. **1969**, *8*, 54-68.

5. Willgerodt, C. *J. Prakt. Chem*. **1886**, *33*, 154-160.

6. Varvoglis, A. *Tetrahedron* **2010**, *66*, 5739–5744.

7. Akiba, K-Y. *Chemistry of Hypervalent Compounds. John Wiley & Sons Inc*. **1999.**

8. Yusubov, M.; Zhdankin. V. *Mendeleev Commun*. **2010**, *20*, 185-242.

9. Yusubov, M.; Zhdankin, V. *Curr. Org. Synth*. **2012**, *9*, 247-272.

10. Martin, J.C. *Science* **1983**, *221*, 509-514.

11. Perkins, W.; Martin, C.; Arduengo, J.; *J. Am. Chem. Soc*. **1980**, *102*, 7753-7759.

12. Powell, W.H. *Pure and Applied Chemistry*, **1984**, *56*, 769-778.

13. Pimentel, C. *J. Chem. Phys*. **1951**, *19*, 446.

14. Hach, J.; Rundle, E. *J. Am. Chem. Soc*. 1951, *73*, 4321-4324.

15. Zhdankin, V. V.; Hypervalent Iodine Chemistry: *John Wiley & Sons Inc*: GB, **2014,** pp 4-6.

16. Farid, U., & Wirth, T. *Encyclopedia of Reagents for Organic Synthesis*. **2012**.

17. Ochiai, M., & Wirth, T. *Topics in Current Chemistry*, Springer, **2003**.

18. Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. *J. Am. Chem. Soc.* **1995**, *117*, 3360.

19. Zhdankin, V. V.; Hypervalent Iodine Chemistry: *John Wiley & Sons Inc*: GB, **2014,** pp 12-14.

20. Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979,** *18*, 239

21. Guerard, K. C.; Sabot, C.; Beaulieu, M. A.; Giroux, M. A; Canesi, S. *Tetrahedron* **2010**, *66*, 5893.

22. Pribram, R. *Justu Liebigs Ann. Chem.* **1907**, *351*, 481-485.

23. Merkushev, E. B.; Novikov, A. N.; Makarchenko, S. S.; Moskal'chuk, A. S.; Glushkova, V. V.; Kogai, T. I.; Polyakova, L. G. *J. Org. Chem. USSR (Engl. Trans.)* **1975**, *11*, 1246−1249.

24. Zhdankin, V. V.; Smart, J. T.; Zhao, P.; Kiprof, P. *Tetrahedron Lett.* **2000**, *41*, 5299−5302.

25. Liang, H.; Ciufolini, M. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 11849.

26. Hypervalent Iodine Chemistry. *In Modern Developments in Organic Synthesis*; Topics in Current Chemistry; Wirth, T., Ed.; *Springer*: Berlin, **2003**; Vol. 224.

27. Fujita, M.; Yoshida, Y.; Miyata, K.; Wakisaka, A.; Sugimura, T. *Angew. Chem., Int. Ed*. **2010**, *49*, 7068−7071.

28. Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175−2177.

29. Uyanik, M.; Yasui, T.; Ishihara, K. *Tetrahedron* **2010**, *66*, 5841−5851.

30. Sreenithya, A.; Patel, C.; Hadad, C.; Sunoj, R. *ACS Catal*., **2017**, *7*, 4189–4196.

31. Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244-12245.

32. Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, Y. *Angew. Chem.* **2005**, *117*, 6349-6352; *Angew. Chem. Int. Ed.* **2005**, 44, 6193-6196.

33. Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244−12245.

34. O'Mahony, G. E.; Ford, A.; Maguire, A. R. *J. Sulfur Chem.* **2013**, *34*, 301−341.

35. Imamoto, T.; Koto, H.; *Chem. Lett*. **1986**, 967-968.

36. Ray III, D. G.; Koser, G. F. *J. Org. chem.* **1992**, *57*, 1607-1610.

37. Hatzigrigoriou, E.; Varvoglis, A.; Bakola-Christianopoulou, M. *J. Org. Chem.* **1990**, *55*, 315−318.

38. Xia, M.; Chen, Z.-C. *Synth. Commun.* **1997**, *27*, 1315−1320.

39. Tohma, H.; Takizawa, S.; Watanabe, H.; Fukuoka, Y.; Maegawa, T.; Kita, Y.; *J. Org. Chem*, **1999**, *64*, 3519-3523.

