Design, Synthesis and Applications of Novel Hypervalent Iodine Reagents

A Thesis Submitted to Cardiff University
in Fulfilment of the Requirements for the
Degree of Doctor of Philosophy
by **Jihan Qurban**

PhD Thesis July 2019
Cardiff University

DECLARATION

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

Signed …… (Jihan Qurban) Date ……..…

STATEMENT 1

This thesis is being submitted in partial fulfillment of the requirements for the degree of …… (insert MCh, MD, MPhil, PhD etc, as appropriate)

Signed …… (Jihan Qurban) Date ……..…

STATEMENT 2

This thesis is the result of my own independent work/investigation, except where otherwise stated, and the thesis has not been edited by a third party beyond what is permitted by Cardiff University's Policy on the Use of Third-Party Editors by Research Degree Students. Other sources are acknowledged by explicit references. The views expressed are my own.

Signed …… (Jihan Qurban) Date ……..…

STATEMENT 3

I hereby give consent for my thesis, if accepted, to be available online in the University's Open Access repository and for inter-library loan, and for the title and summary to be made available to outside organisations.

Signed …… (Jihan Qurban) Date ……..…

STATEMENT 4: PREVIOUSLY APPROVED BAR ON ACCESS

I hereby give consent for my thesis, if accepted, to be available online in the University's Open Access repository and for inter-library loans **after expiry of a bar on access previously approved by the Academic Standards & Quality Committee.**

Signed …… (Jihan Qurban) Date ……..…

Acknowledgements

Thanks for Allah the great for blessing me and giving me the power and persistence to complete my studies.

Nobody can achieve any big goal without getting direct and indirect help and support. Doing a PhD is a milestone in my life, and I would not go through it without the help, support, kindness, time, and efforts of many people. The list is too long, but I will mention some people who had positively affected my research and my life during my PhD studies.

First, my thanks and gratitude to my supervisor, Professor Thomas Wirth, not only for giving me the chance to join his outstanding research group and to work on such an interesting project, but also for the endless support, guidance, and fruitful discussions during all the stages of my PhD. For even criticism, which was always constructive and helped me to improve, acquire new expertise and develop my skills. Working with him was a real pleasure, he gave me the freedom to choose what is of interest for me, his patience and tolerance towards making mistakes and wrong decisions (sometimes), helped me to learn effectively and to build my personality.

Next, I would like to express my thanks and dept to Dr Mohamed Elsherbini for his crucial role and impact on my research, for dedicating time for me, for the fruitful cooperation, for all the help he gave to me in and outside the lab. He was always there for me, answering my questions, correcting my mistakes, and encouraging me when I am down. His constant help, support, and his knowledge and kindness helped me to improve my skills and to trust myself.

Thanks to all the people who were part of the Wirth research group, attended the group meetings and shared the office. Ana, Matt, Simon, Florence, Ravi, Anaïs, Célina, Adam, Rosaria, Agatha, Alex, Svenja, Tomohiro, Wilke, Xiaoping, Micol, Tobi, Filipa, Haifa, Mekhman, Ziyue, Mohamed, Marina, Tom, Rossana, Adele, Alena, Saira, Guilherme, Frauke, Nasser, Wenchao, Xiang-Yang, Abdul, Niklas, Taifur, Jarno, Paulina, Chrissi, Joey and James, without you all, without your suggestions, advice, support and company, my studies / life would be harder, less fun.

My special gratitude to Ana, Flo, and Nasim for proof-reading parts of my thesis. Special thanks to Mohamed for proof-reading the whole thesis and for his advices and tips that helped me a lot during the writing up process.

Thanks to my mentor and examiner Dr. Duncan Browne and Dr. Louis Morill for their valuable suggestions and all the guidance and support they gave to me. I would like to acknowledge all the technical and non-technical staff at the School of Chemistry (Cardiff University). Thanks

to Dr. Benson Kairuki (Cardiff University) for the X-Ray crystallographic analysis, and the EPSRC National Mass Spectrometry Service Centre (Swansea University) for their outstanding service providing mass spectrometric data.

I would like to acknowledge the government of my country, and the University of Um-Alqura (Saudi Arabia) for the generous financial support, without which this work would not be possible.

Finally, I would like to thank my loving husband and my lovely children for all the love, joy, and support they gave to me. Thanks to all my family and friends in Cardiff and in Saudi Arabia for their support, it would have never been the same without all of you. Special thanks to my parents, my sisters and brothers.

Jihan Qurban

Dedicated to my small family: Mustafa, Aya, Abdulrahman, and Lin

LIST OF ABBREVIATIONS

°C	Degree Celsius
μL	Microlitre
Ac	Acetyl
AcOH	Acetic acid
A	Amperes
aq.	Aqueous
APCI	Atmospheric pressure chemical ionisation
Ar	Aryl
C	Concentration
Cat.	Catalytic
Conv.	Conversion
CV	Cyclic voltammetry
d.r.	Diastereomeric ratio
DBU	1,8-Diazabicycloundec-7-ene
DIB	(Diacetoxyiodo)benzene
DCE	1,2-Dichloroethane
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
EDG	Electron donating group
ee	Enantiomeric excess
EI	Electron ionisation
eq.	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron withdrawing group
F mol-1	Faraday per mole
FEP	Fluorinated ethylene propylene
g	Gram
GP	General procedure
GC	Gas chromatography

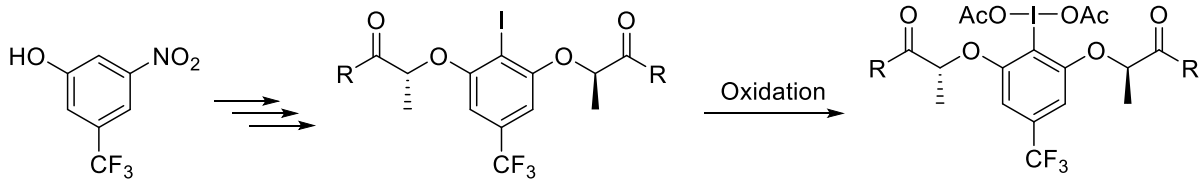
h	Hour(s)
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HOMO	Highest occupied molecular orbital
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectroscopy
Hz	Hertz
i-Pr	Iso-Propyl
IR	Infrared
J	Coupling constant
L	Ligand
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
M	Molarity [mol/l]
mA	milliamperes
m.p.	Melting point
m/z	Mass over charge ratio
m-CPBA	m-chloroperbenzoic acid
Me	Methyl
Mes	Mesityl
MHz	Megahertz
min	Minute(s)
mL	Millilitre
mmol	Millimole
mol%	Mole percentage
N	Normality
nm	nanometre
n-BuLi	n-butylllithium
NMR	Nuclear magnetic resonance
psi	Pounds per square inch
p-TsOH	p-Toluenesulfonic acid
PEEK	Polyether ether ketone
PTFE	Polytetrafluoroethylene
Rf	Retention factor (TLC)

rt	Room temperature
sat.	Saturated
t-Bu	tert-butyl
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
TfO	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Ts	p-toluenesulfonyl
vs	versus
V	Volts

ABSTRACT

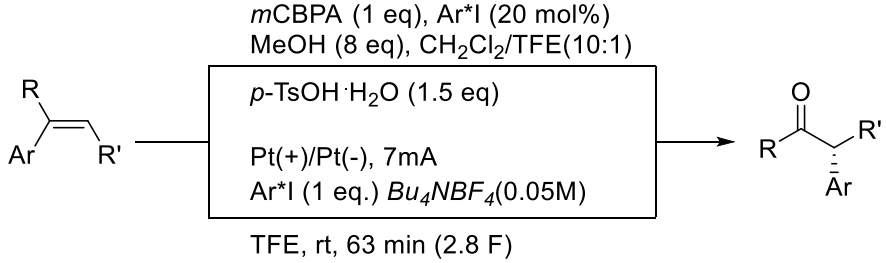
Hypervalent iodine reagents are environmentally benign alternatives to heavy metal oxidants. They are widely used in organic synthesis not only because of the environmentally friendly nature but also due to their readily availability, selectivity and mild reaction conditions. Hypervalent iodine compounds are efficient reagents for a wide range of oxidative transformations such as oxidation of alcohols, phenol dearomatisation, functionalisation of carbonyl compound and alkenes, halogenation, oxidative heterocyclisation, and oxidative rearrangement reactions.

In this thesis, novel electron-deficient chiral hypervalent iodine reagents have been designed and synthesised (Scheme i). The reactivity and selectivity of the newly synthesised reagents have been studied in several stereoselective oxidative transformations.



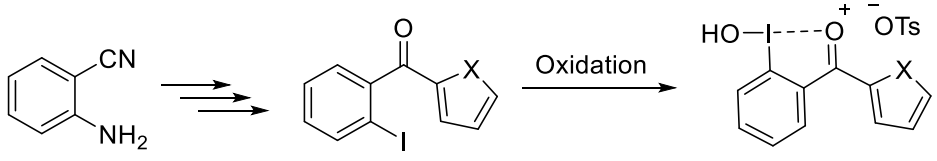
Scheme i. Synthesis of novel electron-deficient lactate-based chiral iodine(III) reagents.

Stereoselective oxidative rearrangement of alkenes into the corresponding *α*-aryl ketone (Scheme ii) was studied using chiral iodoarenes as organocatalysts. In addition, the same transformation was studied using electrochemically generated hypervalent iodine reagent.



Scheme ii. Stereoselective oxidative rearrangement of alkenes.

Finally, the design, synthesis, and characterisation of novel pseudocyclic hypervalent iodine reagents bearing heteroaryl carbonyl moieties is described (Scheme iii). The newly synthesised reagents showed similar and sometimes better reactivity than Koser's reagent.



Scheme iii. Synthesis of novel pseudocyclic hypervalent iodine reagents.

TABLE OF CONTENTS

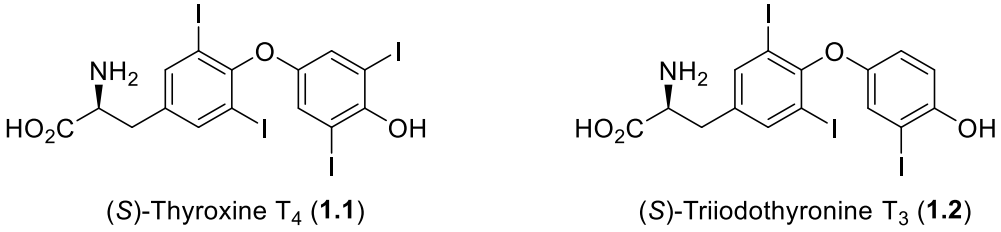
CHAPTER 1

General introduction

1.1. Iodine

Iodine is a non-metal of the halogen group; it is the fifty-third element in the periodic table. Iodine was isolated for the first time by the French chemist Bernard Courtois in the year 1811 from the seaweed's ash. Its deep purple colour is what inspired J. L. Gay Lussac to give its name "Iodine" in 1813, from the word ιώδης (iodes) which means violet in the Greek language. Although iodine forms iodides with a formal oxidation state of -1 with almost all the elements but it can be found in different oxidation states: -1, +1, +3, +5, and +7.

Of all the known isotopes of iodine, ^{127}I is the only stable non-radioactive one. Some of the radioactive isotopes of iodine have medical applications, especially, ^{123}I that is used in the nuclear medicine imaging of the thyroid gland. A gland that regulates the metabolism and produces iodine-containing hormones such as (*S*)-thyroxine T_4 and (*S*)-triiodothyronine T_3 (Figure 1.1).



(*S*)-Thyroxine T_4 (**1.1**) (*S*)-Triiodothyronine T_3 (**1.2**)

Figure 1.1. Thyroid gland iodine-containing hormones.

1.2. Hypervalent iodine compounds

Nowadays, the chemistry of hypervalent iodine reagents is a cornerstone in modern organic synthesis and has gained popularity and widespread recognition and consideration by chemists. The history of hypervalent iodine reagents is long and can be dated back to the year 1886 where the German chemist Conrad Willgerodt[1] prepared the first hypervalent iodine reagent, (dichloroiodo)benzene [$PhICl_2$]. But the chemistry of hypervalent iodine reagents has witnessed a burst and unprecedented development since the beginning of the twenty-first century. The chemical properties and applications of hypervalent iodine reagents are similar to those of heavy metal oxidants with the advantages of being diverse, readily available, mild and environmentally benign.[2–4] Some examples of common hypervalent iodine reagents are depicted in figure 1.2.

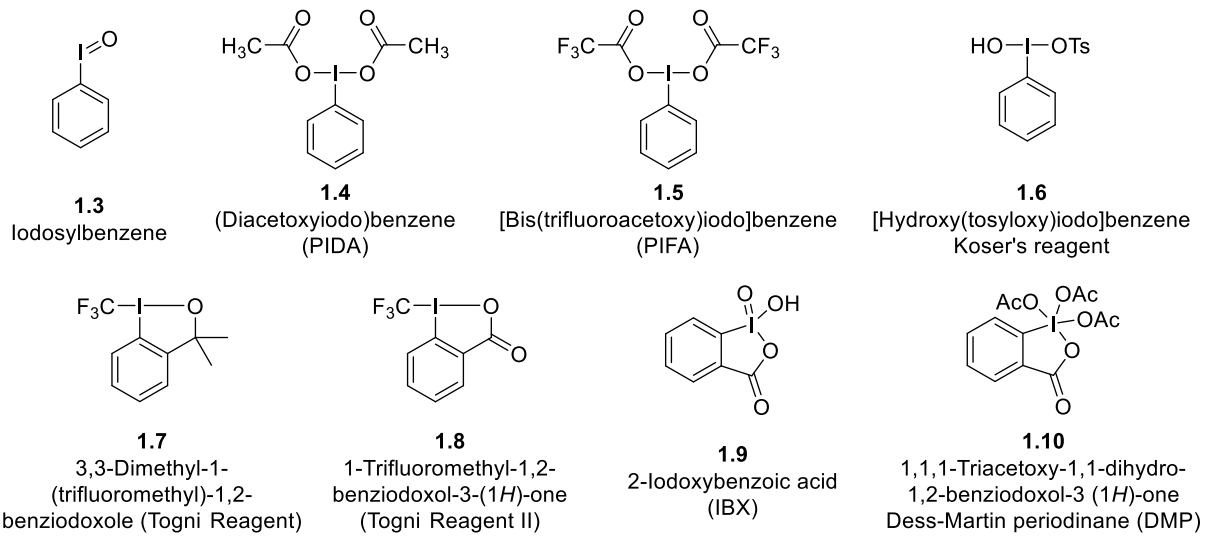


Figure 1.2. Chemical structure of some common hypervalent iodine reagents along with their systematic and common names.

1.2.1. Classification and nomenclature of hypervalent iodine compounds

In hypervalent iodine compounds, iodine exists in higher oxidation states of +3, +5 and +7. Known organic hypervalent iodine compounds belong to the iodine(III) and iodine(V) classes, organic iodine(VII) compounds are not known, only inorganic iodine(VII) compounds such as iodine(VII) fluoride (IF_7), iodine(VII) oxyfluorides and the periodic acid (HIO_4) derivatives are reported in literature. Hypervalent iodine compounds can be classified using Martin–Arduengo *N-X-L* designation for hypervalent compounds (Figure 1.3). Formally, the iodonium ion (structure **A**) is not a hypervalent species as it has only eight valence electrons around the central iodine atom; but, taking into account the closely associated counter ion, iodonium salts are commonly considered ten-electron hypervalent iodine compounds in the modern literature.[5–10]

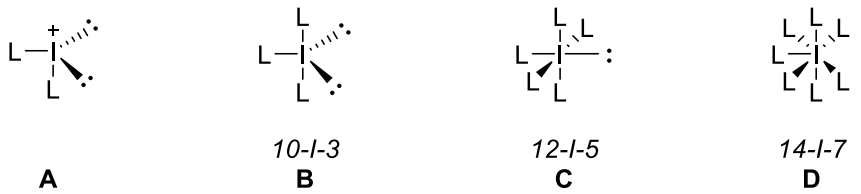


Figure 1.3. Typical structural types of hypervalent iodine compounds.

Historically, iodine(III) derivatives were generally named as iodinanes, while iodine(V) derivatives were named as periodinanes. In 1983 IUPAC recommended using the (lambda

convention) for variable valence in organic nomenclature,[11] therefore, iodinane was replaced by λ^3-iodane for iodine(III) compounds and periodinane was replaced by λ^5-iodane for iodine(V) compounds. However common hypervalent iodine reagents such as $PhI(OAc)_2$, $PhIF_2$, $PhICl_2$, ArIO, $ArIO_2$, among others are not named using the λ nomenclature.

1.2.2. Bonding and structural features

In 1969 J. I. Musher[12] established the definition of "hypervalent" species as molecules or ions of groups 15–18 elements bearing more than eight electrons within a valence shell. The molecular orbital (MO) description of hypervalent bonding in hypervalent compounds as a three-centre-four-electron (3c-4e) bond (Figure 1.4) is widely accepted. The concept of three-centre-four-electron (3c-4e) bond was introduced in the year 1951 by R. E. Rundle[13] and G. C. Pimentel,[14] independently. According to this model the filled 5p orbital of the central iodine atom interacts with the half-filled orbitals of the two ligands L leading to the formation of three molecular orbitals: bonding, nonbonding and antibonding (Figure 1.4).

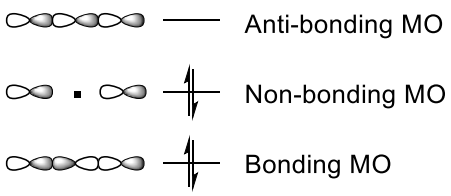


Figure 1.4. Molecular orbital representation of 3c-4e bond in iodine(III) compounds.

The hypervalent bond is highly polarised due to the presence of a node at the central iodine in the highest occupied molecular orbital (HOMO). Hence, the central iodine atom is highly electrophilic. $ArIL_2$ (L = heteroatom ligand) is the most common λ^3-iodane class. In such structures (Figure 1.5a) the more electronegative ligands (L) are collinear and occupy the apical positions, while the carbon substituent (Ar) and both electron pairs occupy the equatorial positions leading to a distorted trigonal bipyramidal geometry. On the other hand, the four ligands (L) in λ^5-iodane of type $ArIL_4$ (Figure 5.1b) occupy the equatorial positions and the carbon ligand (Ar) and the lone pair occupy the apical positions leading to a square bipyramidal geometry.

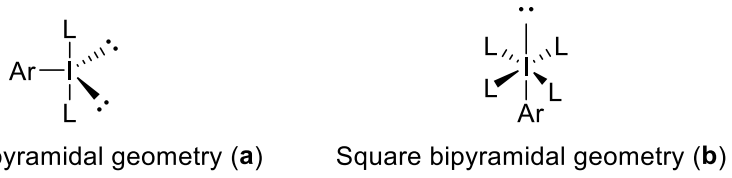


Figure 1.5. a) Geometry of $ArIL_2$ λ^3-iodanes. b) Geometry of $ArIL_4$ λ^5-iodanes.

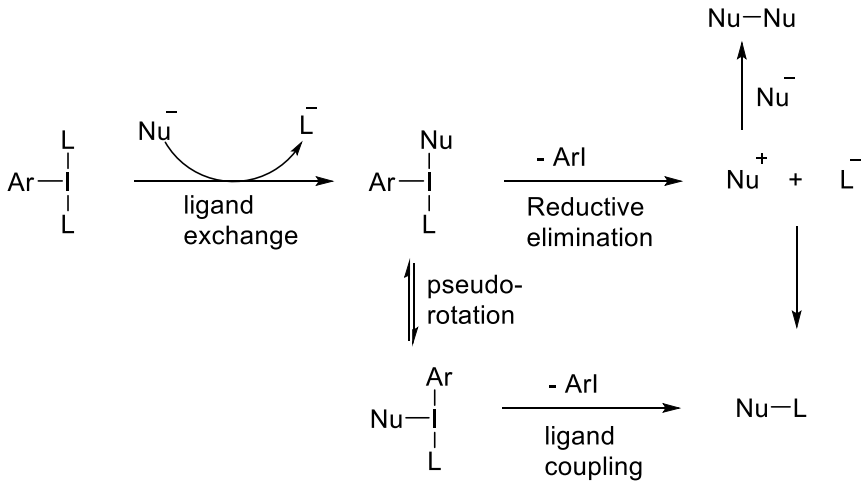
1.2.3. General principles of reactivity

Hypervalent iodine reagents are environmentally benign alternatives to heavy metal oxidants. They are widely used in organic synthesis not only because of the environmentally friendly nature but also due to their readily availability, selectivity and mild reaction conditions. Hypervalent iodine compounds are efficient reagents for a wide range of oxidative transformations such as oxidation of alcohols, phenol dearomatisation, functionalisation of carbonyl compound and alkenes, halogenation, oxidative heterocyclisation, and oxidative rearrangement reactions.

The strong electrophilic nature of hypervalent iodine reagents along with their super leaving group ability (10^6 times of a triflate) when bound to sp^3 carbon are the key facts behind their reactivity, selectivity and versatility.[3] The general reactivity aspects of hypervalent iodine reagents are discussed below.

1.2.3.1. Ligand exchange and reductive elimination

Generally, most reactions involving λ^3-iodanes of type $ArIL_2$ starts with a ligand exchange step, where an external nucleophile (Nu) replaces one of the ligands on the iodine atom followed by either a reductive elimination or a ligand coupling (Scheme 1.1). The reactions involving λ^5-iodanes can be generally explained by a similar mechanism.

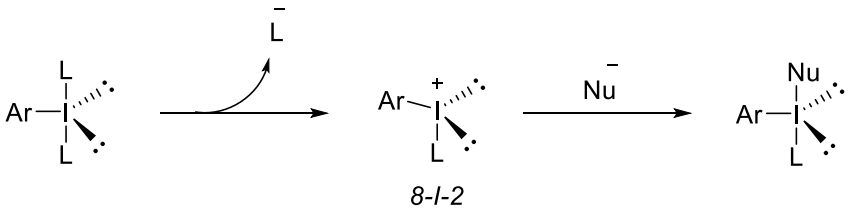


Scheme 1.1. A schematic representation of the reactions involving λ^3-iodanes.

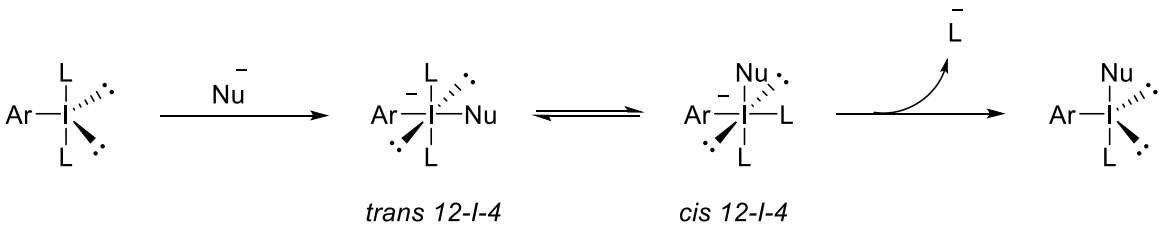
In principle, the ligand exchange step of the reactions of λ^3-iodanes can take place *via* either a dissociative or an associative pathway (Scheme 1.2). In the dissociative mechanism (Scheme 1.2a) one of the ligands at the central iodine atom dissociates leaving a cationic iodonium ion $ArIL^+$ which reacts with a nucleophile forming the ligand exchange product. On the other hand, the associative mechanism (Scheme 1.2b) involves the addition of a nucleophile to the

electrophilic iodine centre forming a *trans 12-I-4* species which isomerises to the *cis 12-I-4* species that undergoes elimination of a ligand (L) leading to the ligand exchange product.

a) Dissociative pathway



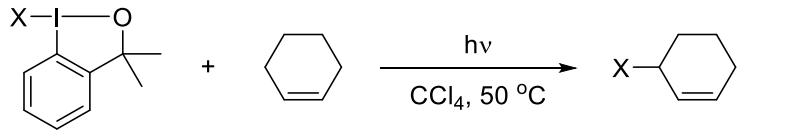
b) Associative pathway



Scheme 1.2. Associative (a) and dissociative (b) pathways of the ligand exchange of λ^3-iodanes.

1.2.3.2. Radical mechanism

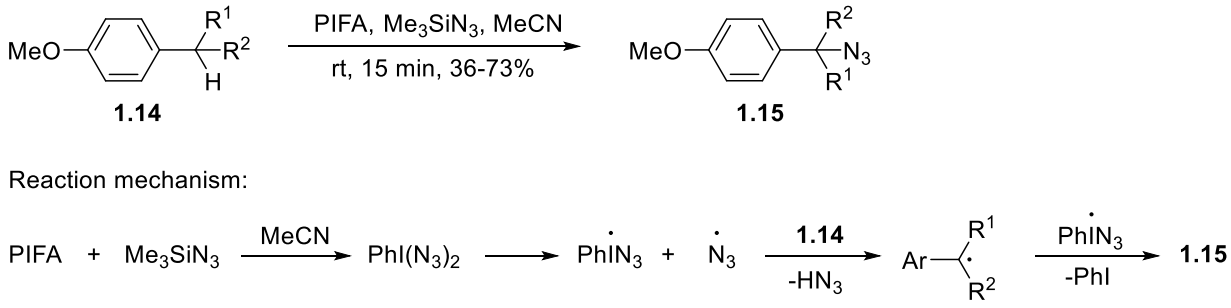
Due to the relatively small bond dissociation energies in hypervalent iodine compounds, homolytic reactions involving free-radical intermediates are relatively common under thermal or photochemical conditions.[15] Typical examples include using halobenziodoxoles of type **1.11** in allylic and benzylic halogenation under photochemical conditions (Scheme 1.3).[16]



1.11: X = Cl, Br **1.12** **1.13:** X = Cl, Br

Scheme 1.3. Radical allylic halogenation using cyclic λ^3-iodanes.

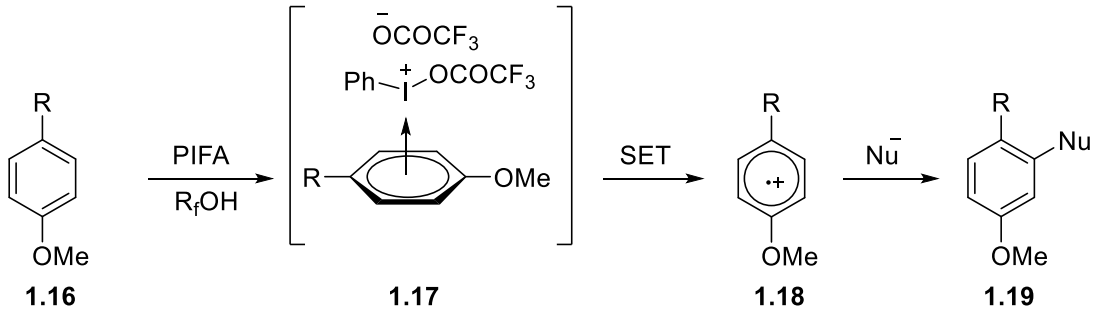
The formation of azide radicals *via* the thermal decomposition of azidoiodanes,[17,18] which can be generated *in situ* from an azide source and a hypervalent iodine reagent [e.g., iodosylbenzene or $PhI(OAc)_2$], is a synthetically useful tool for performing C-H azidation reactions (Scheme 1.4).



Scheme 1.4. Radical benzylic azidation using PIFA/Me_3SiN_3 mixture.

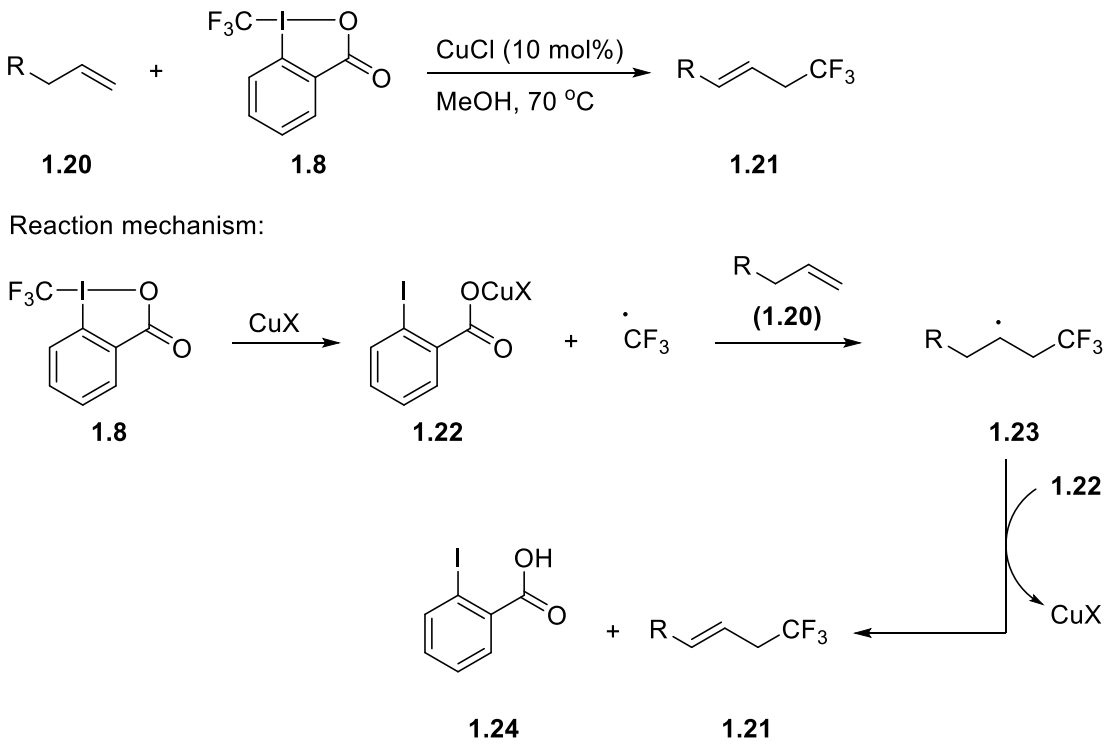
1.2.3.3. Single-electron transfer (SET) mechanism

Reactions of λ^3- or λ^5-iodanes with electron-rich organic substrates can also proceed *via* a single-electron transfer (SET) mechanism. For example, the reaction of PIFA with *p*-substituted phenol ethers **1.16** leads to the formation of the products of nucleophilic aromatic substitution **1.19**. The reaction starts with the formation of the charge-transfer complex **1.17** which undergoes SET to form the radical cation intermediate **1.18** that reacts with external or internal nucleophiles leading to products **1.19** (Scheme 1.5).



Scheme 1.5. Reaction of *p*-substituted phenol ethers **1.16** with PIFA *via* SET mechanism.

Another common reaction of the λ^3-iodanes that involves a SET mechanism is the trifluoromethylation via SET reduction of Togni reagent. Treatment of Togni reagent with a catalytic amount of Cu(I) salt leads to the generation of trifluoromethyl radical which then undergoes radical addition to alkenes leading to allylic trifluoromethylation products **1.21** (Scheme 1.6).[19,20]

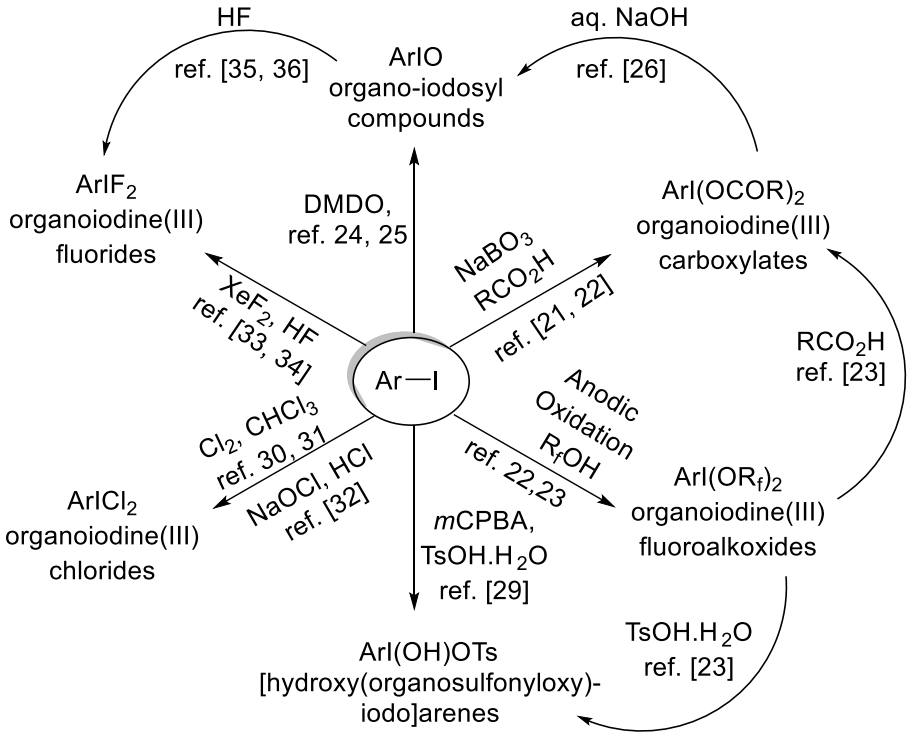


Scheme 1.6. Cu-catalysed allylic trifluoromethylation using Togni reagent.

1.2.4. Preparation of hypervalent iodine reagents

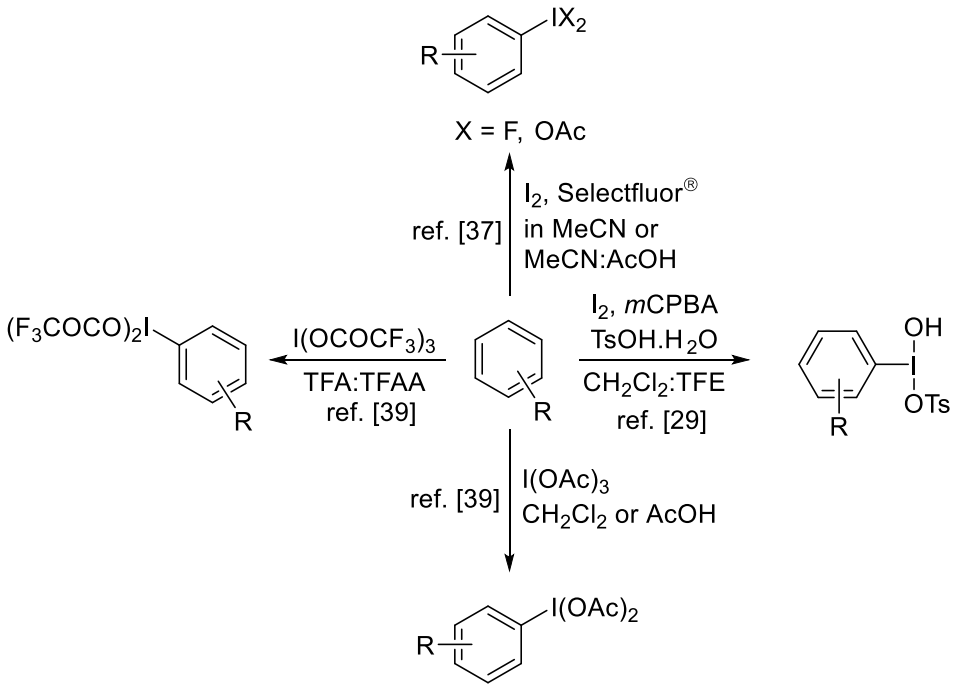
Organic hypervalent iodine reagents can be prepared either by the oxidation of aryl iodide derivatives in the presence of suitable ligands or by the ligand exchange of pre-prepared hypervalent iodine reagents. The oxidation of iodoarenes to the corresponding hypervalent iodine reagents can be achieved using a wide range of chemical oxidants, such as oxone®, selectfluor®, peracids (*m*-chloroperbenzoic acid (*m*CPBA), peracetic acid, etc), hydrogen peroxide, dimethyldioxirane (DMDO), organic hydroperoxides, organic and inorganic hypochlorites, etc.[21] In addition, the anodic oxidation of hypervalent iodine reagents is a feasible process.[22,23] The ligand exchange approach is a common way of altering already prepared hypervalent iodine reagents *via* treatment of prepared λ^3- and λ^5-iodanes with suitable nucleophiles.[21,23]

Some representative examples of the oxidation of iodoarenes into some of the common λ^3-iodane derivatives such as organo-iodosyl compounds,[24–26] organoiodine(III) carboxylates,[27,28] organoiodine(III) fluoroalkoxides,[22,23] [hydroxy(organosulfonyloxy)iodo]arenes,[23,29] organoiodine(III) chlorides,[30–32] and organoiodine(III) fluorides[33–36] are displayed in Scheme 1.7 along with some representative examples of interconversion of common λ^3-iodane derivatives *via* ligand exchange.



Scheme 1.7. Some representative examples of synthesis of λ^3-iodane derivatives *via* oxidation of iodoarenes and ligand exchange approaches.

The synthesis of λ^3-iodane derivatives from the corresponding arenes, elemental iodine and an oxidant such as Selectfluor®[37] or *m*CPBA[29] in one-pot is an interesting alternative strategy for accessing hypervalent iodine reagents (Scheme 1.8). The reaction proceeds smoothly when electron rich arenes are used as substrate. Using iodine triacetate $[I(OAc)_3]$[38] and iodine tris(trifluoroacetate) $[I(OCOCF_3)_3]$[38] allowed the extension of this methodology to less electron rich and even some electron-deficient arenes.[39]



Scheme 1.8. Alternative strategies for the synthesis of λ^3-iodane derivatives starting from the corresponding arenes.

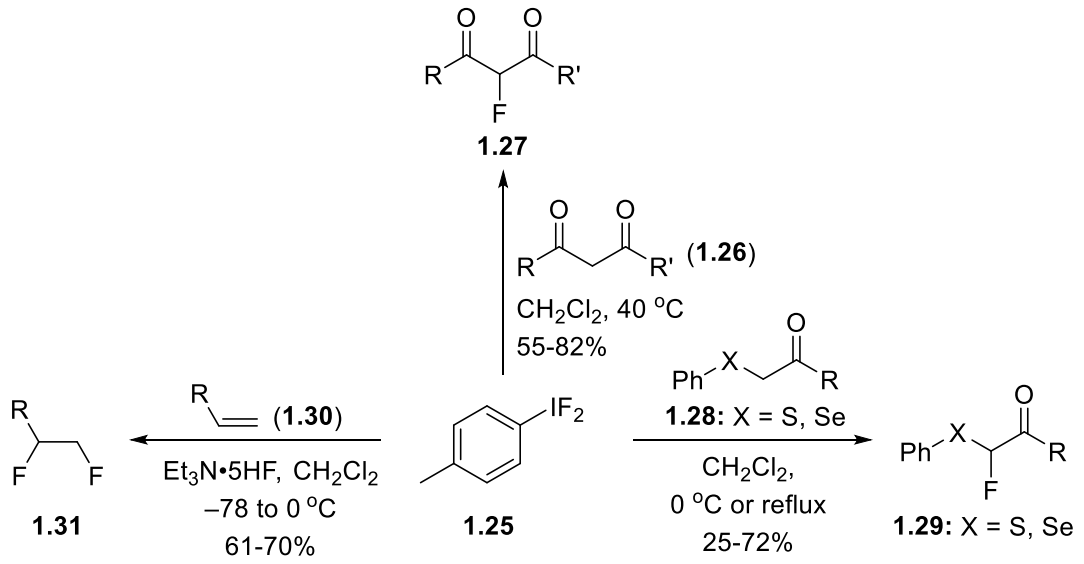
1.2.5. Synthetic applications

The synthetic utility of hypervalent iodine reagents is tremendous and covers a wide range of chemical transformations. In the following sections, an overarching overview and some representative examples of the wide spectrum of the hypervalent iodine chemistry will be presented. A more detailed discussion of the reactivity aspects that were encountered during the research, such as stereoselective transformations, using iodoarenes as organocatalysts, anodic oxidation of aryl iodides, and secondary interactions in hypervalent iodine chemistry will be presented in the following chapters.

1.2.5.1. Halogenation

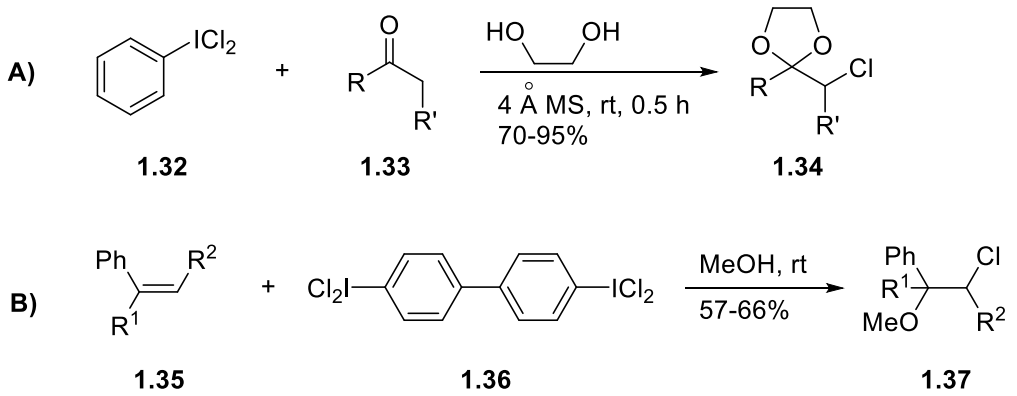
Hypervalent iodine reagents of type $ArIX_2$ where X is a halogen are versatile powerful electrophilic halogenating agents. (Difluoroiodo)arenes and (dichloroiodo)arenes are generally accessible easy to handle compounds. 4-Iodotoluene difluoride (Tol-IF_2)[36] specifically is a powerful selective versatile fluorinating agent. Using Tol-IF_2 monofluorination of *β*-keto esters, *β*-diketones, and *β*-keto amides can be achieved selectively.[40] *α*-Fluorination of sulfides[41,42] and selenides[36] in addition to vicinal

difluorination of alkenes[43] are other examples of the synthetic utility of Tol-IF_2 (Scheme 1.9).



Scheme 1.9. Tol-IF_2 as versatile fluorinating agent.

(Dichloroiodo)arenes especially, (dichloroiodo)benzene ($PhICl_2$), which can be produced in a large scale[30] are widely used as chlorinating agents for various organic substrates. Reaction of $PhICl_2$ with various aliphatic and aromatic ketones **1.33** in ethylene glycol proceeds smoothly to afford the corresponding *α*-chloroketone acetals **1.34** in high to excellent yields (Scheme 1.10 A).[44] The reaction of styrene derivatives **1.35** with 4,4'-bis(dichloroiodo)biphenyl (**1.36**) in the presence of methanol result in the formation of the chloromethoxylation products **1.37** in good yields (Scheme 1.10 B).[31]



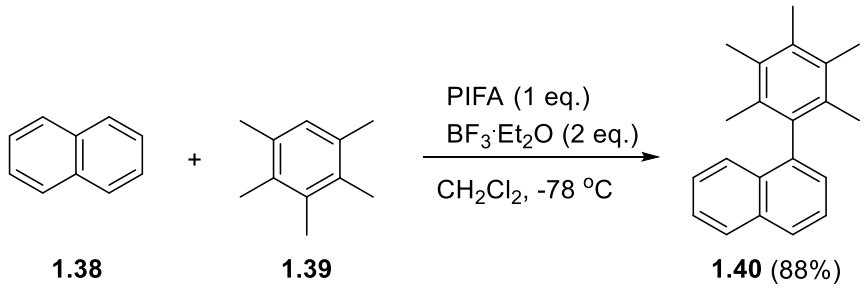
Scheme 1.10. Chlorination using (dichloroiodo)arenes.

Oxidative bromination and iodination using hypervalent iodine reagents are less popular compared to fluorination and chlorination. Stable bromobenziodoxoles have been reported

and applied in the benzylic and allylic bromination[16] in addition to electrophilic bromination of electron-rich arenes and bromolactonisation of 4-pentenoic acid.[45] On the other hand, stable hypervalent iodine reagents with iodide ligands are not reported, but oxidative iodination of aromatic and heteroaromatic compounds can be achieved using molecular iodine in combination with common λ^3-iodanes such as PIDA and PIFA.[46–48]

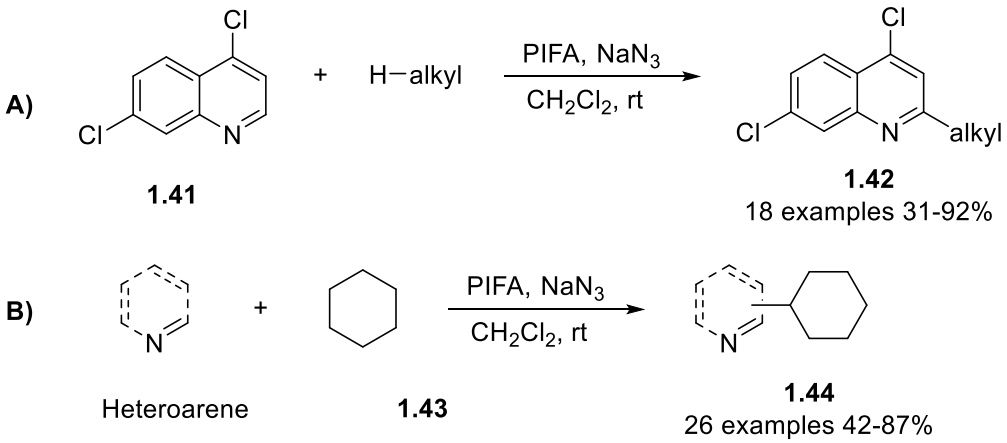
1.2.5.2. Carbon-carbon bond formation

Hypervalent iodine chemistry plays an important role in the metal-free C-C bond formation. The first report of metal-free oxidative cross-biaryl-coupling was reported in 2008 by Dohi *et al.*[49] The cross-coupling of naphthalene and pentamethylbenzene is depicted in Scheme 1.11.



Scheme 1.11. PIFA induced aryl cross-coupling.

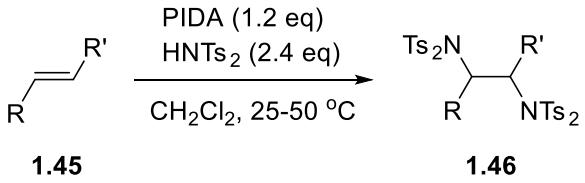
An efficient oxidative cross-coupling of heteroarenes with alkanes has been reported using a mixture of PIFA and sodium azide (NaN_3). A wide range of cross-coupling products were formed smoothly under very mild reaction conditions (Scheme 1.12).[50]



Scheme 1.12. PIFA induced selective oxidative cross-coupling of heteroarenes and alkanes.

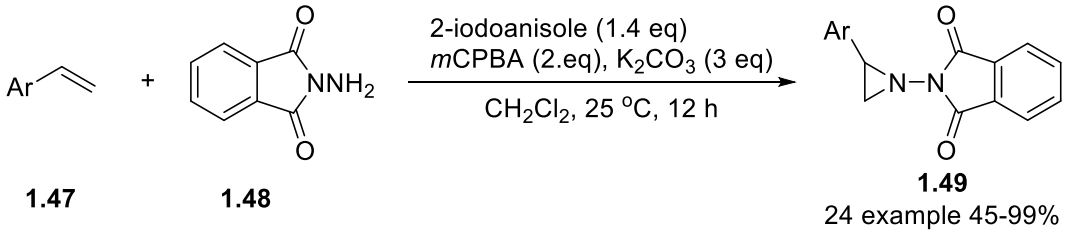
1.2.5.3. Carbon-heteroatom bond formation

Hypervalent iodine reagents have found diverse practical applications in transformations leading to the formation of carbon-heteroatom bonds. Muñiz and co-workers made a good contribution in the field of C-N bond formation.[51–56] One example is the vicinal diamination of alkenes using a combination of PIDA and $HNTs_2$.[57] The reaction is versatile and showed a wide scope of substrates, 60 examples were presented including styrenes, terminal and internal alkenes in addition to cyclic alkenes (Scheme 1.13).



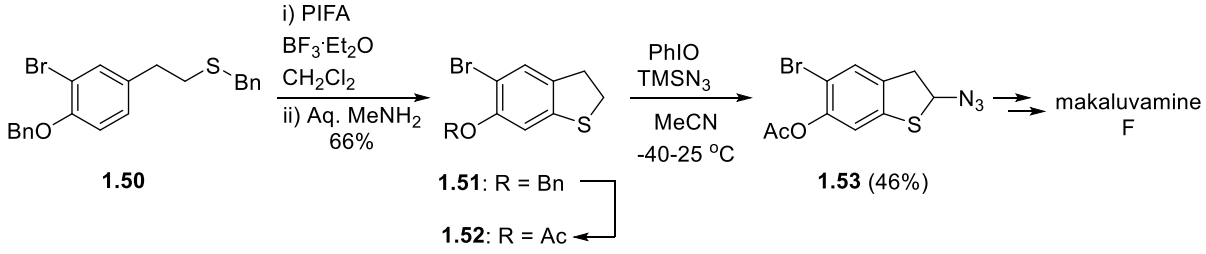
Scheme 1.13. Vicinal diamination of alkenes using PIDA/$HNTs_2$ reagent combination.

Intramolecular aziridination of styrenes was achieved in good to excellent yield under mild reaction conditions using a reagent system composed of 2-iodoanisole, *m*CPBA, and *N*-aminophthalimide (Scheme 1.14).[58]



Scheme 1.14. Aziridination of styrenes using 2-iodoanisole/*m*CPBA.

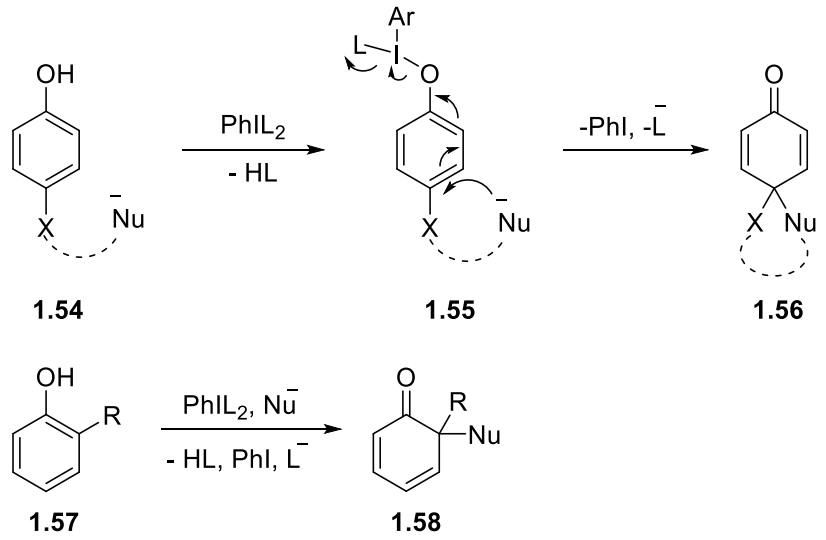
An elegant example of forming C-heteroatom bonds using hypervalent iodine reagents is the construction of the α-amino dihydrobenzothiophene fragment of the alkaloid makaluvamine F via iterative iodine(III) mediated oxidative C-S and C-N bond formations (Scheme 1.15).



Scheme 1.15. Iterative iodine(III) mediated oxidative C-S and C-N bond formation.

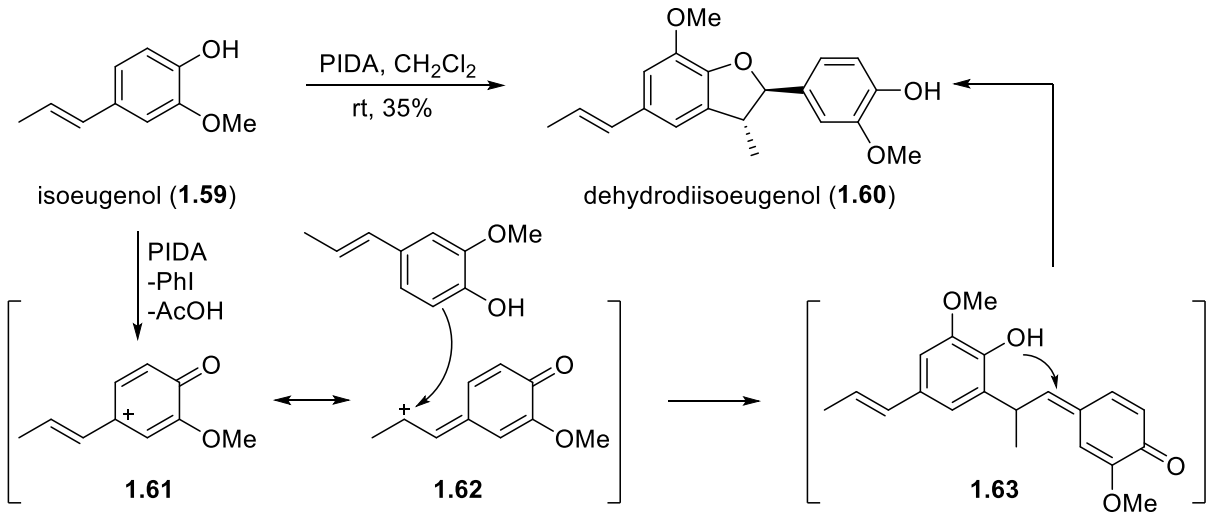
1.2.5.4. Phenol dearomatisation

Phenol dearomatisation is an extensively explored oxidative transformations mediated by hypervalent iodine reagents that finds various applications in the synthesis of natural products and bioactive molecules. A general representation of the oxidative dearomatisation of 4- or 2-substituted phenols of type **1.54** and **1.57** by hypervalent iodine reagents is shown in Scheme 1.16. First the phenolic substrate undergoes ligand exchange with the iodine(III) reagent leading to the formation of phenoxyiodine(III) species **1.55** which then undergoes reductive elimination in the presence of an internal or external nucleophile (Nu) leading to the corresponding cyclohexadienone products of type **1.56** or **1.58**.[59]



Scheme 1.16. General representation of hypervalent iodine mediated phenol dearomatisation.

Treatment of isoeugenol (**1.59**) with PIDA in dichloromethane at room temperature led to the formation of dehydrodiisoeugenol (**1.60**) (Scheme 1.17). The oxidative dimerization of **1.59** is initiated by the formation of *p*-phenoxonium intermediate **1.61** *via* PIDA mediated phenol dearomatisation of **1.59**. Interception of **1.62** with a second molecule of isoeugenol (**1.59**) result in the formation of intermediate **1.63** which undergoes intramolecular nucleophilic ring closure leading to dehydrodiisoeugenol (**1.60**).[60]

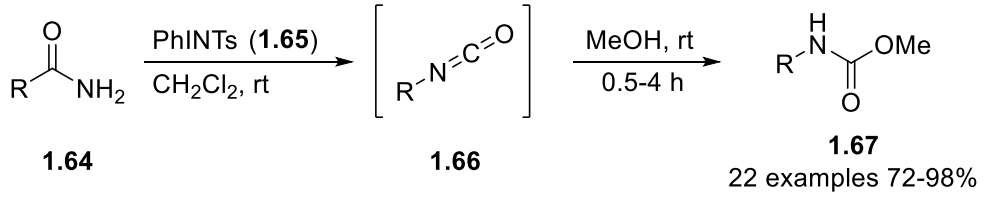


Scheme 1.17. Oxidative dimerisation of isoeugenol **1.59** mediated by PIDA.

1.2.5.5. Oxidative rearrangements

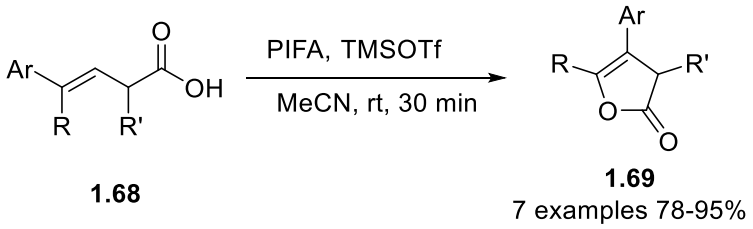
Hypervalent iodine reagents promote a wide range of synthetically useful molecular rearrangement reactions. The ability of hypervalent iodine reagents to react initially as electrophiles in combination with their superior leaving group ability can trigger the migration of various substituents. Hence a wide range of synthetically useful molecular rearrangement reactions have been developed using hypervalent iodine reagents.[61–64]

Hofmann-type rearrangements is one of the early examples of the ability of λ^3-iodanes to promote molecular rearrangement reactions. The reaction can be promoted using a wide range of hypervalent iodine reagents. A wide range of amides **1.64** were smoothly converted into the corresponding carbamates **1.67** in high yield using (tosylimino)phenyl-λ^3-iodane **1.65** vi*a* isocyanate intermediates **1.66** (Scheme 1.18).[65]



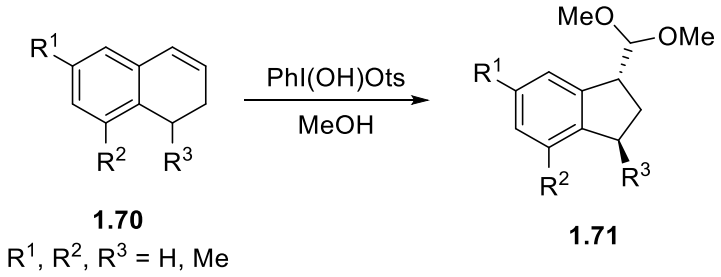
Scheme 1.18. λ^3-iodane mediated Hofmann-type rearrangement of amides to the corresponding carbamates.

The reaction of *β,γ*-unsaturated carboxylic acids **1.68** with PIFA/TMSOTf led to the formation of lactones **1.69** (Scheme 1.19). The reaction proceeds via activation of the double bond with iodine(III) species followed by cyclisation and aryl group migration.[66]



Scheme 1.19. Synthesis of lactone **1.69** *via* PIFA mediated aryl transposition.

Hypervalent iodine reagents promote molecular rearrangement reactions that lead to ring expansion and ring contraction. For example, Koser's reagent promoted the formation of acetal **1.71** *via* ring contraction of 1,2-dihydronaphthalene derivatives **1.70** (Scheme 1.20).[67]

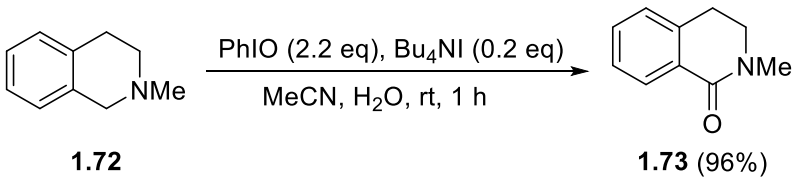


Scheme 1.20. Formation of acetal **1.71** *via* a ring contraction induced by Koser's reagent.

1.2.5.6. Oxidation reactions

Hypervalent iodine reagents are versatile oxidants. They find wide applications in oxidation of benzylic and allylic positions, oxidation of heteroatoms such as sulfur, nitrogen and phosphorus in addition to alcohols.

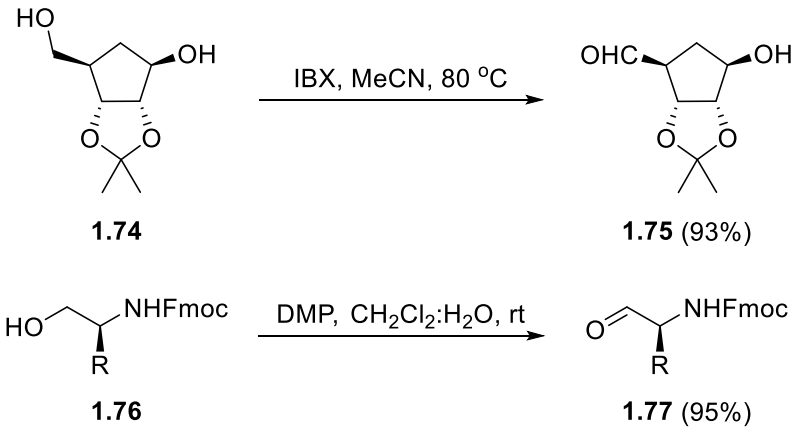
For example, the oxidation of the benzylic position of tetrahydroisoquinoline **1.72** using iodosylbenzene in the presence of catalytic amount of Bu_4NI furnished the corresponding lactam **1.73** in 96% yield (Scheme 1.21).[68]



Scheme 1.21. Oxidation of benzylic position of tetrahydroisoquinoline **1.72** using PhIO.

The oxidative cleavage of the thioacetal protecting groups can be efficiently achieved under mild conditions using λ^3-iodanes.[69–71] On the other hand, λ^5-iodanes such as IBX (**1.9**) and DMP (**1.10**) are excellent selective and mild oxidants for alcohols. The oxidation of alcohols

1.74 and **1.76** to the corresponding aldehydes proceeds smoothly in excellent yields without racemisation using IBX and DMP, respectively (Scheme 1.22).[72,73]



Scheme 1.22. Efficient selective and mild oxidation of alcohols **1.74** and **1.76** to the corresponding aldehydes using IBX and DMP.

1.3. References

[1] C. Willgerodt, *J. Prakt. Chem.* **1885**, *33*, 154–160.

[2] T. Wirth, Ed. , *Hypervalent Iodine Chemistry*, Springer International Publishing, Cham, **2016**.

[3] V. V Zhdankin, Editor., *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds.*, Wiley, **2013**.

[4] A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328–3435.

[5] E. A. Merritt, B. Olofsson, *Angew. Chem. Int. Ed.* **2009**, *48*, 9052–9070.

[6] D. J. Hamnett, W. J. Moran, *Org. Biomol. Chem.* **2014**, *12*, 4156–4162.

[7] E. Zawia, D. J. Hamnett, W. J. Moran, *J. Org. Chem.* **2017**, *82*, 3960–3964.

[8] A. Rodríguez, W. J. Moran, *J. Org. Chem.* **2016**, *81*, 2543–2548.

[9] E. Lindstedt, M. Reitti, B. Olofsson, *J. Org. Chem.* **2017**, *82*, 11909–11914.

[10] D. R. Stuart, *Synlett* **2017**, *28*, 275–279.

[11] W. H. Powell, *Pure Appl. Chem.* **1984**, *56*, 769–778.

[12] J. I. Musher, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 54–68.

[13] R. J. Hach, R. E. Rundle, *J. Am. Chem. Soc.* **1951**, *73*, 4321–4324.

[14] G. C. Pimentel, *J. Chem. Phys.* **1951**, *19*, 446–448.

[15] X. Wang, A. Studer, *Acc. Chem. Res.* **2017**, *50*, 1712–1724.

[16] R. L. Amey, J. C. Martin, *J. Org. Chem.* **1979**, *44*, 1779–1784.

[17] Y. Kita, H. Tohma, T. Takada, S. Mitoh, S. Fujita, M. Gyoten, *Synlett* **1994**, *1994*,

427–428.

[18] F. Fontana, F. Minisci, M. Y. Yong, Z. Lihua, *Tetrahedron Lett.* **1993**, *34*, 2517–2520.

[19] A. T. Parsons, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 9120–9123.

[20] X. Wang, Y. Ye, S. Zhang, J. Feng, Y. Xu, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 16410–16413.

[21] Viktor V. Zhdankin, in *Hypervalent Iodine Chemistry*, John Wiley & Sons Ltd, Chichester, UK, **2013**, pp. 21–143.

[22] M. Elsherbini, T. Wirth, *Chem. Eur. J.* **2018**, *24*, 13399–13407.

[23] M. Elsherbini, B. Winterson, H. Alharbi, A. A. Folgueiras-Amador, C. Génot, T. Wirth, *Angew. Chemie Int. Ed.* **2019**, DOI 10.1002/anie.201904379.

[24] A. Bravo, F. Fontana, G. Fronza, F. Minisci, A. Serri, *Tetrahedron Lett.* **1995**, *36*, 6945–6948.

[25] A. Bravo, F. Fontana, G. Fronza, F. Minisci, L. Zhao, *J. Org. Chem.* **1998**, *63*, 254–263.

[26] H. Saltzman, J. G. Sharefkin, *Org. Synth.* **1963**, *43*, 60.

[27] M. D. Hossain, T. Kitamura, *J. Org. Chem.* **2005**, *70*, 6984–6986.

[28] P. Mizar, A. Laverny, M. El-Sherbini, U. Farid, M. Brown, F. Malmedy, T. Wirth, *Chem. Eur. J.* **2014**, *20*, 9910–9913.

[29] E. A. Merritt, V. M. T. Carneiro, L. F. Silva, B. Olofsson, *J. Org. Chem.* **2010**, *75*, 7416–7419.

[30] A. Zanka, H. Takeuchi, A. Kubota, *Org. Process Res. Dev.* **1998**, *2*, 270–273.

[31] M. S. Yusubov, L. A. Drygunova, V. V. Zhdankin, *Synthesis* **2004**, 2289–2292.

[32] X.-F. Zhao, C. Zhang, *Synthesis* **2007**, 551–557.

[33] M. Zupan, A. Pollak, *J. Fluor. Chem.* **1976**, *7*, 445–447.

[34] A. Gregorcic, M. Zupan, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 517–520.

[35] M. Sawaguchi, S. Ayuba, S. Hara, *Synthesis* **2002**, 1802-1803.

[36] M. A. Arrica, T. Wirth, *European J. Org. Chem.* **2005**, *2005*, 395–403.

[37] C. Ye, B. Twamley, J. M. Shreeve, *Org. Lett.* **2005**, *7*, 3961–3964.

[38] T. Birchall, C. S. Frampton, P. Kapoor, *Inorg. Chem.* **1989**, *28*, 636–639.

[39] T. Hokamp, L. Mollari, L. C. Wilkins, R. L. Melen, T. Wirth, *Angew. Chem. Int. Ed.* **2018**, *57*, 8306–8309.

[40] M. Yoshida, K. Fujikawa, S. Sato, S. Hara, *Arkivoc* **2003**, 36-42.

[41] M. F. Greaney, W. B. Motherwell, *Tetrahedron Lett.* **2000**, *41*, 4467–4470.

[42] M. F. Greaney, W. B. Motherwell, *Tetrahedron Lett.* **2000**, *41*, 4463–4466.

[43] S. Hara, J. Nakahigashi, K. Ishi-i, M. Sawaguchi, H. Sakai, T. Fukuhara, N. Yoneda,

Synlett **1998**, *1998*, 495–496.

[44] J. Yu, C. Zhang, *Synthesis* **2009**, 2324–2328.

[45] D. C. Braddock, G. Cansell, S. A. Hermitage, A. J. P. White, *Chem. Commun.* **2006**, 1442.

[46] E. B. Merkushev, *Synthesis* **1988**, 923–937.

[47] B. Panunzi, L. Rotiroti, M. Tingoli, *Tetrahedron Lett.* **2003**, *44*, 8753–8756.

[48] D.-P. Cheng, Z.-C. Chen, Q.-G. Zheng, *Synth. Commun.* **2003**, *33*, 2671–2676.

[49] T. Dohi, M. Ito, K. Morimoto, M. Iwata, Y. Kita, *Angew. Chem. Int. Ed.* **2008**, *47*, 1301–1304.

[50] A. P. Antonchick, L. Burgmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 3267–3271.

[51] C. Röben, J. A. Souto, Y. González, A. Lishchynskyi, K. Muñiz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9478–9482.

[52] N. Lucchetti, M. Scalone, S. Fantasia, K. Muñiz, *Adv. Synth. Catal.* **2016**, *358*, 2093–2099.

[53] L. Fra, K. Muñiz, *Chem. Eur. J.* **2016**, *22*, 4351–4354.

[54] K. Muñiz, L. Barreiro, R. M. Romero, C. Martínez, *J. Am. Chem. Soc.* **2017**, *139*, 4354–4357.

[55] C. Martínez, A. E. Bosnidou, S. Allmendinger, K. Muñiz, *Chem. Eur. J.* **2016**, *22*, 9929–9932.

[56] A. E. Bosnidou, A. Millán, J. Ceballos, C. Martínez, K. Muñiz, *J. Org. Chem.* **2016**, *81*, 6496–6504.

[57] J. A. Souto, Y. González, A. Iglesias, D. Zian, A. Lishchynskyi, K. Muñiz, *Chem. Asian J.* **2012**, *7*, 1103–1111.

[58] J. Li, J.-L. Liang, P. W. H. Chan, C.-M. Che, *Tetrahedron Lett.* **2004**, *45*, 2685–2688.

[59] S. Quideau, L. Pouységu, P. A. Peixoto, D. Deffieux, in *Wirth T. Hypervalent Iodine Chem. Top. Curr. Chem. Vol 373. Springer, Cham*, **2016**, pp. 25–74.

[60] L. Juhász, L. Kürti, S. Antus, *J. Nat. Prod.* **2000**, *63*, 866–870.

[61] G. Maertens, S. Canesi, in *Wirth T. Hypervalent Iodine Chem. Top. Curr. Chem. Vol 373. Springer, Cham*, **2015**, pp. 223–241.

[62] M. Brown, R. Kumar, J. Rehbein, T. Wirth, *Chem. Eur. J.* **2016**, *22*, 4030–4035.

[63] F. Malmedy, T. Wirth, *Chem. Eur. J.* **2016**, *22*, 16072–16077.

[64] U. Farid, F. Malmedy, R. Claveau, L. Albers, T. Wirth, *Angew. Chem. Int. Ed.* **2013**, *52*, 7018–7022.

[65] A. Yoshimura, M. W. Luedtke, V. V. Zhdankin, *J. Org. Chem.* **2012**, *77*, 2087–2091.

[66] F. V. Singh, J. Rehbein, T. Wirth, *ChemistryOpen* **2012**, *1*, 245–250.

[67] L. F. Silva, F. A. Siqueira, E. C. Pedrozo, F. Y. M. Vieira, A. C. Doriguetto, *Org. Lett.*

2007, *9*, 1433–1436.

[68] W.-J. Huang, O. V. Singh, C.-H. Chen, S.-Y. Chiou, S.-S. Lee, *Helv. Chim. Acta* **2002**, *85*, 1069.

[69] X.-X. Shi, Q.-Q. Wu, *Synth. Commun.* **2000**, *30*, 4081–4086.

[70] T. E. Burghardt, *J. Sulfur Chem.* **2005**, *26*, 411–427.

[71] Y. Wu, X. Shen, Y.-Q. Yang, Q. Hu, J.-H. Huang, *J. Org. Chem.* **2004**, *69*, 3857–3865.

[72] J. More, N. Finney, *Synlett* **2003**, 1307-1310.

[73] A. G. Myers, B. Zhong, M. Movassaghi, D. W. Kung, B. A. Lanman, S. Kwon, *Tetrahedron Lett.* **2000**, *41*, 1359–1362.

CHAPTER 2

Electron-deficient chiral hypervalent iodine reagents

2.1. Introduction

2.1.1. Chiral hypervalent iodine reagents

Asymmetric induction using chiral hypervalent iodine reagents is becoming a cornerstone in asymmetric synthesis. The ability of the chiral hypervalent iodine reagents to induce a wide range of stereoselective transformations under mild reaction condition with a high degree of stereocontrol, in addition to their availability, easy accessibility and diversity make these "greener" reagents reliable alternatives to metal-based chiral reagents, thus minimising the adverse environmental implications of such chemical transformations. Stereoselective oxidations, difunctionalisation of alkenes, 1,2-aryl rearrangement, oxidative dearomatisation and α-functionalisation of carbonyl compounds among others are examples of the value of this chemistry.[1]

The synthesis of chiral hypervalent iodine reagents is dated back to the year 1907 when the first chiral hypervalent iodine reagent (diphenyliodonium tartarate) was synthesised.[2] Despite the long history, the field revived only in the new millennium. Synthesis of chiral hypervalent iodine reagents is usually achieved following one of two main strategies (Figure 2.1A and 2.1B): (i) attachment of chiral ligands to the iodine centres through ligand exchange, the chiral ligands are typically a chiral acid or alcohol, and (ii) introduction of chiral substituent or axial chirality into the iodoarene framework. In addition, chiral reactive ion-pairs of hypervalent iodate anions with chiral cations are also known though less common (Figure 2.1c).[3]

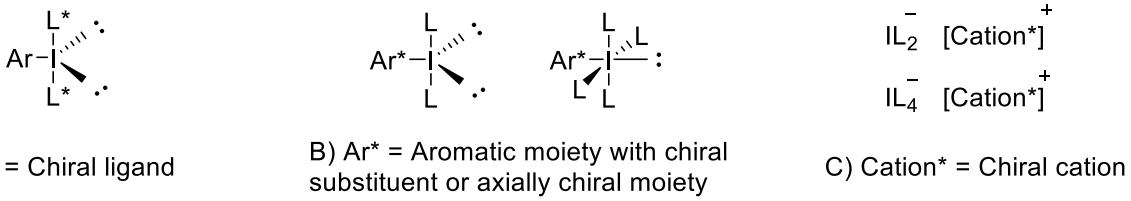
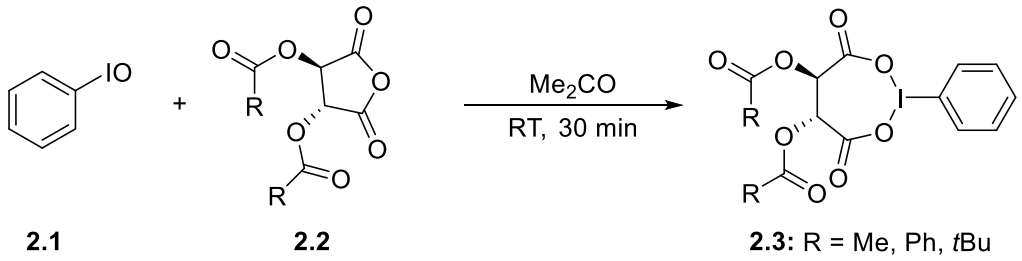


Figure 2.1. General classes of chiral hypervalent iodine reagents.

2.1.1.1. Hypervalent iodine reagents with chiral ligands

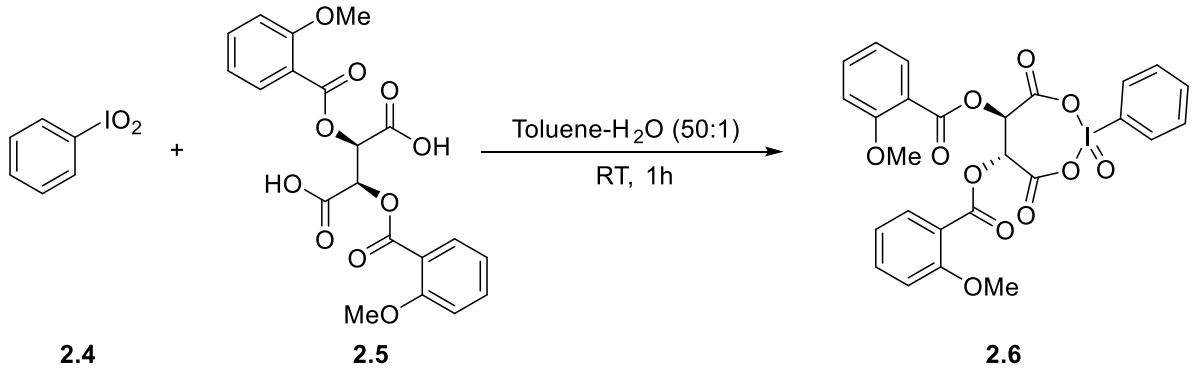
Valuable synthetic applications of chiral hypervalent iodine reagents was pioneered by Imamoto, after about eighty years of the synthesis since the first chiral hypervalent iodine reagent by Pribram. In the year 1986 a new class of chiral hypervalent iodine reagents was synthesised by Imamoto and co-workers.[4] Chiral I(III) reagents of type **2.3** were achieved

via ligand exchange of iodosylbenzene (**2.1**) with different L-tartaric acid anhydride derivatives (**2.2**) (Scheme 2.1).



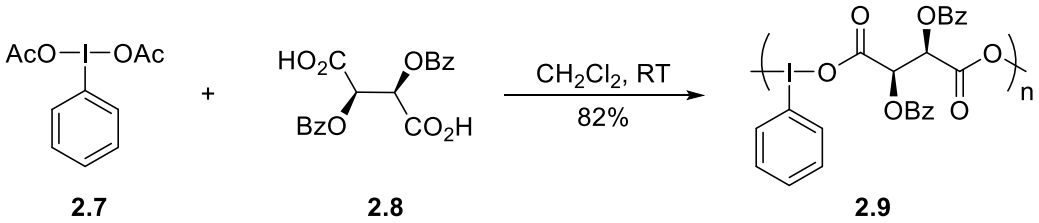
Scheme 2.1. Synthesis of chiral iodine(III) derivatives **2.3**.

Analogously, the chiral I(V) reagent **2.6** was synthesised by Kita *et al.*[5] using $PhIO_2$ (**2.4**) and di(2-methoxy)benzoyl-L-tartaric acid (**2.5**) (Scheme 2.2).



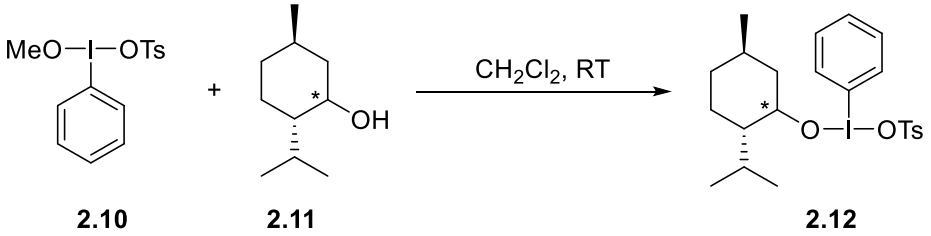
Scheme 2.2. Synthesis of chiral iodine(V) derivatives **2.6**.

In the year 1992 Koser *et al.*[6] prepared an analogue to Imamoto reagents **2.3** using (diacetoxyiodo)benzene (**2.7**) and dibenzoyl-L-tartaric acid (**2.8**) (Scheme 2.3). After extensive analysis the authors found that the real structure of the reaction product is the polymer **2.9** rather than the cyclic form **2.3** previously reported by Imamoto.



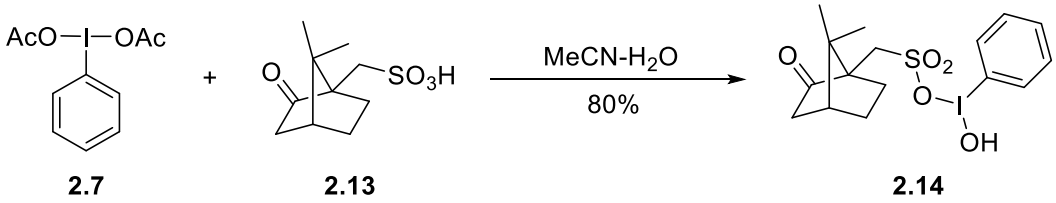
Scheme 2.3. Synthesis of chiral iodine(III) derivatives **2.9**.

The same group also achieved the synthesis of two new chiral I(III) reagents (+)-**2.12** and (-)-**2.12** through ligand exchange of the hypervalent iodine reagent [methoxy(tosyloxy)iodo]benzene (MTIB) (**2.10**) with (+)-menthol and (–)- menthol (Scheme 2.4).[7]



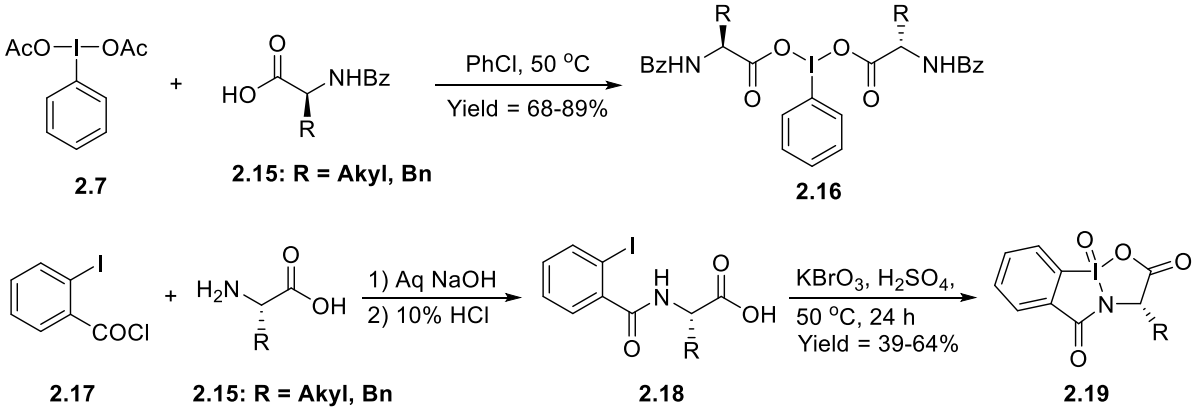
Scheme 2.4. Synthesis of chiral iodine(III) derivatives **2.12**.

(+)-Camphorsulfonic acid (**2.13**) was investigated as a source of chirality by Varvoglis *et al.*[8] to achieve the chiral I(III) **2.14** in 80% yield from (diacetoxyiodo)benzene (**2.7**) (Scheme 2.5).



Scheme 2.5. Synthesis of chiral iodine(III) derivatives **2.14**.

Using amino acids as chiral moieties, Zhdankin *et al.* synthesised a different group of chiral I(III)[9] and I(V)[10] reagents **2.16** and **2.19**, respectively (Scheme 2.6). Ligand exchange of (diacetoxyiodo)benzene (**2.7**) with several *N*-protected amino acids (**2.15**) led to the formation of the chiral iodobenzene dicarboxylate (**2.16**) in high yields. On the other hand, oxidation of the easily accessible 2-iodobenzamides **2.18** with potassium bromate ($KBrO_3$) led to the formation of the chiral benziodazole oxides **2.19** in moderate yields.



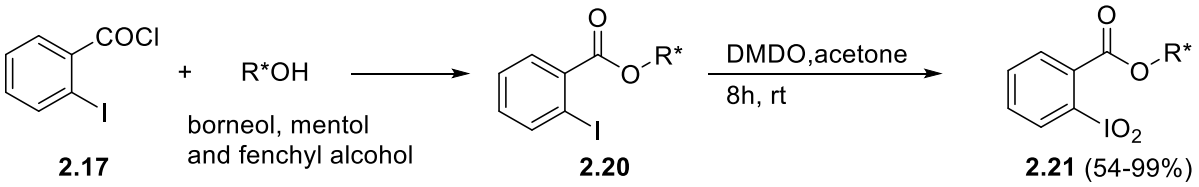
Scheme 2.6. Using amino acids as chiral ligands.

Hypervalent iodine reagents with chiral ligands are typically applied in the stereoselective oxidation of sulfides into the corresponding chiral sulfoxides.

2.1.1.2. Hypervalent iodine reagents with chiral substituents on the iodoarene backbone

In contrast to the synthesis of hypervalent iodine reagents with chiral ligands, the synthesis of hypervalent iodine reagents with chiral substituents in the iodoarene backbone is a very active research area and such kind of reagents are diverse and find wide applications in asymmetric synthesis.

Several strategies to introduce chirality into the iodoarene backbone have been developed. One straightforward strategy is the reaction of 2-iodobenzoic acid or (2-iodophenyl)acetic acid derivative with chiral alcohol or amine. In this context, Wirth et al.[11] synthesised the chiral I(V) reagents **2.21** through the esterification of 2-iodobenzoyl chloride (**2.17**) and chiral alcohols, namely, borneol, menthol and fenchyl alcohol, the esters **2.20** were then oxidized to the corresponding I(V) reagents **2.21** *via* oxidation with dimethyldioxirane (DMDO) in good to excellent yields (Scheme 2.7).



Scheme 2.7. Synthesis of chiral iodine(V) derivatives **2.21**.

Following the aforementioned protocol, the same group reported the synthesis of a wide range of chiral iodoarenes and their application in the α-oxytosylation of ketones, and the lactonisation of 5-oxo-5-phenylpentanoic acid using *m*CPBA as a terminal oxidant (Figure 2.2).[12]

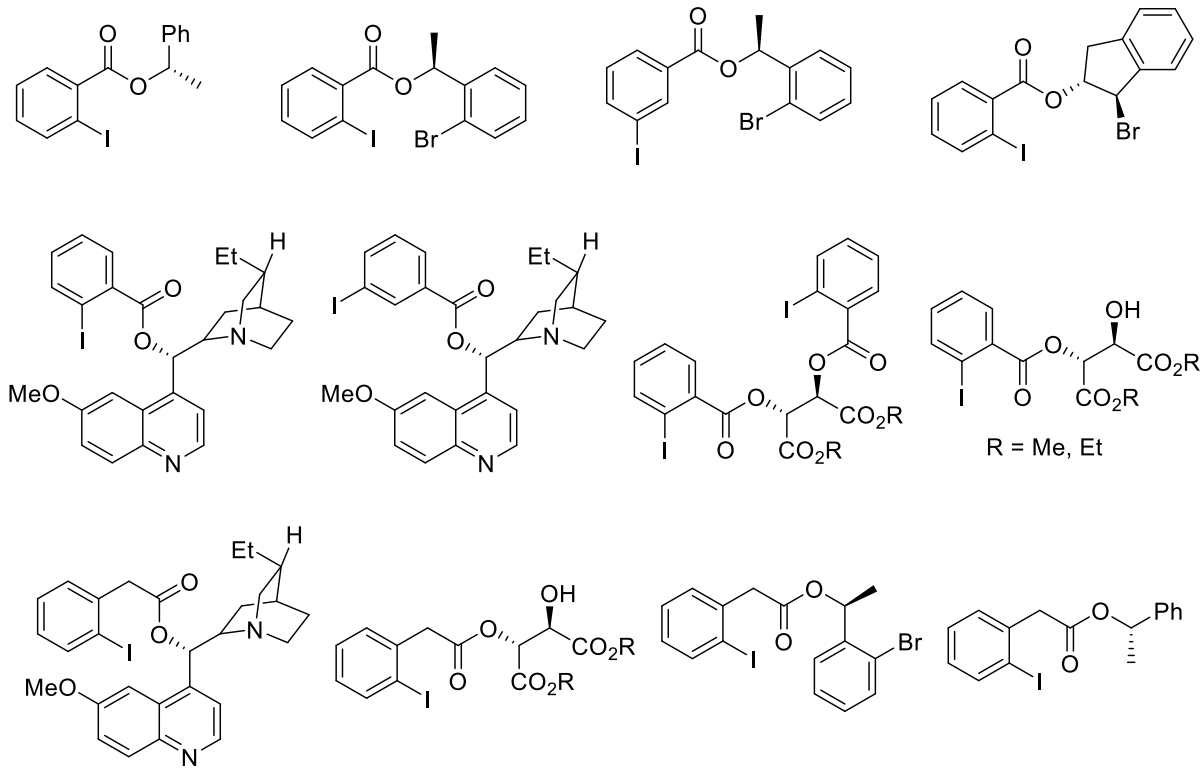


Figure 2.2. Chiral iodoesters as precursors of chiral hypervalent iodine reagents.

In a similar manner, the chiral iodoarenes **2.22** and **2.23** containing norephedrine and pseudo-ephedrine units were synthesised in 72% and 75% yield, respectively, from the corresponding carboxylic acids. The amides were oxidized using *m*CPBA to the corresponding hypervalent iodine species (Figure 2.3).[13]

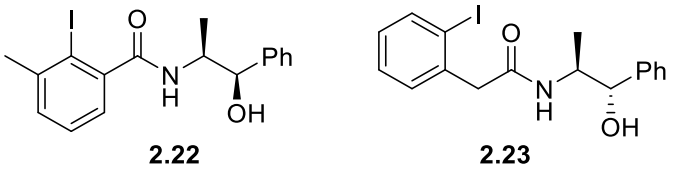


Figure 2.3. Chiral iodoamides as precursorsof chiral hypervalent iodine reagents.

Chiral hypervalent iodine reagents containing chiral units derived from lactic acid and analogous acids (Figure 2.4) are widely used in the stereoselective transformations mediated by chiral hypervalent iodine reagents.[14–20]

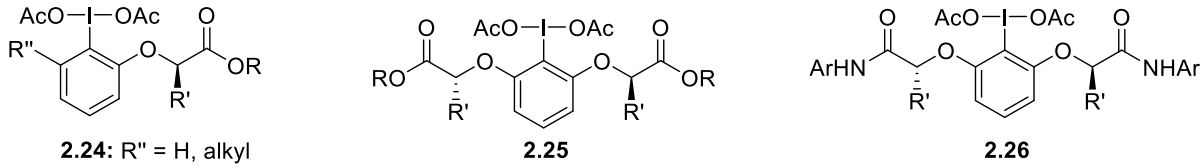
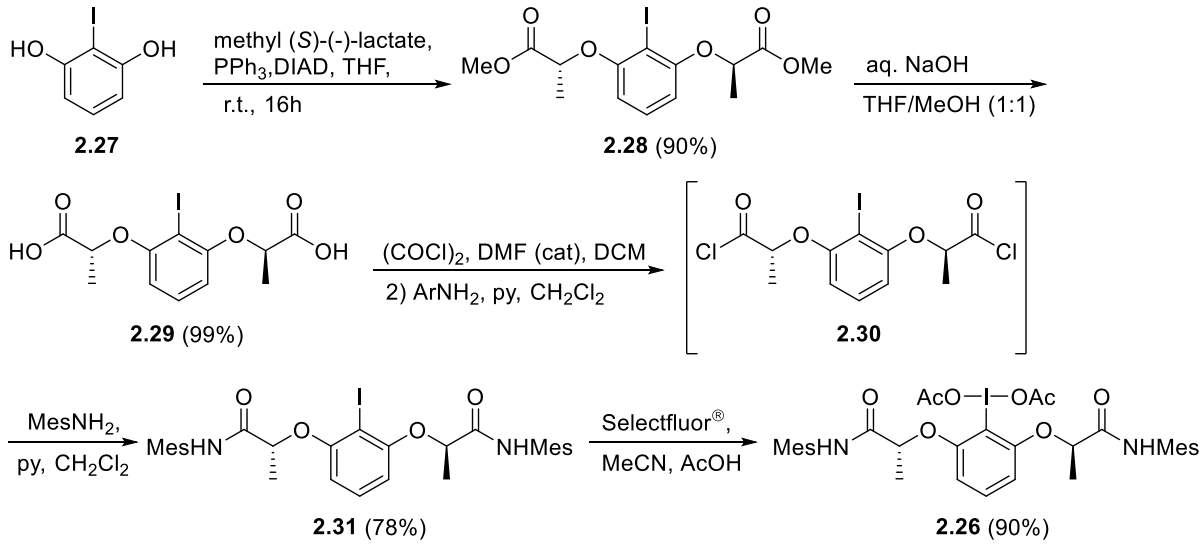


Figure 2.4. Lactate-based and analogous chiral hypervalent iodine reagents.

Synthesis of the chiral hypervalent iodine derivatives **2.26** as a representative example of this widely used group is depicted in scheme 2.8.[16]



Scheme 2.8. Synthesis of C_2-symmetric chiral hypervalent iodine reagent **2.26**.

2.1.1.3. Axially chiral hypervalent iodine reagents

Axially chiral iodoarenes and their corresponding hypervalent iodine reagents attracted the attention of several research groups, examples of such chiral reagents are shown in figure 2.5.[21–28]

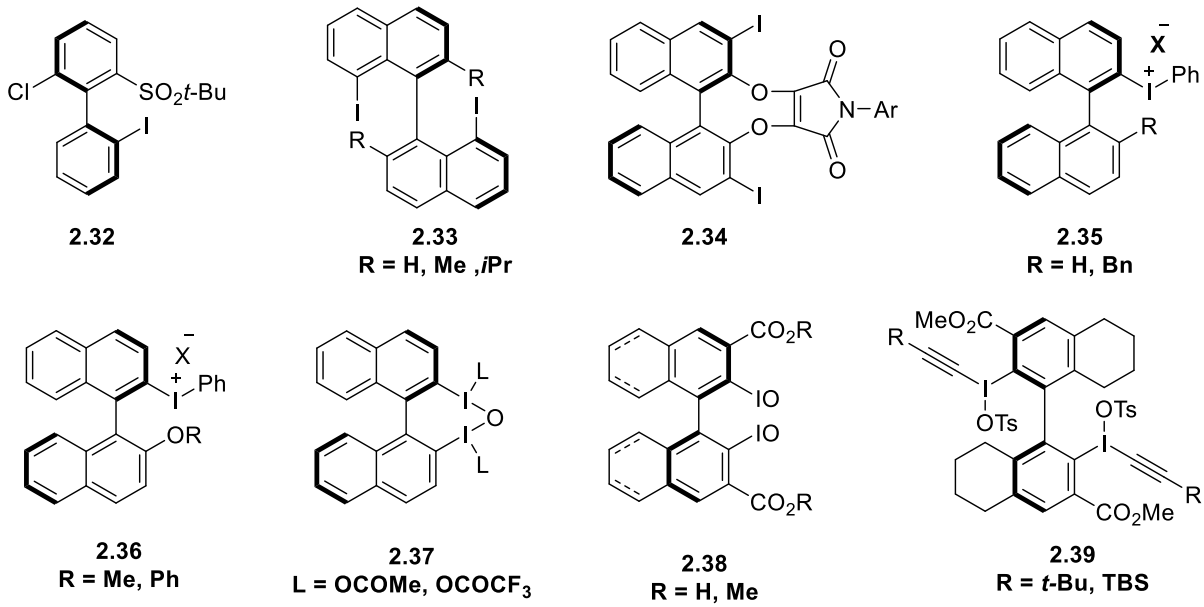
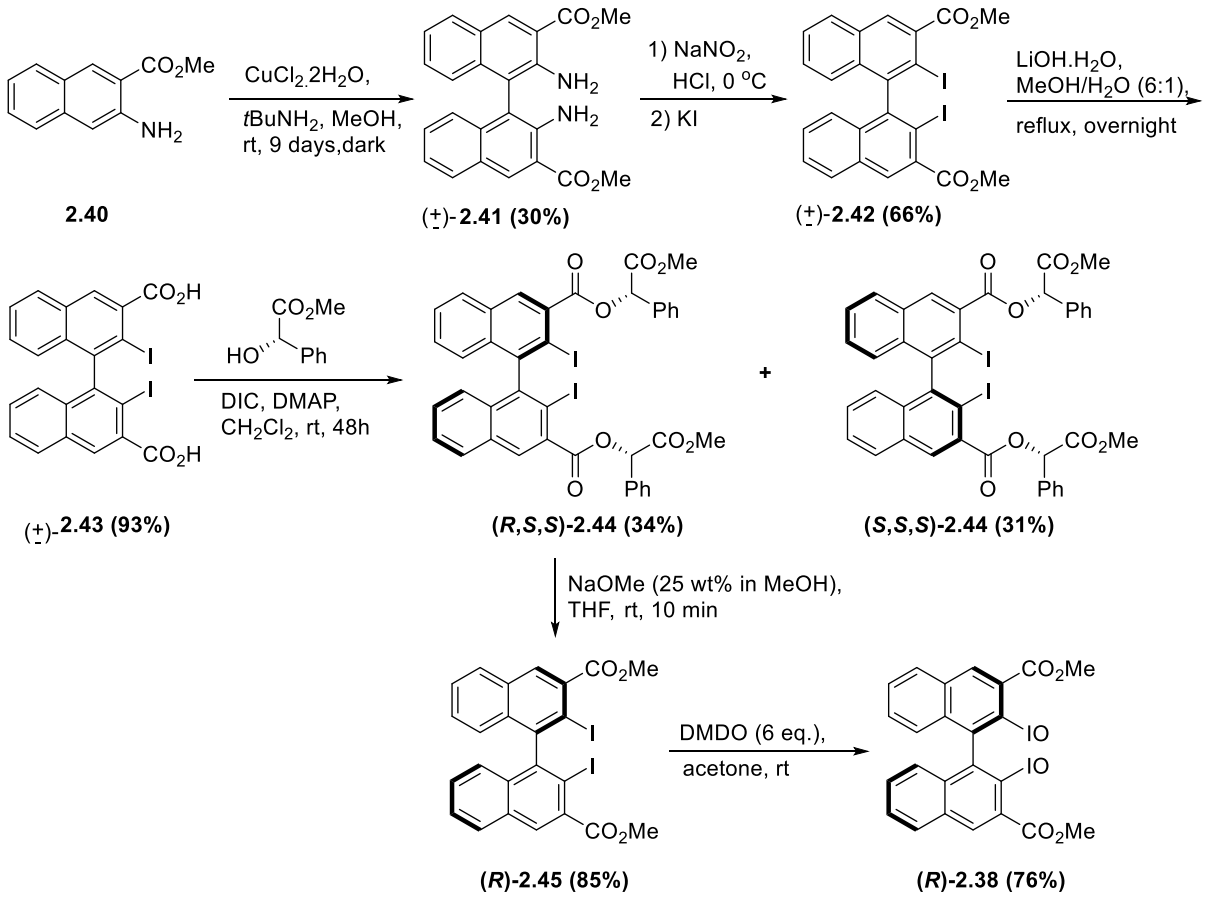


Figure 2.5. Axially chiral iodoarenes and hypervalent iodine reagents.

Synthesis of the axially chiral hypervalent iodine derivatives **2.38** as a representative example of this class of chiral hypervalent iodine reagents is depicted in scheme 2.9.[21]



Scheme 2.9. Synthesis of axially chiral hypervalent iodine reagent **(*R*)-2.38**.

2.1.1.4. Hypervalent iodine reagents with Chiral counter ion

Synthesis and stereoselective applications of chiral hypervalent iodine reagents derived from iodide salts with chiral counter cations are rare in the literature of hypervalent iodine chemistry. Some examples of chiral quaternary ammonium iodides are depicted in figure 2.6.[29]

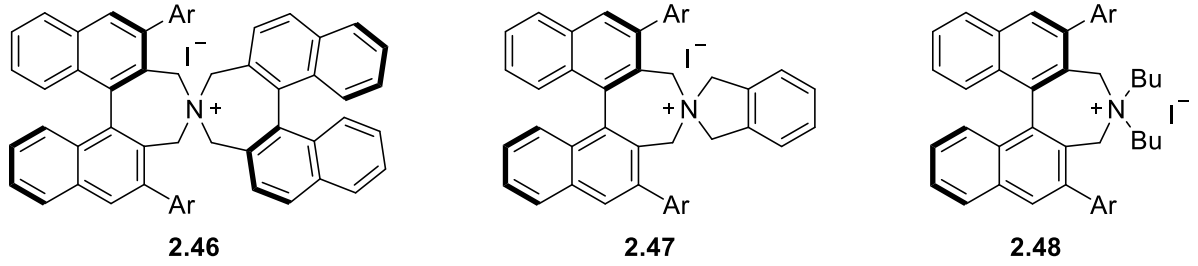
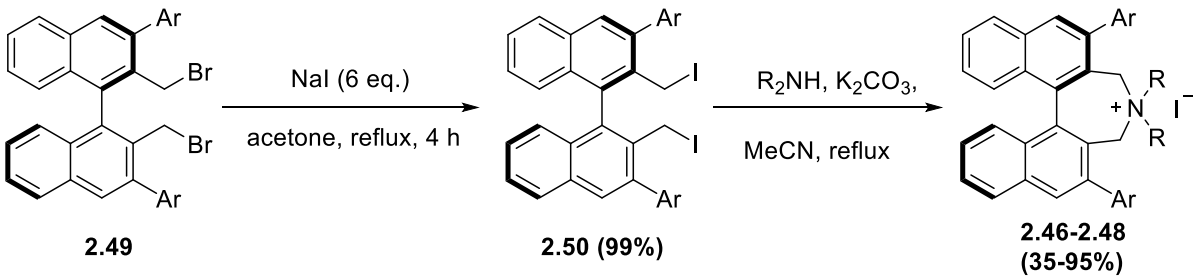


Figure 2.6. Precursors of hypervalent iodine reagents with chiral counter ion.

The salts **2.46-2.48** were synthesised starting from (*R*)-2,2'-bis(bromomethyl)-1,1'-binaphthyl derivatives **2.49** in moderate to excellent yields over two steps (Scheme 2.10).[29]



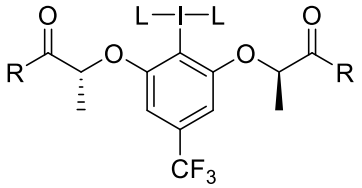
2.49 **2.50 (99%)** **2.46-2.48 (35-95%)**

Scheme 2.10. Synthesis of chiral quaternary ammonium iodides **2.46-2.48**.

2.2. Results and Discussion

2.2.1. Synthesis of novel electron-deficient chiral hypervalent iodine reagents

Among the wide spectrum of chiral hypervalent iodine reagents, the C_2-symmetric lactate-based chiral hypervalent iodine reagents are the most successful in transferring chirality to a wide range of substrates, hence they found application in a variety of valuable enantioselective transformations. As hypervalent iodine reagents are electrophilic at the iodine atom, so introduction of electron withdrawing groups into the aromatic moiety could in principle enhance the electrophilicity of these synthetically important species. The synthesis and application of two novel electron-deficient chiral hypervalent iodine reagents of the general structure **2.51** (Figure 2.7) is described in this chapter.



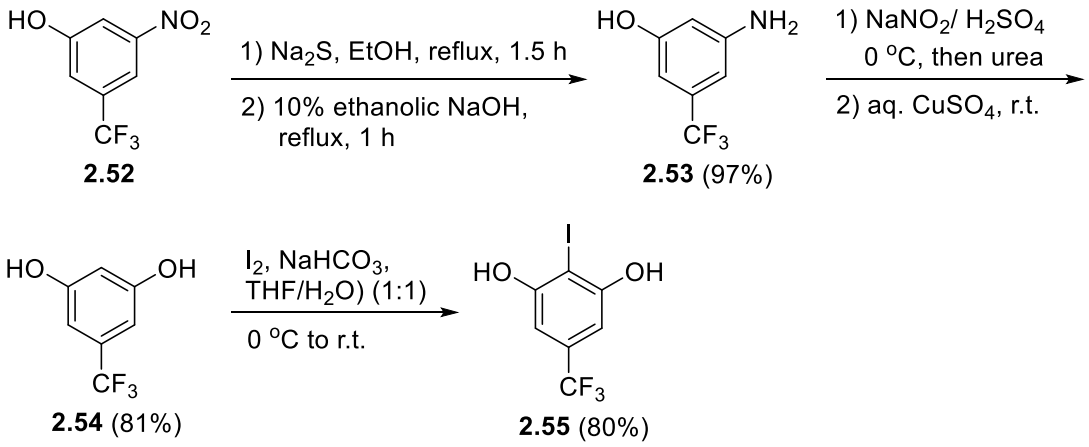
2.51

R = OMe, NHAr
L = heteroatom ligand

Figure 2.7. Lactate based electron-deficient chiral hypervalent iodine reagents.