40. Tohma, H.; Takizawa, S.; Motioka, H.; Maegawa, T.; Kita, Y.; *Chem. Pharm. Bull*. **2000**, *48*, 445-446.

41. Ray III, D. G.; Koser, G. F. *J. Chem. Soc*. **1990**, *112*, 5672-5673.

42. Ochiai, M.; Kitagawa, Y.; Takayama, N.; Takaoka, Y.; Shiro, M. *J. Am. Chem. Soc.* **1999,** *121*, 9233-9234.

43. Jalalian, N.; Olofsson, B. Tetrahedron **2010**, *66*, 5793−5800.

44. Moriarty, R. M.; Prakash, *Acc. Chem. Res.* **1986**, *19*, 244−250.

45. Koser, G. F.; Lodaya, J. S.; Ray, D. G., III; Kokil, P. B. *J. Am. Chem. Soc*. **1988**, *110*, 2987−2988.

46. **a)** Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487−2489. **b)** Lodaya, J. S.; Koser, G. F. *J. Org. Chem*. **1988**, *53*, 210−212. **c)** Moriarty, R. M.; Vaid, R. K.; Ravikumar, V. T.; Vaid, B. K.; Hopkins, T. E. *Tetrahedron.* **1988**, *44*, 1603−1607.

47. Wirth, T.; Hirt, U. H. *Tetrahedron: Asymmetry* **1997**, *8*, 23–26.

48. Richardson, R. D.; Page, T. K.; Altermann, S.; Paradine, S. M.; French, A. N.; Wirth, T. *Synlett* **2007**, 538–542.

49. Farooq, U.; Schäfer, S.; Ali Shah, A. U. H.; Freudendahl, D. M.; Wirth, T. *Synthesis* **2010**, 1023–1029.

50. Yu, J.; Cui, J.; Hou, X.S.; Liu, S.S.; Gao, W.C.; Jiang, S.; Tian, J.; Zhang, C. *Tetrahedron: Asymmetry* **2011**, *22*, 2039-2055.

51. Rodríguez, A.; Moran, W. J. *Synthesis* **2012**, *44*, 1178–1182.

52. **a)** Guilbault, A. A.; Basdevant, B.; Wanie, V. Legault, C. Y. *J. Org. Chem*. **2012**, *77*, 11283–11295. **b)** Guilbault, A. A. Legault, C. Y. *ACS Catal*. **2012**, *2*, 219–222.

53. Suzuki, S.; Kamo, T.; Fukushi, K.; Hiramatsu, T.; Tokunaga, E.; Dohi, T.; Kita, Y.; Shibata, N. *Chem. Sci*. **2014**, *5*, 2754–2760.

54. Berthiol, F. *Synthesis*, **2015**, *47*, 587-603.

55. Parra, A.; Reboredo, S. *Chem. Eur. J*. **2013**, *19*, 17244–17260.

56. Yoshimura, A.; Zhdankin, V.V. *Chem. Rev*. **2016**, *116*, 3328-3435.

57. Souto, J. A.; Martinez, C.; Velilla, I.; Muñiz, K. *Angew. Chem., Int. Ed*. **2013**, *52*, 1324–1328.

58. Zhong, W.; Yang, J.; Meng, X.; Li, Z. *J. Org. Chem*. **2011**, *76*, 9997–10004.

59. Kong, W.; Feige, P.; de Haro, T.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 2469–2473.

60. Hara, S.; Nakahigashi, J.; Ishi-i, K.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett*. **1998**, *39*, 2589–2592

61. Hara, S.; Nakahigashi, J.; Ishi-i, K.; Sawaguchi, M.; Sakai, H.; Fukuhara, T.; Yoneda, N. *Synlett* **1998**, 495–496.

62. Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. *J. Am. Chem. Soc*. **2011**, *133*, 8134–8137.