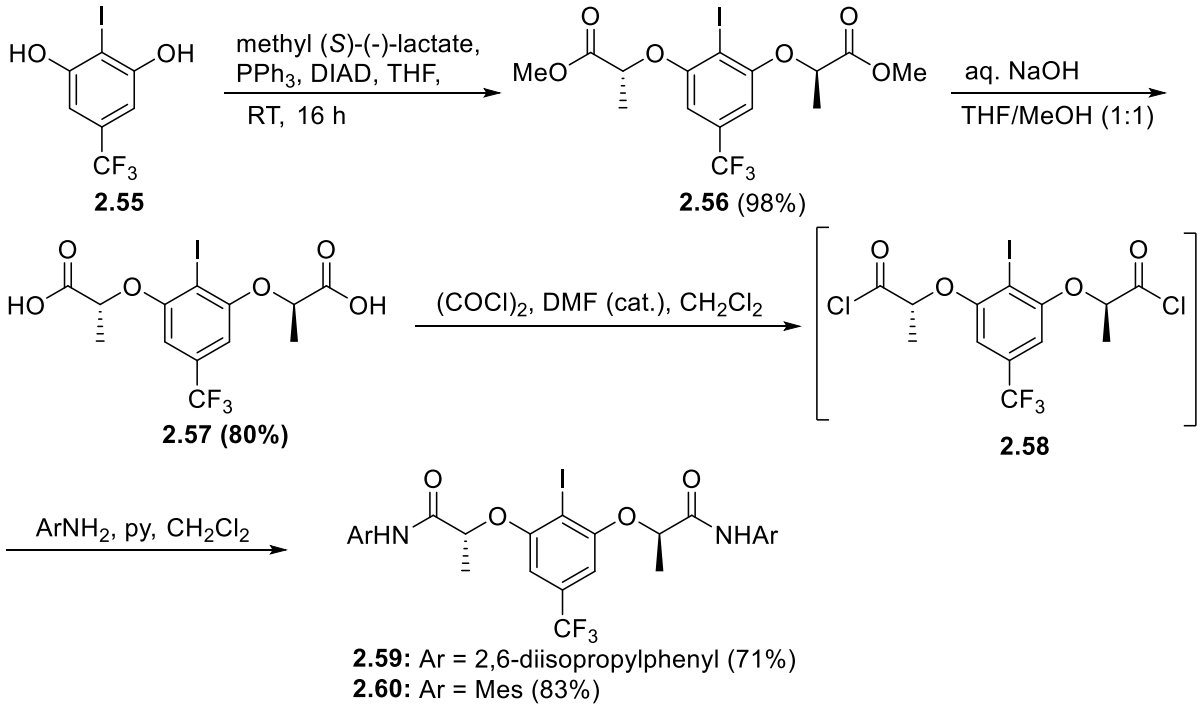
2.2.1.1. Synthesis of novel electron-deficient chiral iodoarenes

To achieve the synthesis of the proposed chiral hypervalent iodine reagents of type **2.51**, the key novel building block, 2-iodo-5-(trifluoromethyl)benzene-1,3-diol (**2.55**) is required. Compound **2.55** was synthesised starting from the commercially available 3-nitro-5-(trifluoromethyl)phenol (**2.52**) in 63% overall yield over 3 steps (Scheme 2.11). The synthesis of **2.55** started with the Zinin reduction[30] of the nitro group of the nitrophenol derivative **2.52** to afford the corresponding amino derivative, 3-amino-5-(trifluoromethyl)phenol (**2.53**)[31] in 97% yield. The amino group of **2.53** is converted into a hydroxy group *via* a Sandmeyer reaction,[32] where the diazotation of **2.53** is followed by treatment with a saturated aqueous solution of $CuSO_4.5H_2O$ led to the formation of the 5-(trifluoromethyl)benzene-1,3-diol (**2.54**) in 81% yield. The iodine was introduced into **2.54** via electrophilic aromatic substitution, where the reaction of diol **2.54** with molecular iodine afforded the desired iodoarene **2.55** in 80% yield.



Scheme 2.11. Synthesis of the novel iodoresorcinol derivative **2.55**.

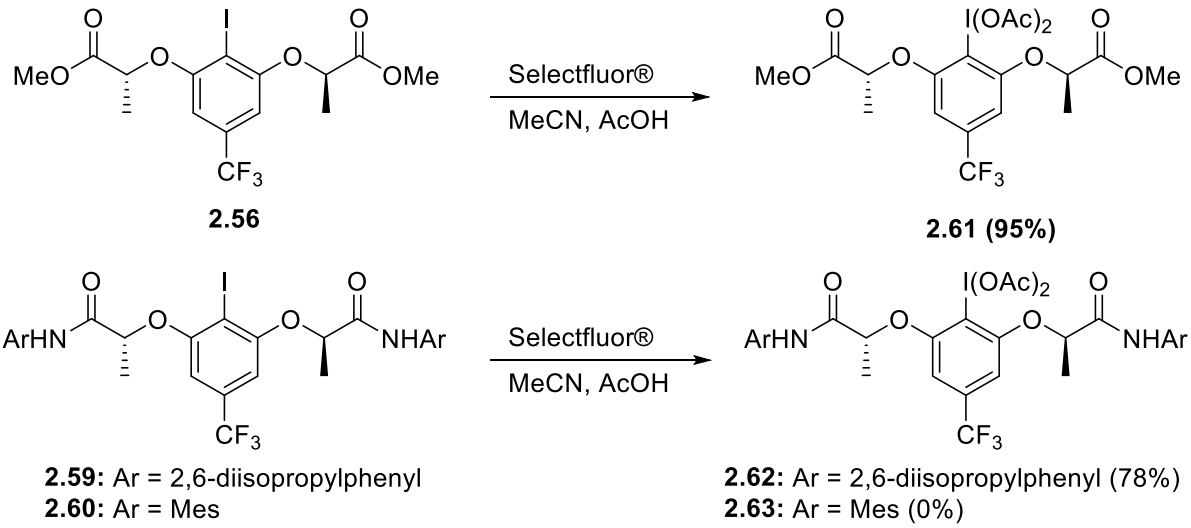
Having the key intermediate **2.55** in hands, the synthesis of the target hypervalent iodine reagents of type **2.51** could be achieved. Hence, the iodoarene **2.55** was reacted with methyl (*S*)-(-)-lactate under Mitsunobu reaction conditions[33] to afford the lactate-based chiral iodoarene **2.56** in 98% yield. Basic hydrolysis of the diester **2.56** in a 1:1 mixture of THF and methanol afforded the dicarboxylic acid **2.57** in 80% yield after acidification. The diacid chloride **2.58** was generated in situ by treatment of the diacid **2.57** with oxalyl chloride, then treated with 2,6-diisopropylaniline and 2,4,6-trimethylaniline to afford the corresponding amides **2.59** and **2.60** in 71% and 83% yields, respectively (Scheme 2.12).



Scheme 2.12. Synthesis of the novel chiral iodoarenes **2.56**, **2.59**, and **2.60**.

2.2.1.2. Oxidation of iodoarene 2.56, 2.59, and 2.60 to the corresponding hypervalent iodine reagents

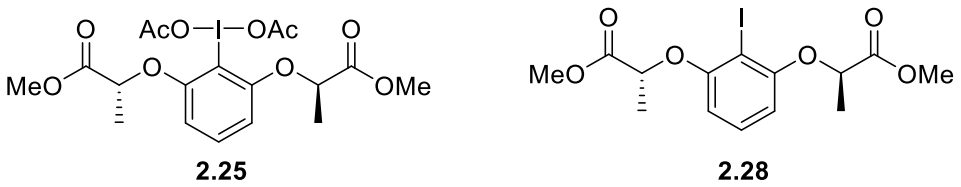
The oxidation of the novel chiral iodoarenes **2.56**, **2.59**, and **2.60** to the corresponding hypervalent iodine species was attempted using previously described[16] method with Selectfluor® in a mixture of acetonitrile and acetic acid (Scheme 2.13). The hypervalent iodine reagents **2.61** and **2.62** were obtained in 95% and 78% yields, respectively. While the oxidation of the iodoarene **2.60** to the corresponding hypervalent iodine reagent **2.63** was unsuccessful under the same reaction conditions and the starting material was recovered after 48 h reaction time. All attempts to oxidise the mesityl amide **2.60** into the corresponding hypervalent iodine reagent using different oxidants such as sodium perborate, *m*CPBA, and Oxone® under various reaction conditions were unsuccessful.



Scheme 2.13. Oxidation of iodoarenes **2.56**, **2.59**, and **2.60** into the corresponding hypervalent iodine reagents.

2.2.2. Synthetic applications of the novel chiral hypervalent iodine reagents 2.61 and 2.62

The reactivity and selectivity of the electron-deficient lactate-based chiral iodoarenes and their corresponding hypervalent iodine reagents were assessed using some typical stereoselective well-known transformations induced by chiral hypervalent iodine reagents in stoichiometric amounts or chiral iodoarenes in a catalytic manner, taking the well-known reagents **2.25** and **2.28** (Figure 2.8)[16,18,33] as reference compounds.



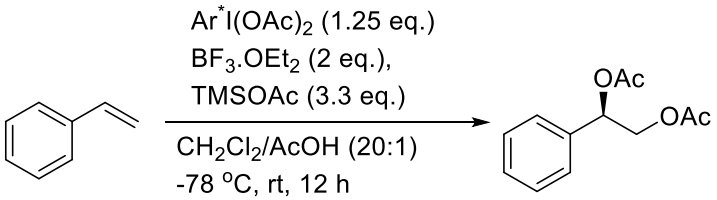
2.25 **2.28**

Figure 2.8. Well-known lactate-based chiral hypervalent iodine reagent **2.25** and its iodoarene precursor **2.28**.

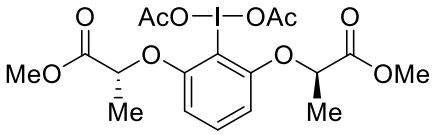
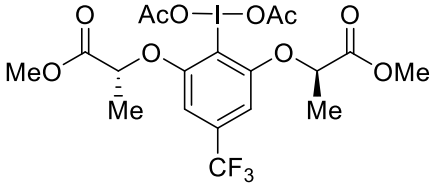
2.2.2.1. Oxidative difunctionalisation of alkenes

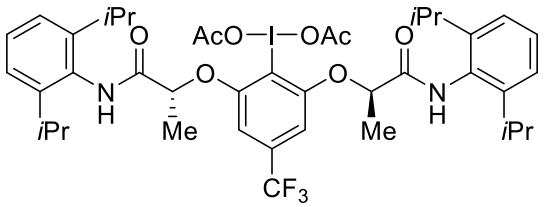
The oxidative difunctionalisation of alkenes is one of the model reactions widely used to investigate the reactivity and selectivity of novel hypervalent iodine reagents.[33–38] Diacetoxylation of styrene was achieved following the literature procedure,[35] where styrene was treated with the chiral hypervalent iodine reagents **2.25**, **2.61**, and **2.62** at low temperature, in the presence of $BF_3.Et_2O$ as activating Lewis acid to afford (*R*)-1,2-diacetoxyethylbenzene (**2.65**) as the major enantiomer (Table 2.1).

Table 2.1. Stereoselective diacetoxylation of styrene using reagent **2.25**, **2.61**, and **2.62**.



2.64 **(*R*)-2.65**

Entry	Hypervalent iodine reagent	**2.65** (Yield%)	**2.65** (ee%)
1	 **2.25**	71	45
2	 **2.61**	67	56

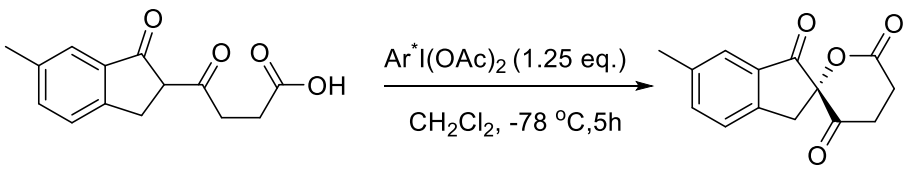
3	 **2.62**	57	54

The results indicate that the newly synthesised reagents **2.61** and **2.62** show better enatiotioselectivity compared to the reference reagent **2.25** where the diacetoxylation product **2.65** was obtained in 56 and 54% ee, respectively with comparable yield in the case of reagent **2.61** and lower yield in case of reagent **2.62**.

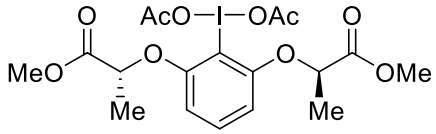
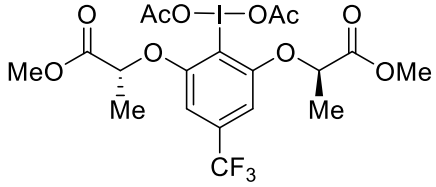
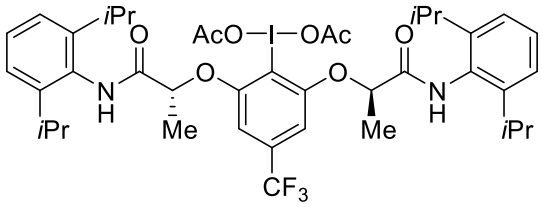
2.2.2.2. Oxyspirolactonisation of keto carboxylic acids

Hypervalent iodine reagents have been successfully utilised to affect the oxylactonisation of a variety of substrates including keto carboxylic acids, unsaturated carboxylic acids, and phenol carboxylic acid derivatives.[12,13,39] Recently, Wirth *et al.*[40] reported the stereoselective oxylactonisation of ketoacids of type **2.66** into the corresponding spirolactones of type **2.67** using electrochemically generated hypervalent iodine regents. Treatment of the keto acid **2.66** with the hypervalent iodine reagents **2.61** and **2.62** in addition to the reference reagent **2.25** lead to the spirolactonisation product **2.67** in all cases. The results (Table 2.2) revealed that the new reagents **2.61** and **2.62** gave the product in slightly higher yield compared to **2.25** and the highest stereoselectivity in case of the reagent **2.61** (63% ee) while the stereoselectivity was the lowest in case of the reagent **2.62** (33% ee). It is noteworthy that using the ester reagents **2.25** and **2.61** lead to the formation **(*S*)-2.67** as the major enantiomer which agrees with the reported stereochemistry by Wirth *et al.*,[40] while the amide reagent **2.62** led to the formation of **(*R*)-2.67** as the major enantiomer.

Table 2.2. Stereoselective spirolactonisation of ketoacid **2.66** using reagent **2.25**, **2.61**, and **2.62**.



2.66 **(*S*)-2.67**

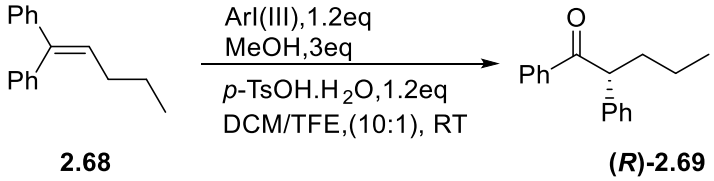
Entry	Hypervalent iodine reagent	**2.67** (Yield%)	**2.67** (ee%)
1	 **2.25**	58	53
2	 **2.61**	60	63
3	 **2.62**	65	33[a]

[a] **(R)-2.67 is** obtained as the major enantiomer.

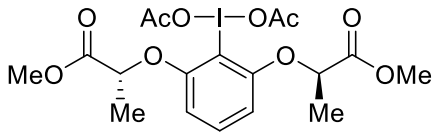
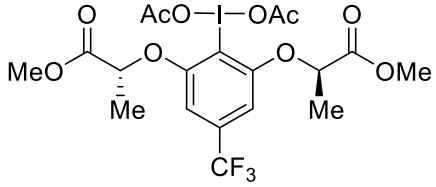
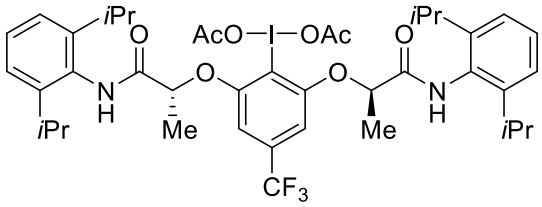
2.2.2.3. Oxidative rearrangement of alkenes

The stereoselective oxidative rearrangement of alkenes mediated by chiral hypervalent iodine reagents[41,42] is an efficient metal-free alternative to transition metal catalysed synthesis of the valuable chiral α-aryl ketones motifs.[43–46] Subjecting the olefinic substrate **2.68** to the oxidative rearrangement conditions reported by Wirth *et al.*[41] but using the electron deficient hypervalent iodine reagents **2.61** and **2.62** led to the desired chiral α-aryl ketone (*R*)-1,2-diphenylpentan-1-one (**2.69**) in good yields and high enantioselectivity. The reagent **2.61** lead to the formation of **2.69** in high yield and slightly higher enantioselectivity compared to the reagent **2.25**, while the reagent **2.62** gave unsatisfactory results (Table 2.3).

Table 2.3. Stereoselective oxidative rearrangement of olefins using reagent **2.25**, **2.61**, and **2.62**.



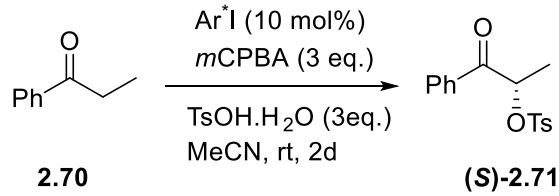
2.68 **(*R*)-2.69**

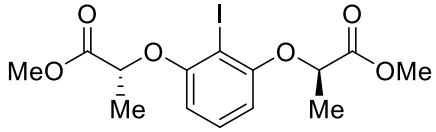
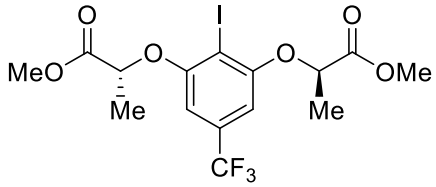
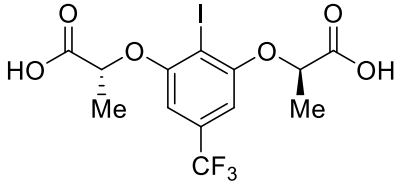
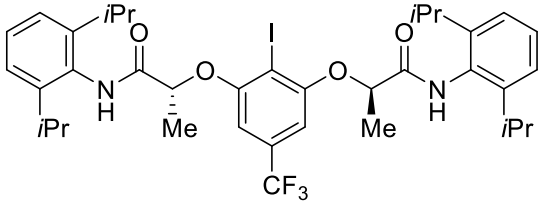
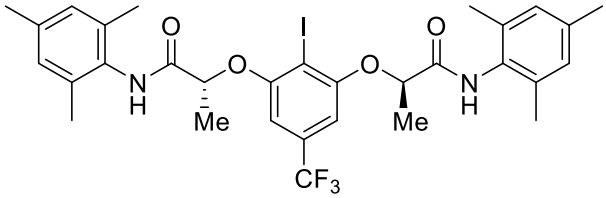
Entry	Hypervalent iodine reagent	**2.69** (Yield%)	**2.69** (ee%)
1	 **2.25**	53	91
2	 **2.61**	65	92
3	 **2.62**	15	78

2.2.2.4. Catalytic α-oxytosylation of ketones

α-Oxytosylation of ketones is another typical reaction mediated by hypervalent iodine reagents.[12,13,25,47–49] The reaction is extensively studied using preformed hypervalent iodine reagents in stoichiometric amounts and iodoarenes as organocatalysts in the presence of terminal oxidants such as *m*CPBA. To investigate the potential applications of the newly prepared electron-deficient lactate-based chiral iodoaren **2.56**, **2.57**, **2.59**, and **2.60** as organocatalysts, the catalytic stereoselective α-oxytosylation of propiophenone (**2.70**) was chosen as a model reaction, applying the literature conditions reported by Legault *et al*.[50] The chiral iodoarene **2.28** was used as a reference. The results (Table 2.4) showed that the five iodoarenes were able to mediate the transformation and the product (*S*)-1-oxo-1-phenylpropan-2-yl 4-methylbenzenesulfonate (**2.71**) was formed in reasonable yields 65-70% using 10 mol% catalyst loading of the ester and amide reagents **2.25**, **2.56**, **2.56**, and **2.60**. Interestingly, the acid reagent **2.57** lead to the formation of the product **(*S*)-2.71** in quantitative yield, albeit in poor stereoselectivity. The enantioselectivity was unsatisfactory for the five catalysts with a maximum of only 16% ee in case of the catalyst **2.56** (Table 2.4).

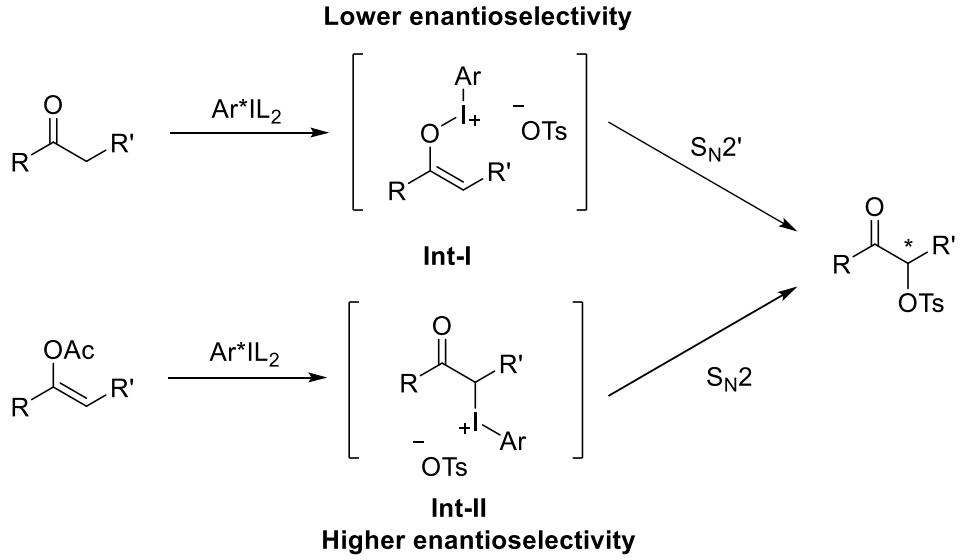
Table 2.4. Catalytic stereoselective α-oxytosylation of propiophenone using chiral iodoarenes **2.28**, **2.56**, **2.57**, **2.59**, and **2.60**.



Entry	Hypervalent iodine reagent	**2.71** (Yield%)	**2.71** (ee%)
1	 **2.28**	70	12
2	 **2.56**	65	16
3	 **2.57**	98	7
4	 **2.59**	70	13
5	 **2.60**	67	2

It's noteworthy that the previously reported stereoselectivities of this type of transformations are usually low to moderate, which might be attributed to the formation of the α-

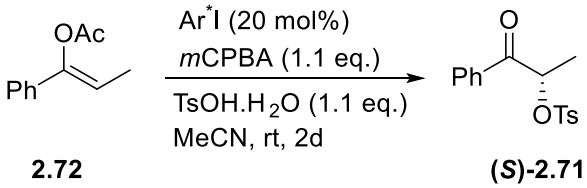
oxytosylation product through S_N2'-type reductive elimination of intermediate iodine(III) species (**Int-I**) bound to the oxygen of the enol tautomer of the carbonyl starting material. Hence, the enantioselectivity of this reaction could be enhanced by preventing the formation of **Int-I** type intermediate by using enol esters as starting materials instead of their corresponding carbonyl substrates (Scheme 2.14).[48] Using enolesters, Legault *et al.*[48] reported high levels of enantioselectivity of α-tosyloxy ketones using chiral hypervalent iodine reagents under stochiometric and catalytic conditions.



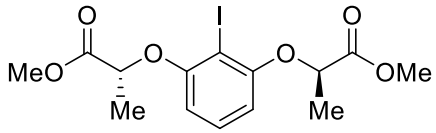
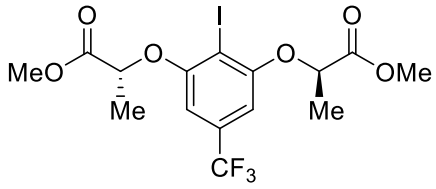
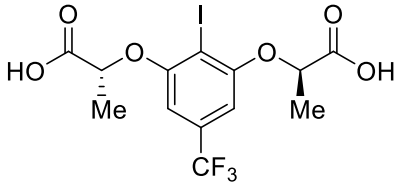
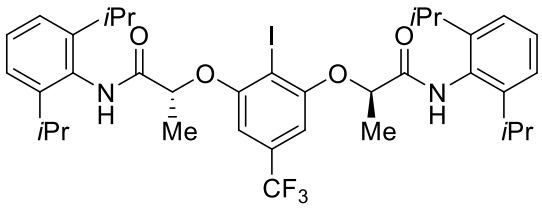
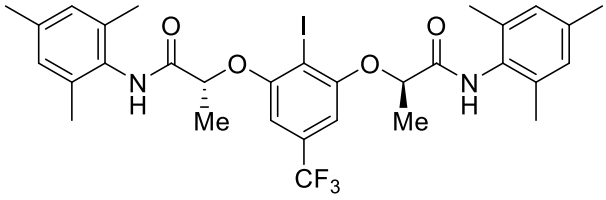
Scheme 2.14. Alternative strategy for *α*-oxytosylation of carbonyl compounds.

Replacing propiophenone by its corresponding enol acetate **2.72** and applying Legault reaction conditions using chiral iodoarenes **2.28, 2.56**, **2.57**, **2.59**, and **2.60** led to the formation of the product (*S*)-1-oxo-1-phenylpropan-2-yl 4-methylbenzenesulfonate (**2.71**) with better enantioselectivity reaching 79% ee (table 2.5).

Table 2.5: Catalytic stereoselective *α*-oxytosylation of propiophenone enol acetate using chiral iodoarenes **2.28**, **2.56**, **2.57**, **2.59**, and **2.60**.



2.72 **(*S*)-2.71**

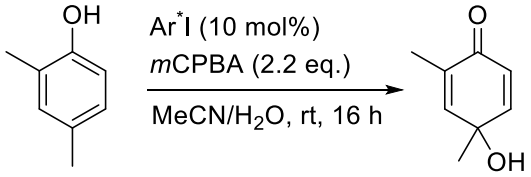
Entry	Hypervalent iodine reagent	**2.71** (Yield%)	**2.71** (ee%)
1	 **2.28**	55	65
2	 **2.56**	64	67
3	 **2.57**	59	65
4	 **2.59**	69	79
5	 **2.60**	66	75

2.2.2.5. Catalytic phenol dearomatisation

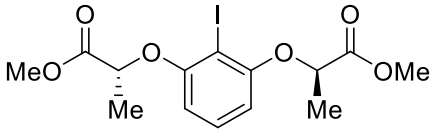
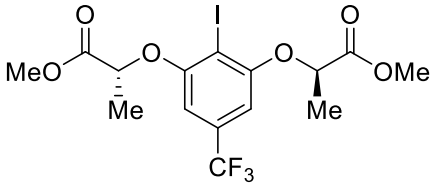
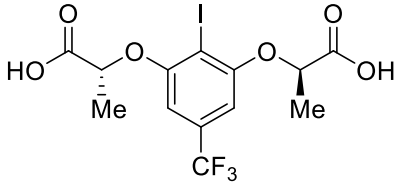
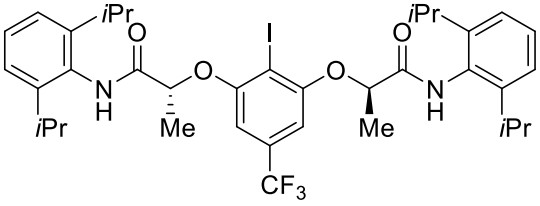
The phenol dearomatisation is not a very good reaction to test the stereoselectivity of chiral hypervalent iodine reagents because the formed stereogenic centre in the product is usually para to the phenol group where the iodine(III) interacts and hence the chiral environment is relatively far away from the reaction site, however, our aim of looking at such a typical reaction of hypervalent iodine reagents is to get more information about the reactivity of the newly synthesised chiral iodoarenes and their potential as more reactive organocatalysts. The oxidative dearomatisation of 2,4-dimethylphenol (**2.73**) was chosen as model reaction

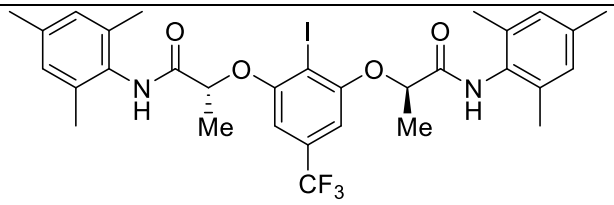
applying the literature reaction condition,[51] but using the chiral iodoarenes **2.56**, **2.57**, **2.59** and **2.60** in addition to **2.28** as a reference catalyst. The results (Table 2.6) show the formation of the desired product **2.74** in high yields (82% and 87%) using the catalysts **2.28** and **2.56**, respectively. The reactivity of the iodoarenes bearing acid **2.57** and amide moieties **2.59** and **2.60** was lower where the product was formed in 71-51% yield. The enantioselectivity was poor (<10%) in all cases as expected.

Table 2.6. Catalytic phenol dearomatisation using chiral iodoarenes **2.28**, **2.56**, **2.57**, **2.59**, and **2.60**.



2.73 **2.74**

Entry	Hypervalent iodine reagent	**2.74** (Yield%)	**2.74** (ee%)
1	 **2.28**	82	3
2	 **2.56**	87	5
3	 **2.57**	71	2
4	 **2.59**	60	8

5	 **2.60**	51	4

2.3. Conclusions and outlook

The synthesis of novel electron deficient lactate-based chiral iodoarenes and hypervalent iodine reagents is described in this chapter. The reactivity and enantioselectivity of the new chiral iodine reagents were investigated using typical hypervalent iodine mediated enantioselective transformations such as the difunctionalisation of alkenes, spirolactonisation, oxidative rearrangement of alkenes, α-oxytosylation of ketones and phenol dearomatisation. In all cases the newly prepared iodine reagents showed either better or comparable reactivity and selectivity to that of the well-known previously prepared lactate-based chiral hypervalent iodine reagents, which could be attributed to the increase of the electrophilicity of the iodine centre as a result of the introduction of the electron-withdrawing trifluoromethyl group. Moreover, the new reagents bearing ester groups were more reactive and more selective compared to the ones bearing amide groups.

It would be interesting to synthesise other electron-deficient chiral hypervalent iodine reagents bearing other electron withdrawing groups (Figure 2.9) and study the kinetics of typical hypervalent iodine mediated oxidative transformation such as diacetoxylation of styrene using the proposed reagents and comparing the results to the known reagents.

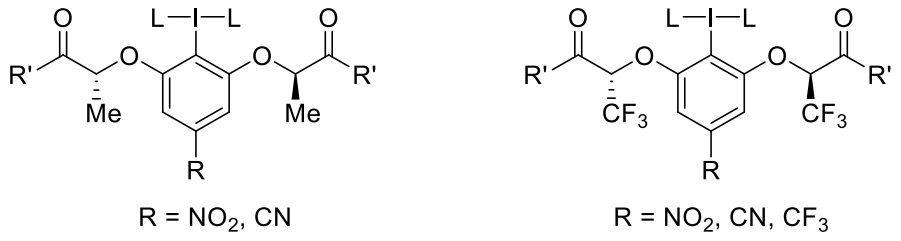


Figure 2.9. Proposed electron-deficient chiral hypervalent iodine reagents.

2.4. References

[1] T. Wirth, Ed. , *Hypervalent Iodine Chemistry*, Springer International Publishing, Cham, **2016**.

[2] R. Pribram, *Liebigs Ann. Chem.* **1907**, *351*, 481–485.

[3] Viktor V. Zhdankin, in *Hypervalent Iodine Chem.*, John Wiley & Sons Ltd, Chichester, UK, **2013**, pp. 21–143.

[4] T. Imamoto, H. Koto, *Chem. Lett.* **1986**, *15*, 967–968.

[5] H. Tohma, S. Takizawa, H. Watanabe, Y. Fukuoka, T. Maegawa, Y. Kita, *J. Org. Chem.* **1999**, *64*, 3519–3523.

[6] D. G. Ray, G. F. Koser, *J. Org. Chem.* **1992**, *57*, 1607–1610.

[7] D. G. Ray, G. F. Koser, *J. Am. Chem. Soc.* **1990**, *112*, 5672–5673.

[8] H. Evangelia, A. Varvoglis, B.-C. Maria, *J. Org. Chem.* **1990**, *55*, 315–318.

[9] A. Y. Koposov, V. V. Boyarskikh, V. V. Zhdankin, *Org. Lett.* **2004**, *6*, 3613–3615.

[10] V. V. Zhdankin, J. T. Smart, P. Zhao, P. Kiprof, *Tetrahedron Lett.* **2000**, *41*, 5299–5302.

[11] S. M. Altermann, S. Schäfer, T. Wirth, *Tetrahedron* **2010**, *66*, 5902–5907.

[12] U. Farooq, S. Schäfer, A. U. H. A. Shah, D. M. Freudendahl, T. Wirth, *Synthesis* **2010**, 1023–1029.

[13] A. Rodríguez, W. Moran, *Synthesis* **2012**, *44*, 1178–1182.

[14] S. M. Banik, J. W. Medley, E. N. Jacobsen, *Science* **2016**, *353*, 51–54.

[15] M. Fujita, S. Okuno, H. J. Lee, T. Sugimura, T. Okuyama, *Tetrahedron Lett.* **2007**, *48*, 8691–8694.

[16] M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem. Int. Ed.* **2010**, *49*, 2175–2177.

[17] M. Uyanik, T. Yasui, K. Ishihara, *Tetrahedron* **2010**, *66*, 5841–5851.

[18] M. Fujita, Y. Yoshida, K. Miyata, A. Wakisaka, T. Sugimura, *Angew. Chem. Int. Ed.* **2010**, *49*, 7068–7071.

[19] W. Kong, P. Feige, T. De Haro, C. Nevado, *Angew. Chem. Int. Ed.* **2013**, *52*, 2469–2473.

[20] H. Wu, Y.-P. He, L. Xu, D.-Y. Zhang, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2014**, *53*,

3466–3469.

[21] C. Bosset, R. Coffinier, P. A. Peixoto, M. El Assal, K. Miqueu, M. Sotiropoulos, L. Pouysøgu, S. Quideau, *Angew. Chem. Int. Ed.* **2014**, *53*, 9860–9864.

[22] S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Buffeteau, D. Cavagnat, A. Chenede, *Angew. Chem. Int. Ed.* **2009**, *48*, 4605–4609.

[23] M. Ochiai, Y. Takaoka, Y. Masaki, Y. Nagao, M. Shiro, *J. Am. Chem. Soc.* **1990**, *112*, 5677–5678.

[24] M. Ochiai, Y. Kitagawa, N. Takayama, Y. Takaoka, M. Shiro, *J. Am. Chem. Soc.* **1999**, *121*, 9233–9234.

[25] S. Brenet, F. Berthiol, J. Einhorn, *Eur. J. Org. Chem.* **2013**, 8094–8096.

[26] G. Levitre, A. Dumoulin, P. Retailleau, A. Panossian, F. R. Leroux, G. Masson, *J. Org. Chem.* **2017**, *82*, 11877–11883.

[27] S. Suzuki, T. Kamo, K. Fukushi, T. Hiramatsu, E. Tokunaga, T. Dohi, Y. Kita, N. Shibata, *Chem. Sci.* **2014**, *5*, 2754–2760.

[28] S. Companys, P. A. Peixoto, C. Bosset, S. Chassaing, K. Miqueu, J.-M. Sotiropoulos, L. Pouysegu, S. Quideau, *Chem. Eur. J.* **2017**, *23*, 13309–13313.

[29] M. Uyanik, H. Okamoto, T. Yasui, K. Ishihara, *Science* **2010**, *328*, 1376–1379.

[30] H. K. Porter, in *Org. React.*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2011**, pp. 455–481.

[31] W. B. Whalley, *J. Chem. Soc.* **1949**, 3016-3020.

[32] T. Cohen, A. G. Dietz, J. R. Miser, *J. Org. Chem.* **1977**, *42*, 2053–2058.

[33] S. Haubenreisser, T. H. Wöste, C. Martínez, K. Ishihara, K. Muñiz, *Angew. Chem. Int. Ed.* **2016**, *55*, 413–417.

[34] T. Hokamp, L. Mollari, L. C. Wilkins, R. L. Melen, T. Wirth, *Angew. Chem. Int. Ed.* **2018**, *57*, 8306–8309.

[35] M. Fujita, M. Wakita, T. Sugimura, *Chem. Commun.* **2011**, *47*, 3983–3985.

[36] Y.-B. Kang, L. H. Gade, *J. Am. Chem. Soc.* **2011**, *133*, 3658–3667.

[37] T. Wirth, U. H. Hirt, *Tetrahedron Asymm.* **1997**, *8*, 23–26.

[38] C. Röben, J. A. Souto, Y. González, A. Lishchynskyi, K. Muñiz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9478–9482.

[39] S. Zhang, F. Lian, M. Xue, T. Qin, L. Li, X. Zhang, K. Xu, *Org. Lett.* **2017**, *19*, 6622–6625.

[40] W.-C. Gao, Z.-Y. Xiong, S. Pirhaghani, T. Wirth, *Synthesis* **2019**, *51*, 276–284.

[41] M. Brown, R. Kumar, J. Rehbein, T. Wirth, *Chem. Eur. J.* **2016**, *22*, 4030–4035.

[42] U. Farid, F. Malmedy, R. Claveau, L. Albers, T. Wirth, *Angew. Chem. Int. Ed.* **2013**, *52*, 7018–7022.

[43] R. Martín, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 7236–7239.

[44] X. Liao, Z. Weng, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 195–200.

[45] S. Lou, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 1264–1266.

[46] R. Takise, K. Muto, J. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2014**, *53*, 6791–6794.

[47] G. Levitre, A. Dumoulin, P. Retailleau, A. Panossian, F. R. Leroux, G. Masson, *J. Org. Chem.* **2017**, *82*, 11877–11883.

[48] B. Basdevant, C. Y. Legault, *Org. Lett.* **2015**, *17*, 4918–4921.

[49] S. M. Altermann, R. D. Richardson, T. K. Page, R. K. Schmidt, E. Holland, U. Mohammed, S. M. Paradine, A. N. French, C. Richter, A. M. Bahar, et al., *Eur. J. Org. Chem.* **2008**, 5315–5328.

[50] A.-A. Guilbault, B. Basdevant, V. Wanie, C. Y. Legault, *J. Org. Chem.* **2012**, *77*, 11283–11295.

[51] K. A. Volp, A. M. Harned, *Chem. Commun.* **2013**, *49*, 3001.

CHAPTER 3

Catalytic oxidative rearrangement of alkenes

3.1. Introduction

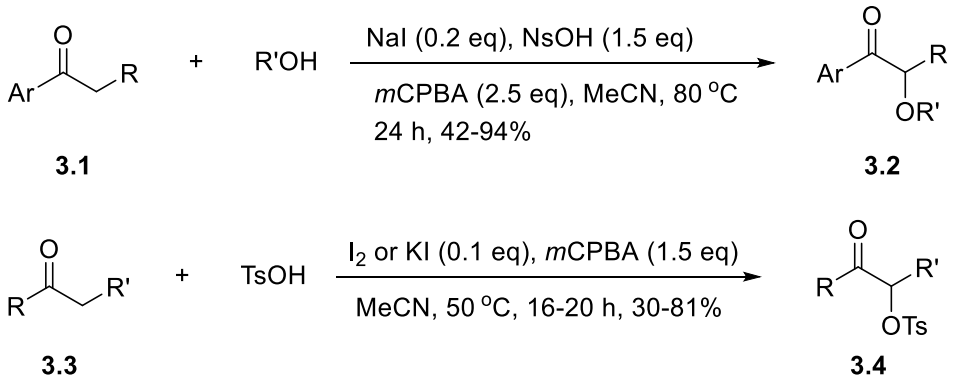
3.1.1. Iodine reagents as organocatalysts

Currently, the chemistry of hypervalent iodine reagents is a well-established field of organic chemistry due to their easy accessibility, mild reaction conditions and environmentally benign nature. Numerous hypervalent iodine reagents with diverse structural features have been synthesised and applied in a wide range of chemical transformations. Traditionally, hypervalent iodine reagents were mainly used as oxidants or co-oxidants in stoichiometric amounts in oxidative transformations, which is considered as a limitation. Although the reactivity patterns of hypervalent iodine reagents are similar to those of the transition metal complexes, the catalytic applications of hypervalent iodine reagents have been less developed compared to their transition metal counterparts.[1–5]

One of the most impressive advancements in the field of hypervalent iodine chemistry is the discovery of catalytic cycles based on hypervalent iodine reagents. Excluding Fuchigami and Fujita's report[6] in 1994 on the catalytic *gem*-difluorination of dithioacetals using electrochemically generated hypervalent iodine reagents, one could date the catalytic applications of the hypervalent iodine reagent to the year 2005, where the groups of Kita,[7] Vinod,[8] and Ochiai[9] independently published their seminal work on chemical transformations catalysed by hypervalent iodine reagents. Later on, the reports on the catalytic applications of hypervalent iodine reagents witnessed a burst and covered almost all the chemical space of the hypervalent iodine chemistry.[3,10–15]

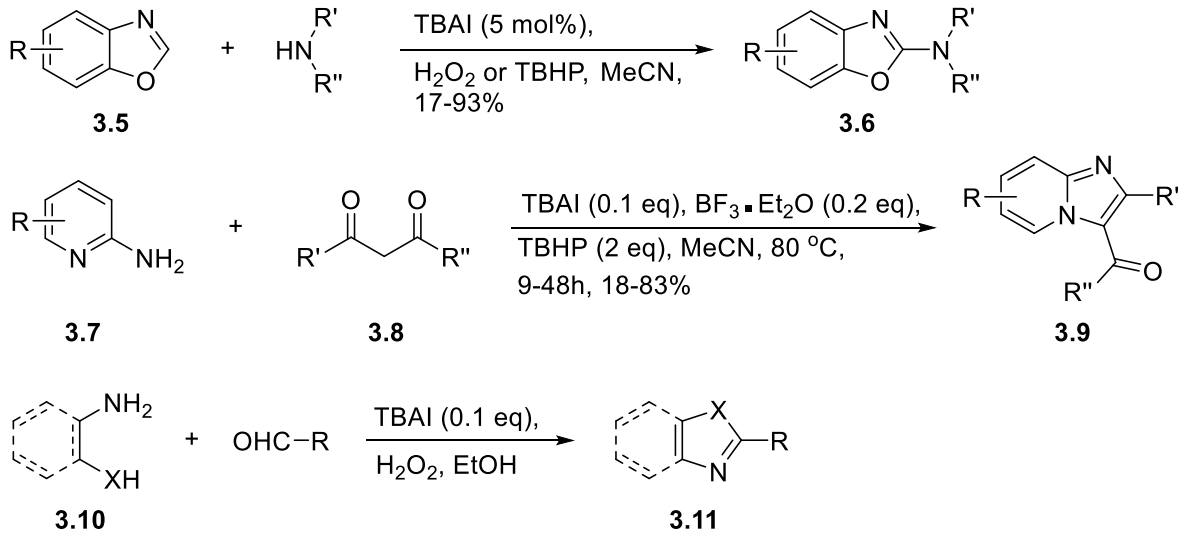
3.1.2. Iodide salts as precatalysts

Molecular iodine and simple iodide salts such as KI, NaI, and quaternary ammonium iodides can be transformed into hypervalent iodine species upon treatment with suitable oxidants and hence they found several applications as precatalysts for hypervalent iodine mediated transformations.[16,17] α-Alkoxylation[18] and α-tosylation[12] of ketones were achieved in moderate to high yields using such catalytic systems (Scheme 3.1).



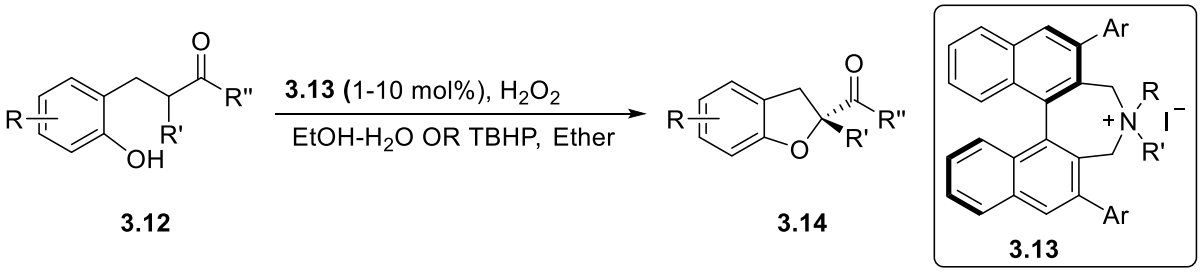
Scheme 3.1. Catalytic α-oxygenation of ketones using iodides as precatalysts

Quaternary ammonium iodides such as tetrabutylammonium iodide (TBAI) are more widely used as precatalysts compared to alkali iodides, which might be attributed to their better solubility in organic solvents. In addition, chiral ammonium iodides can be used in catalytic stereoselective transformations.[19] Some representative examples of the synthetic applications of quaternary ammonium iodides as precatalysts are depicted in Scheme 3.2.[20–22]



Scheme 3.2. Quaternary ammonium iodides as precatalysts.

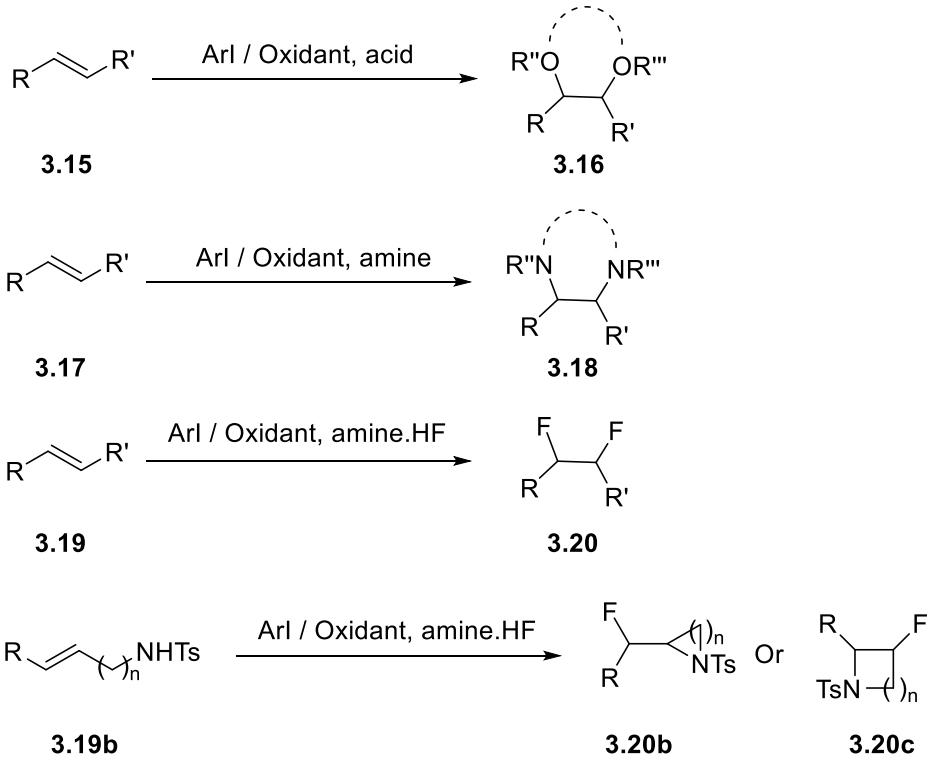
Enantioselective cycloetherification of ketophenols **3.12** into their corresponding chiral 2-acyl-2,3-dihydrobenzofuran derivatives **3.14** (Scheme 3.3) is an impressive catalytic application of iodide salts with chiral quaternary ammonium counter ions (**3.13**) reported by Ishihara *et al*.[19]



Scheme 3.3. Chiral quaternary ammonium iodide salts as organocatalysts.

3.1.3. Iodoarenes as precatalysts

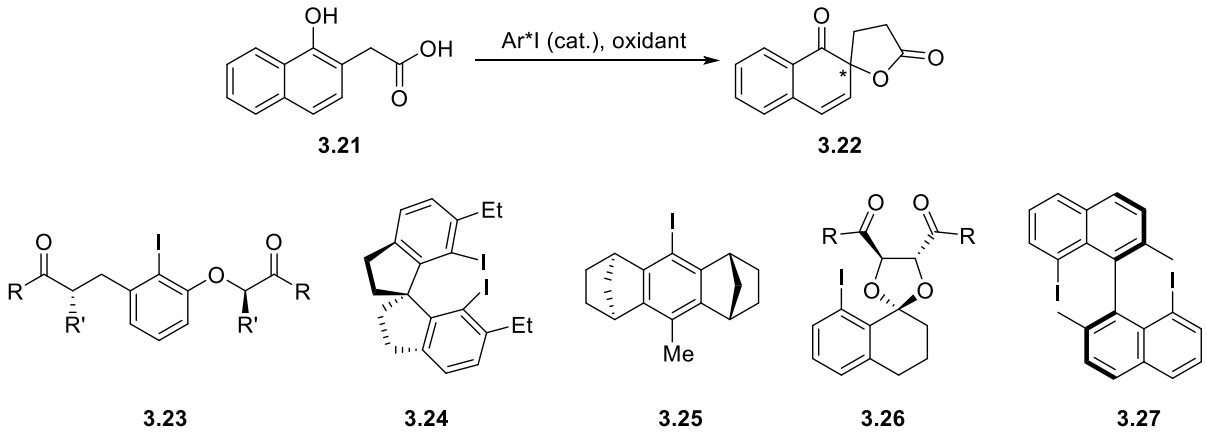
Catalytic cycles based on organic iodine(III) and iodine(V) reagents generated *in situ* from iodoarenes and suitable terminal oxidants have found diverse synthetic application in the field of hypervalent iodine chemistry. Catalytic difunctionalisation of olefins using iodoarene as precatalysts has been extensively studied.[11] Catalytic dioxygenation (**3.16**),[23–27] diamination (**3.18**),[28–30] difluorination (**3.20**),[31–35] and aminofluorination (**3.20b** and **3.20c**)[36–38] were all achieved in high yields and high degrees of stereoselectivity (Scheme 3.4).



Scheme 3.4. Catalytic difunctionalisation of olefins using aryl iodides as precatalysts.

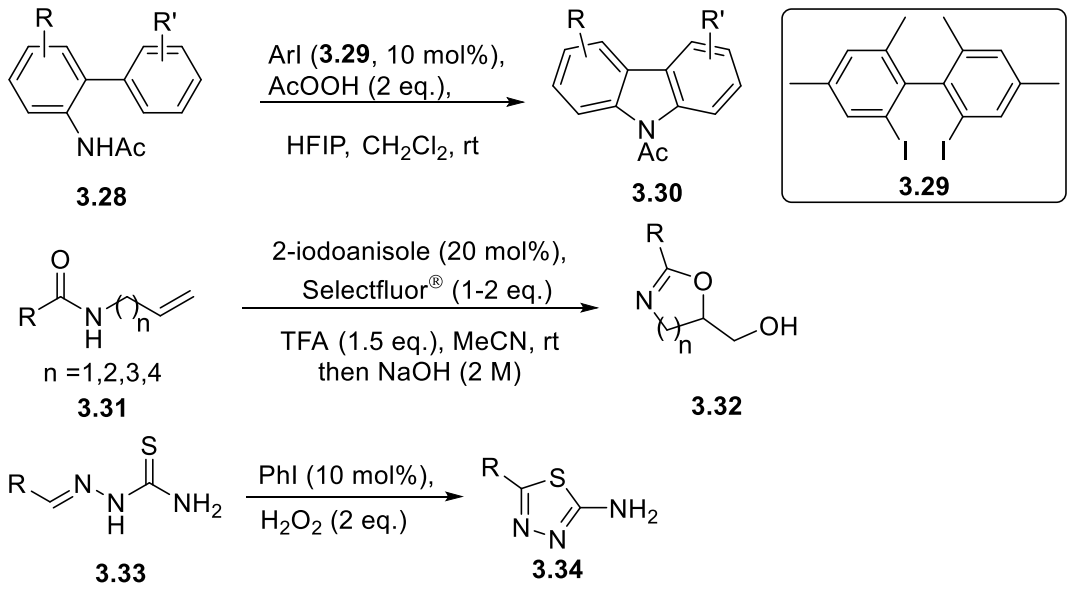
Efficient catalytic protocols of the hypervalent iodine mediated phenol dearomatisation, lactonisation, and lactamisation were developed and improved over years by several research

groups worldwide. A wide range of iodoarenes, from simple iodobenzene derivatives to more complex chiral molecules such as compounds **3.23-3.27**, were successfully used as precatalysts to achieve such transformations in racemic as well as asymmetric manner with high degree of chemo and stereoselectivity.[39–44]



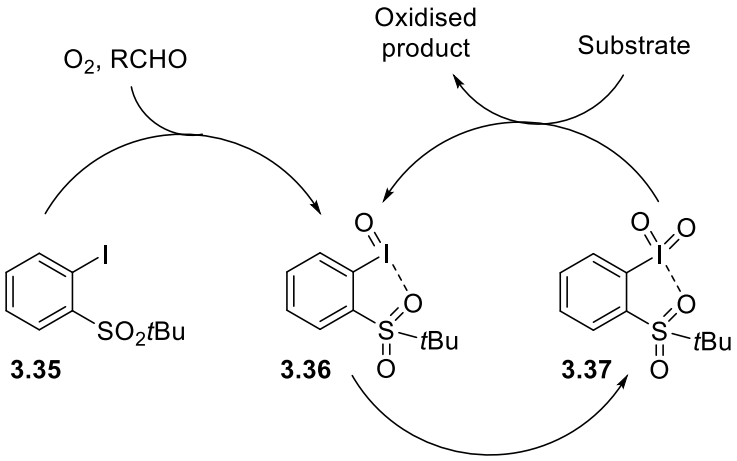
Scheme 3.5. Some examples of chiral iodoarene precatalysts of different classes applied in phenol dearomatisation / spirolactonisation reaction.

Furthermore, the construction of heterocycles of different classes such as carbazoles, benzimidazoles, pyrazoles, oxazoles, thiadiazoles, and many others is another area of the successful application of catalytic cycles based on iodine(III) reagents. Some illustrative examples are shown in Scheme 3.6.[45–48]



Scheme 3.6. Some illustrative examples of catalytic heterocyclisation reactions mediated by hypervalent iodine reagents.

Catalytic applications of hypervalent iodine reagents are not limited to the *in situ* generation of iodine(III) reactive species, catalytic cycles based on iodine(V) reactive species are also well-known.[49–52] In a recent report Powers *et al.*[53] reported the *in situ* generation of several Dess-Martin periodinane (DMP) analogues using several iodoarenes as precatalysts and reactive oxidants generated during aldehyde autoxidation using oxygen as the terminal oxidant. The aerobically generated iodine(V) species showed similar behaviour to DMP, and catalytic oxidation of primary and secondary alcohols, diols, and amino compounds was successfully achieved (Scheme 3.7).

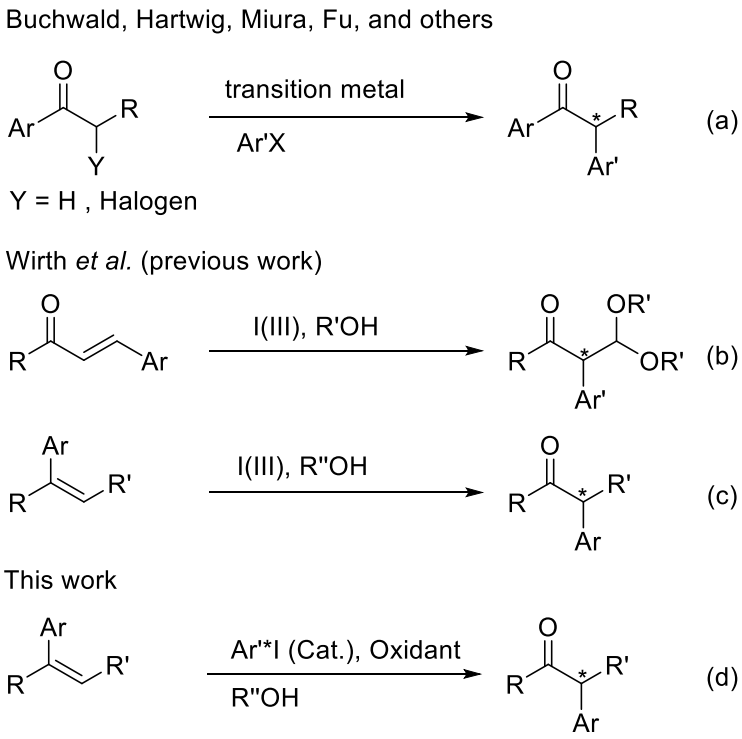


Scheme 3.7. Aerobically generated Dess–Martin periodinane analogue.

3.2. Results and discussion

3.2.1. Stereoselective catalytic oxidative rearrangement of alkenes

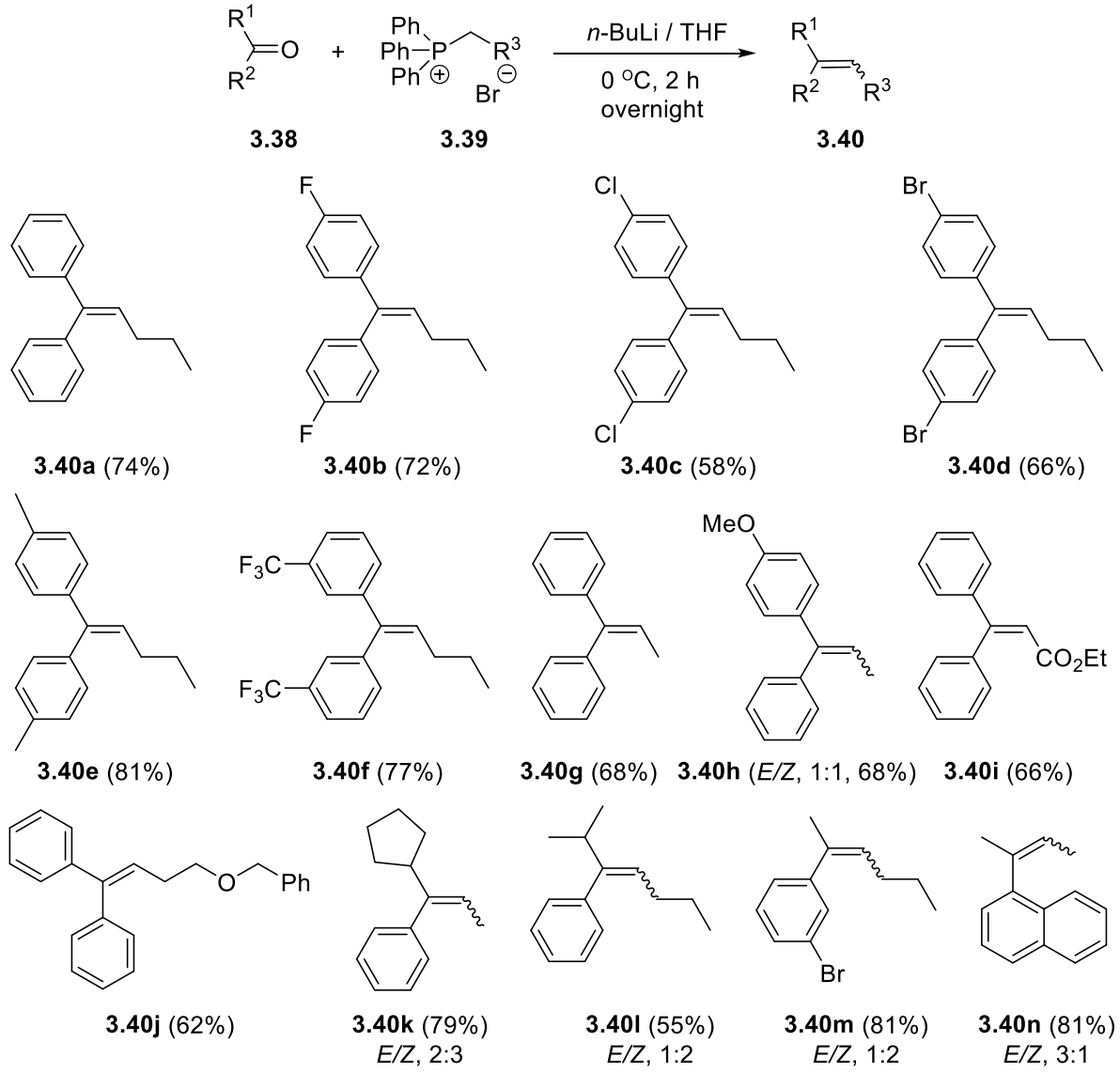
α-Aryl carbonyl compounds are highly desirable compounds, especially for the pharmaceutical industry.[54] A range of transition metal catalysed cross-coupling and intermolecular arylation methods have been developed by several research groups (Scheme 3.8a).[55–63] Our group previously reported a highly efficient metal free synthesis of *α*-aryl carbonyl compounds through the oxidative rearrangement of olefins mediated by hypervalent iodine reagents (Scheme 3.8b,c).[64,65] The aim of this work is to develop a catalytic protocol for the oxidative rearrangement of olefins using chiral iodoarenes as organocatalysts (Scheme 3.8d).



Scheme 3.8. Synthetic strategies of *α*-aryl ketones.

3.2.2. Synthesis of the olefinic substrates

The olefinic substrates **3.40a-n** were synthesised in good to high yields *via* Wittig reaction between the ketone derivatives **3.38** and the appropriate phosphonium salts **3.39** (Scheme 3.9).[65] After purification, when the olefinic products gave a mixture of *E* and *Z* isomers, they were used in the next step without isolation. The *E/Z* ratio was determined by ^{1}H NMR of the purified products.

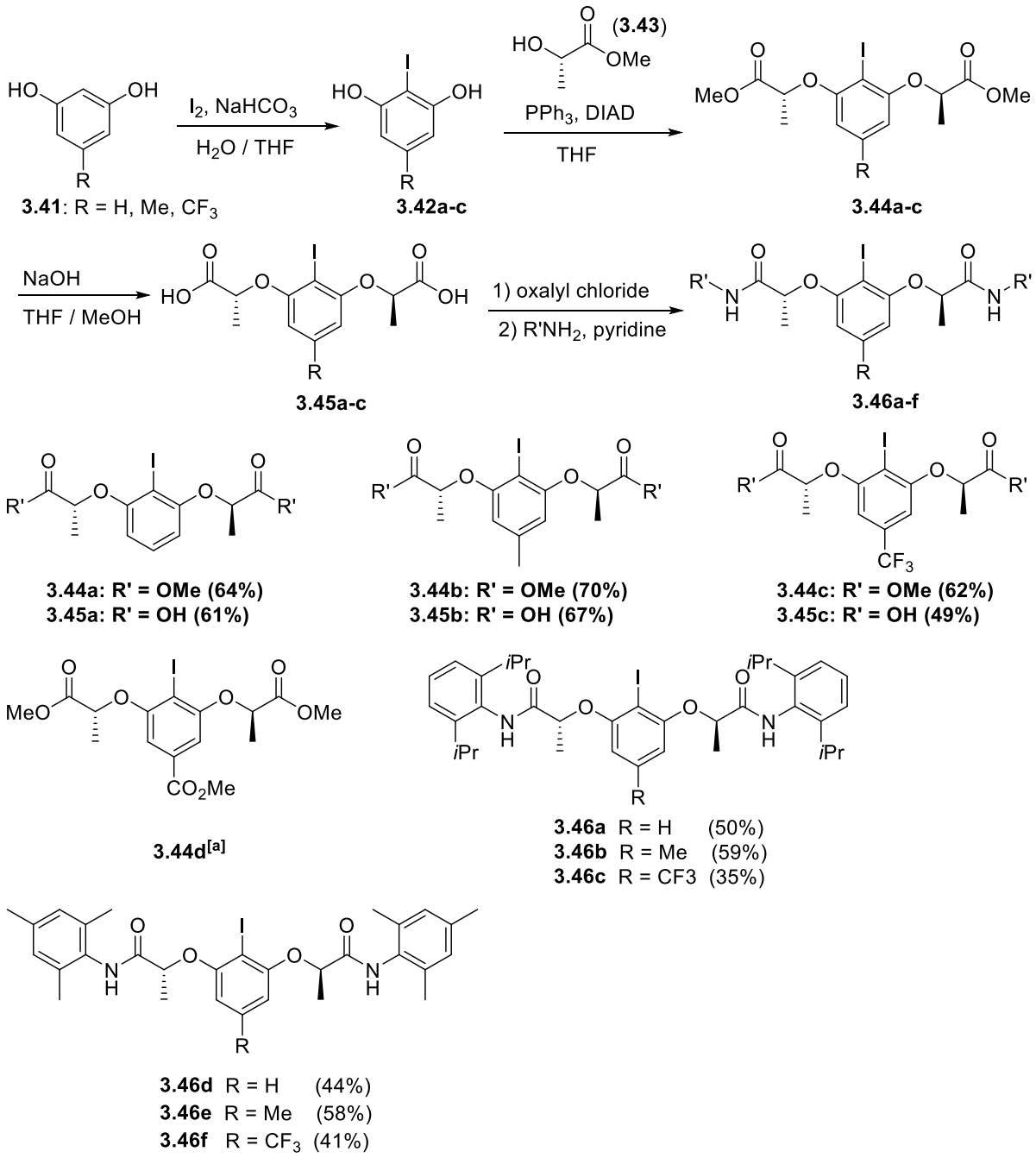


Scheme 3.9. Synthesis of olefinic substrate via Wittig reaction.

3.2.3. Synthesis of the chiral iodoarene catalysts

The chiral iodoarene catalysts used in this study were synthesised according to the pathway depicted in Scheme 3.10. All the catalysts were synthesised starting with the resorcinol derivatives **3.41**. The iodoarene building blocks **3.42** were obtained from resorcinol derivatives **3.41** *via* electrophilic aromatic substitution with molecular iodine. The chirality was introduced into the core structure **3.42** by incorporating a lactate ester moiety *via* Mitsunobu reaction in excellent yields leading to the C_2-symmetric chiral iodoarene catalysts **3.44** bearing ester groups. Basic hydrolysis of the esters **3.44** to the corresponding carboxylic acids **3.45** followed by activation to the corresponding acid chlorides and treatment with the appropriate amines furnished another set of C_2-symmetric chiral iodoarenes **3.46** bearing

amide groups. The overall yields of all the synthesised chiral iodoarenes were satisfactory ranging from 35% to 70%.



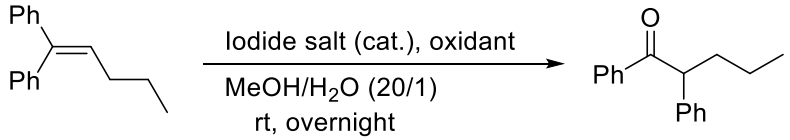
Scheme 3.10. Synthesis of the chiral iodoarene catalysts. [a] Compound **3.44d** was borrowed from my colleague Dr Wen-Chao Gao.

3.2.4. Screening of reaction conditions

To probe the possibility of performing the hypervalent iodine mediated oxidative rearrangement of alkenes catalytically and to get insights on the reaction conditions, the

catalytic oxidative rearrangement of alkene **3.40a** was probed using iodide salts such as Bu_4NI and KI as catalysts and hydrogen peroxide and Oxone® as terminal oxidants. The primary results (Table 3.1) showed that hydrogen peroxide (entry 1) did not lead to the formation of the desired product **3.47**, while Oxone® led to the desired product (entries 2-4). Bu_4NI was a more efficient catalyst than KI. Increasing the amount of Bu_4NI from 10 mol% (entry 2) to 20 mol% (entry 3) led to improvement of the yield of the desired product **3.47** from 34% to 87%.

Table 3.1. Preliminary experiments using iodide salts as catalysts



3.40a **rac-3.47a**

Entry	Catalyst	Oxidant	Yield % (3.47a)
1	Bu_4NI (10 mol%)	H_2O_2 (2 eq.)	----
2	Bu_4NI (10 mol%)	Oxone® (1.5 eq.)	34%
3	Bu_4NI (20 mol%)	Oxone® (1.5 eq.)	87%
4	KI (20 mol%)	Oxone® (1.5 eq.)	56%

With the promising primary results of the catalytic oxidative rearrangement of alkene **3.40a** in hand, the stereoselective catalytic oxidative rearrangements of alkenes using chiral iodoarenes **3.46** as catalysts were studied in detail. Different reaction parameters such as the catalyst structure, catalyst loading, terminal oxidant, and temperature were studied using the alkene **3.40a** as a model substrate.

3.2.4.1. Catalyst screening

The catalytic oxidative rearrangement of the model substrate **3.40a** was investigated using 20 mol% of the chiral esters **3.44a-d,** carboxylic acids **3.45a-c** and amides **3.46a-f** in the presence of one equivalent *m*-chloroperbenzoic acid (*m*CPBA) as the terminal oxidant.

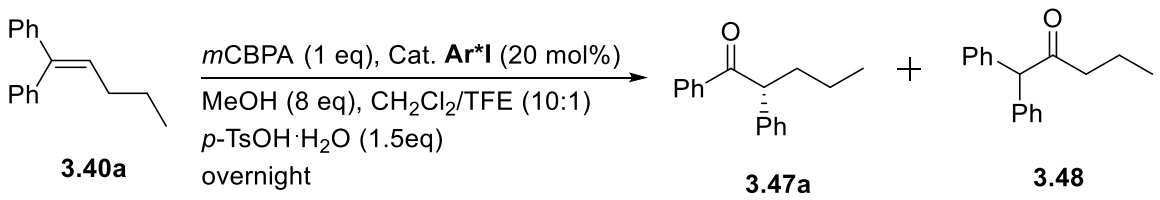
The results (Table 3.2) showed the formation of the desired *α*-aryl ketone **3.47a** in all cases along with the undesired ketone **3.48**. The formation of ketone **3.48** could be attributed to the background reaction between the olefinic substrate **3.40a** and the terminal oxidant (*m*CPBA). Most iodoarene catalysts were able to give the *α*-aryl ketone **3.47a** with reasonable degree of enantioselectivity. The highest asymmetric induction (73%-78% *ee*) was observed in the case of the catalysts **3.46c**, **3.45a** and **3.45c** (Table 3.1, entries 9, 15 and 17), but the yields of the

desired product, the ketone **3.47a** were lower than 20% in all cases. The low yields are due to the predominance of the background reaction that lead to the isolation of the undesired ketone **3.48** in yields higher than the desired ketone (60% in case of catalyst **3.46c**, entry 9). The catalysts **3.44a**, **3.44c and 3.44d** also led to the formation of ketone **3.47a** with good degree of stereoselectivity (67-70% *ee*) (Table 1, entries 1, 7, 10), but the background reaction between the terminal oxidant and the olefinic substrate is still the main reaction and lead to the formation of the ketone **3.48** in 29-45% yield.

The best results were obtained using catalyst **3.44b** (Table 1, entry 3), where the desired *α*-aryl ketone **3.47a** was formed as the major product and isolated in 41% yield, while the undesired ketone **3.48** was formed as a minor product and isolated in 13% yield. The results reveal that the formation of the undesired ketone **3.48** due to the direct oxidation of the olefinic substrate **3.40a** with *m*CPBA is the predominant reaction pathway in all cases except the case of catalyst **3.44b** where its oxidation to the corresponding reactive hypervalent iodine species predominates leading to the formation of the rearranged *α*-aryl ketone **3.47a** as a major product. The predominance of the oxidation of catalyst **3.44b** could be attributed to the presence of the methyl group *para* to the iodine centre which makes the aromatic ring more electron rich, hence rendering the iodine centre easier to oxidise. The poor reaction outcome in case of the other iodoarene catalysts bearing methyl group *para* to the iodine centre such as compounds **3.46b** and **3.46e** could be attributed to the size of the side arms which are bulkier than the side arms of the catalyst **3.44b**. Performing the reaction at 0 ^{o}C did not lead to a significant enhancement of the enantioselectivity and led to a slight decrease of the yield of the desired product **3.47a** (table 3.2 entries 2 and 4).

Increasing the catalyst loading from 20 mol% to 40 mol% did not lead to a significant enhancement of the reaction outcome while lowering the catalyst loading to 10 mol% led to the drop of the yield of the desired ketone **3.47a** to 32% and increase of the yield of the undesired ketone **3.48** to 17% (table 3.2, entries 5 and 6). Generally, the iodoarene catalysts bearing ester groups side chains **3.44a-d** gave higher stereoselectivity than the catalysts bearing amide side chains **3.46a-f**. In view of the above results the chiral iodoarene catalyst **3.44b** (20 mol%) was the catalyst of choice for further optimisations of the reaction conditions.

Table 3.2. Catalyst screening



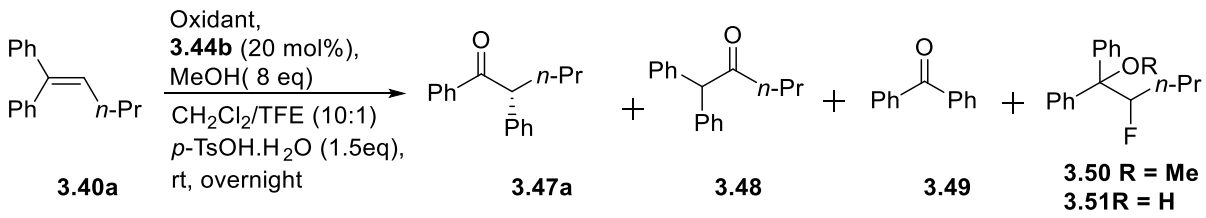
Entry	Ar*I	Yield% (3.47a)	*ee*% (3.47a)	Yield% (3.48)
1	**3.44a**	21	70	29
2[a]	**3.44a**	19	70	26
3	**3.44b**	41	69	13
4[a]	**3.44b**	37	70	11
5[b]	**3.44b**	43	71	10
6[c]	**3.44b**	32	69	17
7	**3.44c**	11	70	40
8	**3.46f**	7	45	49
9	**3.46c**	6	73	60
10	**3.44d**	15	67	45
11	**3.46e**	13	30	26
12	**3.46b**	15	57	45
13	**3.46a**	18	61	40
14	**3.46d**	16	59	46
15	**3.45a**	17	78	27
16	**3.45b**	23	57	24
17	**3.45c**	18	78	21

[a] Temperature = 0 °C; [b] **3.44b** (40 mol%); [c] **3.44b** (10 mol%).

3.2.4.2. Oxidant screening

The catalytic oxidative rearrangement of the model olefinic substrate **3.40a** was investigated using several terminal oxidants in the presence of 20 mol% of the chiral iodoarene catalyst **3.44b**. The outcome of the reaction was largely dependent on the nature and the amount of the stoichiometric oxidant. The results (Table 3.3) revealed that in case of using one or five equivalents of hydrogen peroxide (H_2O_2), *tert*-butyl hydroperoxide (TBHP), or sodium perborate trihydrate ($NaBO_3 \cdot 3H_2O$), there was no reaction at all, and the starting material was recovered unaffected (Table 3.3, entries 1-3). Using peracetic acid (1 eq.), the desired *α*-aryl ketone **3.47a** was not observed in the ^{1}H NMR of the crude reaction mixture, but the ketone **3.48** was the only observed product (13%) (Table 3.3, entry 4). Increasing the amount of peracetic acid to 5 equivalents (table 3.3, entry 5) led to the formation of benzophenone (**3.49**) in 32% yield in addition to 2% of the ketone **3.48** without the formation of the desired ketone **3.47a**. Although, using Oxone® as a terminal oxidant with iodide salts as catalysts led to the formation of racemic **3.47a** in good yields (table 3.1), it was not efficient in oxidizing the chiral iodoarene catalyst **3.44b** and the desired product **3.47a** was obtained in only 6% yield (Table 3.3, entry 6). Using Selectfluor® (1, 1.5, 2 and 5 equivalents) led to the formation of the desired ketone in good enantioselectivity (66-68% *ee*), but in low yields (18% to 21%) along with the oxyfluorination[66,67] products **3.50** and **3.51** (Table 3.3, entries 7, 11, 13, and 15). The formation of compounds **3.50** and **3.51** could be attributed to the background reaction between the olefinic substrate **3.40a** and Selectfluor®. The best results were obtained using one equivalent of *m*CPBA as a terminal oxidant (Table 3.3, entry 8), where the isolated yields of the rearranged *α*-aryl ketone **3.47a** was obtained in 41% yield and 69% *ee*. Increasing the amount of *m*CPBA to 1.5, 2 and 5 eq. (Table 3.3, entries 10, 12, and 14) led to reduction in the yield of the desired ketone **3.47a** and the increase of the amount of ketone **3.48** and benzophenone (**3.49**). Addition of TMSOTf (40 mol%) did not result in enhancement of the reaction outcome (table 3.3, entry 9). The results obtained with the conditions used previously in the catalyst screening could not be improved, therefore, *m*CPBA (1 equivalent) was chosen as the terminal oxidant for the further investigations of the reaction.

Table 3.3. Oxidant screening



3.40a 3.47a 3.48 3.49 3.50 R = Me, 3.51R = H

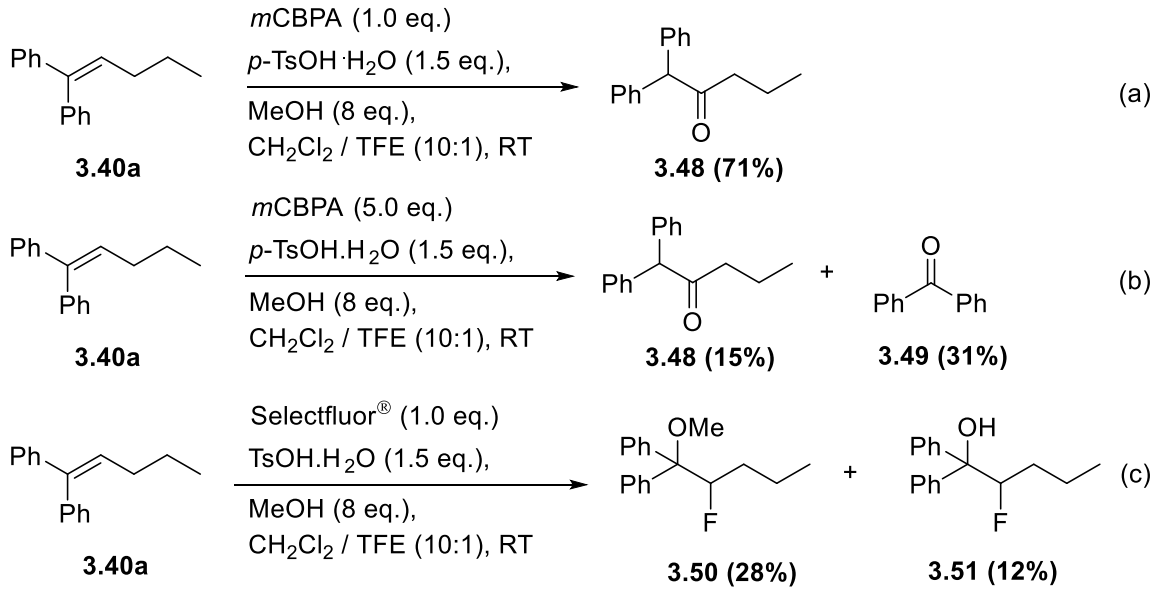
Entry	Oxidant	Yield %					*ee*% (3.47a)
		3.47a	3.48	3.49	3.50	3.51	
1	H_2O_2 (1 or 5 eq.)	----	-----	-----	-----	----	-----
2	TBHP (1 or 5 eq.)	----	-----	-----	-----	----	-----
3	$NaBO_3 \cdot 3H_2O$ (1or5 eq.)	----	-----	-----	-----	----	-----
4	Peracetic acid (1 eq.)	0	13	0	----	----	----
5	Peracetic acid (5 eq.)	0	2	32	----	---	----
6	Oxone® (1 eq.)	6	5	2	----	----	56
7	Selectfluor® (1 eq.)	21	2	-----	23	17	66
8	*m*CPBA (1 eq.)	41	13	0	-----	----	69
9[a]	*m*CPBA (1 eq.)	37	21	0	-----	----	70
10	*m*CPBA (1.5 eq.)	39	19	14	-----	----	67
11	Selectfluor® (1.5 eq.)	19	2	-----	26	14	66
12	*m*CPBA (2 eq.)	38	15	13	---	----	68
13	Selectfluor® (2 eq.)	20	1	----	28	11	68
14	*m*CPBA (5 eq.)	26	35	11	-----	----	71
15	Selectfluor® (5 eq.)	18	2	-----	33	10	67

[a] TMSOTf (40 mol%)

3.2.4.3. Control experiments

To obtain a better understanding of the reaction, especially the formation of the side products, some control experiments were performed in the absence of the iodoarene catalyst to investigate the background reactions between the olefinic substrate **3.40a** and the terminal oxidant (Scheme 3.11). Treatment of the olefin **3.40a** with one equivalent of *m*CPBA led to the formation of the unrearranged ketone **3.48** in 71% yield (Scheme 3.11a). Increasing the amount of *m*CPBA to 5 equivalents led also to the formation of ketone **3.48** in 15% yield along with benzophenone in 31% yield (Scheme 3.11b). Replacing *m*CPBA with Selectfluor® (1 equivalent) led to the oxyfluorination products **3.50** and **3.51** in 40%

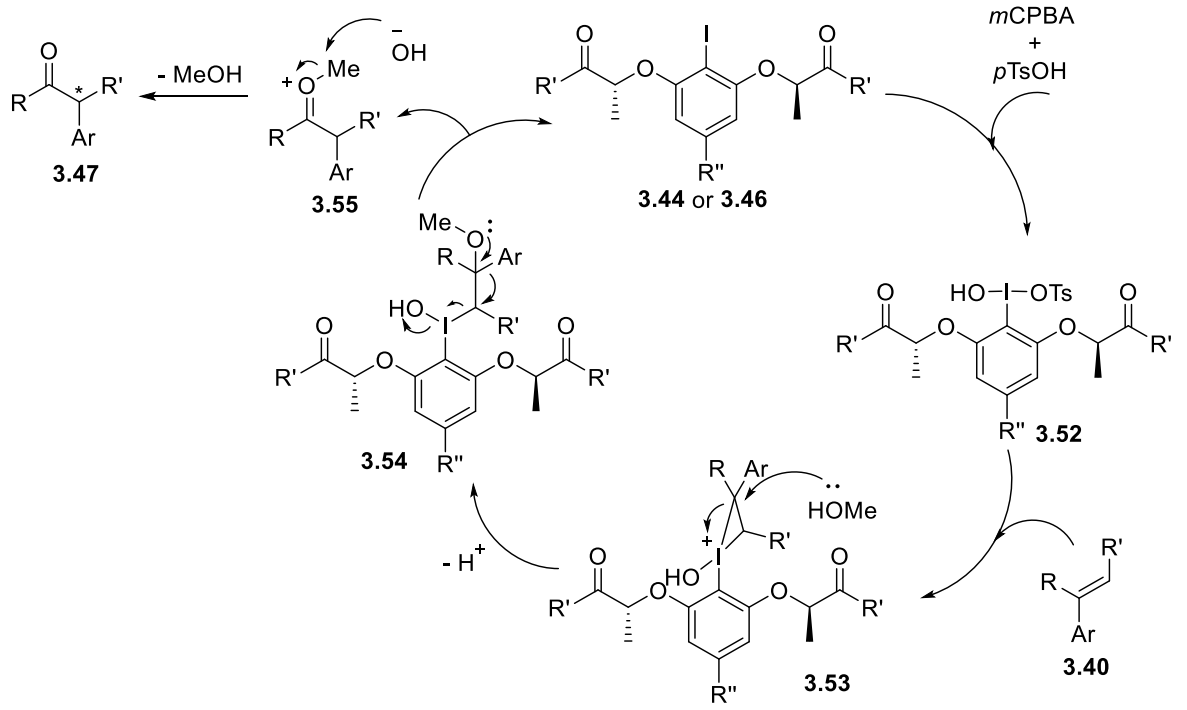
combined yield (Scheme 3.11c). The desired *α*-aryl ketone **3.47** was not observed in the absence of the iodoarene catalyst, indicating that the rearrangement of the olefinic substrate to the *α*-aryl ketone product is mediated by a hypervalent iodine species.



Scheme 3.11. Control experiments.

3.2.5. Reaction mechanism

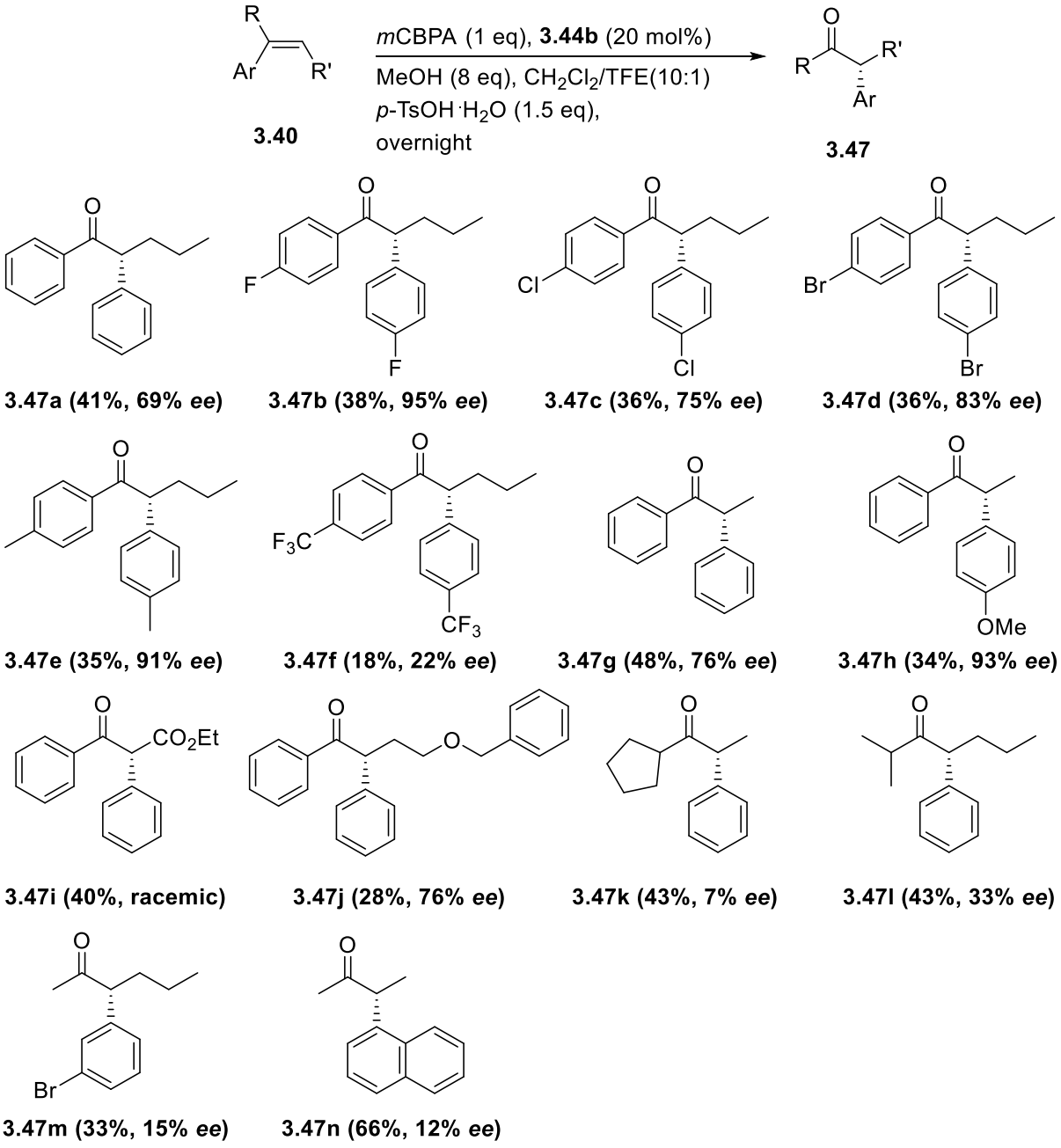
In view of the results of the control experiments (scheme 3.11) and the reaction mechanism of the oxidative rearrangement of olefins using pre-prepared hypervalent iodine reagents as stoichiometric oxidants[65] the catalytic cycle depicted in Scheme 3.12 was proposed. The catalytic cycle starts with the oxidation of the iodoarene catalyst (**3.44** or **3.46**) to the corresponding hypervalent iodine species **3.52**, which undergoes a ligand exchange with the olefinic substrate **3.40** to form the intermediate species **3.53**. Methanol acts as a nucleophile and attacks the electrophilic species **3.53** leading to **3.54** which undergoes a reductive elimination triggered by aryl migration leading to the formation of the desired product **3.47** and the regeneration of the iodoarene catalyst.



Scheme 3.12. A proposed catalytic cycle for the oxidative rearrangement of olefins into *α*-aryl ketones.

3.2.6. Substrate scope

With the optimised reaction conditions in hand, the scope of the catalytic oxidative rearrangement of olefins into *α*-aryl ketones was investigated using different olefinic substrates, varying the electronics and sterics around the double bond (Scheme 3.13).



Scheme 3.13. Substrate scope of the catalytic oxidative rearrangement of alkenes.

The results showed that in all cases the desired α-aryl ketone products were obtained in moderate yields (28% to 48%) except for the ketone **3.47f** bearing the electron withdrawing CF_3 groups in the aromatic rings which was isolated in low yield (18%) and the ketone **3.47n** bearing the electron rich naphthyl moiety which was isolated in good yield (66%). In all the cases of substrates that have two different groups that can migrate, only the products that arise from the migration of the more electron rich group where observed (**3.47h** and **3.47k-3.47n**), which agrees with the involvement of cationic intermediates in the rearrangement

step. The enantiomeric excess of the resulted *α*-aryl ketones ranged from very low values 7%, 12%, and 15% in case of **3.47k**, **3.47n**, and **3.47m**, respectively, and excellent values 95%, 93% and 91% in case of **3.47b, 3.47h** and **3.47e**, respectively. The %*ee* of all the other products were moderate to good ranging from 22% to 76%. Only product **3.47i** was obtained as a racemic mixture, a result that was observed previously using pre-prepared hypervalent iodine reagents in stoichiometric amounts.[65] All the olefinic substrates having two aromatic moieties around the double bond except **3.40f** and **3.40i** led to the corresponding *α*-aryl ketones **3.47a-j** with higher degree of enantioselectivity compared to the olefinic substrates bearing one aromatic moiety only on the double bond. The major enantiomer of all products was assigned the (*R*) configuration by comparing the optical rotation values with those reported in literature.[65]

3.3. Conclusions and outlook

In conclusion, a catalytic protocol for the stereoselective oxidative rearrangement of alkenes to the corresponding *α*-aryl ketones mediated by hypervalent iodine reagents has been developed. A wide range of chiral iodoarene catalysts was screened, and catalyst **3.44b** was the most effective one. In addition, among all the screened terminal oxidants, *m*CPBA proved to be the optimum for this transformation. Under the optimised reaction conditions, several olefinic substrates with various structural features were successfully transformed to the corresponding *α*-aryl ketones. The enantioselectivity of the transformation varied between excellent (> 90% *ee*) for some substrates and low (< 20% *ee*) for some other substrates. The reaction yield was generally moderate due to a background reaction between the olefinic substrates and the terminal oxidant.

Further investigations to supress the background reaction could improve the reaction yield and make the process more practical. As the relatively electron-rich iodoarene **3.44b** was the most efficient catalyst, synthesis of more electron-rich iodoarenes (Figure 3.1) might result in improvement of the reaction outcome.

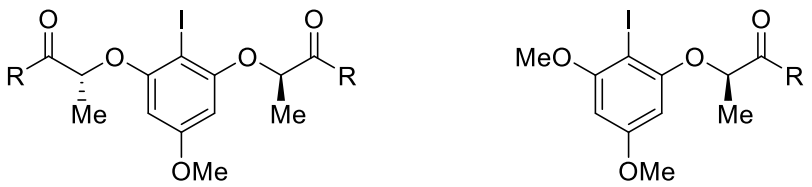


Figure 3.1. Proposed electron-rich chiral iodoarene catalysts.

3.4. References

[1] T. Wirth, Editor., *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis. [In: Top. Curr. Chem., 2016; 373]*., Springer-Verlag, **2016**.

[2] V. V Zhdankin, Editor., *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds.*, Wiley, **2013**.

[3] A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328–3435.

[4] M. Elsherbini, T. Wirth, *Chem. Eur. J.* **2018**, *24*, 13399–13407.

[5] F. V. Singh, T. Wirth, *Synthesis* **2013**, *45*, 2499–2511.

[6] T. Fuchigami, T. Fujita, *J. Org. Chem.* **1994**, *59*, 7190–7192.

[7] T. Dohi, A. Maruyama, M. Yoshimura, K. Morimoto, H. Tohma, Y. Kita, *Angew. Chem. Int. Ed.* **2005**, *44*, 6193–6196.

[8] A. P. Thottumkara, M. S. Bowsher, T. K. Vinod, *Org. Lett.* **2005**, *7*, 2933–2936.

[9] M. Ochiai, Y. Takeuchi, T. Katayama, T. Sueda, K. Miyamoto, *J. Am. Chem. Soc.* **2005**, *127*, 12244–12245.

[10] T. Dohi, Y. Kita, *Chem. Commun.* **2009**, 2073–2085.

[11] X. Li, P. Chen, G. Liu, *Beilstein J. Org. Chem.* **2018**, *14*, 1813–1825.

[12] W. Guo, O. Vallcorba, A. Vallribera, A. Shafir, R. Pleixats, J. Rius, *ChemCatChem* **2014**, *6*, 468–472.

[13] T. Yagyu, Y. Takemoto, A. Yoshimura, V. V. Zhdankin, A. Saito, *Org. Lett.* **2017**, *19*, 2506–2509.

[14] A. Parra, S. Reboredo, *Chem. Eur. J.* **2013**, *19*, 17244–17260.

[15] S. Ghosh, S. Pradhan, I. Chatterjee, *Beilstein J. Org. Chem.* **2018**, *14*, 1244–1262.

[16] M. Uyanik, K. Ishihara, *ChemCatChem* **2012**, *4*, 177–185.

[17] G.-L. Gao, Q. Chen, *Curr. Organocatalysis* **2017**, *4*, 33–47.

[18] C. Zhu, Y. Zhang, H. Zhao, S. Huang, M. Zhang, W. Su, *Adv. Synth. Catal.* **2015**, *357*, 331–338.

[19] M. Uyanik, H. Okamoto, T. Yasui, K. Ishihara, *Science* **2010**, *328*, 1376–1379.

[20] T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner, B. J. Nachtsheim, *Org. Lett.* **2011**, *13*, 3754–3757.

[21] L. Ma, X. Wang, W. Yu, B. Han, *Chem. Commun.* **2011**, *47*, 11333–11335.

[22] C. Zhu, Y. Wei, *ChemSusChem* **2011**, *4*, 1082–1086.

[23] S. Haubenreisser, T. H. Wöste, C. Martínez, K. Ishihara, K. Muñiz, *Angew. Chem. Int. Ed.* **2016**, *55*, 413–417.

[24] T. Wöste, K. Muñiz, *Synthesis* **2016**, *48*, 816–827.

[25] M. Shimogaki, M. Fujita, T. Sugimura, *Eur. J. Org. Chem.* **2013**, *2013*, 7128–7138.

[26] C. Gelis, A. Dumoulin, M. Bekkaye, L. Neuville, G. Masson, *Org. Lett.* **2017**, *19*, 278–281.

[27] W. Zhong, S. Liu, J. Yang, X. Meng, Z. Li, *Org. Lett.* **2012**, *14*, 3336–3339.

[28] K. Muñiz, L. Barreiro, R. M. Romero, C. Martínez, *J. Am. Chem. Soc.* **2017**, *139*, 4354–4357.

[29] P. Mizar, A. Laverny, M. El-Sherbini, U. Farid, M. Brown, F. Malmedy, T. Wirth, *Chem. Eur. J.* **2014**, *20*, 9910–9913.

[30] A. Kong, S. Blakey, *Synthesis* **2012**, *44*, 1190–1198.

[31] S. M. Banik, J. W. Medley, E. N. Jacobsen, *J. Am. Chem. Soc.* **2016**, *138*, 5000–5003.

[32] I. G. Molnár, R. Gilmour, *J. Am. Chem. Soc.* **2016**, *138*, 5004–5007.

[33] E. M. Woerly, S. M. Banik, E. N. Jacobsen, *J. Am. Chem. Soc.* **2016**, *138*, 13858–13861.

[34] T. Kitamura, K. Muta, J. Oyamada, *J. Org. Chem.* **2015**, *80*, 10431–10436.

[35] S. M. Banik, J. W. Medley, E. N. Jacobsen, *Science* **2016**, *353*, 51–54.

[36] S. Suzuki, T. Kamo, K. Fukushi, T. Hiramatsu, E. Tokunaga, T. Dohi, Y. Kita, N. Shibata, *Chem. Sci.* **2014**, *5*, 2754–2760.

[37] T. Kitamura, A. Miyake, K. Muta, and J. Oyamada, *J. Org. Chem.* **2017**, *82*, 11721–11726.

[38] K. M. Mennie, S. M. Banik, E. C. Reichert, E. N. Jacobsen, *J. Am. Chem. Soc.* **2018**, *140*, 4797–4802.

[39] M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem. Int. Ed.* **2010**, *49*, 2175–2177.

[40] T. Dohi, N. Takenaga, T. Nakae, Y. Toyoda, M. Yamasaki, M. Shiro, H. Fujioka, A. Maruyama, Y. Kita, *J. Am. Chem. Soc.* **2013**, *135*, 4558–4566.

[41] T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer, Y. Kita, *Angew. Chem. Int. Ed.* **2008**, *47*, 3787–3790.

[42] S. J. Murray, H. Ibrahim, *Chem. Commun.* **2015**, *51*, 2376–2379.

[43] K. A. Volp, A. M. Harned, *Chem. Commun.* **2013**, *49*, 3001.

[44] T. Dohi, H. Sasa, K. Miyazaki, M. Fujitake, N. Takenaga, Y. Kita, *J. Org. Chem.* **2017**, *82*, 11954–11960.

[45] A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angew. Chem. Int. Ed.* **2011**, *50*, 8605–8608.

[46] A. Alhalib, S. Kamouka, W. J. Moran, *Org. Lett.* **2015**, *17*, 1453–1456.

[47] A. Yoshimura, K. R. Middleton, A. D. Todora, B. J. Kastern, S. R. Koski, A. V. Maskaev, V. V. Zhdankin, *Org. Lett.* **2013**, *15*, 4010–4013.

[48] Y. Han, Y. Sun, A. Abdukader, B. Liu, D. Wang, *Catal. Letters* **2018**, *148*, 3486–3491.

[49] A. Schulze, A. Giannis, *Synthesis* **2006**, 257–260.

[50] J. N. Moorthy, K. N. Parida, *J. Org. Chem.* **2014**, *79*, 11431–11439.

[51] M. Uyanik, R. Fukatsu, K. Ishihara, *Org. Lett.* **2009**, *11*, 3470–3473.

[52] J. N. Moorthy, K. Senapati, K. N. Parida, S. Jhulki, K. Sooraj, N. N. Nair, *J. Org. Chem.* **2011**, *76*, 9593–9601.

[53] A. Maity, S.-M. Hyun, A. K. Wortman, D. C. Powers, *Angew. Chem. Int. Ed.* **2018**, *57*, 7205–7209.

[54] J. Magano, J. R. Dunetz, Eds. , *Transition Metal-Catalyzed Couplings in Process Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2003**.

[55] M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109.

[56] R. Martín, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 7236–7239.

[57] X. Liao, Z. Weng, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 195–200.

[58] P. M. Lundin, J. Esquivias, G. C. Fu, *Angew. Chem. Int. Ed.* **2009**, *48*, 154–156.

[59] S. Lou, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 1264–1266.

[60] L. Fan, S. Takizawa, Y. Takeuchi, K. Takenaka, H. Sasai, *Org. Biomol. Chem.* **2015**, *13*, 4837–4840.

[61] R. Takise, K. Muto, J. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2014**, *53*, 6791–6794.

[62] J. A. Fernández-Salas, E. Marelli, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2015**, *21*, 3906–3909.

[63] C. C. C. Johansson, T. J. Colacot, *Angew. Chem. Int. Ed.* **2010**, *49*, 676–707.

[64] U. Farid, F. Malmedy, R. Claveau, L. Albers, T. Wirth, *Angew. Chem. Int. Ed.* **2013**, *52*, 7018–7022.

[65] M. Brown, R. Kumar, J. Rehbein, T. Wirth, *Chem. Eur. J.* **2016**, *22*, 4030–4035.

[66] J.-F. Zhao, X.-H. Duan, H. Yang, L.-N. Guo, *J. Org. Chem.* **2015**, *80*, 11149–11155.

[67] Q. Yang, L.-L. Mao, B. Yang, S.-D. Yang, *Org. Lett.* **2014**, *16*, 3460–3463.

CHAPTER 4

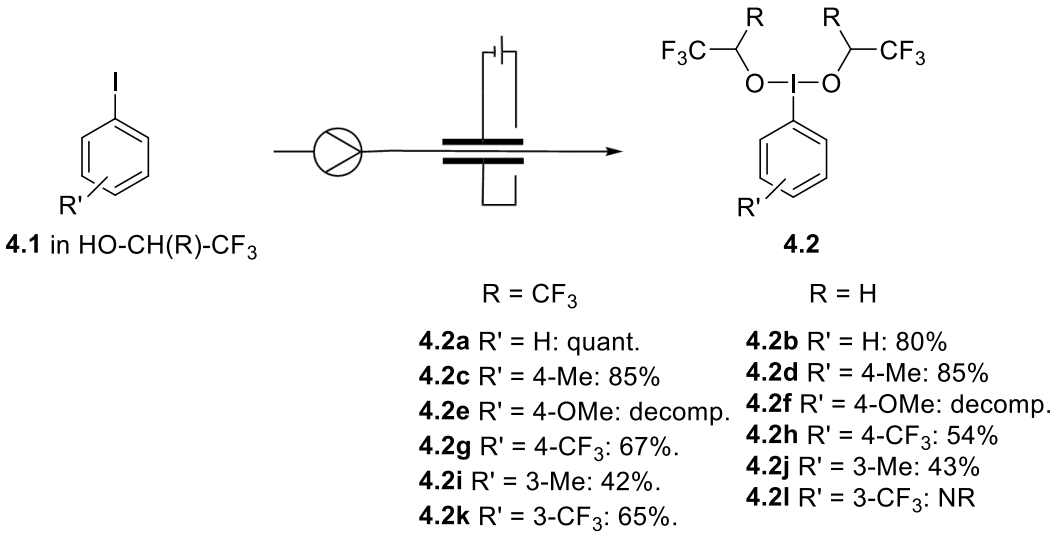
Indirect electrochemical oxidative rearrangement of alkenes

4.1. Introduction

Hypervalent iodine reagents are versatile oxidants, widely used in synthetic organic chemistry.[1–3] Oxidative couplings,[4–6] phenol dearomatisations,[7,8] oxidative formation of heterocycles,[9–12] aminations,[13,14] halogenations,[15–17] arylations,[18–20] and rearrangements[21–24] are some synthetic applications of the wide spectrum of hypervalent iodine chemistry. The widespread of hypervalent iodine reagents in synthetic organic chemistry is due to their environmentally benign nature, easy availability, and versatility, in addition to mild reaction conditions. However, the synthesis of hypervalent iodine reagents relies mainly on chemical oxidation of iodine(I) compounds. Hence, large amounts of expensive and/or hazardous chemical oxidants[25] are consumed and a lot of waste is produced in order to obtain the benign hypervalent iodine reagents. Electrochemical synthesis of hypervalent iodine compounds *via* the anodic oxidation of iodine(I) counterparts represents a promising and more sustainable alternative approach.[26,27] Undeniably, organic electrochemistry[28–34] is witnessing a resurgence and is gaining more and more popularity. The inherent eco-friendly nature of the electrochemical methods (due to using electric current instead of oxidizing and reducing agents), in addition to scalability, mild conditions, and chemoselectivity are the key factors that make electrochemical methods attractive alternatives to the conventional organic synthesis techniques.