63. Gelis, C.; Dumoulin, A.; Bekkaye, M.; Neuville, L.; Masson, G. *Org. Lett.* **2017**, *19*, 278−281.

64. Haubenreisser, S.; Wöste, T. H.; Martínez, C.; Ishihara, K.; Muñiz, K. *Angew. Chem., Int. Ed*. **2016**, *55*, 413–417.

65. Banik, S. M.; Medley, J. W.; & Jacobsen, E. N. *J. Am. Chem. Soc*. **2016**, *138*, 5000–5003.

66. Purkait, N., Okumura, S., Souto, J. A., & Muniz, K. *Org. Lett*. **2014**, *16*, 4750−4753.

67. Alhalib, A.; Kamouka, S.; Moran, W. J. *Org. Lett*. **2015**, *17*, 1453-1456.

68. Kamouka, S.; **(2017)** *Development of Enantioselective and Catalytic Cyclisation Reactions Using Hypervalent Iodine Compounds.* Doctoral thesis, University of Huddersfield.

69. **a)** Justik, M. W.; Koser, G. F. *Molecules* **2005**, *10*, 217−225. **b)** Silva, L. F.; Vasconcelos, R. S.; Nogueira, M. A. *Org. Lett*. **2008**, *10*, 1017−1020.

70. Silva, L. F.; Siqueira, F. A.; Pedrozo, E. C.; Vieira, F. Y. M.; Doriguetto, A. C. *Org. Lett*. **2007**, *9*, 1433−1436.

71. Miki, Y.; Fujita, R.; Matsushita, K. I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2533−2536.

72. Farid, U.; Malmedy, F.; Claveau, R.; Albers, L.; Wirth, T. *Angew. Chem., Int. Ed*. **2013**, *52*, 7018−7022.

73. Malmedy, F.; Wirth, T. *Chem. - Eur. J*. **2016**, *22*, 16072− 16077.

74. Roche, S.P; Porco, J.A. Jr. *Angew. Chem. Int. Ed*. **2011**, *50*, 4068–4093

75. Zhuo, C-X.; Zhang, W.; You, S-L. *Angew. Chem. Int. Ed*. **2012**, *51*, 12662–12686.

76. Ding, Q.; Ye, Y.; Fan, R. *Synthesis*. **2004**, *45*, 1–16.

77. Ding, Q.; Zhou, X.; Fan R. *Org Biomol Chem*. **2014**, *12*, 4807–4815.

78. Wang, D-S.; Chen, Q-A.; Lu, S-M.; Zhou, Y-G. *Chem Rev*. **2012**, *112*, 2557–2590.

79. Roche, S-P.; Youte, T.; Tre´guier, B. *Tetrahedron*. **2015**, *71*, 3549–3591.

80. Quideau, S.; Pouyse´gu, L.; Deffieux, D. *Synlett*. **2008**, 467–495.

81. Magdziak, D.; Meek, SJ.; Pettus, TRR. *Chem Rev*. **2004**, *104*, 1383–1429.

82. Yakura, T.; Konishi. T. *Synlett* **2007**, *5*, 765-768.

83. Yakura, T.; Omoto, M.; Yamauchi, Y.; Tian, Y.; Ozono, A. *Tetrahedron* **2010**, *66*, 5833-5840.

84. Yakura, T.; Omoto, M. *Chem. Pharma. Bull*. **2009**, *57*, 643-645.

85. Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 6193-6196.

86. Traore, M.; Ahmed-Ali, S.; Peuchmaur, M.; Wong, Y-S. *Tetrahedron*, **2010,** *66*, 5863-5872.

87. Dohi, T.; Maruyama, A.; takenage, n.; Senami, K.; Minamitsuji, Y.; Fujioka, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 3787-3790.

88. Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2175-2177.

89. Uyanik, M.; Yasui, T.; Ishihara, K. *Tetrahedron* **2010**, *66*, 5841-5851.

90. Uyanik, M.; Ishihara, K. *Yuki Gosei Kagaku Kyokaishi* **2012**, *70*, 1116-1122.

91. Dohi, T.; Takenaga, N.; Nakae, T.; Yamasaki, Y.; Shiro, M.; Fujioka, H.; Maruyama, A.; Kita, Y. *J. Am. Chem. Soc*. **2013**, *135*, 4558–4566.

92. Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed*. **2013**, *52*, 9215-9218.

93. Volp, K. A.; Harned, A. M. *Chem. Commun*. **2013**, *49*, 3001–3003.

94. Ganji, B.; Ariafard, A. *Org. Biomol. Chem*., **2019**, *17*, 3521-3528.

95. Dohi, T.; Uchiyama, T.; Yamashita, D.; Washimi, N.; Kita, Y. *Tetrahedron Lett*. **2011**, *52*, 2212–2215.

96. De Castro, C. M.; Nahori, M. A.; Dumarey, C. H.; Varqaftiq, B. B.; Bachelet, M. *Eur. J. Pharmacol.* **1995**, *294*, 669.

97. (a) Xiao, S.-J.; Zhang, M.-S.; Chen, F.; Ding, L.-S.; Zhou, Y. *J. Asian Nat. Prod. Res.* **2016**, *18*, 719. Also, see: (b) Zhang, Y.-M.; Su, M.-S.; Shao, F.; Yang, M.; Zhang, P.-Z. *Chem. Nat. Prod.* **2018**, *54*, 1118.

98. Boehm, Marcus F.; Martinborough, E.; Moorjani, M.; Tamiya, J.; Huang, L.; Fowler, T.; Novak, A.; Meghani, P.; Brahmachary, E.; Yeager, A-R. *PCT Int. Appl.* **2012**, pp 369.

99. Zhang, L.; Wang, X.; Wang. J.; Grinberg, N.; Krishnamurthy, D.; Senanayake, C-H. *Tetrahedron Lett*. **2009**, *50*, 2964-2966.

100. Lambruschini, C.; Basso, A.; Moni, L.; Pinna, A.; Riva, R.; Banfi, L. *Eur. J. Org. Chem*. **2018**, *39*, 5445-5455.

101. Liu, L-P.; Yu, L-M.; Zhang, Z-M.; Yan, X-F. *Asian. J. Chem*. **2012**. *25*, 4121-4122.

102. Kita, Y.; Tohma, H.; Masanao, I.; Hatanaka, K.; Yakura, T. *Tetrahedron Lett.* **1991**, *32*, 4321–4324.

103. Tsujiyama, S.; Suzuki, K.; Guthrie, D. B.; Gibney, H. M.; Curran, D. P. *Org. Syn.* **2007**, *84*, 272-284.

104. Berliner, M-A.; Cordi, E-M.; Dunetz, J-R.; Price, K-E. *Org. Process Res. Dev.* **2010**, *14*, *1*, 180-187.

105. Zeng, F.; Alper, H. *Org. Lett.* **2010**, *12*, *16*, 3642-3644.

106. Hequan, Y.; Sun, T.; Aijun, L.; Jinyi, X.; Xiaoming, W. *Faming Zhuanli Shenqing* **2015**, pp 11.

107. Krishnamurthy, R.; Natarajan, S. *Synthetic Communications* **1992**, *22*, 3189-95.

108. Lei, Y.; Minhao, h.; Tianfeng, X. et al. *Eur. J. Med. Chem*. **2017**, *126*, 1107-1117.

109. Behzad, Z.; Davood, S. *Syn. Comm.* **2006**, *36*, 2699-2704.

110. Wei, J.; Bi, Y.; Wang, Y.; Shi, X. *Faming Zhuanli Shenqing.* **2007**, pp 19.

111. Mallakpour, S.; Dinari,, M. *Polymer Bulletin.* **2013**, *70*, 1049-1064.

112. Orlandi, M.; Benaglia, M.; Tosi, F.; Annunziata, R.; Cozzi, F. *J. Org. Chem.* **2016**, *81*, *7*, 3037-3041.

113. João, H. PhD thesis, *University of Huddersfield*, **2014**.

114. Sashida, H.; Satoh, H. *Chem. Pharm. Bull.* **2004**, *52*, 413-417.

115. Morishita, K.; Murayama, S.; Araki, T.; Aoki, I.; Karasawa, S. *J. Org. Chem.* **2016**, *81*, *18*, 8351-8362.

116. Zhou, Z.; Li; Y.; Han, B.; Meggers, E. *Chem. Sci.* **2017**, *8*, 5757-5763.

117. Romina Wechsel, R.; Raftery, J.; Cavagnat, D.; Guichard, G.; Clayden, J. *Angew. Chem. Int. Ed*. **2016**, *55*, 33, 9657–9661.