4.1.1. Anodic oxidation of iodoarenes

Recently, an efficient continuous electrochemical generator of hypervalent iodine reagents was developed in our laboratory.[27] The anodic oxidation of iodobenzene derivatives in fluorinated alcohols to the corresponding hypervalent iodine reagents was achieved under flow conditions using glassy carbon as anode and platinum as cathode (Scheme 4.1). Coupling the stream of the electrochemically generated hypervalent iodine reagents with a second stream of various substrates effected a wide range of oxidative transformations in a coupled flow / manner (Figure 4.1). Although, the generated hypervalent iodine reagents with ligands derived from fluorinated alcohols are not bench stable their utilisation immediately in flow is advantageous, in addition, they were easily transformed to the classical bench stable hypervalent iodine reagents *via* ligand exchange.



Scheme 4.1. Anodic oxidation of iodobenzene derivatives under flow conditions. (Reproduced from ref.[27] with kind permission from Wiley).

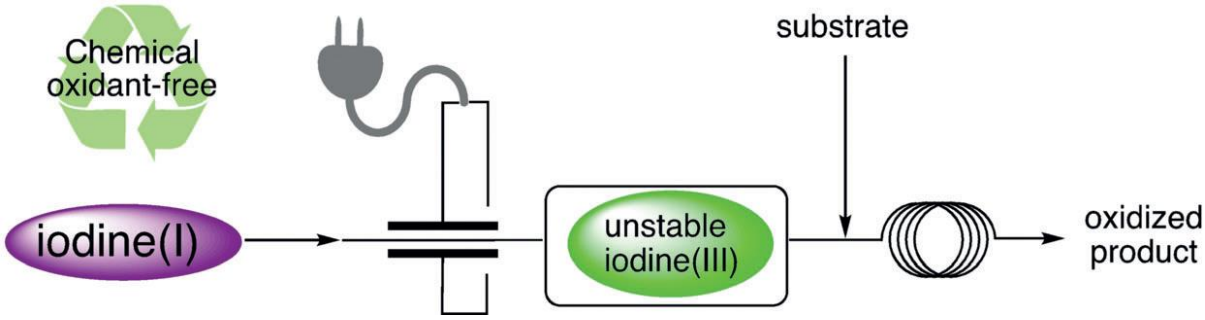
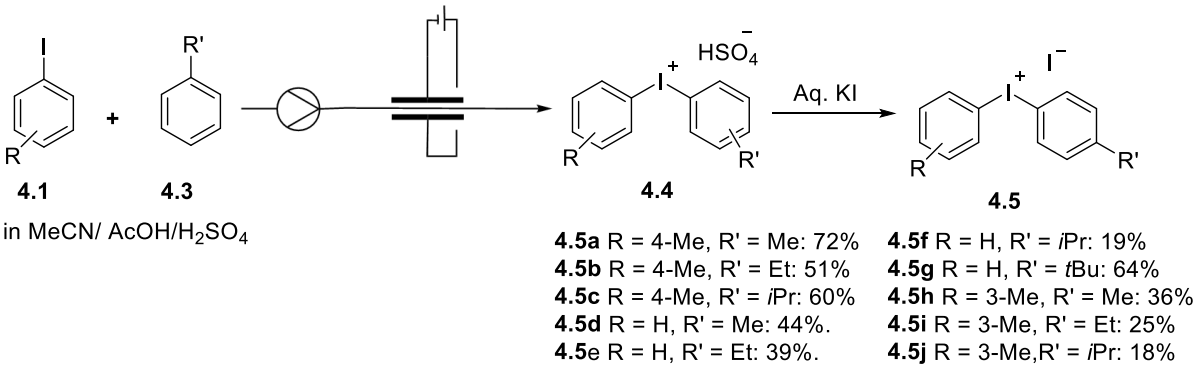


Figure 4.1. Electrochemical generation / utilization of hypervalent iodine reagent under flow conditions. (Reproduced from ref.[27] with kind permission from Wiley).

A simple protocol for the synthesis of diaryliodonium salts was also developed earlier in our laboratory[35] using our first-generation electrochemical flow cell[36–40]. Injecting the substrates (iodoarene/arene) solution in MeCN/Ac_2O/H_2SO_4 mixture through the reactor inlet (80 µL/min), while applying a constant current (30 mA) led to the formation of diaryliodonium salts that are precipitated in the form of iodides upon treatment with potassium iodide, and collected by simple filtration (Scheme 4.2). The diaryliodonium salts **4.5** were obtained in modest to good yields (18 – 72%). The method is operationally simple and highlighted the feasibility of using electrolysis under flow conditions in iodine chemistry.



Scheme 4.2. Electrochemical synthesis of iodonium salts **4.5** in flow.[35]

Synthesis of diaryliodonium salts via anodic oxidation in batch electrolysis was first described by Miller and Hoffmann in 1966.[41] Later on, after Miller and Hoffmann's report by about 35 years, Peacock and Pletcher [42,43] proved the synthetic feasibility and generality of the electrochemical generation of iodonium salts in batch-type cells.

4.1.2. Anodic oxidative heterocyclizations mediated by hypervalent iodine reagents

The electrochemically generated hypervalent iodine reagent [bis(trifluoroethoxy)-iodo]benzene **4.2b** (Figure 4.2) was developed as an alternative to the commercially available reagents such as (diacetoxyiodo)benzene (PIDA) and [bis(trifluoroacetoxy)iodo]benzene (PIFA) by the Nishiyama group.[44,45]

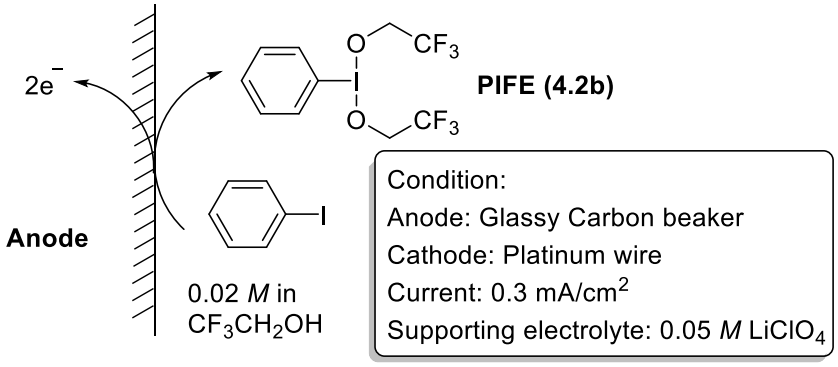
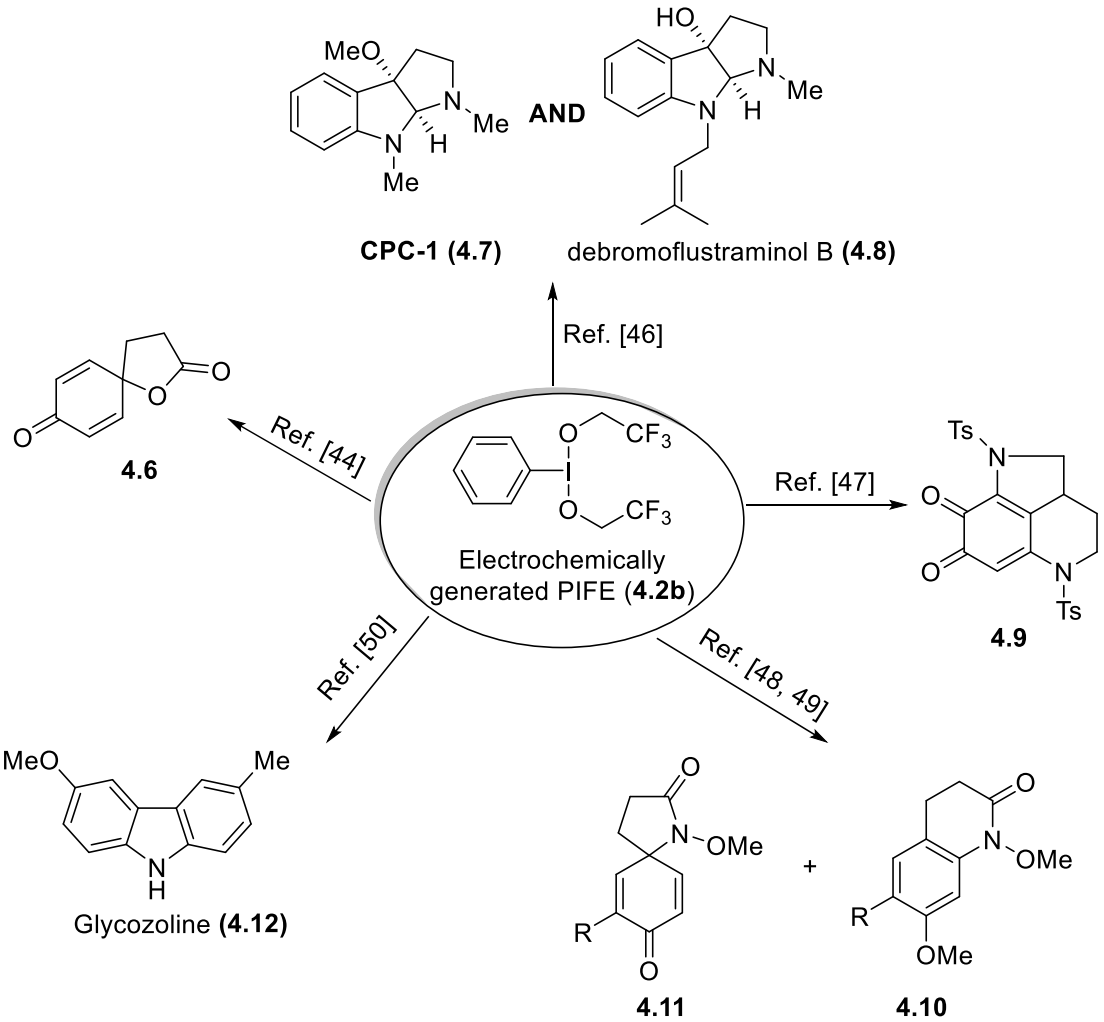


Figure 4.2. Electrochemical generation of the hypervalent iodine reagent (PIFE).[44] (Reproduced from ref.[26] with kind permission from Wiley).

The reactivity of **4.2b** (Scheme 4.3) is comparable and sometimes superior to PIDA and PIFA, which is illustrated by its successful applications in the construction of a variety of oxygen and nitrogen-containing scaffolds, natural products and the oxidation of the naturally occurring xanthone derivatives (Mangostins).[44–51]



Scheme 4.3. Synthetic applications of the electrochemically generated hypervalent iodine reagent **4.2b**.

A novel recyclable iodine(I)/iodine(III) redox mediator for electrosynthesis was developed by Francke and co-workers.[52] The iodine(I) precursor **4.13** was synthesised from iodobenzene in 45% yield over three steps. The tethered alkylammonium group eliminates the need of supporting electrolytes during electrolysis and made the recovery and recycling of **4.13** easy. The authors studied the anodic oxidation of the ionically tagged aryl iodide **4.13** in fluorinated alcohols and proved the formation of the corresponding hypervalent iodine reagents **4.14** and **4.15** (Figure 4.3).[52]

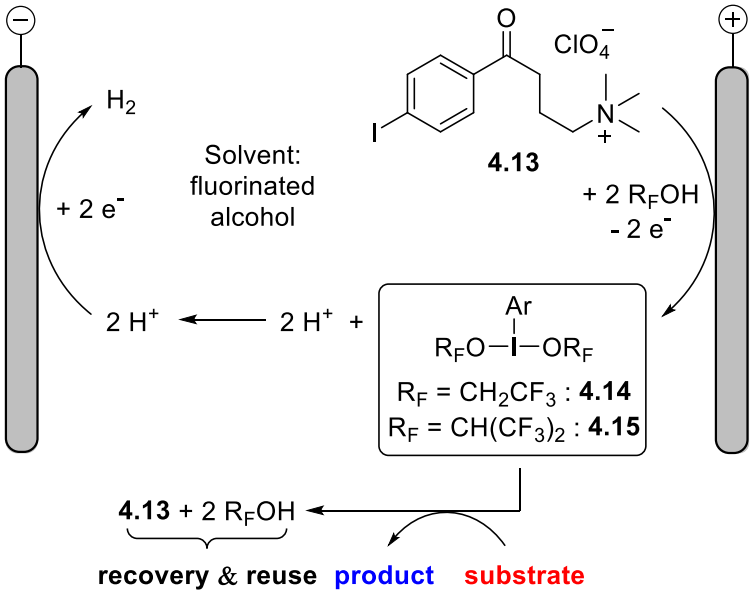
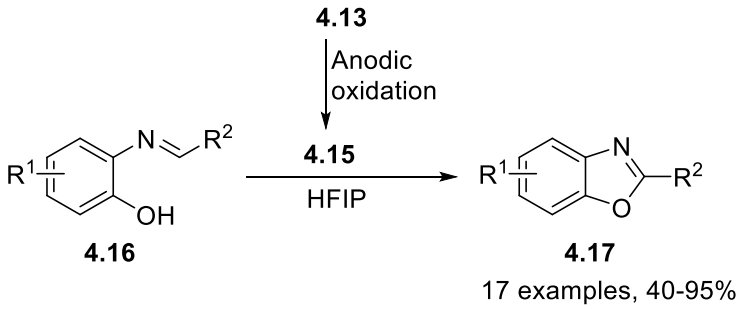


Figure 4.3. A iodine(I)/iodine(III) redox couple as a mediatory system for electrosynthesis.[52] (Reproduced from ref.[52] with kind permission from ACS publications)

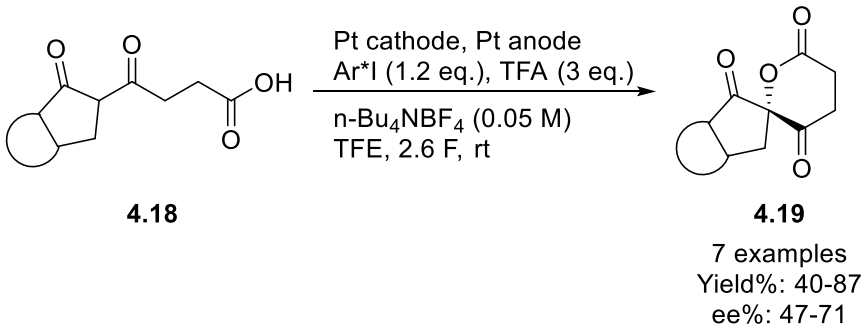
Application of the anodically generated hypervalent iodine reagent **4.15** in the indirect electrosynthesis of benzoxazoles **4.17,** demonstrated its efficiency as an ex-cell mediator for oxidative transformations. The reaction proceeds smoothly and a wide range of 2-(benzylideneamino)phenol substrates **4.16** were transformed into the corresponding benzoxazoles generally in good to excellent yields (Scheme 4.4)[53].



Scheme 4.4. Indirect anodic synthesis of benzoxazoles **4.17**.[53] (Reproduced from ref.[26] with kind permission from Wiley).

Anodic oxidation of iodoarenes to the corresponding hypervalent iodine reagents is not limited to simple iodobenzene derivatives. Recently Wirth *et al.*[54] reported the electrochemical oxidation of chiral iodoarenes into the corresponding chiral hypervalent iodine reagents. The anodically generated chiral hypervalent iodine reagents were

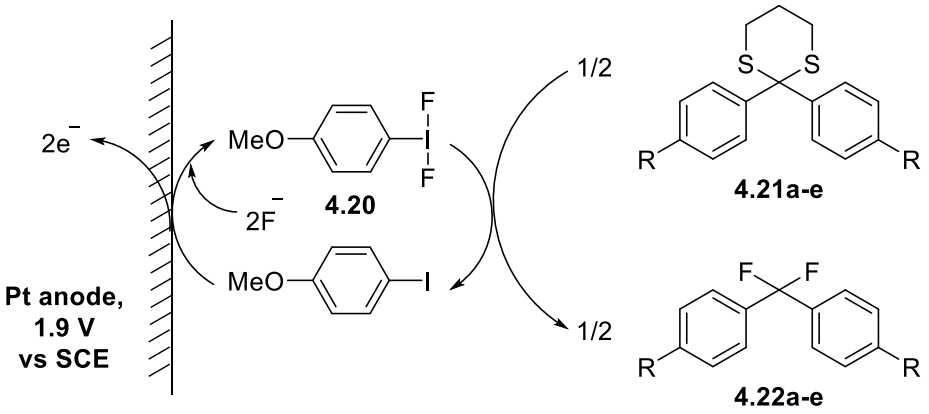
successfully applied as in-cell mediators for the stereoselective spirolactonisation of various diketo acids (Scheme 4.5).



Scheme 4.5. Enantioselective indirect electrochemical spirolactonisation.[54]

4.1.3. Anodic fluorination mediated by hypervalent iodine reagents

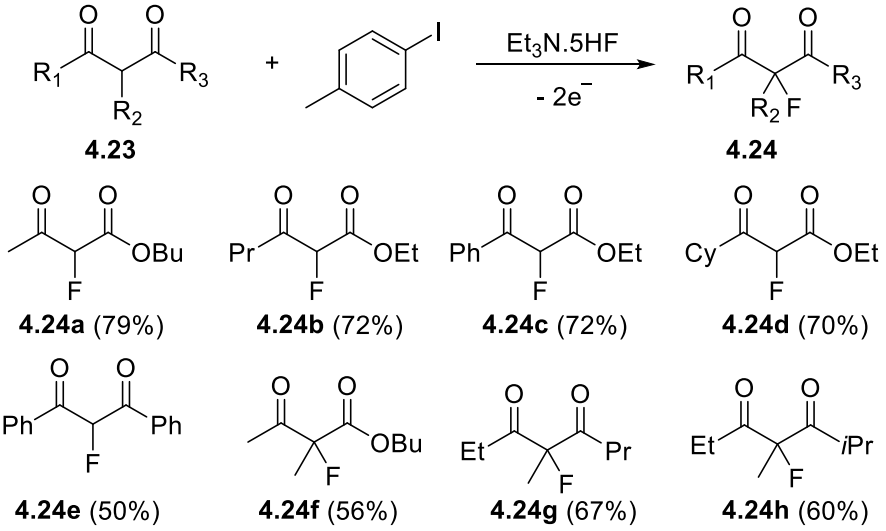
(Difluoroiodo)arenes $ArIF_2$ are very useful fluorinating agents. But their direct preparation requires powerful fluorinating reagents, in addition their separation and crystallisation are very difficult as they are highly hygroscopic and easily hydrolysable compounds.[25] Hence, their electrochemical generation and their use as in-cell and ex-cell mediators for the indirect anodic fluorination of various classes of organic molecules attracted the attention of chemists for long time. In fact, the first electrochemical synthesis of (difluoroiodo)benzene ($PhIF_2$) is dated back to the year 1960 when Schmidt and Meinert[55] reported its preparation *via* the electrolysis of acetonitrile solution of iodobenzene in the presence of silver fluoride that acted as a supporting electrolyte and as fluorine source. In the 1990 the electrochemically generated (difluoroiodo)arenes were successfully used as mediators for the indirect anodic *gem*-difluorination of dithioketals.[56,57] The reaction was carried out both ex-cell and in-cell. The in-cell version of the reaction enabled the catalytic use of aryliodides, where the *gem*-difluorinated products **4.22** were obtained in high yields using only 5 mol% of 4-iodoanisole (Scheme 4.6).



4.22a R = H: 69%[55], 81%[56]
4.22b R = Me: 78%[56]
4.22c R = OMe: 78%[55], 86%[56]
4.22d R = Cl: 98%[55], 61%[56]
4.22e R = F: 96%[55], 66%[56]

Scheme 4.6. Mechanism and scope of *gem*-difluorination of dithioketals. (Reproduced from ref.[26] with a kind permission from Wiley).

Similarly, the valuable fluorinating agent, 4-iodotoluene difluoride (Tol-IF_2) has been synthesised electrochemically and was successfully applied in the indirect anodic fluorination of β-dicarbonyl compounds as an in-cell mediator. [58] Thus, the potentiostatic electrolysis (1.5 V vs Ag/Ag^+) of a 1:1 mixture of 4-iodotoluene and β-dicarbonyl substrates **4.23** in Et_3N•5HF in an undivided cell led to the α-fluoro-β-dicarbonyl products **4.24** in good yields (Scheme 4.7). Interestingly, the monofluorinated compounds **4.24a-e** were obtained selectively as main products in good yields when unsubstituted β-dicarbonyl compounds were used as substrates.



Scheme 4.7. Indirect anodic fluorination of β-dicarbonyl compounds.

Moreover, recyclable polystyrene-supported iodobenzene[59] **4.25** and a task-specific ionic liquid[60] **4.26** derived from iodophenol (Figure 4.4) were applied successfully in the indirect anodic fluorination reactions, facilitating the workup, recovery and reuse of the iodine mediators.

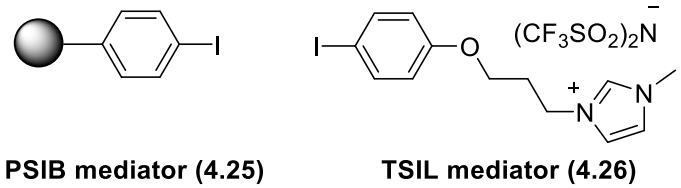
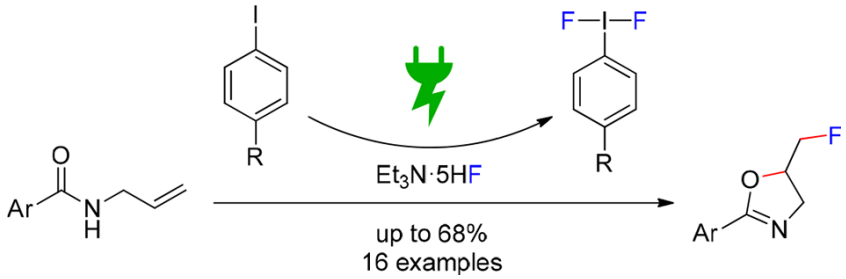


Figure 4.4. Recyclable iodine mediators.

Recently Waldvogel and co-workers[61] reported the synthesis of 2-oxazolines via fluorocyclization of *N*-allylcarboxamide mediated by electrochemically generated (difluoroiodo)arenes $ArIF_2$ (Scheme 4.8).



Scheme 4.8. Indirect anodic fluorocyclisation of *N*-allylcarboxamides. (Reproduced from ref.[61] with a kind permission from ACS).

4.2. Results and discussion

The investigation of the indirect anodic oxidative rearrangement of alkenes into the corresponding α-aryl ketones mediated by electrochemically generated hypervalent iodine reagents commenced with screening of chiral iodoarene precursors (Figure 4.5) applying the standard conditions of the indirect anodic spirolactonization of diketo acids (*vide supra*) previously developed in our laboratory.[54]

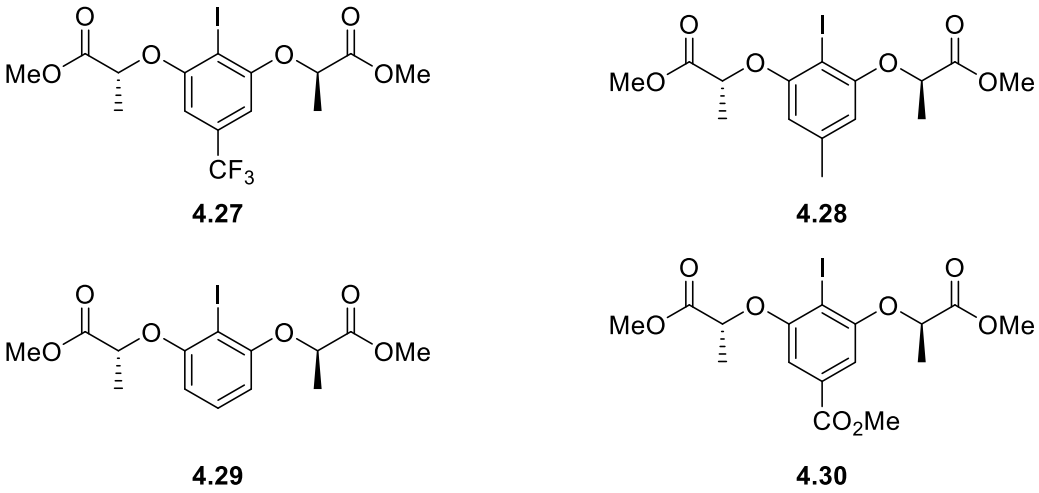


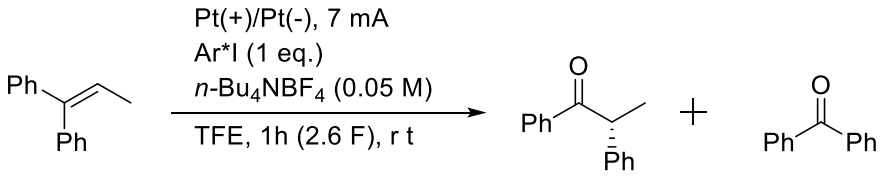
Figure 4.5. Chiral iodoarene precursors.

The results (Table 4.1) showed the formation of the desired *α*-aryl ketone **4.32a** in all cases along with benzophenone (**4.33**). The desired product α-aryl ketone **4.32a** was obtained with all the tested iodoarene catalysts. The yield was very low in the case of catalysts **4.27** and **4.30** (Table 4.1, entries 1,4), where the desired product was obtained in 10% and 20%, respectively, along with 20% and 12% of benzophenone, respectively. Both catalysts **4.28** and **4.29** (Table 4.1, entries 2,3) led to the formation of **4.32a** in 35% yield along with benzophenone, 8% and 16%, respectively. These results are in line with the structural features of the utilised iodoarenes, where the presence of electron-withdrawing groups in case of catalysts **4.27** and **4.30** should lead to increase of their oxidation potentials, which is reflected in the low yield of the product α-aryl ketone **4.32a** that is formed through the I(III) mediated oxidative rearrangement of alkene **4.31a** and the increase of the amount of benzophenone that is formed as result of the background direct electrochemical cleavage[62] of the starting alkene.

In contrast to the results of the catalytic oxidative rearrangement of alkenes, discussed in the previous chapter (chapter 3), the more electron rich catalyst **4.28** led to the lowest

enantioselectivity (41 ee%) of the desired product **4.32a** (Table 4.1, entry 2). The electron-deficient catalysts **4.27** and **4.30** led to the formation of the α-aryl ketone **4.32a** with higher enantioselectivity, 50 and 52 ee%, respectively (Table 4.1, entries 1 and 4). The highest enantioselectivity (55 ee%) was obtained when using the catalyst **4.29** (Table 4.1, entry 3). In view of these results, catalyst **4.29** showed the highest reactivity and selectivity under the tested reaction conditions, hence it was chosen as the optimum catalyst to study other reaction parameters.

Table 4.1: Catalyst screening



4.31a **4.32a** **4.33**

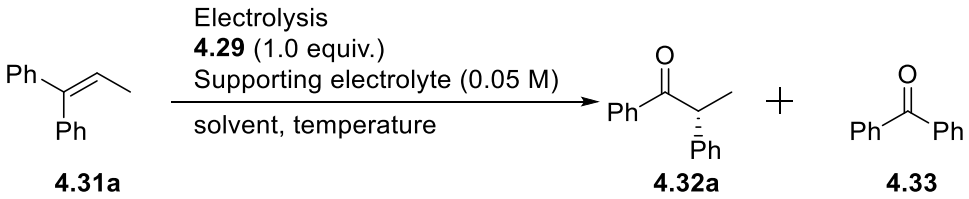
Entry	Ar*I	**4.32**		**4.33** Yield%
		Yield%	ee%	
1	**4.27**	10	50	20
2	**4.28**	35	41	8
3	**4.29**	35	55	16
4	**4.30**	20	52	12

After establishing the optimum chiral iodoarene catalyst, other reaction parameters, such as electrodes, solvents, supporting electrolyte and passed charge were investigated. The results (Table 4.2) showed that changing the anode material from platinum to carbon: graphite and glassy carbon lead to decrease in the yield of the desired product, where the α-aryl ketone **4.32a** was obtained in 19% and 23% yield, respectively (Table 4.2, entries 2,3). Therefore, platinum pair (anode and cathode) was chosen as the optimum electrode pair. Changing the supporting electrolyte from *n*-Bu_4NBF_4 to $LiClO_4$ led to a decrease of the yield of **4.32a** to 20% (Table 4.2, entry 4), while, when Et_4NCl was used as a supporting electrolyte (Table 4.2, entry 5) the desired product **4.32a** was not observed, only a trace amount of

benzophenone was noticed in the crude ^{1}H NMR. Hence, *n*-Bu_4BF_4 was used as the supporting electrolyte for the subsequent experiments.

Changing the solvent from 2,2,2-trifluoroethanol (TFE) to 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) or acetonitrile (MeCN) did not lead to the formation of the desired product **4.32a** (Table 4.2, entries 6,7). Using a mixture of TFE and dichloromethane (8:2) led to the formation of **4.32a** in a lower yield (10%) (Table 4.2, entry 8). The aforementioned observations of the results of the solvent screening experiments are in agreement with what was previously observed for the indirect anodic spirolactonisation of diketo acids (*vide supra*) previously developed in our laboratory.[54] Hence TFE was chosen as the optimum solvent for the reaction. As the stereoselectivity is usually enhanced by lowering the temperature the reaction was performed at 0 ^oC and -20 ^oC instead of room temperature (Table 4.2, entries 9,10). At 0 ^oC the α-aryl ketone **4.32a** was formed in lower yield (10%) without any impact on the enantioselectivity (54 ee%). Doing the reaction at -20 ^oC led to enhancement of the enantioselectivity, where the product **4.32a** was formed in 63 ee%, but in only 5% yield. Increasing the iodoarene from 1.0 equivalent to 1.2 equivalent didn't lead to a significant improvement of the reaction yield (Table 4.2, entry 11). On the other hand, decreasing the amount of the iododoarene **4.29** to 0.5 equivalent (Table 4.2, entry 12) led to a significant reduction in the reaction yield where the desired α-aryl ketone **4.32a** was formed in only 10% yield. Increasing the passed charge from 2.6 F to 2.8 F led to the slight increase of the reaction yield from 35% to 38% (Table 4.2, entry 13), but any further increase of charge beyond 2.8 F didn't lead to any improvement of the reaction yield (Table 4.2, entries 14,15). In contrast to the results of oxidative rearrangement of alkenes using stochiometric amounts of hypervalent iodine reagent[23] or catalytic amounts of chiral iodoarene (presented in chapter 3), addition of methanol to the electrolysis mixture led to reduction of the reaction yield (Table 4.2, entries 16, 17).

Table 4.2: Optimisation of reaction parameters



4.31a **4.32a** **4.33**

Entry	Solvent	Anode	Supporting Electrolyte	Charge	Temp.	**4.32**		**4.33** Yield%
						Yield%	ee%	
1	TFE	Pt	*n*-Bu_4NBF_4	2.6 F	rt	35	55	16
2	TFE	graphite	*n*-Bu_4NBF_4	2.6 F	rt	19	53	10
3	TFE	GC	*n*-Bu_4NBF_4	2.6 F	rt	23	51	7
4	TFE	Pt	$LiClO_4$	2.6 F	rt	20	26	6
5	TFE	Pt	Et_4NCl	2.6 F	rt	---	---	trace
6	HFIP	Pt	*n*-Bu_4NBF_4	2.6 F	rt	trace	---	14
7	MeCN	Pt	*n*-Bu_4NBF_4	2.6 F	rt	---	---	11
8	TFE:DCM (8:2)	Pt	*n*-Bu_4NBF_4	2.6 F	rt	10	45	7
9	TFE	Pt	*n*-Bu_4NBF_4	2.6 F	0 °C	10	54	5
10	TFE	Pt	*n*-Bu_4NBF_4	2.6 F	-20 °C	5	63	4
11[a]	TFE	Pt	*n*-Bu_4NBF_4	2.6 F	rt	42	55	15
12[b]	TFE	Pt	*n*-Bu_4NBF_4	2.6 F	rt	10	54	19
13	TFE	Pt	*n*-Bu_4NBF_4	2.8 F	rt	38	55	15
14	TFE	Pt	*n*-Bu_4NBF_4	3.0 F	rt	36	54	17
15	TFE	Pt	*n*-Bu_4NBF_4	3.5 F	rt	35	55	17
16[c]	TFE	Pt	*n*-Bu_4NBF_4	2.6 F	rt	15	n.d	19
17[d]	TFE	Pt	*n*-Bu_4NBF_4	2.6 F	rt	13	n.d	22

[a] **4.29** (1.2 equiv.); [b] **4.29** (0.5 equiv.); [c] MeOH (3 equiv.) was added; [d] MeOH (8 equiv.) was added; GC = glassy carbon; n.d = not determined.

In view the above results, the optimum reaction conditions were determined as following (Table 4.2, entry 13):

Electrodes: Pt (anode) and Pt (Cathode)

Charge: 2.8 F

Solvent: TFE

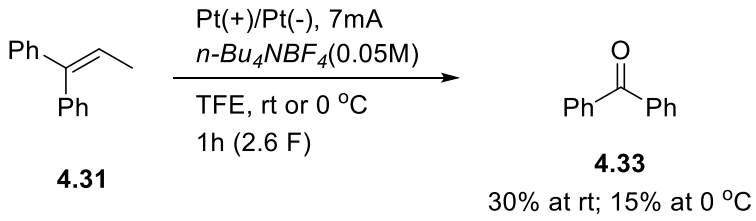
Supporting electrolyte: *n*-Bu_4NBF_4 (0.05 M)

Temperature: room temperature

Chiral iodoarene: **4.29** (1.0 equivalent)

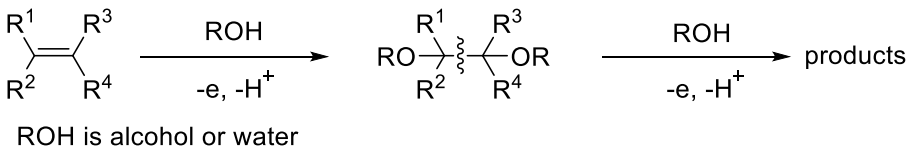
4.2.1. Control Experiments

To get more insights into the reaction, some control experiments have been carried out. Performing the electrolysis in the absence of the iodoarene applying the condition of entry 1 of table 4.2 (Scheme 4.9) led to the formation of benzophenone in 30% yield without the detection of the desired α-aryl ketone **4.32a**. Repeating the same experiment exactly, but at 0 ^oC led to the formation of benzophenone in lower yield (15%).



Scheme 4.9. Control experiments; the electrolysis in the absence of iodoarene.

The above control experiments show clearly that benzophenone is formed as a result of the background direct electrochemical cleavage[62] of the starting alkene. The electrochemical cleavage of alkenes to the corresponding ketones or acetals requires the presences of water and alcohol respectively. This is a two-step process; where vicinal dioxygenation of olefinic double bond takes place first followed by the cleavage of the C-C σ-bond of the formed dioxygenated species (Scheme 4.10).[62]



Scheme 4.10. Electrochemical cleavage of the alkenes.

The electrolysis of the chiral iodoarene **4.29** applying conditions of entry 1 (Table 4.2), but in the absence of the olefinic substrate was performed and monitored by ^{1}H NMR. The results showed that the conversion of iodoarene **4.29** to the corresponding iodine(III) species increases with time (with the passed charge) as expected, but interestingly, it reached a maximum of (40%) after 60 min (2.6 F) after which the conversions started to decline and only the starting material **4.29** was present after 90 min (3.9 F).[1] This behaviour of the anodic oxidation of the iodoarene mediator explains the low yield of the desired α-aryl ketone **4.32a** when the electrolysis is done in the presence of the olefinic substrate.

4.2.2. Cyclic voltammetry

More understanding of the reaction could be obtained *via* cyclic voltammetry studies. Hence, cyclic voltammetry measurements of the chiral iodoarenes **4.27-430** (Figures 4.6 and 4.7) showed a strong relation between the oxidation potential and the observed reactivity of compounds **4.27-430** (Table 4.1). The more electron rich reagents **4.28** and **4.29** that gave the highest product yields (35%) showed relatively lower oxidation potentials, 1.86 V and 2.00 V respectively, compared to the electron-deficient reagents **4.27** and **4.30** that showed oxidation potentials of 2.35 V and 2.15 V respectively, and led to the formation of the product **4.32a** in 10% and 20% respectively. In addition, the cyclic voltammetry of the olefinic substrate **4.31a** (Figure 4.8) showed oxidation potential of 2.15 V which is in the same range of the oxidation potentials of the chiral iodoarenes **4.27-430**, which could explain the background direct anodic oxidation of the olefinic substrate **4.31a**. It is noteworthy that the oxidation potential of the chiral iodoarene **4.28** (1.86 V) is very close to the reported oxidation potential of iodobenzene (1.80 V).[27]

[1] This observation was also observed during the anodic oxidation of a new class of permanently charged iodoarenes developed in our laboratory (Bethan Winterson and Thomas Wirth, unpublished results).

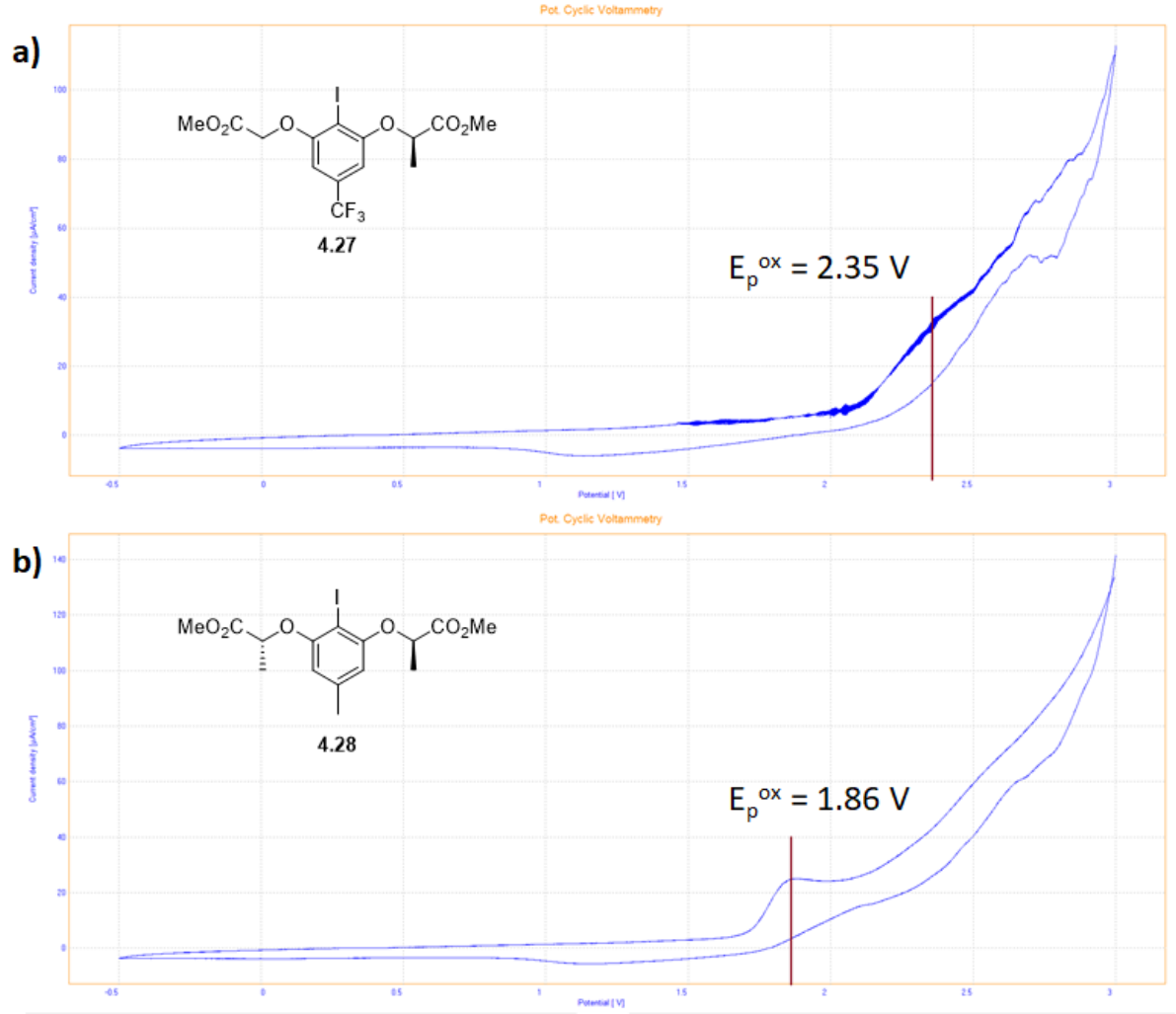


Figure 4.6. Cyclic voltammograms of compounds **4.27** (a) and **4.28** (b). Oxidative cyclic voltammograms of the substrates (2 mM) measured in acetonitrile containing 0.1 M of Bu_4NClO_4 at 100 mV/s scan rate. Working electrode: glassy carbon (3 mm diameter); Platinum wire as a counter electrode and Ag/AgCl in 3M NaCl as a reference electrode.

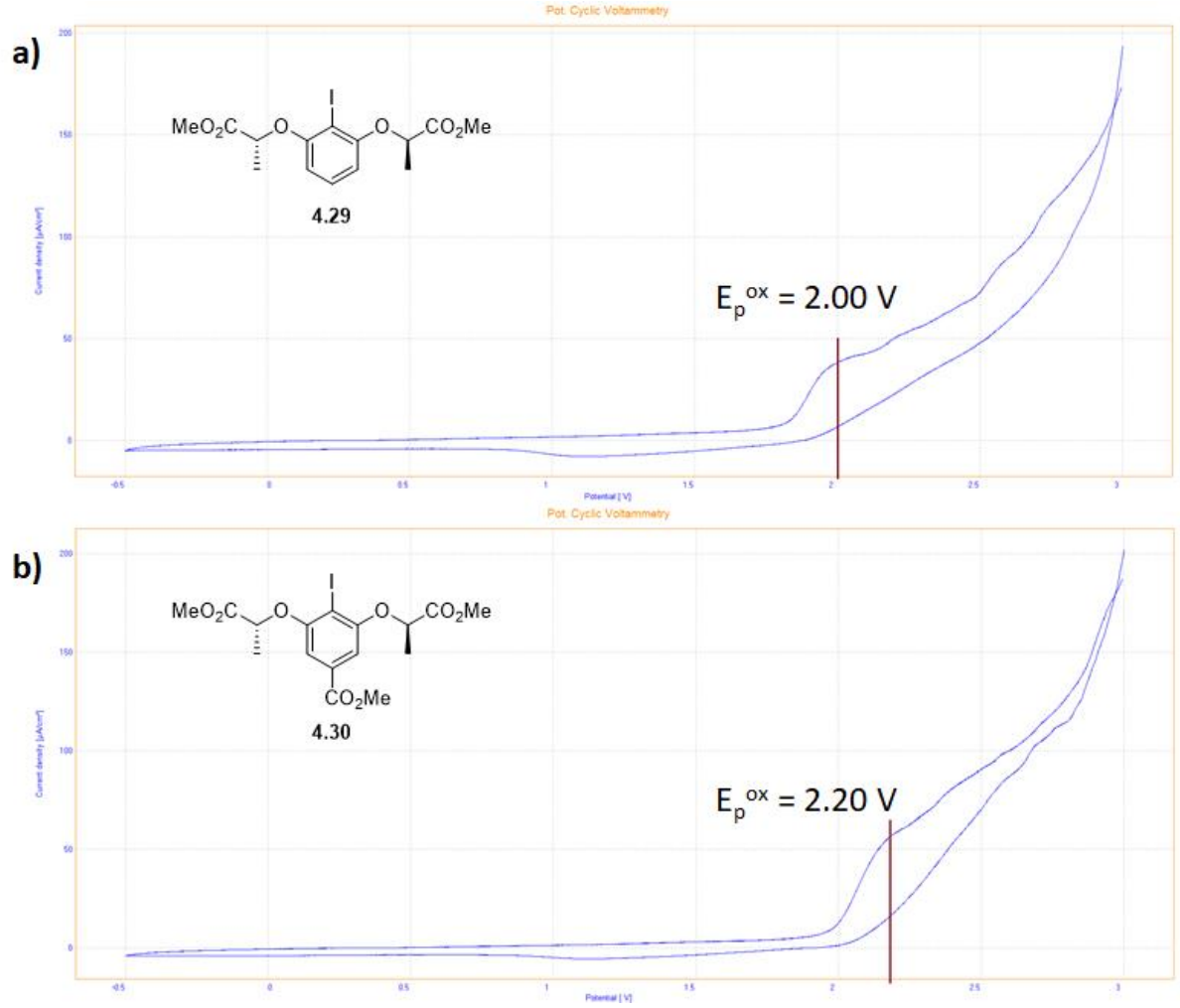


Figure 4.7. Cyclic voltammograms of compounds **4.29** (a) and **4.30** (b). Oxidative cyclic voltammograms of the substrates (2 mM) measured in acetonitrile containing 0.1 M of Bu_4NClO_4 at 100 mV/s scan rate. Working electrode: glassy carbon (3 mm diameter); Platinum wire as a counter electrode and Ag/AgCl in 3M NaCl as a reference electrode.

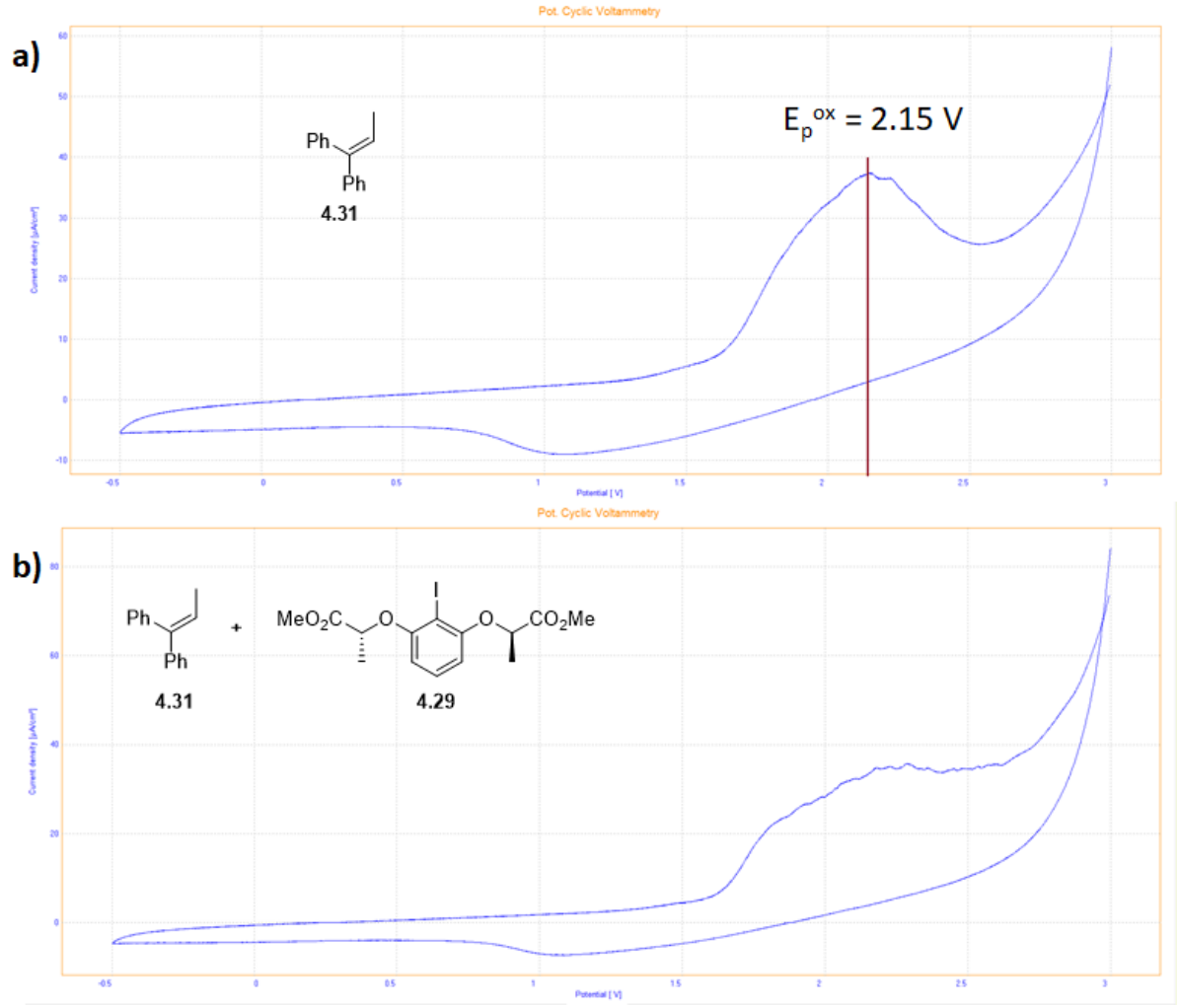
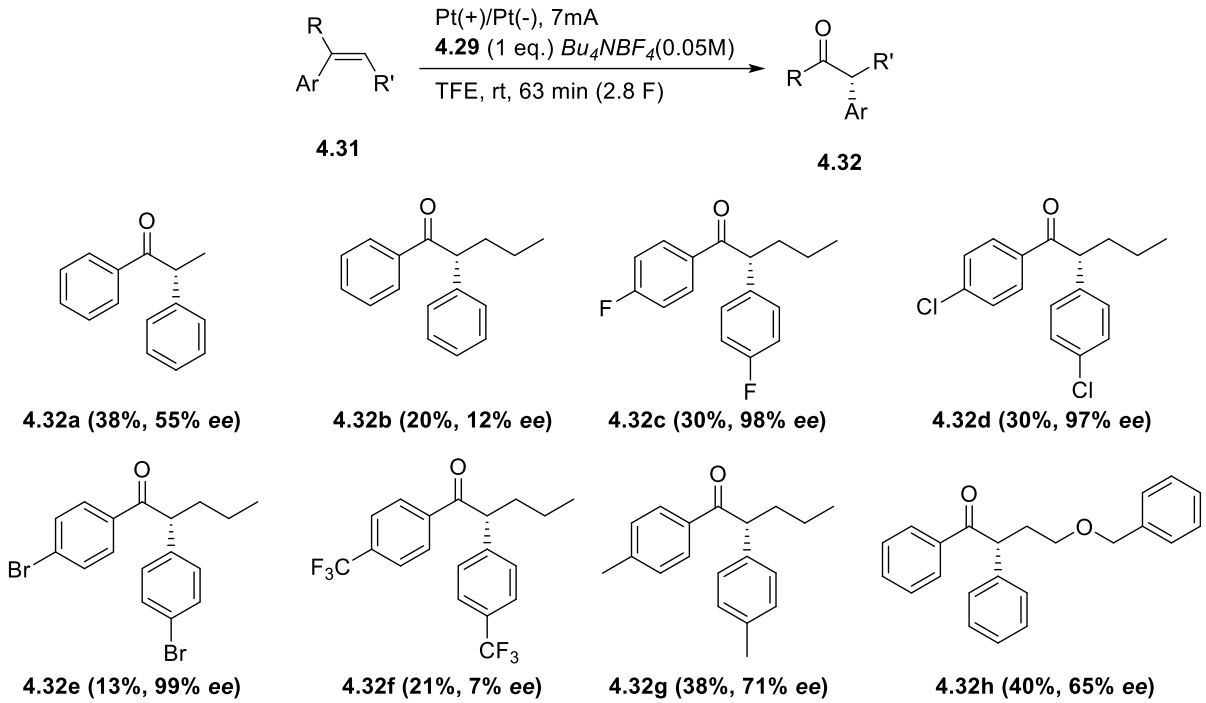


Figure 4.8. Cyclic voltammograms of compounds **4.31** (a) and a mixture of **4.31** and **4.29** (b). Oxidative cyclic voltammograms of the substrates (2 mM) measured in acetonitrile containing 0.1 M of Bu_4NClO_4 at 100 mV/s scan rate. Working electrode: glassy carbon (3 mm diameter); Platinum wire as a counter electrode and Ag/AgCl in 3M NaCl as a reference electrode.

4.2.3. Substrate scope

The scope of substrates of the indirect anodic oxidative rearrangement of alkenes was investigated applying the optimised reaction conditions (Table 4.2, entry 13). Eight different alkenes were used, the corresponding into *α*-aryl ketones were obtained in all cases (Scheme 4.11).



Scheme 4.11. Substrate scope of the indirect anodic stereoselective oxidative rearrangement of alkenes.

The results showed that the desired *α*-aryl ketone products were obtained in low yields. Although the yields calculated based on the olefinic substrates are low (13% to 40%), taking into that the maximum conversion of iodoarene **4.29** to the corresponding active iodine(III) species is 40% (*vide supra*) it turns out that the limiting reagent is the electrochemically generated iodine(III) species. Hence, calculating the yields based on the amount of the anodically generated iodine(III) species (40%), the yields of the oxidative rearrangement process ranges from 33% to 100%, which means that improving the anodic oxidation of the iodoarenes to corresponding hypervalent iodine species could in principle lead to a very efficient oxidative rearrangement process.

Regarding the enantioselectivity, the ee% of the formed *α*-aryl ketones was very low, 7% and 12% in case of products **4.32f** and **4.32b,** respectively. Interestingly, alkenes bearing halogens at the para position of the aromatic ring gave the corresponding *α*-aryl ketones in excellent enantioselectivity. The ee% was excellent, 98%, 97%, and 99% in the case of compounds **4.32c, 4.32d,** and **4.32e**, respectively. Compounds **4.32a**, **4.32g**, and **4.32h** led to the corresponding *α*-aryl ketones in moderate enantioselectivity (38-71% ee).

4.3. Conclusion and outlook

In conclusion, the indirect anodic stereoselective oxidative rearrangement of alkenes to the corresponding *α*-aryl ketones mediated by electrochemically generated hypervalent iodine reagents has been investigated. The primary results demonstrated the feasibility of this approach, although detailed studies to improve the outcome of the reaction are needed. Under the primary optimised reaction conditions, eight alkenes were successfully transformed into the corresponding *α*-aryl ketones in yields from 12-40%, the enantioselectivity ranged between 7 to 99% ee. Although the yields reached 40% maximum, but the control experiments showed that the maximum conversion of the chiral iodoarene **4.29** to the corresponding active hypervalent iodine species at the anode is the bottleneck as the maximum conversion was only 40% which puts an upper limit of the oxidative rearrangement process. Hence, detailed studies of the anodic oxidation of the lactate-based chiral iodoarenes are needed in order to improve the outcome of the anodic oxidation process and solving this problem could in principle lead to better outcome of the overall process.

4.4. References

[1] T. Wirth, Editor., *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis. [In: Top. Curr. Chem., 2016; 373]*., Springer-Verlag, **2016**.

[2] V. V Zhdankin, Editor., *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds.*, Wiley, **2013**.

[3] A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328–3435.

[4] T. Dohi, Y. Kita, *Top. Curr. Chem.* **2016**, *373*, 1–24.

[5] S. Shang, D. Zhang-Negrerie, Y. Du, K. Zhao, *Angew. Chem. Int. Ed.* **2014**, *53*, 6216–6219.

[6] M. Hori, J.-D. Guo, T. Yanagi, K. Nogi, T. Sasamori, H. Yorimitsu, *Angew. Chem. Int. Ed.* **2018**, 57, 4663-4667.

[7] D. C. Smith, E. Vitaku, J. T. Njardarson, *Org. Lett.* **2017**, *19*, 3508−3511.

[8] A. M. Harned, *Tetrahedron Lett.* **2014**, *55*, 4681–4689.

[9] K. S. Gayen, N. Chatterjee, S. Khamarui, P. K. Tarafdar, *Eur. J. Org. Chem.* **2017**, 425–439.

[10] Z. Yun, R. Cheng, J. Sun, D. Zhang-Negrerie, Y. Du, *Adv. Synth. Catal.* **2018**, *360*, 250–254.

[11] A. A. Almasalma, E. Mejía, *Eur. J. Org. Chem.* **2018**, *2018*, 188–195.

[12] R. Kamal, V. Kumar, R. Kumar, *Chem. Asian J.* **2016**, *11*, 1988–2000.

[13] K. Kiyokawa, T. Watanabe, L. Fra, T. Kojima, S. Minakata, *J. Org. Chem.* **2017**, *82*, 11711−11720.

[14] P. Mizar, A. Laverny, M. El-Sherbini, U. Farid, M. Brown, F. Malmedy, T. Wirth, *Chem. Eur. J.* **2014**, *20*, 9910–9913.

[15] V. W. Pike, *J. Label. Compd. Radiopharm.* **2017**, 1–32.

[16] A. M. Arnold, A. Ulmer, T. Gulder, *Chem. Eur. J.* **2016**, *22*, 8728–8739.

[17] R. K. Pluta, P. E. Krach, L. Cavallo, L. Falivene, M. Rueping, *ACS Catal.* **2018**, *8*, 2582–2588.

[18] Z. Jia, E. G. Lvez, R. M. Sebastian, R. Pleixats, A. Alvarez-Larena, E. Martin, A. Vallribera, A. Shafir, *Angew. Chem. Int. Ed.* **2014**, *53*, 11298 –11301.

[19] M. Hartmann, Y. Li, C. Muck-Lichtenfeld, A. Studer, C. Mück-Lichtenfeld, A. Studer, *Chem. Eur. J.* **2016**, *22*, 3485–3490.

[20] E. Stridfeldt, E. Lindstedt, M. Reitti, J. Blid, P. O. Norrby, B. Olofsson, *Chem. Eur. J.* **2017**, *23*, 13249–13258.

[21] F. V. Singh, T. Wirth, *Synthesis* **2013**, *45*, 2499–2511.

[22] F. Malmedy, T. Wirth, *Chem. Eur. J.* **2016**, *22*, 16072–16077.

[23] M. Brown, R. Kumar, J. Rehbein, T. Wirth, *Chem. Eur. J.* **2016**, *22*, 4030–4035.

[24] U. Farid, F. Malmedy, R. Claveau, L. Albers, T. Wirth, *Angew. Chem. Int. Ed.* **2013**, *52*, 7018–7022.

[25] Viktor V. Zhdankin, V. V. Zhdankin, in *Hypervalent Iodine Chemistry*, John Wiley & Sons Ltd, Chichester, UK, **2013**, pp. 21–143.

[26] M. Elsherbini, T. Wirth, *Chem. Eur. J.* **2018**, *24*, 13399–13407.

[27] M. Elsherbini, B. Winterson, H. Alharbi, A. A. Folgueiras-Amador, C. Génot, T. Wirth, *Angew. Chemie Int. Ed.* **2019**, DOI 10.1002/anie.201904379.

[28] O. Hammerich, B. Speiser, Editors., *Organic Electrochemistry: Revised and Expanded, Fifth Edition.*, CRC Press, **2016**.

[29] T. Fuchigami, M. Atobe, S. Inagi, Editors., *Fundamentals and Applications of Organic Electrochemistry: Synthesis, Materials, Devices.*, Wiley, **2014**.

[30] S. R. Waldvogel, A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, *Angew. Chem. Int. Ed.* **2018**, 57, 5594-5619.

[31] M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319.

[32] E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, *2*, 302–308.

[33] J.-I. Yoshida, K. Kataoka, R. Horcajada, A. Nagaki, *Chem. Rev.* **2008**, *108*, 2265–2299.

[34] D. Pletcher, *Electrochem. Commun.* **2018**, *88*, 1–4.

[35] K. Watts, W. Gattrell, T. Wirth, *Beilstein J. Org. Chem.* **2011**, *7*, 1108–1114.

[36] A. Folgueiras, T. Wirth, *Sci. Synthesis* **2018**, 147-189.

[37] A. A. Folgueiras-Amador, K. Philipps, S. Guilbaud, J. Poelakker, T. Wirth, *Angew. Chemie Int. Ed.* **2017**, *56*, 15446–15450.

[38] A. A. Folgueiras-Amador, X. Y. Qian, H. C. Xu, T. Wirth, *Chem. Eur. J.* **2018**, *24*, 487–491.

[39] A. A. Folgueiras-Amador, T. Wirth, *J. Flow Chem.* **2017**, *7*, 94–95.

[40] D. Pletcher, R. A. Green, R. C. D. Brown, *Chem. Rev.* **2018**, 118, 4537-4591.

[41] L. L. Miller, A. K. Hoffmann, *J. Am. Chem. Soc.* **1967**, *89*, 593–597.

[42] M. J. Peacock, D. Pletcher, *Tetrahedron Lett.* **2000**, *41*, 8995–8998.

[43] M. J. Peacock, D. Pletcher, *J. Electrochem. Soc.* **2001**, *148*, D37–D42.

[44] Y. Amano, S. Nishiyama, *Heterocycles* **2008**, *75*, 1997–2003.

[45] D. Kajiyama, T. Saitoh, S. Nishiyama, *Electrochem.* **2013**, *81*, 319–324.

[46] D. Kajiyama, T. Saitoh, S. Yamaguchi, S. Nishiyama, *Synthesis* **2012**, *44*, 1667–1671.

[47] K. Inoue, Y. Ishikawa, S. Nishiyama, *Org. Lett.* **2010**, *12*, 436–439.

[48] Y. Amano, S. Nishiyama, *Tetrahedron Lett.* **2006**, *47*, 6505–6507.

[49] Y. Amano, K. Inoue, S. Nishiyama, *Synlett* **2008**, 0134–0136.

[50] D. Kajiyama, K. Inoue, Y. Ishikawa, S. Nishiyama, *Tetrahedron* **2010**, *66*, 9779–9784.

[51] Y. Nishiyama, Y. Amano, T. Ogamino, S. Nishiyama, *Electrochemistry* **2006**, *74*, 609–611.

[52] T. Broese, R. Francke, *Org. Lett.* **2016**, *18*, 5896–5899.

[53] O. Koleda, T. Broese, J. Noetzel, M. Roemelt, E. Suna, R. Francke, *J. Org. Chem.* **2017**, *82*, 11669–11681.

[54] W.-C. Gao, Z.-Y. Xiong, S. Pirhaghani, T. Wirth, *Synthesis* **2019**, *51*, 276–284.

[55] H. Schmidt, H. Meinert, *Angew. Chem.* **1960**, *72*, 109–110.

[56] T. Fuchigami, T. Fujita, *J. Org. Chem.* **1994**, *59*, 7190–7192.

[57] T. Fujita, T. Fuchigami, *Tetrahedron Lett.* **1996**, *37*, 4725–4728.

[58] S. Hara, T. Hatakeyama, S. Q. Chen, K. Ishi-I, M. Yoshida, M. Sawaguchi, T. Fukuhara, N. Yoneda, *J. Fluor. Chem.* **1998**, *87*, 189–192.

[59] T. Sawamura, S. Kuribayashi, S. Inagi, T. Fuchigami, *Adv. Synth. Catal.* **2010**, *352*, 2757–2760.

[60] T. Sawamura, S. Inagi, T. Fuchigami, *Org. Lett.* **2010**, *12*, 644–646.

[61] J. D. Haupt, M. Berger, S. R. Waldvogel, *Org. Lett.* **2019**, *21*, 242–245.

[62] Y. N. Ogibin, G. I. Nikishin, *Russ. Chem. Rev.* **2001**, *70*, 543–576.

CHAPTER 5

Secondary interactions in hypervalent iodine chemistry

5.1. Introduction

The chemistry of hypervalent iodine compounds has expanded largely during the last two decades. Due to their readily availability, easy handling and diversity, organic hypervalent iodine reagents are widely used in modern synthetic organic chemistry. Their electrophilic nature, in addition to their superior leaving group ability (~10^6 times of triflate) are the key features behind their unique reactivity.[1,2] Hence, hypervalent iodine reagents found a wide range of synthetic applications, especially selective oxidative transformations including, but not limited to, oxidative C–C, C–heteroatom and heteroatom–heteroatom couplings,[3–8] oxidative rearrangements,[9–12] difunctionalisation of alkenes,[13–15] and dearomatisation of phenols.[16–20] Moreover, hypervalent iodine compounds are environmentally friendly alternatives to heavy metal oxidants as a result of their low toxicity and mild reaction conditions.

Ishihara, Muñiz, and co-workers[21] shed light on the crucial role of secondary interactions in the high selectivity of the C_2-symmetric lactate-based chiral hypervalent iodine reagents. Based on X-ray analysis of amide derivatives **5.1** and **5.2**, they demonstrated that hydrogen bonding lead to structurally defined molecular hypervalent iodine reagents (Figure 5.1) that accounts for the high asymmetric induction achieved using this family of reagents.

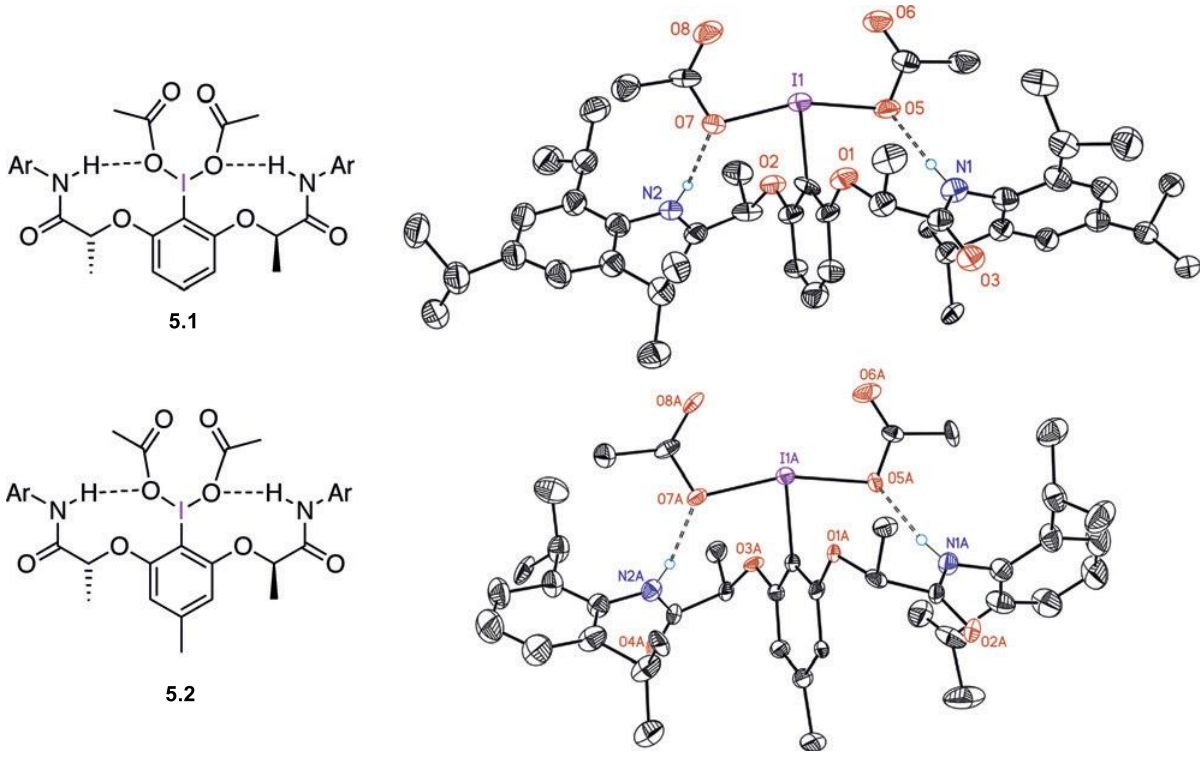


Figure 5.1. Intramolecular hydrogen-bonding properties of chiral hypervalent iodine compounds **5.1** (Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$) and **5.2** (Ar = 2,6-*i*Pr$_2$C$_6$H$_3$). All hydrogen atoms except the N-H groups are omitted for clarity. (Reproduced from ref.[21] with kind permission from Wiley).

Moreover, Muñiz *et al.*[22] introduced the concept of Lewis base adduct formation as a kinetic factor in iodine(I/III) catalysis, as they demonstrated the positive influence of the 2-pyridinyl substituent on the catalytic performance of aryl iodides in vicinal difunctionalisation of alkenes under iodine(III) Catalysis. X-ray analysis proved the presence of a strong interaction between the electrophilic iodine(III) centre and the neighbouring pyridine nitrogen (Figure 5.2).

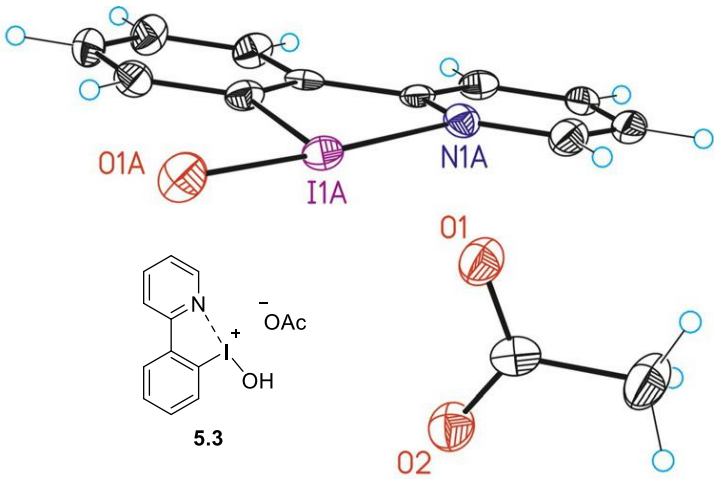
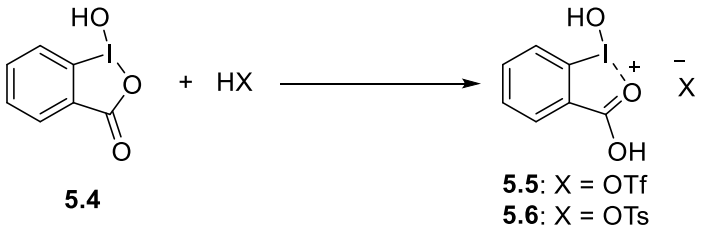


Figure 5.2. Intramolecular solid-state structures of compound **5.3**. (Reproduced from ref.[22] with a kind permission from Wiley).

In a similar context, Zhdankin *et al.*[23,24] reported new pseudocyclic benziodoxole triflate and tosylate **5.5** and **5.6** *via* the treatment of 1-hydroxybenziodoxolone (**5.4**) with triflic and *p*-toluenesulfonic acid, respectively (Scheme 5.1). The X-ray analysis of these compounds revealed that the carbonyl group oxygen acted as a Lewis base and shows a strong intramolecular interaction with the electrophilic iodine(III) centre.



Scheme 5.1. Preparation of benziodoxole-based pseudocyclic structures.

Various hypervalent iodine reagents incorporating nitrogen-containing heterocyclic units, especially pyridine moieties have been reported (Figure 5.3).[22,25–31] Interaction of the heteroatoms with the iodine(III) centre was observed in most cases.

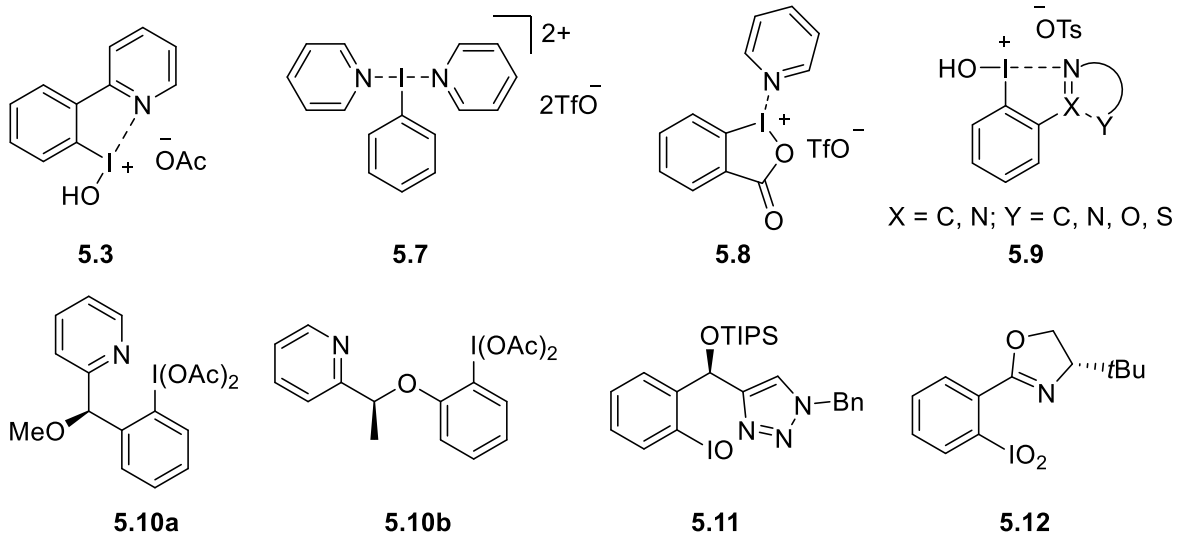
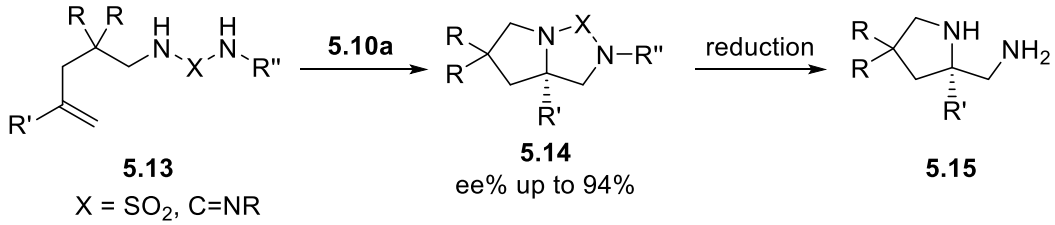


Figure 5.3. Some hypervalent iodine reagents containing heterocycles.

The pyridine containing chiral hypervalent iodine reagents **5.10a** and **5.10b** were developed previously in our laboratory. Reagent **5.10a** proved to be very efficient reagent for the enantioselective intramolecular diamination of olefins (Scheme 5.2).[27]



Scheme 5.2. Stereoselective intramolecular deamination of alkenes using reagent **5.10a**.

Although there is no crystal structure provided for the hypervalent iodine reagent **5.10a** due to its instability, the ^{1}H NMR provided a strong evidence of the coordination of the pyridine nitrogen to the iodine(III) centre, which accounts for the high selectivity of reagent **5.10a** in the above diamination reaction compared to other tested reagents.[27] On the other hand, the solid-state structure of reagent **5.10b** (Figure 5.4) showed no interaction between the pyridine nitrogen and the iodine(III) centre, which was manifested in its low selectivity in the stereoselective rearrangement of arylketones to the corresponding α-arylated esters.[28]

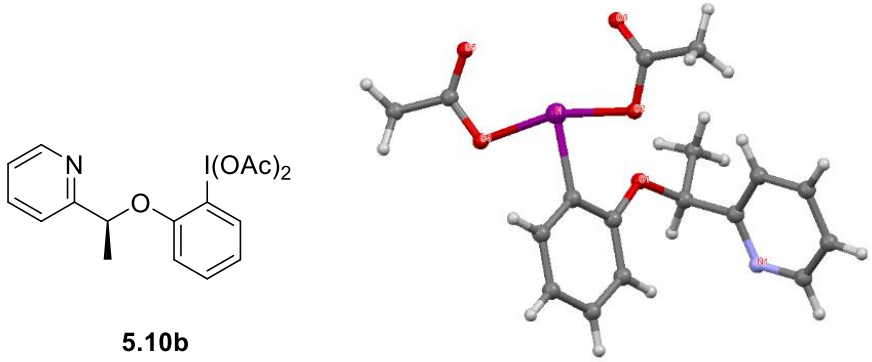


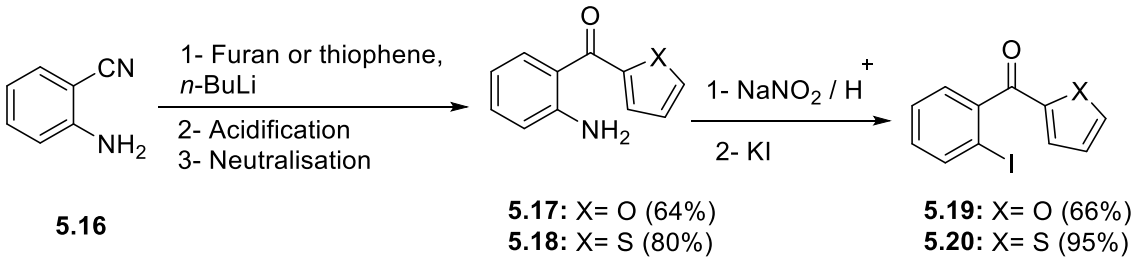
Figure 5.4. Solid-state structure of reagent **5.10b**. (Reproduced from Ref.[28] a kind permission from Wiley)

As hypervalent iodine reagents are electrophilic in nature, heteroatoms in the vicinity of the electrophilic iodine centre affect the structural features, reactivity and selectivity of hypervalent iodine reagents.[21,22,27] The aim of this project is to synthesise a series of hypervalent iodine reagents with different heteroatoms in the proximity of the electrophilic iodine(III) centre to get structural information about the effect of secondary interactions between the heteroatoms and the I(III) centre on the reactivity and selectivity of hypervalent iodine reagents.

5.2. Results and discussion

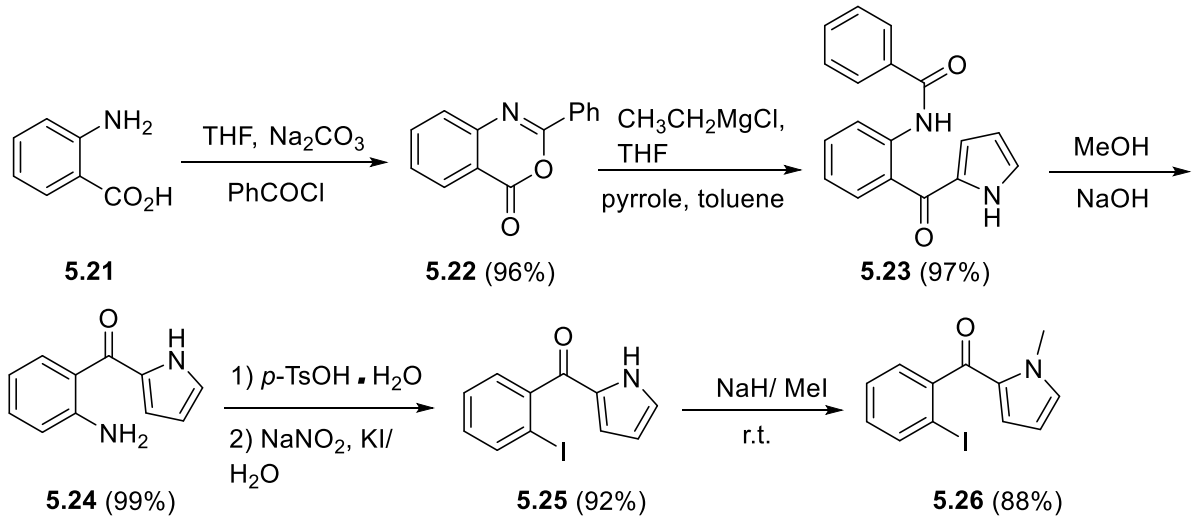
5.2.1. Synthesis of new iodoarenes containing 5-membered heterocycles

The iodoketone precursors **5.19** and **5.20** were prepared in 44% and 77% yield respectively, over two steps starting from 2-aminobenzonitrile (**5.16**) (Scheme 5.3). The addition of the lithiated heterocycles, generated *in situ* through the deprotonation of furan and thiophene using *n*-BuLi, to **5.16** led to the formation of the aminoketones **5.17** and **5.18** in 64% and 80% yield respectively,[32] after acidification and neutralisation. The formed aminoketones were then transformed into the corresponding iodoketones **5.19** and **5.20** in 66% and 95% yield respectively, *via* a Sandmeyer[33] reaction (Scheme 5.3).



Scheme 5.3. Synthesis of iodoketones bearing furan and thiophene moieties.

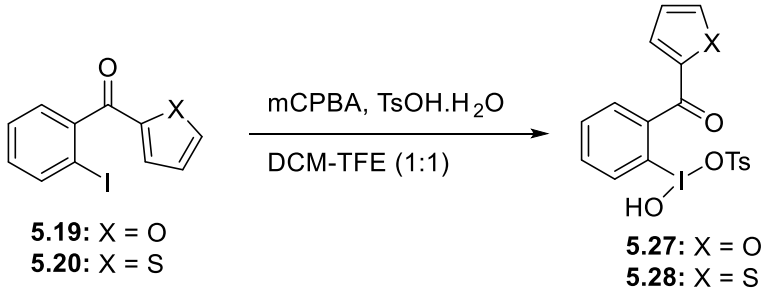
On the other hand, the pyrrole analogue **5.26** was prepared in 75% overall yield following a different synthetic route (Scheme 5.4).[34,35] The synthesis starts with the reaction of anthranilic acid **5.21** with benzoyl chloride to form the benzoxazine derivative **5.22** in 96% yield. Treatment of **5.22** with a pre-stirred mixture of pyrrole and ethylmagnesium chloride led to the formation of the protected aminoketone **5.23** in 97% yield. Basic hydrolysis of **5.23** led to the formation of the free aminoketone **5.24** in a quantitative yield, which undergoes Sandmeyer[33] reaction to afford the iodoketone **5.25** in 92% yield. *N*-Methylation of **5.25** afforded the desired iodoketone **5.26** in 88% yield.



Scheme 5.4. Synthesis of iodoketones bearing a pyrrole moiety.

5.2.2. Oxidation of the prepared iodoarenes

As the main objective of this project is to study the effect of the secondary interactions between the electrophilic iodine(III) centres and the nearby heteroatoms on the structure and reactivity of hypervalent iodine reagents, and as the iodoketones **5.19, 5.20, 5.25,** and **5.26** have all the necessary features for such study, the oxidation of compounds **5.19, 5.20, 5.25,** and **5.26** into the corresponding hypervalent iodine reagents was attempted. Although the oxidation of simple iodoarenes usually proceeds smoothly,[36] the oxidation of **5.19, 5.20, 5.25,** and **5.26** was cumbersome. A wide range of oxidants and oxidation protocols was investigated, but either there was no reaction at all, or the reaction mixture was very complex to isolate the oxidised products in a pure form. In many cases the ^{1}H NMR of the crude reaction mixture showed downfield peaks compared to the starting material peaks which is usually a sign of the oxidation of iodine(I) species into the corresponding iodine(III) species, but the isolation of the products was unsuccessful. Only the oxidation of furan and thiophene derivatives **5.19** and **5.20** using *m*-chloroperbenzoic[37] acid in the presence of *p*-TsOH monohydrate was successful and the products were isolated in pure form (Scheme 5.5).



Scheme 5.5. Oxidation of iodoketones **5.19** and **5.20**.

Based on their ^{1}H NMR and ^{13}C NMR data, the chemical structures **5.27** and **5.28** were initially suggested for the products of the above oxidation, but the easy solubility of these products in water left some doubt about the actual chemical structure of the formed hypervalent iodine species and suggested the possibility of the iodonium salt form. To answer the question of the actual structure of these products and to achieve the project main objective, a crystal structure was necessary. The oxidation products of **5.19** and **5.20** were recrystallised from hexane-dichloromethane and characterised by single crystal X-ray crystallography. The solid-state structure of the products ruled out the initially expected Koser's[38] type structures **5.27** and **5.28** with a close tosylate–iodine distance and confirmed the pseudocyclic[39] forms **5.29** (Figure 5.5) and **5.30** (Figure 5.6) manifesting the Lewis-base assisted activation[22,39] of the iodine centre.

Analysis of the X-ray data of tosylate **5.29** (Figure 5.5) showed the presence of a strong intramolecular interaction of 2.342 Å between the carbonyl oxygen and the hypervalent iodine atom besides one short iodine-oxygen covalent bond [I(1)-O(1) = 1.945 Å] and the iodine-carbon covalent bond [I(1)-C(1) = 2.080 Å]. The observed angle [O(1)-I(1)-O(2)] of the iodonium ion fragment of **5.29** (167.7º) is in good agreement with the distorted T-shaped geometry characteristic to hypervalent iodine(III) compounds.[22–24]

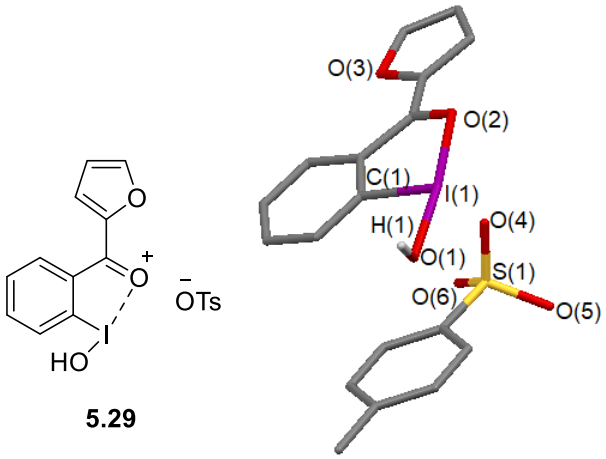
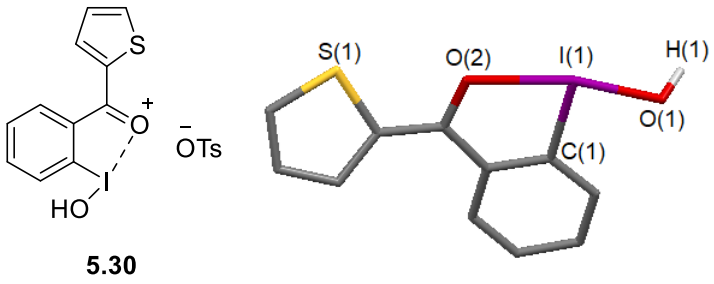


Figure 5.5. X-ray crystal structure of compound **5.29.** Hydrogen atoms bound to carbon atoms were removed for clarity. Selected bond lengths and angles: **5.29**: I(1)-O(1) 1.945 Å, I(1)-O(2) 2.342 Å, I(1)-C(1) 2.080 Å, O(1)-I(1)-O(2) 167.7°.

Crystallisation of the oxidation product of the thiophene derived iodoketone **5.20** was not easy, but a relatively good crystal was obtained after repeated crystallisation for several times. Regardless of the low quality of the obtained crystals, a crystal structure

showing only the cationic fragment of product **5.30** was obtained (Figure 5.6). Similar to product **5.29**, the analysis of the X-ray data of product **5.30** showed the presence of a strong intramolecular interaction of 2.326 Å between the carbonyl oxygen and the hypervalent iodine atom besides one short iodine-oxygen covalent bond [I(1)-O(1) = 1.943 Å] and iodine-carbon covalent bond [I(1)-C(1) = 2.155 Å] with an observed angle [O(1)-I(1)-O(2)] of 166.7º indicating a distorted T-shaped geometry characteristic to hypervalent iodine(III) compounds.[22–24] The iodonium ion of **5.30** showed a secondary interaction (2.830 Å) between the coordinated carbonyl oxygen (O(2)) and the sulfur atom (S(1)) of the thiophene ring which is relatively short compared to a distance of 3.560 Å between the furan oxygen (O(3)) and the coordinated carbonyl oxygen (O(2)) of compound **5.29**.



5.30

Figure 5.6. X-ray crystal structure the cationic fragment of compound **5.30**. Hydrogen atoms bound to carbon atoms were removed for clarity. Selected bond lengths and angles: **5.30**: I(1)-O(1) 1.943 Å, I(1)-O(2) 2.326 Å, I(1)-C(1) 2.155 Å, O(1)-I(1)-O(2) 166.7°.

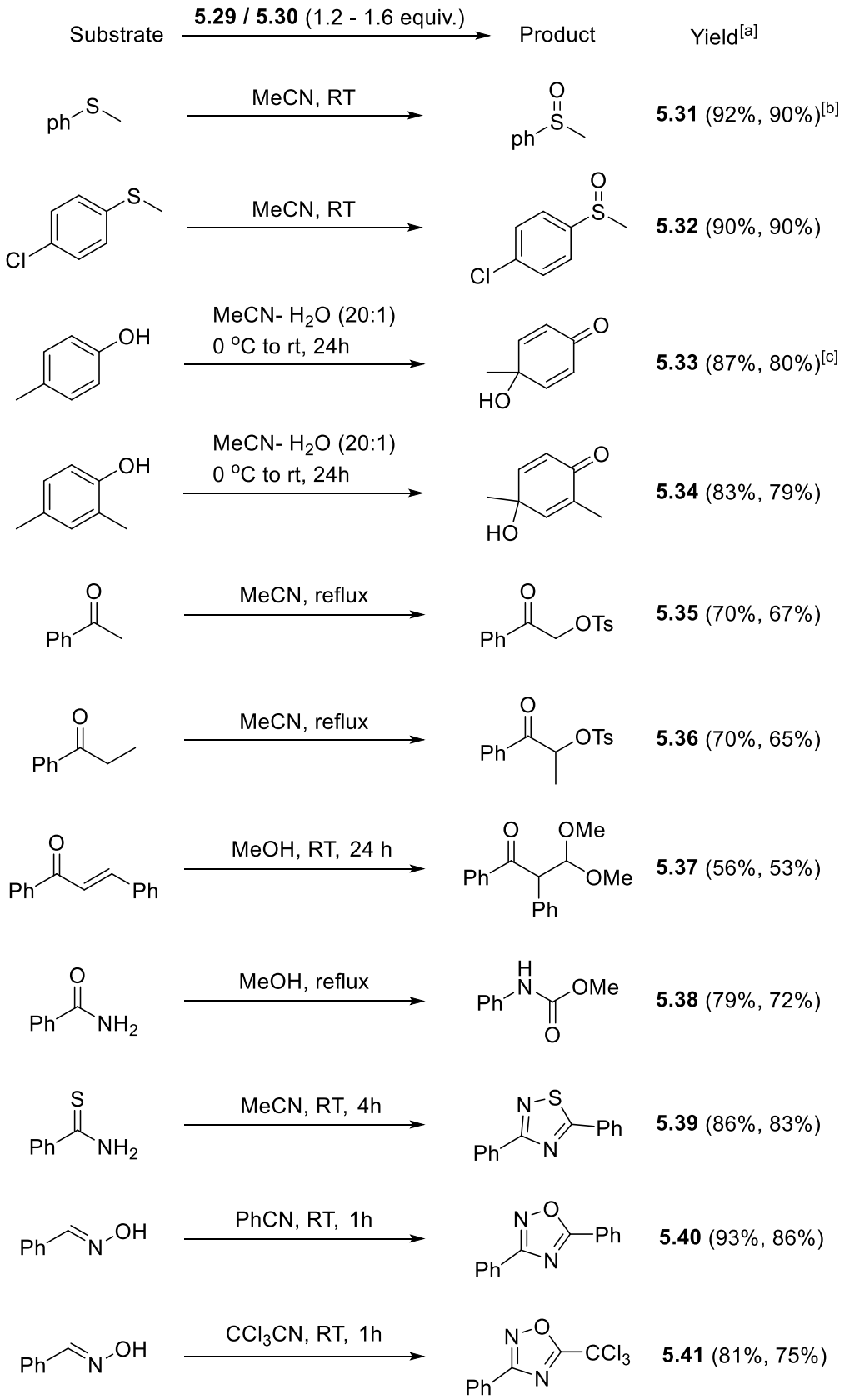
Comparing the X-ray data of both reagents **5.29** and **5.30** shows that the intramolecular interaction between the carbonyl oxygen and the iodine(III) centre is relatively stronger in case of compound **5.30** compared to compound **5.29**. In addition, compound **5.30** shows a secondary interaction between the sulfur of the thiophene ring and the coordinated carbonyl oxygen, while a similar secondary interaction is not observed between the furan oxygen and the coordinated carbonyl oxygen of compound **5.29**. These findings extracted from the X-ray data of both compounds **5.29** and **5.30** could suggest that the thiophene derivative **5.30** might be relatively more stable and less reactive compared to its furan analogue **5.29**.

5.2.3. Synthetic applications

A broad range of potential synthetic applications of hypervalent iodine reagents **5.29** and **5.30** as versatile oxidising reagents is demonstrated (Table 5.1). Generally, all the reactions with both reagents lead to the formation of the expected products in moderate to excellent yields. The furan-derived reagent **5.29** proved to be more

reactive than its thiophene analogue **5.30** which might be attributed to the presence of additional secondary interaction in the case of compound **5.30** rendering it more stable and hence less reactive (*vide supra*).

Sulfoxides **5.31** and **5.32** were obtained in excellent yields (90-92%) *via* the oxidation of the corresponding sulfides using **5.29** and **5.30**. Oxidising thioanisole under the same conditions but using Koser's reagent led to the isolation of **5.31** in 80% yield. Phenol dearomatisation of *p*-cresol and 2,4-dimethylphenol lead to the corresponding ketones **5.33** and **5.34** in 79 - 87% yield. When Koser's reagent was used as the oxidant for the oxidative dearomatisation of *p*-cresol, the corresponding ketone **5.33** was obtained in 74% yield. Both compounds **5.29** and **5.30** affected the *α*-tosyloxylation of acetophenone and propiophenone in good yields. Performing the α-tosyloxylation of propiophenone in a catalytic manner using 10 mol% of iodoarenes **5.19**, **5.20**, and **5.26** as organocatlysts in the presence of mCPBA as a terminal oxidant lead to the formation of the product **5.36** albeit in low yields, 21%, 10%, and 13%, respectively. In addition, the oxidative rearrangement of benzalacetophenone mediated by **5.29** and **5.30** in methanol afforded the corresponding *α*-aryl ketone **5.37** in 56% and 53% yield, respectively. Moreover, Hofmann rearrangement[11] of benzamide in methanol led to the corresponding carbamate **5.38** in good yield. Reagents **5.29** and **5.30** are efficient oxidants for oxidative heterocyclisations. 3,5-Diphenyl-1,2,4-thiadiazole (**5.39**) was obtained in 86% and 83% yield *via* oxidative dimerisation of thiobenzamide using reagents **5.29** and **5.30**, respectively. In the same context, the reaction of benzaldehyde oxime with **5.29** and **5.30** in acetonitrile and 2,2,2-trichloroacetonitrile proceed smoothly to afford 1,2,4-oxadiazoles **5.40** and **5.41** in high yields. All these reactions are summarised in table 5.1.



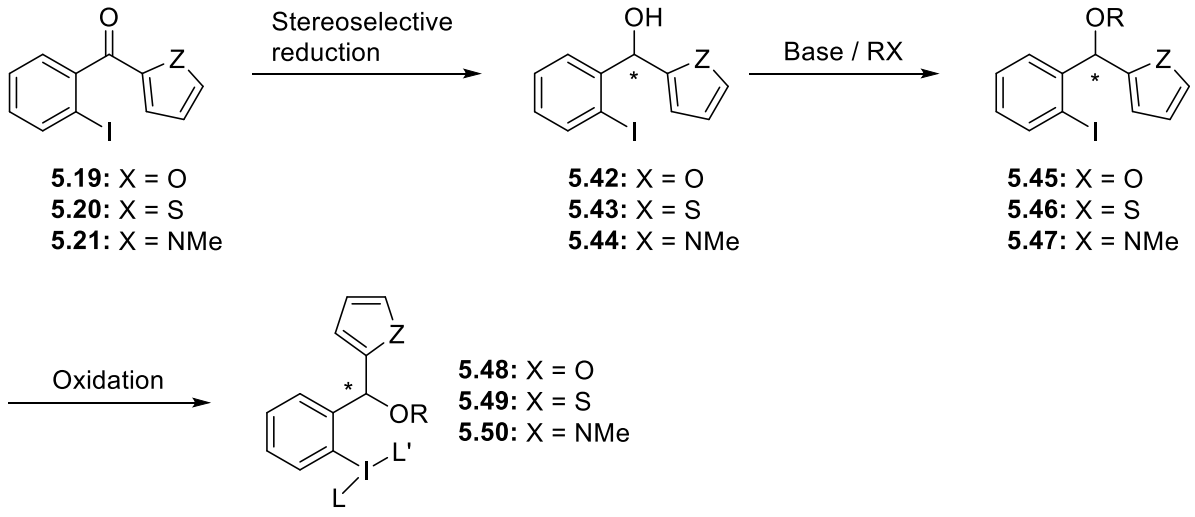
[a] Using **5.29** and **5.30**, respectively; [b] 80% using Koser's reagent; [c] 74% using Koser's reagent.

Table 5.1. Synthetic applications of reagents **5.29** and **5.30**.

5.3. Conclusions and outlook

In conclusion, the synthesis and structural elucidation of two new hypervalent iodine reagents **5.29** and **5.30** is reported. The X-ray analysis of **5.29** and **5.30** showed the presence of strong intramolecular interaction (2.342 and 2.326 Å) between the carbonyl oxygen and the hypervalent iodine atom of compounds **5.29** and **5.30**, respectively. Reagents **5.29** and **5.30** are versatile reagents for a wide range of oxidative transformations such as oxidation of sulfides, phenol dearomatisation, oxidative rearrangements and heterocyclisations. In general, both reagents lead to the formation of the products in moderate to excellent yields. Moreover, the furan derived reagent **5.29** shows higher reactivity than its thiophene analogue **5.30** in most cases.

For future work, it would be of great interest to reduce the newly prepared iodoketones **5.19, 5.20,** and **5.26** into the corresponding alcohols. Performing the reduction in a stereoselective way will lead to the formation of chiral alcohols.[40–44] Protection of the alcohol functionality followed by oxidation should in principle lead to the formation of novel chiral hypervalent iodine reagents (Scheme 5.6).[27] It would be of great interest to get information about the structural features of the proposed hypervalent iodine reagents of type **5.48-5.50** and to study the extent and effect of secondary interactions in such molecules on the reactivity and selectivity of such reagents in stereoselective transformations. In addition, it could be of interest to study the catalytic applications of the proposed chiral iodoarenes of type **5.45-5.47** in stereoselective transformations relying on iodine(I) / iodine(III) catalytic cycles.



Scheme 5.6. Future work, synthesis of chiral iodine(I)/iodine(III) compounds with 5- membered heterocycles.

5.4. References

[1] V. V Zhdankin, *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds.*, Wiley, **2013**.

[2] T. Wirth, Editor., *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis. [In: Top. Curr. Chem., 2016; 373].*, Springer-Verlag, **2016**.

[3] S. Ghosh, S. Pradhan, I. Chatterjee, *Beilstein J. Org. Chem.* **2018**, *14*, 1244–1262.

[4] G.-L. Gao, Q. Chen, *Curr. Organocatal.* **2017**, *4*, 33–47.

[5] A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328–3435.

[6] S. Kamouka, W. J. Moran, *Beilstein J. Org. Chem.* **2017**, *13*, 1823–1827.

[7] C. Martínez, A. E. Bosnidou, S. Allmendinger, K. Muñiz, *Chem. Eur. J.* **2016**, *22*, 9929–9932.

[8] A. Alhalib, S. Kamouka, W. J. Moran, *Org. Lett.* **2015**, *17*, 1453–1456.

[9] M. Brown, R. Kumar, J. Rehbein, T. Wirth, *Chem. Eur. J.* **2016**, *22*, 4030–4035.

[10] Z. Zhao, Z. Peng, Y. Zhao, H. Liu, C. Li, J. Zhao, *J. Org. Chem.* **2017**, *82*, 11848–11853.

[11] F. V. Singh, T. Wirth, *Synthesis* **2013**, *45*, 2499–2511.

[12] J. Qurban, M. Elsherbini, T. Wirth, *J. Org. Chem.* **2017**, *82*, 11872–11876.

[13] X. Li, P. Chen, G. Liu, *Beilstein J. Org. Chem.* **2018**, *14*, 1813–1825.

[14] K. Muñiz, L. Barreiro, R. M. Romero, C. Martínez, *J. Am. Chem. Soc.* **2017**, *139*, 4354–4357.

[15] C. Martínez, E. G. Pérez, Á. Iglesias, E. C. Escudero-Adán, K. Muñiz, *Org. Lett.* **2016**, *18*, 2998–3001.

[16] T. Dohi, N. Takenaga, T. Nakae, Y. Toyoda, M. Yamasaki, M. Shiro, H. Fujioka, A. Maruyama, Y. Kita, *J. Am. Chem. Soc.* **2013**, *135*, 4558–4566.

[17] D. C. Smith, E. Vitaku, J. T. Njardarson, *Org. Lett.* **2017**, *19*, 3508−3511.

[18] S. J. Murray, H. Ibrahim, *Chem. Commun.* **2015**, *51*, 2376–2379.

[19] A. M. Harned, *Tetrahedron Lett.* **2014**, *55*, 4681–4689.

[20] C. Bosset, R. Coffinier, P. A. Peixoto, M. El Assal, K. Miqueu, M. Sotiropoulos, L. Pouysøgu, S. Quideau, *Angew. Chem. Int. Ed.* **2014**, *53*, 9860–9864.

[21] S. Haubenreisser, T. H. Wöste, C. Martínez, K. Ishihara, K. Muñiz, *Angew. Chem. Int. Ed.* **2016**, *55*, 413–417.

[22] K. Aertker, R. J. Rama, J. Opalach, K. Muñiz, *Adv. Synth. Catal.* **2017**, *359*, 1290–1294.

[23] A. Yoshimura, K. C. Nguyen, S. C. Klasen, A. Saito, V. N. Nemykin, V. V. Zhdankin, *Chem. Commun.* **2015**, *51*, 7835–7838.

[24] A. Yoshimura, S. C. Klasen, M. T. Shea, K. C. Nguyen, G. T. Rohde, A. Saito, P. S.

Postnikov, M. S. Yusubov, V. N. Nemykin, V. V. Zhdankin, *Chem. Eur. J.* **2017**, *23*, 691–695.

[25] R. Weiss, J. Seubert, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 891–893.

[26] V. V. Zhdankin, A. Y. Koposov, N. V. Yashin, *Tetrahedron Lett.* **2002**, *43*, 5735–5737.

[27] P. Mizar, A. Laverny, M. El-Sherbini, U. Farid, M. Brown, F. Malmedy, T. Wirth, *Chem. Eur. J.* **2014**, *20*, 9910–9913.