118. Dobrijov, G-M.; Valcheva, V.; Nikolova, Y.; Ugrinova, I.; Pasheva, E.; Dimitrov, V. *Eur. J. Med. Chem.* **2013**, *63*, 468-473.

119. Li, Q; Xu, K; Song, P; Dai, Y; Yang, L; Pang, X. *Dyes. Pigm*. **2014**, *109*, 169-174.

120. Araki, H.; Suzuki, R.; Nozawa, D.; Ota, H.; Futamura, A.; Abe, M.; Amada, H.; Konishi, I.; Ogata, U. *Jpn. Kokai Tokkyo Koho.* **2015**, pp 110.

121. Brunner, H.; Poleschak, I. *Zeitschrift fuer Naturforschung, B: Chem. Sci.* **1997**, *52*, 1997.

122. Madera, A-Marie.; Poon, D.; Smith, A. *PCT Int. Appl.* **2011**, pp 118.

123. Hunt, T.; Atherton, H.; Collingwood, S.; Coote, K.; Czarnecki, S.; et al. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2877-2879.

124. Weiberth, F-J.; Bourque, A-J.; Elenbaas, S.; Hanna, R.; Powers, M-R.; Siegel, C.; Zhao, J. *Synthesis* **2017**, *49*, 4133-4136.

125. Rezanka, T.; Sigler, K. *Eur. J. Org. Chem*. **2006**, *18*, 4277-4284.

126. Basavaprabhu, H.; Sureshbabu, V. *Org. Biomol. Chem*. **2012**, *10*, 2528-2533.

127. Reddy, Rao, G-V.; Subramanyam, R-V.; Iyengar, D-S. *Syn. Comm*. **2000**, *30*, 2233-2237.

128. Rodríguez, A.; Moran, W. *Synthesis* **2012**, *44*, 1178-1182.

129. McKillop, A.; Kemp, D. *Tetrahedron* **1989**, *45*, 3299-3306.

130. Fujita, M.; Yoshida, Y.; Miyata, K.; Wakisaka, A.; Sugimura, T. *Angew. Chem. Int. Ed* **2010**, *49*, 7068-7071.

131. Matthies, D.; *Arch. Pharm*. **1968**, *301*, 867-872.

132. Lambruschini, C.; Basso, A.; Moni, L.; Pinna, A.; Riva, R.; Banfi, L. *Eur. J. Org. Chem.* **2018**, *39*, 5445-5455.

133. Schneider, A-E.; Manolikakes, G. *J. Org. Chem.* **2015**, *80*, *12*, 6193-6212.

134. Thomsen, I.; Torssell, K. B. Acta *Chem. Scan*, **1991**, *45*, 539-542.

135. Berliner, M-A.; Cordi, E-M. ; Dunetz, J-R.; Price, K-E. *Org. Process Res. Dev*. **2010**, *14*, 180.

136. Banik, S-M.; Medley, J-W.; Jacobsen, E. *J. Am. Chem. Soc.* **2016**, *138*, *15*, 5000-5003.

137. Smith, W.; Ho, O. *J. Org. Chem*. **1990**, *55*, 2543-2545.

138. James, C-W.; Kenner, J.; Stubbings, W-C. *J. Chem. Soc., Trans.*, **1920**, *117*, 773-776.

139. Tauk, L.; Schröder, A-P.; Decher, G.; Giuseppone, *Nat. Chem*. **2009**, *1*, 649-656.

140. Sani, M.; Fossati, G.; Huguenot, F.; Zanda, M. *Angew. Chem., Int. Ed*. **2007**, *46*, 3526-3529.

141. Casimir, J-R.; Guichard, G.; Briand, J-P. *J. Org. Chem.* **2002**, *67*, 3764-3768.

142. Lin, C-C.; Hsieh, T-H.; Liao, P-Y.; Liao, Z-Y.; Chang, C-W.; Shih, Y-C.; Yeh, W-H.; Chien, T-C. *Org. Lett.* **2014**, *16*, 892-895.