[28] F. Malmedy, T. Wirth, *Chem. Eur. J.* **2016**, *22*, 16072–16077.

[29] C. Hempel, C. Maichle-Mössmer, M. A. Pericàs, B. J. Nachtsheim, *Adv. Synth. Catal.* **2017**, *359*, 2931–2941.

[30] J. K. Boppisetti, V. B. Birman, *Org. Lett.* **2009**, *11*, 1221–1223.

[31] A. Boelke, E. Lork, B. J. Nachtsheim, *Chem. Eur. J.* **2018**, *24*, 18653–18657.

[32] V.-H. Nguyen, L. Vendier, M. Etienne, E. Despagnet-Ayoub, P.-A. R. Breuil, L. Magna, D. Proriol, H. Olivier-Bourbigou, C. Lorber, *Eur. J. Inorg. Chem.* **2012**, *2012*, 97–111.

[33] E. B. Merkushev, *Synthesis* **1988**, 923–937.

[34] C. C. Llopart, J. A. Joule, *Arkivoc* **2004**, 20.

[35] G. Rotas, A. Kimbaris, G. Varvounis, *Tetrahedron* **2011**, *67*, 7805–7810.

[36] V. V. Zhdankin, in *Hypervalent Iodine Chem.*, John Wiley & Sons Ltd, Chichester, UK, **2013**, pp. 21–143.

[37] E. A. Merritt, V. M. T. Carneiro, L. F. Silva, B. Olofsson, *J. Org. Chem.* **2010**, *75*, 7416–7419.

[38] G. F. Koser, R. H. Wettach, *J. Org. Chem.* **1977**, *42*, 1476–1478.

[39] A. Yoshimura, M. S. Yusubov, V. V. Zhdankin, *Org. Biomol. Chem.* **2016**, *14*, 4771–4781.

[40] A. Hirao, S. Itsuno, S. Nakahama, N. Yamazaki, *J. Chem. Soc. Chem. Commun.* **1981**, 315.

[41] E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1989**, *30*, 6275–6278.

[42] E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1986–2012.

[43] C. Wang, A. Pettman, J. Basca, J. Xiao, *Angew. Chem. Int. Ed.* **2010**, *49*, 7548–7552.

[44] T. J. Greshock, D. M. Johns, Y. Noguchi, R. M. Williams, *Org. Lett.* **2008**, *10*, 613–616.

CHAPTER 6
Experimental Part

6.1. General methods

The reactions were performed using standard laboratory equipment. In all the reactions, standard reagent grade solvents and chemicals from Sigma Aldrich, Alfa Aesar, Acros Organic and FluoroChem were used without further purification, unless otherwise specified. All air sensitive reactions were carried out under argon or nitrogen atmosphere using oven dried glassware. All reactions were stirred using a stirrer plate and a magnetic stirrer bar and heating if necessary, over a hotplate with a temperature probe control and adapted heating block. Lower temperatures were achieved using ice/water bath (0 ºC) or dry ice/acetone bath (-78 ºC). Dry ether and THF were collected from a solvent purification system (SPS) from the company MBRAUN (MB SPS-800). Dry CH_2Cl_2 was distilled over calcium hydride under nitrogen atmosphere. Büchi rotavapors were used for solvent evaporations (reduced pressure up to 8 mbar) and a high vacuum apparatus was used to further dry the products.

Thin-layer chromatography (TLC) was performed on pre-coated aluminium sheets of Merck silica gel 60 F254 (0.20 mm) and visualised by UV radiation (254 nm). Automated column chromatography was performed on a Biotage® Isolera Four using Biotage® cartridges SNAP Ultra 10 g, SNAP Ultra 25 g, SNAP Ultra 50 g, SNAP Ultra 100 g, Telos® 12 g and Telos® 20 g. Manual column chromatography was performed using silica gel 60 (Merck, 230-400 mesh) under pressure (Flash Chromatography). The solvents used for the purification are indicated in the text and were purchased from Fischer Scientific as laboratory grade.

^{1}H NMR and ^{13}C NMR spectra were measured on Bruker DPX 300, 400 or 500 apparatus and were referenced to the residual proton solvent peak (^{1}H: $CDCl_3$, δ 7.26 ppm; DMSO-d_6, δ 2.54 ppm) and solvent ^{13}C signal ($CDCl_3$, δ 77.2 ppm, DMSO-d_6, δ 39.5 ppm). Chemical shifts δ were reported in ppm, multiplicity of the signals was declared as followed: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, dd = doublet of doublets, m = multiplet, b = broad; and coupling constants (*J*) in Hertz.

Mass spectrometric measurements were performed by the EPSRC Mass Spectrometry Facility in Swansea University on a Waters Xevo G2-S and on a Thermo Scientific LTQ Orbitrap XL machine for high-resolution mass spectroscopy (HRMS) or by R. Jenkins, R. Hick, T. Williams and S. Waller at Cardiff University on a Water LCR Premier XE-TOF. Ions were generated by the Atmospheric Pressure Ionisation Techniques (APCI), Electrospray (ESI), Electron Ionisation (EI) or Nanospray Ionisation (NSI). The molecular ion peak values quoted for either

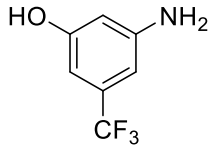
molecular ion $[M]^+$, molecular ion plus hydrogen $[M+H]^+$, molecular ion plus sodium $[M+Na]^+$ or molecular ion plus potassium $[M+K]^{+\cdot}$

IR spectra were recorded on a Shimadzu FTIR Affinity-1S apparatus. Wavenumbers are quoted in cm^{-1}. All compounds were measured neat directly on the crystal of the IR machine. Melting points were measured using a Gallenkamp variable heater with samples in open capillary tubes.

X-Ray crystallographic studies were carried out at the X-Ray Crystallography Service at Cardiff University. The data were collected on an Agilent SuperNova Dual Atlas diffractometer with a mirror monochromator, equipped with an Oxford cryosystems cooling apparatus. Crystal structures were solved and refined using SHELX. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted in idealised positions. The structure was solved by a direct method and refined by a full matrix least-squares procedure on F2 for all reflections (SHELXL-97).

6.2. Experimental data for chapter 2: Electron-deficient chiral hypervalent iodine reagents

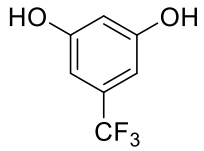
3-Amino-5-(trifluoromethyl)phenol (2.53)[1]



3-Nitro-5-(trifluoromethyl)phenol (**2.52**) (5.0 g, 24.1 mmol, 1 equiv.) dissolved in ethanol (25 mL) was refluxed during the gradual addition (15 min) of a solution of sodium sulfide (25 g, 104 mmol, 4.3 equiv) in ethanol (100 mL). After 1.5 h, hot 10% ethanolic sodium hydroxide solution (12.5 mL) was added, heating continued for 1 hour, then the alcohol removed under reduced pressure. The residue was acidified with hydrochloric acid (2 M) and then neutralised by the addition of sodium hydrogen carbonate solution and extracted with ether (4 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure affording 3-amino-5-hydroxybenzotrifluoride **2.53** as a red solid (4.15 g, 23.4 mmol, 97%).

m.p.: 83 – 85 ºC; IR (solid) ν/cm^{-1}: 3375, 3284, 3061, 2958, 749; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.50 (s, 1H), 6.45 (s, 1H), 6.30 (s, 1H), 4.98 (br s, 1H), 3.84 (br s, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.9, 148.4, 133.0 (q, *J* = 32.2 Hz), 123.9 (q, *J* = 272.4 Hz), 104.8 (two carbons), 102.7 ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ = -63.20 ppm.; HRMS: m/z calculated for $C_7H_7F_3NO$ $[M+H]^+$ = 178.0474; found: 178.0488.

5-(trifluoromethyl)benzene-1,3-diol (2.54)

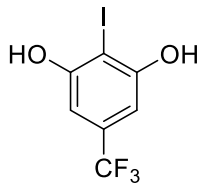


3-Amino-5-(trifluoromethyl)phenol (**2.53**) (3.98 g, 22.47 mmol) was dissolved in a mixture of water (14 mL) and concentrated sulfuric acid (16 mL). After cooling to 0 ºC, a solution of sodium nitrite (1.5 g) in water (8 mL), was added slowly, after 15 minutes, the excess nitrous acid was destroyed by addition of urea. Then the cooled solution was added to a heated saturated solution of copper sulfate (200 mL). Then left to cool down to the room temperature and extracted with ether (4 x 50 ml), the combined extracts were dried over anhydrous $MgSO_4$,

filtered, and concentrated under reduced pressure affording 3,5-dihydroxybenzotrifluoride **2.54** as a red solid (3.24 g, 18.2 mmol, 81%).

m.p.: 87 – 89 ºC; IR (solid) ν/cm^{-1}: 3269, 2853, 1253, 713; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (s, 2H), 6.50 (s, 1H), 5.44 (br s, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 157.2, 133.0 (q, *J* = 32.7 Hz), 123.8 (q, *J* = 272.2 Hz), 106.1, 105.3 ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ = -63.08 ppm; HRMS: m/z calculated for $C_7H_6F_3O_2$ $[M+H]^+$ = 179.0314; found: 179.0320.

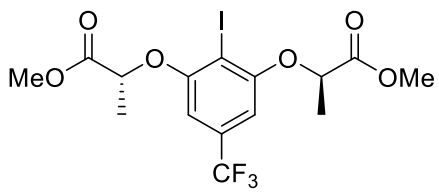
2-iodo-5-(trifluoromethyl)benzene-1,3-diol (2.55)



3,5-Dihydroxybenzotrifluoride (**2.54**) (2.14 g, 12 mmol, 1 equiv.) was dissolved in H_2O/THF (1:1) (250 mL). After cooling to 0 ºC, iodine (3.12 g, 12.6 mmol, 1.05 equiv.) was added followed by slow addition of $NaHCO_3$ (1.108 g, 13.2 mmol, 1.1 equiv.). The resulting reaction mixture was stirred for 10 min at 0 ºC, then allowed to warm to room temperature and stirred for 40 min. The reaction was then quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution (10 mL). After extraction with EtOAc (4 x 40 mL), the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (8:2 Hex/EtOAc) afforded the pure product **2.55** as a yellow solid (2.92 g, 9.61 mmol, 80%).

m.p.: 91 – 92 ºC; IR (solid) ν/cm^{-1}: 3277, 1250, 1010; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.80 (s, 2H), 5.55 (s, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.2, 133.2 (q, *J* = 33.3 Hz), 123.4 (q, *J* = 272.5 Hz), 104.4, 81.6 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): δ = –63.32 ppm; HRMS m/z: $[M]^+$ calculated for $C_7H_4F_3IO_2$ = 303.9206; found: 303.9208.

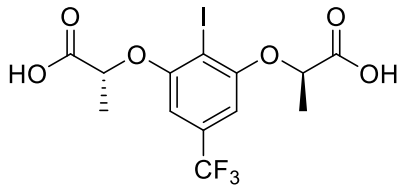
Dimethyl-2,2'-((2-iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))(2R,2'R)-dipropionate (2.56)



2-iodo-5-(trifluoromethyl)benzene-1,3-diol **(2.55)** (1.3 g, 4.28 mmol, 1 eq), was dissolved in (25 mL) dry THF under an argon atmosphere. After addition of methyl (s)-lactate (0.897 g, 9.4 mmol, 2.2 eq), triphenylphosphine (2.6 g, 9.83 mmol, 2.3 eq) and diisopropyl azodicarboxylate (2 g, 10.26 mmol, 2.4 eq) the reaction mixture was stirred for 16 h at room temperature and then concentrated under reduced pressure. Purification by flash column chromatography (8:2 Hexane/EtOAc) afforded the pure product as a white solid (2.0 g, 98 %, 4.19 mmol).

m.p.: 69-71 °C; $[\alpha]_D^{20}$: - 90.5 (c = 0.243, $CHCl_3$); IR (solid) ν/cm^{-1}: 1739, 1244, 1109; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.58 (s, 2H, Ar*H*), 4.83 (q, *J* = 6.8 Hz, 2H, O-C*H*(CH_3)-), 3.77 (s, 6H, COOC*H*$_3$), 1.73 (d, *J* = 6.8 Hz, 6H, O-CH(C*H*$_3$)-) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.6, 158.7, 132.3 (q, *J* = 33.0 Hz), 123.6 (q, *J* = 273.0 Hz), 103.8, 85.3, 74.5, 52.7, 18.6 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): δ -62.94 ppm; HRMS: m/z calculated for $C_{15}H_{16}F_3IO_6Na$ $[M+Na]^+$ = 498.9841; found: 498.9760.

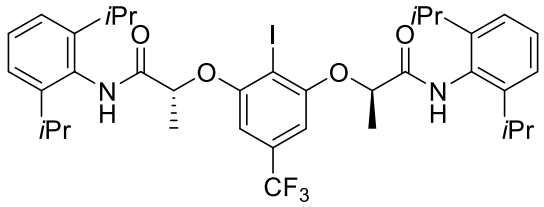
(2R,2'R)-2,2'-((2-Iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))dipropionic acid (2.57)



Dimethyl2,2'-((2-iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))(2R,2'R)-dipropionate (**2.56**) (1.68 g, 3.53, 1 equiv.) was dissolved in THF/MeOH (1:1) (20 mL). After addition of aqueous NaOH (2 M, 10 mL, 20 mmol, 5.6 eq) the reaction mixture was stirred for 6 h at room temperature and then acidified with aqueous HCl (3 M, 10 mL). After extraction with EtOAc (3 x 20 mL) the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, affording the product as a white solid (1.27 g, 80 %, 2.83 mmol).

m.p.: 127-128 °C; $[\alpha]_D^{20}$: - 47.8 (c = 0.6, CH_3CN); IR (solid) ν/cm^{-1}: 2991,1705, 1242, 1110; ^{1}H NMR (500 MHz, DMSO): δ 13.18 (s, 2H, O*H*), 6.74 (s, 2H, Ar*H*), 5.11 (q, *J* = 6.7 Hz, 2H, O-C*H*(CH_3)-), 1.57 (d, *J* = 6.7 Hz, 6H, -O-CH(C*H*$_3$)-) ppm; ^{13}C NMR (126 MHz, CD_3OD) δ: 174.5, 160.3, 132.8 (q, *J* = 32.8 Hz), 125.1 (q, *J* = 271.6 Hz), 103.9, 85.3, 75.2, 18.8 ppm; ^{19}F NMR (471 MHz, DMSO): δ -61.34 ppm; HRMS: m/z calculated for $C_{13}H_{11}F_3IO_6$ $[M-H]^-$ = 446.9553; found: 446.9569.

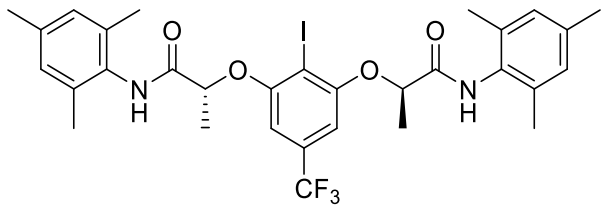
(2R,2'R)-2,2'-((2-Iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))bis(N-(2,6-diisopropylphenyl)propanamide) (2.59)



(2R,2'R)-2,2'-((2-iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))dipropionic acid (**2.57**) (1.344 g, 3.0 mmol, 1 equiv.) was suspended in (30 mL) dry DCM under an argon atmosphere. After addition of oxalyl chloride (1.33 g, 10.5 mmol, 3.5 equiv.) and a catalytic amount of DMF the reaction mixture was stirred for 3 h at room temperature and then concentrated in vacuum. The crude product was re-dissolved in (16 mL) dry DCM under an argon atmosphere and 2,6-diisopropylaniline (2.632 g, 15 mmol, 5 equiv.) as well as pyridine (0.95 g, 12 mmol, 4 eq) were added. The reaction mixture was stirred for 16 h at room temperature and quenched by the addition of aqueous HCl (3 M, 10 mL). After extraction with DCM (3 X 10 mL), the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (8:2→2:2 Hex/EtOAc) afforded the product as a yellow solid (1.63 g, 71 %, 2.13 mmol).

m.p.: 230 -233 ^{O}C; $[\alpha]_D^{20}$ - 503 (c = 0.286, $CHCl_3$); IR (solid) ν/cm^{-1}: 3203, 1660, 1249, 1101; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (s, 2H, N*H*), 7.32 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.19 (d, *J* = 7.8 Hz, 4H, Ar*H*), 6.92 (s, 2H, Ar*H*), 5.10 (q, *J* = 6.6 Hz, 2H, O-C*H*(CH_3)-), 3.0-2.85 (m, 4H, -C*H*(CH_3)$_2$), 1.83 (d, *J* = 6.5 Hz, 6H, O-CH(C*H*$_3$)-), 1.20 (d, *J* = 6.8 Hz, 12H, -CH(C*H*$_3$)$_2$), 1.15-1.0 (m, 12H, -CH(C*H*$_3$)$_2$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 169.9, 157.6, 146.3, 133.7 (q, *J* = 33 Hz), 129.9, 128.9, 123.8, 122.9, 103.9, 85.0, 76.8, 28.9, 22.6, 18.9 ppm (Fluorine coupling not found); ^{19}F NMR (471 MHz, $CDCl_3$): δ = -62.9 ppm; HRMS: m/z calculated for $C_{37}H_{47}F_3IN_2O_4$ $[M+H]^+$ = 767.2533; found: 767.2521.

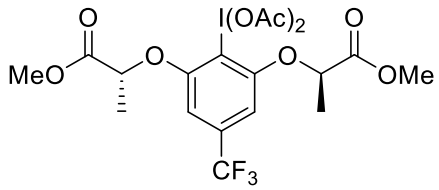
(2R,2'R)-2,2'-((2-Iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))bis(N-mesitylpropanamide)(2.60)



(2R,2'R)-2,2'-((2-iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))dipropionic acid (**2.57**) (1.286 g, 2.87 mmol, 1 equiv.) was suspended in (29 mL) dry DCM under an argon atmosphere. After addition of oxalyl chloride (1.276 g, 10 mmol, 3.5 equiv.) and a catalytic amount of DMF the reaction mixture was stirred for 3 h at room temperature and then concentrated in vacuo. The crude product was re-dissolved in (4 mL) dry DCM under an argon atmosphere and 2,4,6-trimethylaniline (1.54 g, 11.389 mmol, 5 equiv.) as well as pyridine (0.882 g, 11.164 mmol, 4 equiv.) were added. The reaction mixture was stirred for 16 h at room temperature and quenched by addition of aqueous HCl (3 M). After extraction with DCM, the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (8:2→2:2 Hex/EtOAc) afforded the product as a white solid (1.63 g, 83 %, 2.38 mmol).

m.p.: 293-297 ^{O}C; $[\alpha]_D^{20}$: -740 (c = 1.0, $CHCl_3$); IR (solid) ν/cm^{-1}: 3257,1670, 1250, 1150; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 2H, N*H*), 6.91 (s, 4H, Mes*H*), 6.86 (s, 2H, Ar*H*), 5.04 (q, *J* = 6.6 Hz, 2H, O-C*H*(CH_3)-), 2.25 (s, 6H, Mes-CH_3), 2.15 (s, 12H, Mes-CH_3), 1.81 (d, *J* = 6.7 Hz, 6H, O-CH(CH_3)-) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 169.1, 157.6, 137.5, 135.2, 130.0, 129.2, 128.9, 122.1, 104.0, 85.1, 76.8, 21.1, 18.9, 18.4 ppm (Fluorine coupling not found); ^{19}F NMR (471 MHz, $CDCl_3$): δ = -63.00 ppm; HRMS: m/z calculated for $C_{31}H_{35}F_3IN_2O_4$ $[M+H]^+$ = 683.1594; found: 683.1594.

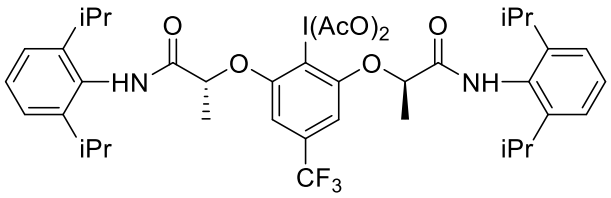
Dimethyl-2,2'-((2-(diacetoxy-λ^3-iodanyl)-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))(2R,2'R)-dipropionate (2.61)



Dimethyl 2,2'-((2-iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))(2R,2'R)-dipropionate **(2.56)** (0.238 g, 0.5 mmol, 1 equiv.) and Selectfluor® (0.885 g, 2.5 mmol, 5 equiv.) were dissolved in CH_3CN (30 mL) and glacial acetic acid (10 mL) under N_2. The reaction mixture was stirred at room temperature till completion (TLC). The reaction mixture was concentrated under vacuum then water (50 mL) was added to the residue and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give **2.61** as a white solid (0.28 g, 95%, 0.47 mmol); the product was used without further purification.

m.p.: 195-197 ^{O}C; **[α]$_D^{20}$**: -65 (c = 0.4, $CHCl_3$); IR (Neat) ν/cm^{-1}: 2997.4, 1741, 1259, 1109; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.78 (s, 2H, Ar*H*), 4.93 (q, *J* = 6.8 Hz, 2H, -O-C*H*(CH_3)-), 3.77 (s, 6H, -COOC*H*$_3$), 1.99 (s, 6H, OAc), 1.70 (d, *J* = 6.8 Hz, 6H, -O-CH(C*H*$_3$)-) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.3, 170.8, 157.1, 137.08 (q, *J* = 33.1 Hz), 122.9 (q, *J* = 273.7 Hz), 110.4, 103.4, 74.9, 52.8, 20.5, 18.3 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): δ = -63.7 ppm

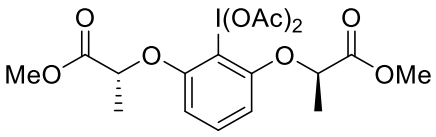
(2R,2'R)-2,2'-((2-(Diacetoxy-λ^3-iodanyl)-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))bis(N-(2,6-diisopropylphenyl)propanamide) (2.62)



(2R,2'R)-2,2'-((2-iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))bis(N-(2,6-diisopropylphenyl)propanamide) (**2.59**) (191.7 mg, 0.25 mmol), Selectfluor® (0.885 g, 2.5 mmol, 10 eq) were dissolved in CH_3CN (30 mL) and glacial acetic acid (10 mL) under N_2. The reaction mixture was stirred at room temperature till completion (TLC). The reaction mixture was concentrated under vacuum then water (50 mL) was added to the residue and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give **2.62** as a white solid (0.156 g,78%, 0.176 mmol); the product was used without further purification.

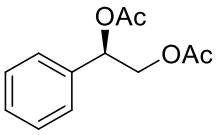
m.p.:220-222 ^{o}C; [α]$_D^{20}$: -60 (c = 0.1666, $CHCl_3$); IR (Solid) ν/cm^{-1}: 3100, 1663, 1259, 1015; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 2H, N*H*), 7.34-7.27 (m, 2H, Ar*H*), 7.19 (s, 2H, Ar*H*), 7.12 (s_{br}, 4H, Ar*H*), 5.22 (q, *J* = 6.7 Hz, 2H, -O-C*H*(CH_3)-), 2.99 (m, 4H, -C*H*(CH_3)$_2$), 1.92 (d, *J* = 6.6 Hz, 6H, -O-CH(C*H*$_3$)-), 1.45 (s, 6H, OAc), 1.3-0.8 (m, 24H, -CH(C*H*$_3$)$_2$) ppm; ^{13}C NMR (101 MHz, CDCl3) δ 176.9, 169.9, 169.8, 157.6, 156.5, 146.2, 129.4 (dd, *J* = 105.0, 21.7 Hz), 123.8, 103.1, 77.0, 76.8, 28.9, 23.6, 19.7, 19.4, 18.8 ppm (Fluorine coupling not found). ^{19}F NMR (471 MHz, $CDCl_3$): δ = -63.045 ppm.

Dimethyl 2,2'-((2-(diacetoxy-l3-iodanyl)-1,3-phenylene)bis(oxy))(2R,2'R)-dipropionate (2.25)



Prepared according to literature.[2] Dimethyl-2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2R,2'R)-dipropionate (102 mg, 0.25 mmol), Selectfluor® (0.885 g, 2.5 mmol, 10 eq) were dissolved in CH_3CN (30 mL) and glacial acetic acid (10 mL) under N_2. The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated under vacuum then water (50 mL) was added to the residue and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give **2.25** as a white solid Yield: (0.1235 g, 95%, 0.2347 mmol); **$[\alpha]_D^{20}$**: - 18.46° (c = 1.48 $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 2H), 4.86 (q, *J* = 6.8 Hz, 2H), 3.75 (s, 6H), 1.97 (s, 6H), 1.68 (d, *J* = 6.8 Hz, 6H) ppm; **^{13}C NMR** (125 MHz, CDCl3): δ = 176.8, 171.2, 156.6, 135.1, 106.9 106.2, 74.4, 52.3, 20.3, 18.1 ppm. Spectroscopic data in a good agreement with literature.[2,3]

(*R*)-1-Phenylethane-1,2-diyl diacetate (2.65)

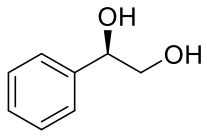


A mixture of hypervalent iodine reagents **2.25, 2.61** or **2.62** (0.375 mmol, 1.25 equiv.) and styrene (34.4 μL, 0.3 mmol, 1 equiv.) was dissolved in a mixture of CH_2Cl_2 (3 mL) and glacial acetic acid (0.15 mL) containing trimethylsilyl acetate (0.15 mL, 0.99 mmol, 3.3 equiv.). Boron trifluoride diethyl etherate (75µL, 0.6 mmol, 2.0 equiv.) was added at -78 °C with stirring. The reaction mixture left to warm up to room temperature overnight. Water (5 mL) was then added followed by extraction with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (*n*hexane: EtOAc = 90:10) to afford diacetate **2.65** as a pale-yellow oil (44 mg, 67%, 0.1979 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.31 (m, 5H), 6.01 (dd, *J* = 7.9, 4.0 Hz, 1H), 4.33 (dd, *J* = 11.9, 4.0 Hz, 1H), 4.28 (dd, 11.9, 7.9 Hz, 1H), 2.12 (s, 3H), 2.06 (s, 3H) ppm; ^{13}C NMR

(126 MHz, $CDCl_3$) δ = 170.8, 170.3, 136.6, 128.8, 128.7, 126.8, 73.4, 66.2, 21.3, 20.9 ppm. Spectroscopic data are in a good agreement with literature.[4]

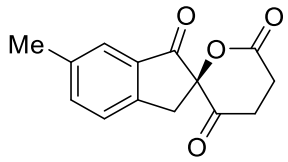
(*R*)-1-Phenylethane-1,2-diol



For the purpose of determining the enantiomeric excess of **2.65**, it was hydrolysed to the corresponding diols following a literature procedure.[5] Diacetate **2.65** (22.2 mg, 0.1 mmol, 1 equiv.) was dissolved in methanol (1 mL) and K_2CO_3 (20.7 mg, 0.15, 1.5 equiv.) was added. The reaction mixture was stirred at room temperature for 4 h, then acidified with HCl (3 M, 1 mL). The mixture was concentrated under reduced then extracted with CH_2Cl_2 (3 X 3 mL), the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure. The crude mixture was purified by flash column chromatography (*n*-hexane:EtOAc = 75:25).

$[\alpha]_D^{20}$: - 68.8º (c = 0.8333 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7. 39 – 7.28 (m, 5H), 4.83 (dd, *J* = 8.1, 3.5 Hz, 1H), 3.77 (dd, *J* = 11.3, 3.5 Hz, 1H), 3.67 (dt, *J* = 11.3, 8.1 Hz, 1H), 2.60 (br. s, 1H), 2.19 (br. s, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 140.6, 128.7, 128.2, 126.2, 74.8, 68.3 ppm; HPLC: Lux® 5 μm Cellulose-1, LC Column (250 x 4.6 mm), *n*-hexane/i-PrOH = 95/5, 0.7 mL/min, 209 nm, t_R (major, *R*) = 28.7 min, t_R (minor, *S*) = 32.2 min, *ee* = 56%. Spectroscopic data are in a good agreement with literature.[6]

(*S*)-6-Methyl-4',5'-dihydrospiro[indene-2,2'-pyran]-1,3',6'(3H)-trione (2.67)



A mixture of hypervalent iodine reagents **2.25, 2.61** or **2.62** (0.3 mmol, 2.0 equiv) and 4-(6-methyl-1-oxo-2,3-dihydro-1*H*-inden-2-yl)-4-oxobutanoic acid (**2.66**)[7] (37 mg, 0.15 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (2 mL) and the solution was cooled to –78 °C. The reaction mixture was stirred at –78 °C for 5 h. Saturated aq. $NaHCO_3$ solution (5 mL) was then added and diluted with CH_2Cl_2 (5 mL), phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous MgSO4, filtered and removed under vacuum. The crude mixture was purified

by flash column chromatography (*n*hexane: EtOAc = 80:20) to afford **2.67** as colourless solid (21.6 mg, 60%, 0.0884 mmol).

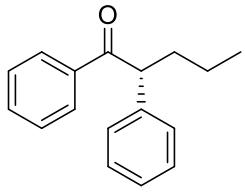
m.p.: 165-168 ºC; $[\alpha]_D^{20}$: + 17.65 (c = 0.57 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 3.77 – 3.62 (m, 2H), 3.29 (d, *J* = 16.8 Hz, 1H), 3.03 – 2.95 (m, 1H), 2.85 – 2.79 (m, 2H), 2.40 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 202.0, 197.4, 169.2, 149.5, 139.0, 138.5, 132.7, 126.0, 125.7, 93.2, 38.7, 33.6, 27.3, 21.2 ppm; HPLC : YMC Chiral Amylose-C column, hexane/i-PrOH = 85/15, 0.8 mL/min, 20 °C, 254 nm, t_R (minor, *R*) = 34.2 min, t_R (major, *S*) = 37.6 min; ee = 63%. Spectroscopic data are in a good agreement with literature.[7]

(*R*)-2.67

Isolated from the above reaction in case of reagent **2.62**.

$[\alpha]_D^{20}$: - 13.91 (c = 0. 767 $CHCl_3$); HPLC : YMC Chiral Amylose-C column, hexane/i-PrOH = 85/15, 0.8 mL/min, 20 °C, 254 nm, t_R (major, *R*) = 34.2 min, t_R (minor, *S*) = 37.6 min; *ee* = 33%.

(*R*)-1,2-diphenylpentan-1-one (2.69)

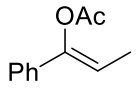


To a mixture of hypervalent iodine reagents **2.25, 2.61** or **2.62** (0.11 mmol, 1.2 equiv.) and of 1,1-diphenylpentene **2.68** (20 mg, 0.09 mmol, 1 equiv.), and methanol (11 μL, 0.27 mmol, 3 equiv.) in CH_2Cl_2:TFE (10:1) (1.5 mL) at –78 ºC, was added TsOH.H_2O (21 mg, 0.11 mmol, 1.2 eq). The reaction was stirred for 4 h at -78 ºC then 16 h at room temperature, then quenched with a 1:1 mixture of aqueous sat. $NaHCO_3$ and sat. $Na_2S_2O_3$ (0.5 mL). Water (4 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were filtered through a TELOS® phase Separator and concentrated under vacuum to give the crude product. The desired aryl ketone was isolated by TLC (hexane/ethyl acetate 9:1. to give the product **2.69** as a colorless (13 mg, 65%).

$[\alpha]_D^{20}$: - 150º (c = 0.67 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.26 – 7.20(m, 4H), 7.15 – 7.10 (m, 1H), 4.49 (t, *J* = 7.2 Hz, 1H), 2.13 – 2.04 (m, 1H), 1.80 – 1.68 (m, 1H), 1.30 – 1.14 (m, 2H), 0.85 (t, *J* = 7.2

Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.3, 140.0, 137.2, 132.9, 129.0, 128.8, 128.6, 128.4, 127.1, 53.6, 36.3, 21.0, 14.2 ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*-PrOH = 99.5/0.5, 1.0 mL/min, 10 ºC, 243 nm; t_R (*S*) = 9.2 min, t_R (*R*) = 11.9 min; ee = 92%. Spectroscopic data are in a good agreement with literature.[8]

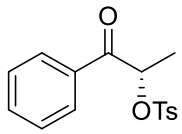
(*Z*)-1-Phenylprop-1-en-1-yl Acetate (2.72)



n-Butyllithium (3.84 ml, 9.6 mmol, 2.5 M in hexane, 1.2 equiv.) was added to a cooled (−78 °C) solution of diisopropylamine (1.34 ml, 9.6 mmol, 1.2 equiv.) in THF (40 mL) under argon. After stirring for 30 min, propiophenone (1.073 ml, 8 mmol, 1 equiv.) was added, stirring was continued for additional 45 min, acetic anhydride (1.5 ml, 16 mmol, 2 equiv.) was then added. Stirring was continued for additional 30 min at −78 °C and another 30 min at room temperature. The reaction mixture was then poured into a saturated aq. $NaHCO_3$ solution (90 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel with EtOAc:hexanes (5:95 to 20:80) to provide **2.72** as a colourless oil (1.32 g, 94%, 7.491 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.38 – 7.26 (m, 3H), 5.93 (q, *J* = 6.9 Hz, 1H), 2.33 (s, 3H), 1.74 (m, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 168.9, 147.1, 135.2, 128.6, 128.1, 124.4, 112.8, 20.9, 11.8 ppm. Spectroscopic data are in a good agreement with literature.[9]

(*S*)-1-oxo-1-phenylpropan-2-yl 4-methylbenzenesulfonate (2.71)



Method A:

Propiophenone (40 mg, 0.3 mmol, 1 equiv.) was added to a mixture of chiral aryl iodides **2.28**, **2.56**, **2.59** or **2.60** (0.03 mmol, 0.1 equiv.), *m*-CPBA (202 mg, 0.9 mmol, 3 equiv.) and *p*-TsOH•H_2O (171 mg, 0.9 mmol, 3 equiv.) in MeCN (2 mL) at room temperature. The solution was then stirred for 48 h. Saturated aqueous $Na_2S_2O_3$ solution (5 mL) was added, the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic phases were washed with

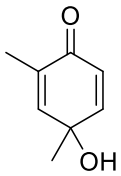
sat. aq $NaHCO_3$ (1 X 10 mL) and brine (1 X 10 mL), then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel with Et_2O/hexanes (20:80) to give pure **2.71** as a white solid (58.5 mg, 0.1922 mmol, 65%, *ee = 16%*,).

Method B:

A mixture of chiral iodoarene **2.28, 2.56, 2.59** or **2.60** (0.084 mmol, 0.2 equiv.), *m*-CPBA (9.4 mg, 0.042 mmol, 0.1 equiv.) and *p*-TsOH hydrate (7.9 mg, 0.042 mmol, 0.1 equiv.) was dissolved in MeCN (0.5 mL). A solution of **2.72** (74 mg, 0.421 mmol, 1 equiv.), *m*-CPBA (94, 0.421 mmol, 1 equiv.) and *p*-TsOH hydrate (80, 0.421 mmol, 1 equiv.) in 2.5 mL of acetonitrile was added with stirring over 12 h *via* a syringe pump. Stirring continued for additional one hour. Saturated aqueous solution of $Na_2S_2O_3$ (5 mL) was added and the resulting mixture was extracted with EtOAc (3 X 5 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (1 X 10 mL) and brine (1 X 10 mL), then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel with Et_2O/hexanes (5:95 to 20:80) to give pure **2.71** as a white solid (90 mg, 69%, 79% *ee*, 0.2957 mmol).

m.p.: 76-78 ^oC; $[\alpha]_D^{20}$: - 5.4 (c = 0.7333 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 6.3 Hz, 2H), 5.78 (q, *J* = 6.9 Hz, 1H), 2.41 (s, 3H), 1.60 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 195.0, 145.2, 134.0, 133.8, 133.6, 129.9, 128.9, 128.1, 77.5, 21.8, 18.9 ppm; ; HPLC : YMC Chiral Amylose-C column, hexane/i-PrOH = 85/15, 0.7 mL/min, 25 °C, 254 nm, t_R (minor, *R*) = 16.2 min, t_R (major, *S*) = 17.8 min; ee = 79%. Spectroscopic data are in a good agreement with literature.[10,11]

4-hydroxy-2,4-dimethylcyclohexa-2,5-dien-1-one (2.74)



2,4-dimethylphenol (**2.73)** (0.33 mmol, 1 equiv) and chiral iodoarenes **2.28, 2.56, 2.59** or **2.60** (0.033 mmol, 10 mol%) were dissolved in a mixture of MeCN/H_2O (2 mL, 9:1). *m*-CPBA (0.726 mmol, 2.2 equiv) was added and the reaction mixture was stirred at –5 °C for 5 h then at room temperature overnight. The reaction was quenched with saturated aq $Na_2S_2O_3$ solution

(4 mL) and saturated aq. $NaHCO_3$ solution (4 mL). The mixture was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered, and removed under reduced pressure. Purification by flash column chromatography (silica gel, *n*-hexane/EtOAc, 85:15) to afford pure **2.74** as a white solid (27 mg, 0.195 mmol, 60%, ee = 8%).

m.p.: 63- 66 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.84 (dd, *J* = 10.0, 3.1 Hz, 1H), 6.64 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.11 (d, *J* = 9.9 Hz, 1H), 2.29 – 2.15 (br, 1H), 1.87 (s, 3H), 1.46 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 186.1, 151.8, 147.4, 134.0, 127.2, 67.7, 27.0, 15.7 ppm. Spectroscopic data are in a good agreement with literature.[12]

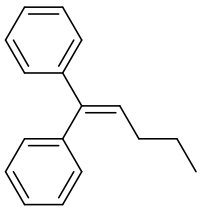
6.3. Experimental data for chapter 3: Catalytic oxidative rearrangement of alkenes

6.3.1. Synthesis of olefinic substrate

General procedure A: Wittig olefination[8]

Alkylphosphonium bromide (1.2 equiv.) was suspended in THF at 0 °C, followed by the addition *n*-BuLi (1.2 equiv.) or NaH (60% in mineral oil, 2 equiv.) dropwise with stirring. After dissolution of the salt the solution of the appropriate ketone (1.0 eq) in THF was added dropwise at 0 °C. Stirring was continued at room temperature and stirred overnight. Saturated aqueous solution of amm. chloride was added and the mixture was extracted with diethyl ether (3X). The combined organic phases were washed with brine (1X), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified with column chromatography (hexane: ethyl acetate, 1:0→10:1) to afford the pure alkene.

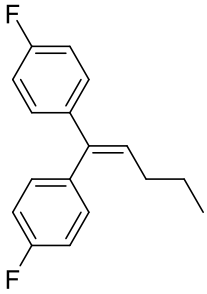
1,1-Diphenylpentene (3.40a)



Butyltriphenylphosphonium bromide (5.26 g, 13.18 mmol), *n*-BuLi (2.1 M in hexane, 6.28 mL, 13.18 mmol) and benzophenone (2.0 g, 10.98 mmol) were reacted according to general olefination procedure to afford **3.40a** as a colorless oil (1.776 g, 74%, 7.99 mmol).

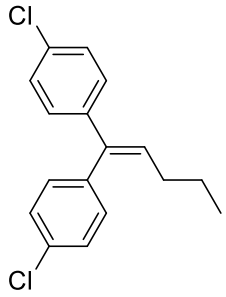
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.23 (m, 10H), 6.16 (t, *J* = 7.4 Hz, 1H), 2.17 (q, *J* = 7.4 Hz, 2H), 1.54 (sext, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H) ppm; 13C NMR (75 MHz, CDCl3): δ = 143.1, 141.7, 140.5, 130.3, 130.1 (2C), 128.3 (2C), 128.3 (2C), 127.4 (2C), 126.9, 126.8, 31.9, 23.4, 14.1 ppm. Spectroscopic data are in a good in agreement with literature.[8]

1,1-Bis(4-fluorophenyl)pentene (3.40b)



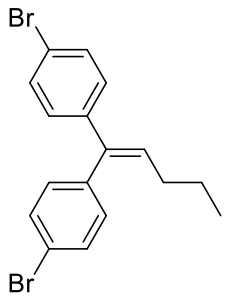
Butyltriphenylphosphonium bromide (2.63 g, 6.6 mmol), *n*-BuLi (2.1 M in hexane, 3.14 mL, 6.6 mmol) and 4,4'-fluorobenzophenone (1.2 g, 5.5 mmol) were reacted according to general olefination procedure to afford **3.40b** as a colorless oil (1.008 g, 72%, 3.902 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.02 (m, 6H), 6.96 – 6.91 (m, 2H), 6.00 (t, *J* = 7.2 Hz, 1H), 2.05 (q, *J* = 7.2 Hz, 2H), 1.45 (sext, *J* = 7.2 Hz, 2H), 0.89 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.7 (d, *J* = 252 Hz), 134.0 (d, *J* = 3 Hz), 132.8 (d, *J* = 9 Hz), 128.3 (d, *J* = 8 Hz), 127.7 (d, *J* = 8 Hz), 115.9 (d, *J* = 22 Hz), 115.7 (d, *J* = 21 Hz), 115.3 (d, *J* = 21 Hz), 32.7, 19.8, 14.3 ppm. Spectroscopic data are in a good in agreement with literature.[8]

1,1-Bis(4-chlorophenyl)pentene (3.40c)



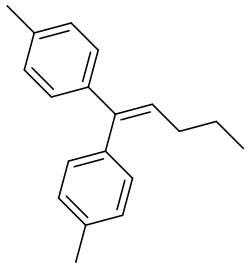
Butyltriphenylphosphonium bromide (2.04 g, 5.1 mmol), *n*-BuLi (1.7 M in hexane, 3.0s mL, 5.1 mmol) and 4,4'-dichlorobenzophenone (1.066 g, 4.24 mmol) were reacted according to general olefination procedure to afford **3.40c** as a colorless oil (580 mg, 58%, 1.99 mmol).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 8.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 8.9 Hz, 2H), 6.10 (t, *J* = 7.9 Hz, 1H), 2.09 (q, *J* = 7.9 Hz, 2H), 1.48 (sext, *J* = 6.9 Hz, 2H), 0.92 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 141.0, 139.6, 138.3, 133.0, 132.8, 131.4 (2C), 131.3, 128.6 (2C), 128.5 (2C), 128.4 (2C), 31.9, 23.1, 14.0 ppm. Spectroscopic data are in a good in agreement with literature.[8]

,1-Bis(4-bromophenyl)pentene (3.40d)



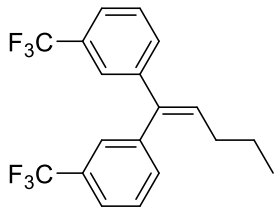
Butyltriphenylphosphonium bromide (2 g, 5 mmol), *n*-BuLi (1.6 M in hexane, 3.12 mL, 5 mmol) and 4,4'-dibromobenzophenone (1.42 g, 4.18 mmol) were reacted according to general olefination procedure to afford **6x** as a colorless oil (1.056 g, 66%, 2.78 mmol).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.07 – 6.02 (m, 4H), 6.08 (t, *J* = 8.2 Hz, 1H), 2.07 (q, *J* = 8.2 Hz, 2H), 1.46 (sext, *J* = 7.2 Hz, 2H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 141.4 (2C), 139.7, 138.8, 131.7 (2C), 131.6 (2C), 131.4 (2C), 128.9 (2C), 121.3, 121.1, 32.0, 23.1, 13.9 ppm. Spectroscopic data are in a good in agreement with literature.[8]

1,1-Bis(4-methylphenyl)pentene (3.40e)



Butyltriphenylphosphonium bromide (2 g, 5 mmol), *n*-BuLi (2.45 M in hexane, 2.04 mL, 5 mmol) and 4,4'-dimethylbenzophenone (878 mg, 4.18 mmol) were reacted according to general olefination procedure to afford **3.40e** as a colorless oil (810 mg, 81%, 3.24 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.9 Hz, 2H), 7.14 (dd, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 4H), 6.04 (t, *J* = 6.9 Hz, 1H), 2.40 (s, 3H), 2.34 (s, 3H), 2.11 (q, *J* = 6.9 Hz, 2H), 1.47 (sext, *J* = 6.9 Hz, 2H), 0.91 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 141.4, 140.5, 137.7, 136.5, 136.4, 130.0 (2C), 129.2, 128.9 (2C), 128.8 (2C), 127.3 (2C), 32.0, 23.4, 21.4, 21.2, 14.0 pp. Spectroscopic data are in a good in agreement with literature.[8]

1,1-Bis(3-(trifluoromethyl)phenyl)pentene (3.40f)

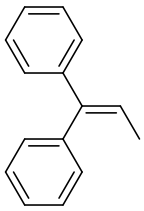


Butyltriphenylphosphonium bromide (2.00 g, 5 mmol), *n*-BuLi (1.75 M in hexane, 2.86 mL, 5 mmol) and 3,3'-bis(trifluoromethyl)benzophenone (1.048 g, 4.18 mmol) were reacted

according to general olefination procedure to afford **3.40f** as a colorless oil (1.155 g, 77%, 3.22 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.56 – 7.46 (m, 3H), 7.44 (s, 1H), 7.41 – 7.32 (m, 2H), 7.29 (d, *J* = 7.9 Hz, 1H), 6.20 (t, *J* = 7.9 Hz, 1H), 2.09 (q, *J* = 7.9 Hz, 2H), 1.54 – 1.44 (sext, *J* = 7.9 Hz, 2H), 0.92 (t, *J* = 7.9 Hz, 3H) ppm. Spectroscopic data are in a good in agreement with literature.[8]

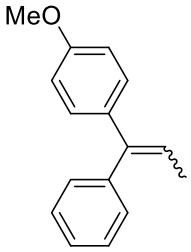
1,1-Diphenylpropen (3.40g)



Ethyltriphenylphosphonium bromide (3 g, 8.08 mmol), *n*-BuLi (3.24 mL, 8.08 mmol) and benzophenone (1.228 g, 6.74 mmol) were reacted according to general olefination procedure to afford **3.40g** as a colourless solid (863.6 mg, 68 %, 4.55 mmol).

m.p.: 48-51 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.3 Hz, 2H, ArH), 7.32 – 7.17 (m, 8H, ArH), 6.18 (q, *J* = 7.0 Hz, 1H, C=CHCH3), 1.76 (d, *J* = 7.0 Hz, 3H, C=CHCH3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.1, 142.5, 140.1, 130.2 (2C), 128.3 (2C), 128.2 (2C), 127.3 (2C), 127.0, 126.9, 124.3, 15.9 ppm. Spectroscopic data are in a good in agreement with literature.[8]

1-(4-Anisyl)-1-phenylpropene (3.40h) (*E/Z*, 1:1)

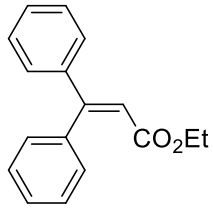


Ethyl triphenylphosphonium bromide (2.44 g, 6.58 mmol), *n*-BuLi (2.1 M in hexane, 3.14 mL, 6.58 mmol) and 4-methoxybenzophenone (1.168 g, 5.5 mmol) were reacted according to general olefination procedure to afford **3.40h** as a white solid (750 mg, 75%, 3.344 mmol).

m.p.: 47-50 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2H), 7.31 – 7.09 (m, 15H), 6.94-6.88 (m, 2H), 6.82-6.77 (m, 2H), 6.12 (q, *J* = 7.0, 1H), 6.08 (q, *J* = 7.0, 1H), 3.84 (s, 3H), 3.79

(s, 3H), 1.78 (d, *J* = 7.0 Hz, 3H), 1.74 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.7, 158.6, 143.5, 142.1, 142.0, 140.4, 135.9, 132.4, 131.3, 130.2, 128.4, 128.2, 128.2, 127.4, 126.9, 126.8, 124.0, 122.6, 113.6, 113.6, 55.4, 55.4, 15.9, 15.8 ppm. Spectroscopic data are in a good in agreement with literature.[8]

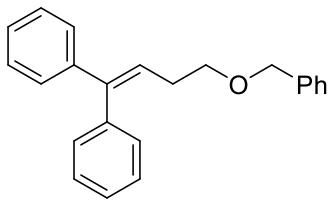
Ethyl-3,3-diphenylacrylate (3.40i)



Prepared from triethyl phosphonoacetate (654 *μL*, 3.3 mmol), sodium hydride (60% in mineral oil, 132 mg, 5.34 mmol) and benzophenone (500 mg, 2.74 mmol) in THF (10 ml) according to the literature.[13] Column chromatography (hexane:ethyl acetate, 4:1→2:1) afforded **3.40i** as a colorless oil (455 mg, 66%, 1.803 mmol);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 8H), 7.17 – 7.10 (m, 2H), 6.29 (s, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 1.04 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.2, 156.6, 140.9, 139.1, 129.5, 129.3 (2C), 128.5 (2C), 128.4 (2C), 128.2, 128.0 (2C), 117.6, 60.2, 14.1 ppm; Spectroscopic data are in a good in agreement with literature.[8,13]

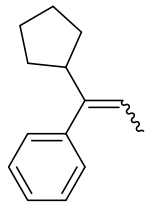
4-Benzyloxy-1,1-diphenyl-but-1-ene (3.40j)



(3-(Benzyloxy)propyl)triphenylphosphonium bromide (3.22 g, 6,58 mmol), *n*-BuLi (2.1 M in hexane, 3.14 mL, 6.58 mmol) and benzophenone (1 g, 5.5 mmol) were reacted according to general olefination procedure to afford **3.40j** as a colorless oil (1.07 g, 62 %, 3.4 mmol).

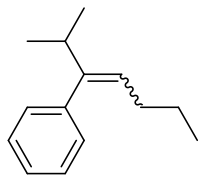
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.10 (m, 15H), 6.08 (t, *J* = 7 Hz, 1H), 4.43 (s, 2H), 3.49 (t, *J* = 7 Hz, 2H), 2.39 (q, *J* = 7 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.4, 142.7, 140.1, 138.6, 137.7, 132.6, 130.2, 130.0, 128.5, 128.3, 128.2, 128.0, 127.8, 127.7, 127.4, 127.1 (2C), 125.9, 72.9, 70.1, 30.6 ppm. Spectroscopic data are in a good in agreement with literature.[8]

1-Cyclopentyl-1-phenylpropene (3.40k) (*E/Z*, 2:3)



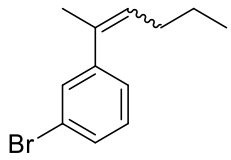
Ethyl triphenylphosphonium bromide (2.44 g, 6.58 mmol), *n*-BuLi (2.1 M in hexane, 3.14 mL, 6.58 mmol) and cyclopentyl phenyl ketone (958 mg, 5.5 mmol) were reacted according to general olefination procedure to afford **3.40k** as a colorless oil (790 mg, 79%, 4.241 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.6 Hz, 1.4H), 7.30 – 7.18 (m, 4H),), 7.17 – 7.12 (m, 2H),), 7.12 – 7.08 (m, 1.3H), 5.56 (qd, *J* = 6.7, 1.2 Hz, 0.7H (*E*)), 5.43 (q, *J* = 6.9 Hz, 1H (*Z*)), 3.07 (tt, *J* = 10.6, 7.7 Hz, 1H (*Z*)), 2.72 – 2.60 (m, 0.7H (*E*)), 1.88 – 1.66 (m, 7H), 1.66-1.50 (m, 7H), 1.50 – 1.45 (m, 2H), 1.45 – 1.30 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.4, 145., 144.1, 141.8, 129.0, 128.7, 127.9, 127.7, 126.2, 126.1, 123.9, 119.1, 48.4, 41.3, 31.7, 31.3, 25.3, 24.7, 14.6, 13.7ppm. Spectroscopic data are in a good in agreement with literature.[8]

2-Methyl-3-phenyl-4-heptene (3.40l) (*E/Z*, 1:2)



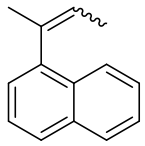
Butyltriphenylphosphonium bromide (2.0 g, 5 mmol), *n*-BuLi (1.6 M in hexane, 3.14 mL, 5 mmol) and isobutyrophenone (626 μL, 4.18 mmol) were reacted according to general olefination procedure to afford **3.40l** as a colorless oil (435 mg, 55 %, 2.31 mmol).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 2H), 7.18 – 7.15 (m, 2H), 7.15 – 7.13 (m, 0.5H), 7.13 – 7.06 (m, 2H), 7.01 – 6.97 (m, 1H), 5.32 (td, *J* = 7.3, 1.1 Hz, 0.5H (*E*)), 5.17 (t, *J* = 7.3 Hz, 1H (*Z*)), 2.97 (sept, *J* = 7.0 Hz, 1H (*Z*)), 2.46 (sept, *J* = 7.0 Hz, 0.5H (*E*)), 2.1 (q, *J* = 7.3 Hz, 2H (*Z*)), 1.71 (q, *J* = 7.3 Hz, 1H (*E*)), 1.43 – 1.32 (m, 2H (*Z*)), 1.29 – 1.17 (m, 1H (*E*)), 0.96 (d, *J* = 7.0 Hz, 6H (*Z*)), 0.93 (d, *J* = 6.9 Hz, 3H (*E*)), 0.89 (t, *J* = 7.3 Hz, 3H (*Z*)), 0.74 (t, *J* = 7.3 Hz, 1.5H (*E*)) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 147.6, 146.9, 143.7, 141.7, 129.1, 129.1, 128.9, 127.8, 127.6, 126.2, 126.2, 124.7, 36.1, 30.9, 29.9, 29.4, 23.3, 23.2, 22.1, 22.0, 14.1, 13.9 ppm. Spectroscopic data are in a good in agreement with literature.[8]

2-(3-Bromophenyl)-2-hexene (3.40m) (*E/Z*, 1:2)



Butyltriphenylphosphonium bromide (3 g, 7.52 mmol), *n*-BuLi (1.8 M in hexane, 4.18 mL, 7.52 mmol) and 3'-bromoacetophenone (828 μL, 6.26 mmol) were reacted according to general olefination procedure to afford **3.40m** as a colorless oil (1.215 g, 81%, 5 mmol).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 0.5H), 7.43 – 7.27 (m, 3H), 7.24 – 7.14 (m, 1.5H), 7.11 (d, *J* = 7.4 Hz, 1H), 5.81 (t, *J* = 6.8 Hz, 0.5H (*E*)), 5.50 (t, *J* = 7.0 Hz, 1H(*Z*)), 2.19 (q, *J* = 6.8 Hz, 1H (*E*)), 2.01 (s, 4.5H), 1.95 (q, *J* = 7.1 Hz, 2H (*Z*)), 1.49 (sext, *J* = 7.0 Hz, 1H (*E*)), 1.36 (sext, *J* = 6.9 Hz, 2H (*Z*)), 0.98 (t, *J* = 7.1 Hz, 1.5H (*E*)), 0.87 (t, *J* = 7.2 Hz, 3H (*Z*)) ppm. Spectroscopic data are in a good in agreement with literature.[8]

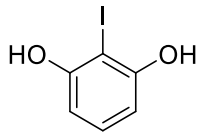
1-(But-2-en-2-yl)naphthalene (3.40n) (*E/Z*, 3:1)



Ethyl triphenylphosphonium bromide (2.44 g, 6.58 mmol), *n*-BuLi (2.1 M in hexane, 3.14 mL, 6.58 mmol) and 1-acetylnapthalene (936 mg, 5.5 mmol) were reacted according to general olefination procedure to afford **3.40n** as a colorless oil (810 mg, 81%, 4.44 mmol).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.06 (m, 0.38H), 8.01 (dd, *J* = 6.0, 3.5 Hz, 1H), 7.99 – 7.9 (m, 1.5H), 7.89 – 7.80 (m, 1.4H), 7.62 – 7.49 (m, 4.2H), 7.36 (dd, *J* = 13.8, 7.0 Hz, 1.4H), 5.92 (q, J = 6.9 Hz, 1H (*E*)), 5.72 (q, *J* = 6.8 Hz, 0.35H (*Z*)), 2.22 (d, *J* = 0.9 Hz, 4H (*E* + *Z*)), 1.99 (d, *J* = 6.7 Hz, 1H (*Z*)), 1.48 (dd, *J* = 6.8, 0.9 Hz, 3H (*E*)) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.4, 140.6, 135.9, 135.8, 133.9, 133.9, 131.5, 131.0, 128.5, 128.4, 126.9, 126.1, 125.9, 125.7, 125.7, 125.7, 125.6, 125.3, 125.1, 123.4, 26.2, 18.8, 15.0, 14.1 ppm. Spectroscopic data are in a good in agreement with literature.[8]

6.3.2. Synthesis of iodoarene catalysts

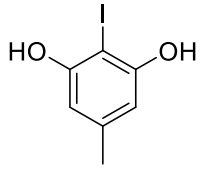
2-Iodobenzene-1,3-diol (3.42a)



Resorcinol (**3.41a**) (10 g, 90.82 mmol, 1 equiv.) was dissolved in (70 mL) H_2O and cooled to 0 ^oC with ice-bath. Molecular iodine (24.20 g, 95.359 mmol, 1.05 equiv.) was added with stirring followed by addition of solid $NaHCO_3$ (8.39 g, 99.9 mmol, 1.1 equiv.) portion wise. The reaction mixture was stirred at 0 ^oC for additional 10 min and then left to warm to room temperature. Saturated aqueous $Na_2S_2O_3$ solution was then added. The mixture was extracted with EtOAc (3 X 50 mL). The combined organic layers were washed with brine (2 X 50 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by recrystallization from chloroform to afford pure **3.42a** as a white solid (14.91 g, 70%, 63.18 mmol).

m.p.: 90-93 ^0C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.11 (t, *J* = 8.1 Hz, 1H, Ar*H*), 6.56 (d, *J* = 8.1 Hz, 2H, Ar*H*), 5.31 (s, 2H, O*H*) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.77, 130.53, 107.45, 77.78 ppm. Spectroscopic data in a good agreement with literature.[4]

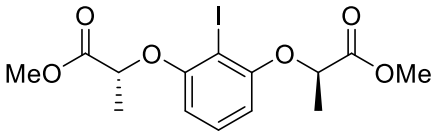
2-Iodo-5-methylbenzene-1,3-diol (3.42b)



Orcinol (**3.41b**) (1.5 g, 12.083 mmol, 1 eq) was dissolved in 1:1 mixture of H_2O and THF (240 mL) and cooled to 0^oC. Molecular iodine (3.220 g, 12.687 mmol, 1.05 equiv.) was added with stirring followed by addition of solid $NaHCO_3$ (1.117 g, 13.291 mmol, 1.1 equiv.) portion wise. The reaction mixture was stirred at 0 ^oC for additional 10 min and then left to warm to room temperature. Saturated aqueous $Na_2S_2O_3$ solution was then added. The mixture was extracted with EtOAc (3 X 15 mL). The combined organic layers were washed with brine (2 X 15 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by recrystallization from chloroform to afford pure **3.42b** as a white solid (2.17g, 72%, 8.6788 mmol).

m.p.: 106- 108 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.42 (s, 2H, Ar*H*), 5.19 (s, 2H, O*H*), 2.28 (s, 3H, ArCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.4, 141.2, 108.4, 73.6, 21.2 ppm. Spectroscopic data in a good agreement with literature.[4]

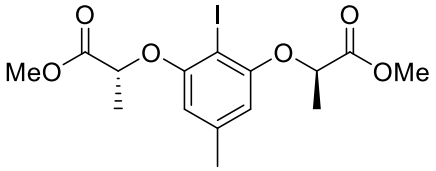
Dimethyl-2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate (3.44a)



Under an argon atmosphere, 2-iodobenzene-1,3-diol (**3.42a**) (1.3 g, 5.5 mmol, 1 equiv.) was dissolved in dry THF (40 ml), followed by the addition of methyl (*S*)-lactate (1.26 g, 12.1 mmol, 2.2 equiv.), triphenylphosphine (3.44 g, 13.12 mmol, 2.3 equiv.) and diisopropyl azodicarboxylate (2.66 g, 13.2 mmol, 2.4 equiv.). The reaction mixture was stirred at room temperature for 16 h, then concentrated under reduced pressure. The crude product was purified by flash column chromatography (5:1 Hexane/EtOAc) to afford pure **3.44a** (1.8 g, 90%, 4.4097 mmol).

[α]$_D^{20}$: -18.0 (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (t, *J* = 8.3 Hz, 1H), 6.37 (d, *J* = 8.3 Hz, 2H), 4.77 (q, *J* = 6.8 Hz, 2H), 3.75 (s, 6H), 1.70 (d, *J* = 6.8 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.3, 158.4, 129.8, 107.6, 80.8, 74.4, 52.5, 18.8 ppm. Spectroscopic data in a good agreement with literature.[4]

Dimethyl-2,2'-((2-iodo-5-methyl-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate (3.44b)

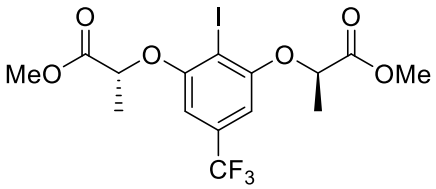


Under an argon atmosphere, 2-iodo-5-methylbenzene-1,3-diol (**3.42b**) (1 g, 4 mmol, 1 equiv.) was dissolved in dry THF (25 mL), followed by the addition of methyl (*S*)-lactate (0.916 g, 8.8 mmol, 2.2 equiv.), triphenylphophine (2.4 g, 9.2 mmol, 2.3 equiv.) and diiospropyl azodicarboxylate (1.94 g, 9.6 mmol, 2.4 equiv.). The reaction mixture was stirred at room temperature for 16 h, then concentrated under reduced pressure. The crude product was purified by flash column chromatography (10:1→7:1 Hex/EtOAc) to afford pure **3.44b** (1.649 g, 97%, 3.9056 mmol).

m.p.: 188-191 ^{o}C; [α]$_D^{20}$: - 5.45^{o} (c = 0.7333 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.20 (s, 2H, Ar*H*), 4.75 (q, *J* = 6.8 Hz, 2H, -O-C*H*(CH_3)-), 3.75 (s, 6H, -COOCH_3), 2.25 (s, 3H, ArCH_3),

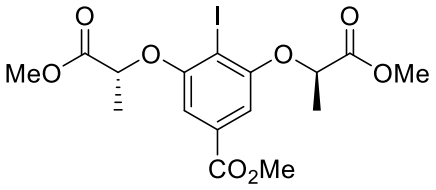
1.69 (d, *J* = 6.8 Hz, 6H, -O-CH(C*H*$_3$)-) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.4, 158.1, 140.3, 108.3, 76.9, 74.3, 52.5, 22.0, 18.8 ppm. Spectroscopic data in a good agreement with literature.[4]

Dimethyl-2,2'-((2-iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate (3.44c)



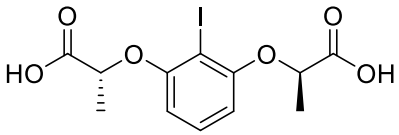
The synthesis and characterisation of the title compound were described under chapter 2 (see compound **2.56**).[14]

Dimethyl-2,2'-((2-iodo-5-(methoxycarbonyl)-1,3-phenylene)bis(oxy))(2*R*,2'*R*) dipropionate (3.44d)



The title compound was borrowed from my colleague Dr Wen-Chao Gao.[7]

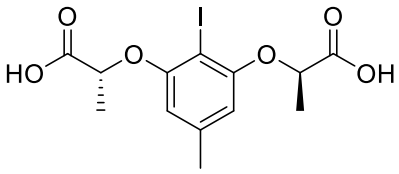
(2*R*,2'*R*)-2,2'-(2-Iodo-1,3-phenylene)bis(oxy)dipropanoic acid (3.45a)



Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate (**3.44a**) (1.53 g, 3.75 mmol, 1 equiv.) was dissolved in a 1:1 mixture of THF and MeOH (20 mL), followed by the addition of a 2 M aqueous solution of NaOH (10 ml, 20.0 mmol, 5.3 equiv.). The reaction mixture was stirred at room temperature for 6 h, then acidified with 3 M aqueous HCl. The mixture was extracted with EtOAc (3 X 15 mL), the combined organic layers were washed with brine (2 X 15), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford **3.45a** as a white solid (1.33 g, 95%, 3.4988 mmol).

m.p.: 99 – 101 ºC; $[\alpha]_D^{20}$: - 4.9º (c = 0.8333 CH_3CN); ^{1}H NMR (500 MHz, DMSO): δ 13.04 (s, 2H, COO*H*), 7.21 (t, *J* = 8.3 Hz, 1H, Ar*H*), 6.42 (d, *J* = 8.3 Hz, 2H, Ar*H*), 4.85 (q, *J* = 6.8 Hz, 2H, -O-C*H*(CH_3)-), 1.55 (d, *J* = 6.8 Hz, 6H, -O-CH(C*H*$_3$)-C(=O)-) ppm; ^{13}C NMR (101 MHz, DMSO) δ = 172.7, 157.7, 129.7, 106.0, 79.6, 72.8, 18.4 ppm . Spectroscopic data in a good agreement with literature.[4]

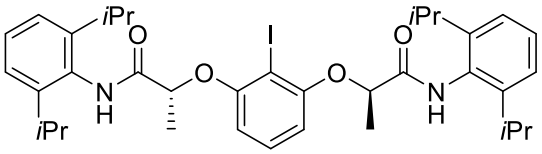
(2*R*,2'*R*)-2,2'-((2-Iodo-5-methyl-1,3-phenylene)bis(oxy))dipropanoic acid (3.45b)



As described for the synthesis of (**3.45a)**, dimethyl 2,2'-((2-iodo-5-methyl-1,3 phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate (**3.44b**) (1g, 2.36 mmol, 1 eq) and aqueous NaOH (2 M, 6.6 mL, 13.216 mmol, 5.6 eq) were stirred in 26 mL THF/MeOH (1:1) for 4 h at room temperature. Work-up afforded **3.45b** as a white solid (0.9 g, 96 %, 2.283 mmol).

m.p.: 152-154 ºC; $[\alpha]_D^{20}$: - 32.78º (c = 0.8333 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30 (s, 2H, Ar*H*), 4.83 (q, *J* = 6.9 Hz, 2H, -O-C*H*(CH_3)-), 2.31 (s, 3H, ArC*H*$_3$), 1.73 (d, *J* = 6.9 Hz, 6H, -O-CH(C*H*$_3$)-) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 174.8, 157.3, 140.9, 108.7, 77.0, 73.9, 22.0, 18.5 ppm. Spectroscopic data in a good agreement with literature.[4]

(2*R*,2'*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))bis(*N*-(2,6-diisopropylphenyl)propanamide) (3.46a)

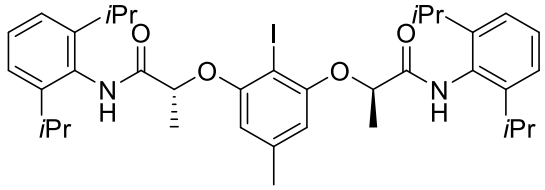


A suspension of (2*R*,2'*R*)-2,2'-(2-iodo -1,3- phenylene)bis(oxy)dipropanoic acid (**3.45a**) (0.873 g, 2.296 mmol, 1 equiv.), oxalyl chloride (1.02 g, 8.039 mmol, 3.5 equiv.) and a catalytic amount of DMF were stirred in 25 mL dry CH_2Cl_2 for 3 h at room temperature under argon. The reaction mixture was concentrated under reduced pressure. The crude product (acid chloride) was dissolved in dry DCM (12 mL), followed by the addition of 2,6-diisopropylaniline (2.04 g, 11.485 mmol, 5 equiv.) and pyridine (0.725 g, 9.186 mmol, 4 equiv.) under argon. The reaction mixture was stirred at room temperature for 16 h. Aqueous HCl (3 M) was then added, the resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL), the

combined organic layers were dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure. The crude product was purified by recrystallisation from methanol to afford pure **3.46a** as a white solid (1.312g, 82 %, 1.878 mmol).

m.p.:219-222 °C; $[\alpha]_D^{20}$: - 81° (c = 0.6666 $CHCl_3$); IR (Solid) ν/cm^{-1}: 3050, 1724, 1602, 1560; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 2H, N*H*), 7.40 (t, *J* = 8.3 Hz, 1H, Ar*H*), 7.31 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.18 (d, *J* = 7.8 Hz, 4H, Ar*H*), 6.70 (d, *J* = 8.4 Hz, 2H, Ar*H*), 5.06 (q, *J* = 6.6 Hz, 2H, -O-C*H*(CH_3)-), 3.1-2.8 (m, 4H, Ar-C*H*(CH_3)$_2$), 1.80 (d, *J* = 6.7 Hz, 6H, -O-CH(C*H*$_3$)-), 1.19 (d, *J* = 6.8 Hz, 12H, Ar-CH(C*H*$_3$)$_2$), 1.13 (d, *J* = 5.6 Hz, 12H, Ar-CH(C*H*$_3$)$_2$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.52, 157.03, 146.20, 130.63, 130.04, 128.64, 123.56, 107.12, 80.55, 76.10, 28.71, 23.61, 18.65 ppm; HRMS m/z calculated for $C_{36}H_{47}IN_2O_4$ $[M+H]^+$ = 699.2641; found: 699.2640.

(2*R*,2'*R*)-2,2'-((2-Iodo-5-methyl-1,3-phenylene)bis(oxy))bis(*N*-(2,6 diisopropylphenyl)propanamide) (3.46b)

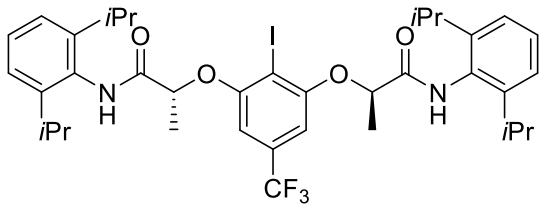


As described for the synthesis of **3.46a**, (2*R*,2'*R*)-2,2'-(2-iodo-5-methyl-1,3-phenylene)bis(oxy)dipropanoic acid (**3.45b**) (300 mg, 0.761 mmol, 1 equiv.), oxalyl chloride (338 mg, 2.664 mmol, 3.5 eq) and a catalytic amount of DMF were stirred at room temperature in dry DCM (8 mL) for 3 h under argon. The reaction mixture was concentrated under reduced pressure. The crude product was re-dissolved in dry CH_2Cl_2 (5 mL) and treated with 2,6-diisopropylaniline (675 mg, 3.806 mmol, 5 equiv.) and pyridine (241 mg, 3.044 mmol, 4 equiv.). The reaction mixture was stirred at room temperature for 16 h under argon. Work-up and purification by flash column chromatography (8:2→1:1 Hex/EtOAc) afforded pure **3.46b** as a white solid (0.4752 g, 88 %, 0.6667 mmol).

m.p.: 113-116 °C; $[\alpha]_D^{20}$: - 38.86° (c = 0.6 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (s, 2H, N*H*), 7.31 (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.18 (d, *J* = 7.7 Hz, 4H, Ar*H*), 6.54 (s, 2H, Ar*H*), 5.03 (q, *J* = 6.6 Hz, 2H, -O-C*H*(CH_3)-), 3.11-2.85 (m, 4H, Ar-C*H*(CH_3)$_2$), 2.40 (s, 3H, ArC*H*$_3$), 1.80 (d, *J* = 6.6 Hz, 6H, -O-CH(C*H*$_3$)-), 1.19 (d, *J* = 6.7 Hz, 12H, Ar-CH(C*H*$_3$)$_2$), 1.17-1.03 (m, 12H, Ar-CH(C*H*$_3$)$_2$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.85, 156.88, 146.32, 141.73, 130.12,

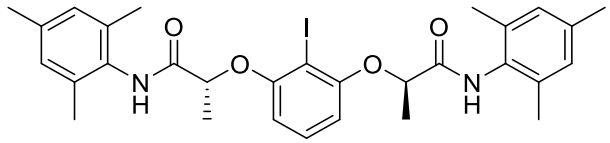
128.76, 123.67, 108.21, 76.41, 76.14, 28.83, 23.72, 22.09, 18.91 ppm. Spectroscopic data in a good agreement with literature.[4]

(2*R*,2'*R*)-2,2'-((2-Iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))bis(N-(2,6-diisopropylphenyl)propanamide) (3.46c)



The synthesis and characterisation of the title compound were described under chapter 2 (see compound **2.59**).[14]

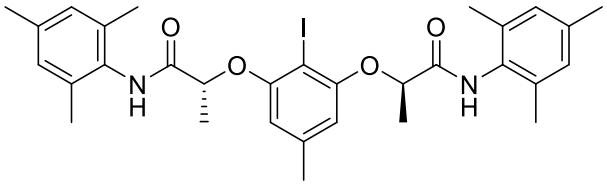
(2*R*,2'*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))bis(*N*-mesitylpropanamide) (3.46d)



A suspension of (2R,2'R)-2,2'-(2-iodo-1,3-phenylene)bis(oxy)dipropanoic acid (**3.45a**) (700 mg, 1.841 mmol, 1 equiv.) in dry DCM (20 mL) was treated with oxalyl chloride (818 mg, 6.445 mmol, 3.5 equiv.) and a catalytic amount of DMF under an argon atmosphere. The mixture was stirred at room temperature for 3 h, then concentrated under reduced pressure. The crude product (acid chloride) was dissolved in dry DCM (9 mL) and treated with and 2,4,6-trimrthylaniline (996 mg, 7.366 mmol, 4 equiv.) and pyridine (583 mg, 7.366 mmol, 4 equiv.) under argon. The reaction mixture was stirred at room temperature for 16 h. Aqueous HCl (3 M) was then added, the resulting mixture was extracted with CH_2Cl_2 (3 X 10 mL), the combined organic layers were dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure to afford **3.46d** as a white solid (0.83 g, 73%, 1.351 mmol).

m.p.: 238 – 240 ºC; $[\alpha]_D^{20}$: - 109.46º (c = 0.6333 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (s, 2H, N*H*), 7.35 (t, *J* = 8.3 Hz, 1H, Ar*H*), 6.93 (s, 4H, Ar*H*(Mes)), 6.67 (d, *J* = 8.4 Hz, 2H, Ar*H*), 5.01 (q, *J* = 6.7Hz, 2H, -O-C*H*(CH_3)-), 2.27 (S, 6H, ArC*H*$_3$(Mes)), 2.15 (S, 12H, ArC*H*$_3$(Mes)), 1.78 (d, *J* = 6.7 Hz, 6H, -O-CH(C*H*$_3$)-) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.8, 157.1, 137.4, 135.2, 130.8, 130.2, 129.2, 107.2, 80.7, 76.3, 21.1, 18.9, 18.4 ppm. Spectroscopic data in a good agreement with literature.[4]

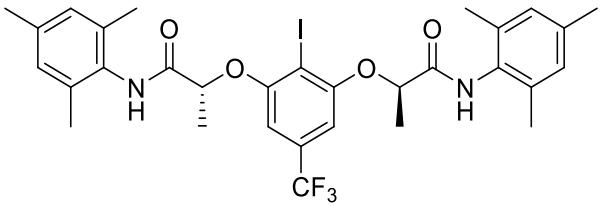
(2*R*,2'*R*)-2,2'-((2-Iodo-5-methyl-1,3-phenylene)bis(oxy))bis(*N*-mesitylpropanamide) (3.46e)



As described for the synthesis of **3.46d**, (2*R*,2'*R*)-2,2'-(2-iodo-5-methyl-1,3-phenylene)bis(oxy)dipropanoic acid (**3.45b**) (542 mg, 1.375mmol, 1 equiv.), oxalyl chloride (609 mg, 4.440 mmol, 3.5 equiv.) and a catalytic amount of DMF were stirred in 15 mL dry DCM for 3 h at room temperature under an argon atmosphere. The reaction mixture was concentrated *in vacuo* and the crude product, 2,4,6-trimethylaniline (742 mg, 5.074 mmol, 4 equiv.) and pyridine (434 mg, 5.074 mmol, 4 equiv.) were stirred in 7 mL dry DCM for 16 h at room temperature under an argon atmosphere. Work-up and purification by flash column chromatography (8:2→2:2 Hex/EtOAc) afforded **3.46e** as a white solid (0.7396 g, 86 %, 1.1767 mmol).

m.p.: 163 – 164 ºC; $[\alpha]_D^{20}$: - 91.31º (c = 0.7666 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 2H, N*H*), 6.90 (s, 4H, Mes*H*), 6.47 (s, 2H, Ar*H*), 4.98 (q, *J* = 6.6 Hz, 2H, -O-C*H*(CH_3)-), 2.35 (s, 3H, ArC*H*$_3$), 2.27 (s, 6H, Mes-C*H*$_3$), 2.14 (s, 12H, Mes-C*H*$_3$), 1.78 (d, *J* = 6.6 Hz, 6H, -O-CH(C*H*$_3$)-) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.9, 156.8, 141.6, 137.4, 135.2, 130.2, 129.2, 108.3, 76.5, 76.2, 22.0, 21.1, 19.0, 18.4 ppm. Spectroscopic data in a good agreement with literature.[4]

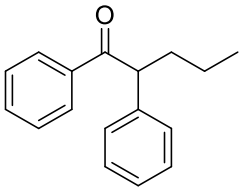
(2*R*,2'*R*)-2,2'-((2-Iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))bis(N-mesitylpropanamide)(3.46f)



The synthesis and characterisation of the title compound were described under **chapter 2** (see compound **2.60**).[14]

6.3.3. Catalytic oxidative rearrangement of alkenes

1,2-diphenylpentan-1-one (rac-3.47a)



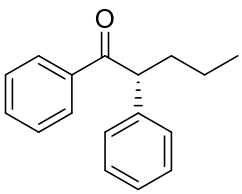
To a stirred mixture of alkene **3.40a** (28.0 mg, 0.13 mmol, 1 equiv.) an Bu_4NI (9.6 mg, 0.026 mmol, 0.2 equiv.) in MeOH/H_2O (20:1, 2 mL) was added Oxone® (120 mg, 0.95 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature. The reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were filtered through a TELOS Phase Separator and concentrated under vacuum. The crude material was purified by preparative TLC (Hexane/EtOAC, 9:1) to give pure **rac-3.47a** as a colourless oil (27 mg, 0.113 mmol,).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.26 – 7.20(m, 4H), 7.15 – 7.10 (m, 1H), 4.49 (t, *J* = 7.2 Hz, 1H), 2.13 – 2.04 (m, 1H), 1.80 – 1.68 (m, 1H), 1.30 – 1.14 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.3, 140.0, 137.2, 132.9, 129.0, 128.8, 128.6, 128.4, 127.1, 53.6, 36.3, 21.0, 14.2 ppm. Spectroscopic data are in a good in agreement with literature.[8]

General procedure B: Catalytic asymmetric oxidative rearrangement of alkenes

$TsOH.H_2O$ (1.5 equiv.) was added to the solution of aryl alkene (1.0 equiv.), iodoarene **3.44b** (0.2 equiv.), *m*CPBA (1.0 equiv.), methanol (8.0 equiv.) in CH_2Cl_2/TFE (10:1) under argon. The reaction mixture was stirred at 0 °C for 4 h, then at room temperature for additional 16 h. The reaction was quenched with a (1:1) mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution. Then diluted with water and extracted with CH_2Cl_2 (3X). The combined organic phases were filtered through a TELOS Phase Separator and concentrated under vacuum to give the crude product.

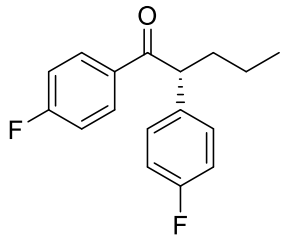
(*R*)-1,2-diphenylpentan-1-one (3.47a)



Following the general procedure B. 1,1-Diphenylpentene (66.5 mg, 0.3 mmol), catalyst **3.44b** (25.3 mg, 0.06 mmol), *m*CPBA (67 mg, 0.3 mmol), TsOH•H_2O (85.5 mg, 0.45 mmol) and methanol (97 μL, 2.4 mmol). The product was obtained as a colourless oil (48.3 mg, 41%, 0.2027 mmol, 69% ee).

$[\alpha]_D^{20}$: - 143.5º (c = 0.7666 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.26 – 7.20(m, 4H), 7.15 – 7.10 (m, 1H), 4.49 (t, *J* = 7.2 Hz, 1H), 2.13 – 2.04 (m, 1H), 1.80 – 1.68 (m, 1H), 1.30 – 1.14 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.3, 140.0, 137.2, 132.9, 129.0, 128.8, 128.6, 128.4, 127.1, 53.6, 36.3, 21.0, 14.2 ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*- PrOH = 99.5/0.5, 1.0 mL/min, 10 ºC, 243 nm; t_R (*S*) = 9.2 min, t_R (*R*) = 11.9 min; 69% *ee*. Spectroscopic data are in a good in agreement with literature.[8]

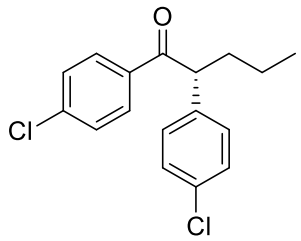
(*R*)-1,2-bis(4-fluorophenyl)pentan-1-one (3.47b)



Following the general procedure B. 1,1-Bis(4-fluorophenyl)pentene (155 mg, 0.6 mmol), catalyst **3.44b** (50.6 mg, 0.12 mmol), *m*CPBA (134 mg, 0.6 mmol), TsOH•H_2O (171 mg, 0.9 mmol) and methanol (194 μL, 4.8 mmol). The product was obtained as a colourless oil (60.9 mg, 38%, 0.222 mmol, 95% ee,).

$[\alpha]_D^{20}$: - 75.99º (c = 0.8333 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.86 (m, 2H), 7.21 – 7.14 (m, 2H), 7.02 – 6.95 (m, 2H), 6.93 – 6.87 (m, 2H), 4.42 (t, *J* = 7.3 Hz, 1H), 2.10 – 1.96 (m, 1H), 1.75 – 1.64 (m, 1H), 1.27 – 1.10 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.6, 165.7 (d, *J* = 255.0 Hz), 162.0 (d, *J* = 245.7 Hz), 135.4 (d, *J* = 3.2 Hz), 133.3 (d, *J* = 3.0 Hz), 131.3 (d, *J* = 9.3 Hz), 129.8 (d, *J* = 8.0 Hz), 115.9 (d, *J* = 13.6 Hz), 115.8 (d, *J* = 14.0 Hz), 52.6, 36.3, 20.9, 14.1 ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*- PrOH = 99.5/0.5, 1.0 mL/min, 10 ºC, 265 nm; t_R (*R*) = 11.4 min, t_R (*S*) = 12.3 min; 95% *ee*. Spectroscopic data are in a good agreement with literature.[8]

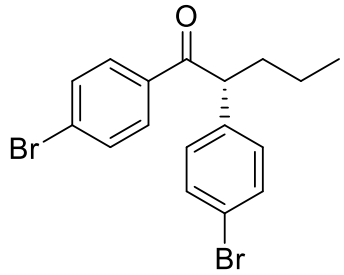
(*R*)-1,2-bis(4-chlorophenyl)pentan-1-one (3.47c)



Following the general procedure B. 1,1-Bis(4-chlorophenyl)pentene (87 mg, 0.3 mmol), catalyst **3.44b** (25.3 mg, 0.06 mmol), *m*CPBA (67 mg, 0.3 mmol), TsOH•H_2O (85.5 mg, 0.45 mmol) and methanol (97 μL, 2.4 mmol). The product was obtained as a colourless oil (32.4 mg, 36%, 0.1055 mmol, 75% ee).

$[\alpha]_D^{20}$: - 35.2º (c = 0.8333 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.23 – 7.19 (m, 2H), 7.15-7.13 (m, 2H), 4.39 (t, *J* = 7.3 Hz, 1H), 2.09 – 1.96 (m, 1H), 1.75 – 1.65 (m, 1H), 1.27 – 1.11 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 198.7, 139.6, 138.0, 135.1, 133.1, 130.1 (2C), 129.6 (2C), 129.2 (2C), 129.0 (2C), 52.8, 36.1, 20.9, 14.1ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*- PrOH = 99.5/0.5, 1.0 mL/min, 10 ºC, 265 nm; t_R (*S*) = 14.3 min, t_R (*R*) = 16.0 min; 75% *ee*. Spectroscopic data are in a good in agreement with literature.[8]

(*R*)-1,2-bis(4-bromophenyl)pentan-1-one (3.47d)

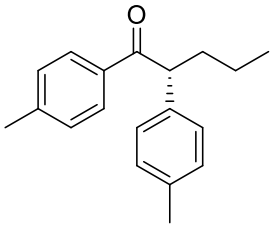


Following the general procedure B. 1,1-Bis(4-bromophenyl)pentene (114 mg, 0.3 mmol), catalyst **3.44b** (25.3 mg, 0.06 mmol), *m*CPBA (67 mg, 0.3 mmol), TsOH•H_2O (85.5 mg, 0.45 mmol) and methanol (97 μL, 2.4 mmol). The product was obtained as a colourless oil (39.6 mg, 36%, 0.0999 mmol, 83% ee).

$[\alpha]_D^{20}$: - 21.6º (c = 0.8333 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 4.44 (t, *J* = 7.2 Hz, 1H), 2.14 – 2.07 (m, 1H), 1.81 – 1.74 (m, 1H), 1.34 – 1.20 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 198.6, 138.4, 135.4, 132.1 (2C), 131.9 (2C), 130.1 (2C),

129.9 (2C), 128.2, 121.1, 52.8, 35.9, 20.8, 14.0 ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*- PrOH = 99.5/0.5, 1.0 mL/min, 10 ºC, 226 nm; t_R (*S*) = 10.3 min, t_R (*R*) = 13.8 min; 83% *ee*. Spectroscopic data are in a good in agreement with literature.[8]

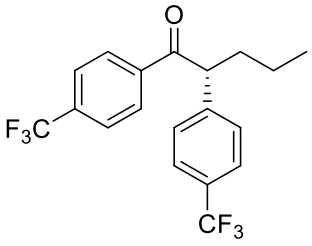
(*R*)-1,2-di-*p*-tolylpentan-1-one (3.47e)



Following the general procedure B. 1,1-Bis(4-methylphenyl)pentene (150 mg, 0.6 mmol), catalyst **3.44b** (50.6 mg, 0.12 mmol), *m*CPBA (134 mg, 0.6 mmol), TsOH•H_2O (171 mg, 0.9 mmol) and methanol (194 μL, 4.8 mmol). The product was obtained as a colourless oil (52.5 mg, 35%, 0.197 mmol, 91% ee,);

$[\alpha]_D^{20}$: - 62º (c = 0.8333 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8 Hz, 2H), 7.22 – 7.17 (m, 4H), 7.09 (d, *J* = 8 Hz, 2H), 4.51 (t, *J* = 7.3 Hz, 1H), 2.35 (s, 3H), 2.28 (s, 3H), 2.19 – 2.09 (m, 1H), 1.85 – 1.74 (m, 1H), 1.38 – 1.20 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.0, 143.6, 137.1, 136.5, 134.6, 129.6 (2C), 129.3 (2C), 128.9 (2C), 128.2 (2C), 52.9, 36.2, 21.7, 21.1, 21.0, 14.2 ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*- PrOH = 99.5/0.5, 1.0 mL/min, 10 ºC, 254 nm; t_R (*S*) = 12.7 min, t_R (*R*) = 18.2 min; 91% *ee*. Spectroscopic data are in a good in agreement with literature.[8]

(*R*)-1,2-bis(4-(trifluoromethyl)phenyl)pentan-1-one (3.47f)

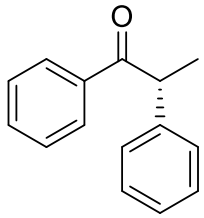


Following the general procedure B. 1,1-Bis(3-(trifluoromethyl)phenyl)pentene (107 mg, 0.3 mmol), catalyst (**3.44b**) (25.3 mg, 0.06 mmol), *m*CPBA (67 mg, 0.3 mmol), TsOH•H_2O (85.5 mg, 0.45 mmol) and methanol (97 μL, 2.4 mmol). The product was obtained as a colourless oil (20 mg, 18%, 0.0534 mmol, 22% ee).

$[\alpha]_D^{20}$: - 40.8º (c = 0.8333 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.51 (app d, *J* = 7.9 Hz, 2H), 7.46 –

7.41 (m, 1H), 4.62 (t, *J* = 7.3 Hz, 1H), 2.25 – 2.13 (m, 1H), 1.92 – 1.79 (m, 1H), 1.39 – 1.20 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.3, 138.4, 135.3, 132.3 (2C), 131.8 (2C), 131.7, 131.3, 130.2 (2C), 129.7 (2C), 128.3, 121.2, 53.4, 36.3, 20.9, 14.1 ppm (Fluorine coupling not found); HPLC: YMC Chiral Amylose-C column, hexane/*i*-PrOH = 99.75/0.25 1.0 mL/min, 10 ºC, 345 nm; t_R (*S*) = 5.4 min, t_R (*R*) = 6.3 min; 22% *ee*. Spectroscopic data are in a good in agreement with literature.[8]

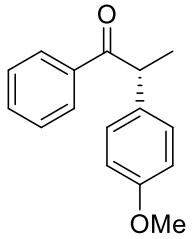
(*R*)-1,2-diphenylpropan-1-one (3.47g)



Following the general procedure B. 1,1-Diphenylpropene (58 mg, 0.3 mmol), catalyst **3.44b** (25.3 mg, 0.06 mmol), *m*CPBA (67 mg, 0.3 mmol), TsOH•H_2O (85.5 mg, 0.45 mmol) and methanol (97 μL, 2.4 mmol). The product was obtained as a colourless oil (28.8 mg, 48%, 0.137 mmol, 76% ee).

$[\alpha]_D^{20}$: - 186.95º (c = 0.7666 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7 Hz, 2H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.31– 7.30 (m, 4H), 7.22 (app sext, *J* = 4 Hz, 1H), 4.71 (q, *J* = 6.9 Hz, 1H), 1.56 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 200.5, 141.6, 136.6, 132.9, 129.1 (2C), 128.9 (2C), 128.6 (2C), 127.9 (2C), 127.0, 48.0, 19.6 ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*- PrOH = 98/2, 1.0 mL/min, 10 ºC, 280 nm; t_R (*S*) = 7.3 min, t_R (*R*) = 8.3 min; 76% *ee*. Spectroscopic data are in a good in agreement with literature.[8]

(*R*)-2-(4-methoxyphenyl)-1-phenylpropan-1-one (3.47h)

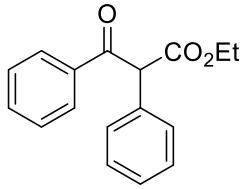


Following the general procedure B. 1-(4-Anisyl)-1-phenylpropene (127 mg, 0.6 mmol), catalyst **3.44b** (50.6 mg, 0.12 mmol), *m*CPBA (134 mg, 0.6 mmol), TsOH•H_2O (171 mg, 0.9

mmol) and methanol (194 μL, 4.8 mmol). The product was obtained as a colourless oil (34 mg, 34%, 0.1415 mmol, 93% ee,).

$[\alpha]_D^{20}$: - 125.4° (c = 0.8666 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.9 Hz, 2H), 7.50 – 7.45 (m, 1H), 7.41 – 7.35 (m, 2H), 7.22 – 7.18 (m, 2H), 6.85 – 6.79 (m, 2H), 4.64 (q, *J* = 6.8 Hz, 1H), 3.75 (s, 3H), 1.51 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.7, 158.6, 136.6, 133.6, 132.8, 128.9, 128.9, 128.6, 114.5, 55.3, 47.1, 19.6 ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*- PrOH = 99.0/1.0, 1.0 mL/min, 10 ºC, 229 nm; t_R (*R*) = 19 min, t_R (*S*) = 23.5 min; 93% *ee*. Spectroscopic data are in a good in agreement with literature.[8]

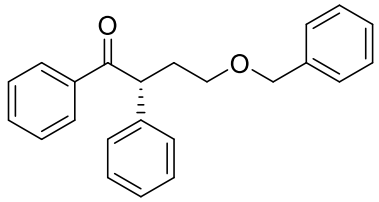
Ethyl 3-oxo-2,3-diphenylpropanoate (3.47i)



Following the general procedure B. Ethyl-3,3-diphenylacrylate (75.7 mg, 0.3 mmol), catalyst **3.44b** (25.3 mg, 0.06 mmol), *m*CPBA (67 mg, 0.3 mmol), TsOH•H_2O (85.5 mg, 0.45 mmol) and methanol (97 μL, 2.4 mmol). The product was obtained as a colourless oil (32 mg, 40%, 0.119 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, *J* = 7.4 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.41 – 7.22 (m, 7H), 5.58 (s, 1H), 4.24 – 4.13 (m, 2H), 1.21(t, *J* = 7.4 Hz, 3H) ppm. Spectroscopic data are in a good in agreement with literature.[8]

(*R*)-4-(benzyloxy)-1,2-diphenylbutan-1-one (3.47j)

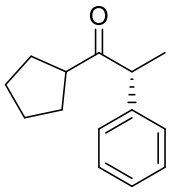


Following the general procedure B. 4-Benzyloxy-1,1-diphenyl-but-1-ene (188.6 mg, 0.6 mmol), catalyst **3.44b** (50.6 mg, 0.12 mmol), *m*CPBA (134 mg, 0.6 mmol), TsOH•H_2O (171 mg, 0.9 mmol) and methanol (194 μL, 4.8 mmol). The product was obtained as a colourless oil (53.2 mg, 28%, 0.161 mmol, 76% ee,).

$[\alpha]_D^{20}$: - 34° (c = 1.0 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.1 Hz, 2H), 7.29 – 7.22 (m, 9H), 7.19 – 7.14 (m, 1H), 4.86 (t, *J* =

7.3 Hz, 1H), 4.41 (s, 1H), 3.50 – 3.42 (m, 1H), 3.39 – 3.32 (m, 1H), 2.54 – 2.43 (m, 1H), 2.13 – 2.02 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.0, 139.3, 138.7, 137.1, 133.1, 129.3, 129.2, 129.0, 128.8, 128.7, 128.1, 128.0, 127.5, 73.1, 67.7, 50.0, 34.1 ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*- PrOH = 99.0/1.0, 1.0 mL/min, 10 ºC, 238 nm; t_R (*S*) = 18.9 min, t_R (*R*) = 19.5 min; 76% *ee*. Spectroscopic data are in a good in agreement with literature.[8]

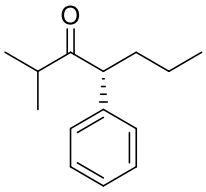
(*R*)-1-cyclopentyl-2-phenylpropan-1-one (3.47k)



Following the general procedure B. 1-Cyclopentyl-1-phenylpropene (168 mg, 0.9 mmol), catalyst **3.44b** (76 mg, 0.18 mmol), *m*CPBA (201 mg, 0.9 mmol), TsOH•H_2O (257 mg, 1.35 mmol) and methanol (582 μL, 7.2 mmol). The product was obtained as a colourless oil (25.8 mg, 43%, 0.1275 mmol, 7% ee,).

$[\alpha]_D^{20}$: - 174º (c = 0.6666 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 2H), 7.19 – 7.13 (m, 3H), 3.79 (q, *J* = 6.9 Hz, 1H), 2.87 – 2.75 (m, 1H), 1.79 – 1.72 (m, 1H), 1.64 – 1.38 (m, 8H), 1.32 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 214.0, 141.1, 128.9, 128.2, 127.1, 52.7, 50.1, 30.7, 29.2, 26.3, 18.2 ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*- PrOH = 99.0/1.0, 1.0 mL/min, 10 ºC, 229 nm; t_R (*S*) = 7.1 min, t_R (*R*) = 7.7 min; 7% *ee*. Spectroscopic data are in a good in agreement with literature.[8]

(*R*)-2-methyl-4-phenylheptan-3-one (3.47l)

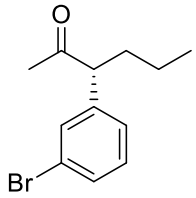


Following the general procedure B. 2-Methyl-3-phenyl-4-heptene (56.5 mg, 0.3 mmol), catalyst **3.44b** (25.3 mg, 0.06 mmol), *m*CPBA (67 mg, 0.3 mmol), TsOH•H_2O (85.5 mg, 0.45 mmol) and methanol (97 μL, 2.4 mmol). The product was obtained as a colourless oil (25.8 mg, 43%, 0.1263 mmol, 33% ee).

$[\alpha]_D^{20}$: - 240º (c = 0.9 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.12 (m, 5H), 3.79 (t, *J* = 7 Hz, 1H), 2.65 (hept, *J* = 7 Hz, 1H), 1.98 – 1.85 (m, 1H), 1.67 – 1.59 (m, 1H), 1.20 – 1.08 (m, 2H), 1.07 (d, *J* = 7 Hz, 3H), 0.87 – 0.74 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 214.4,

139.3, 128.8 (2C), 128.4 (2C), 127.1, 57.1, 39.8, 35.1, 20.9, 19.0, 18.2, 14.3 ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*- PrOH = 99.75/0.25, 1.0 mL/min, 10 ºC, 223 nm; t_R (*R*) = 4.9 min, t_R (*S*) = 5.2 min; 33% *ee*. Spectroscopic data are in a good in agreement with literature.[8]

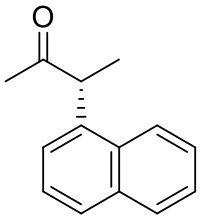
(*R*)-3-(3-bromophenyl)hexan-2-one (3.47m)



Following the general procedure B. 2-(3-Bromophenyl)-2-hexene (67.5 mg, 0.3 mmol), catalyst **3.44b** (25.3 mg, 0.06 mmol), *m*CPBA (67 mg, 0.3 mmol), TsOH•H_2O (85.5 mg, 0.45 mmol) and methanol (97 μL, 2.4 mmol). The product was obtained as a colourless oil (33 mg, 33%, 0.104 mmol, 15% ee).

$[\alpha]_D^{20}$: - 20.6º (c = 0.8333 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.16 – 7.12 (m, 1H), 3.58 (t, *J* = 7.4 Hz, 1H), 2.05 (s, 3H), 2.04 – 1.90 (m, 1H), 1.70 – 1.60 (m, 1H), 1.28 – 1.11 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 207.6, 141.2, 131.1, 130.2 (2C), 126.6, 122.8, 59.0, 33.9, 29.0, 20.5, 13.8 ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*-PrOH = 99.5/0.5, 1.0 mL/min, 10 ºC, 254 nm; t_R (*S*) = 8.3 min, t_R (*R*) = 9.3 min; 15% *ee*. Spectroscopic data are in a good in agreement with literature.[8]

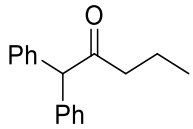
(*R*)-3-(naphthalen-1-yl)butan-2-one (3.47n)



Following the general procedure B. 1-(But-2-en-2-yl)naphthalene (109.4 mg, 0.6 mmol), catalyst **3.44b** (50.6 mg, 0.12 mmol), *m*CPBA (134 mg, 0.6 mmol), TsOH•H_2O (171 mg, 0.9 mmol) and methanol (194 μL, 4.8 mmol). The product was obtained as a colourless oil (39 mg, 66%, 0.197 mmol, 12% ee,).

$[\alpha]_D^{20}$: - 16.9º (c = 1.3 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.91 – 7.88 (m, 1H), 7.84 – 7.77 (m, 1H), 7.58 – 7.43 (m, 3H), 7.33 (dd, *J* = 7, 1.0 Hz, 1H), 4.45 (q, *J* = 7 Hz, 1H), 2.01 (s, 3H), 1.56 (d, *J* = 7 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.7, 137.1, 134.3, 131.6, 129.3, 128.0, 126.7, 126.0, 125.9, 125.3, 123.2, 50.2, 28.2, 17.1 ppm; HPLC: YMC Chiral Amylose-C column, hexane/*i*-PrOH = 99.0/1.0, 1.0 mL/min, 10 ºC, 254 nm; t_R (*S*) = 7.0 min, t_R (*R*) = 7.6 min; 12% *ee*. Spectroscopic data are in a good in agreement with literature.[8]

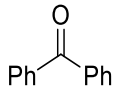
1,1-diphenylpentan-2-one (3.48)



$TsOH.H_2O$ (85.5 mg, 0.45 mmol, 1.5 equiv.) was added to the solution of 1,1-Diphenylpentene (66.7 mg,0.3 mmol, 1.0 equiv.), *m*CPBA (51.7 mg, 0.3 mmol, 1.0 equiv.), methanol (97 μL, 2.4 mmol, 8.0 equiv.) in CH_2Cl_2/TFE (10:1)(3.5 mL) under argon. The reaction mixture was stirred at 0 ºC for 4 h, then at room temperature for additional 16 h. The reaction was quenched with a (1:1) mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution. Then diluted with water and extracted with CH_2Cl_2 (3X3 mL). The combined organic phases were filtered through a TELOS Phase Separator and concentrated under vacuum. The crude material was purified by preparative TLC to give pure **3.48** as a colourless oil (50.8 mg, 0.213 mmol, 71%,).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.2 Hz, 4H), 7.30 – 7.22 (m, 6H), 5.14 (s, 1H), 2.54 (t, *J* = 7.3 Hz, 2H), 1.63 (sex, *J* = 7.4 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H) ppm. Spectroscopic data are in a good agreement with literature.[15]

Benzophenone (3.49)

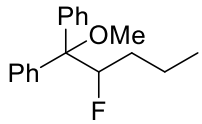


Isolated from the above reaction but using *m*-CPBA (1.5 equiv.). (15.5 mg, 0.085 mmol, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.3 Hz, 4H), 7.59 (t, *J* = 7.4 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 4H) ppm. Spectroscopic data are in a good agreement with literature.[16]

Oxyfluorination products 3.50 and 3.51

TsOH.H_2O (85.5 mg, 0.45 mmol, 1.5 equiv.) was added to the solution of 1,1-diphenylpentene (**3.40a**) (66.7 mg,0.3 mmol, 1.0 equiv.), Selectfluor® (106.3 mg, 0.3mmol, 1.0 equiv.), methanol (97 μL, 2.4 mmol, 8.0 equiv.) in CH_2Cl_2/TFE (10:1)(3.5 mL) under argon. The reaction mixture was stirred at 0 ^oC for 4 h, then at room temperature for additional 16 h. The reaction was quenched with a (1:1) mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ solution. Then diluted with water and extracted with CH_2Cl_2 (3X3 mL). The combined organic phases were filtered through a TELOS Phase Separator and concentrated under vacuum.

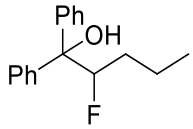
(2-Fluoro-1-methoxypentane-1,1-diyl)dibenzene (3.50)



colorless oil (22.9 mg, 0.084 mmol, 28%).

IR (neat) ν/cm^{-1}: 3024, 2958, 1076; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 6.99 (m, 10H, Ar*H*), 5.39 – 5.17 (m, 1H, C*H*F), 3.12 (s, 3H, OMe), 1.54 – 1.40 (m, 2H, C$H_2$$CH_2CH_3$), 1.40 – 1.22 (m, 2H, CH_2CH_2CH_3), 0.80 (t, *J* = 7.0 Hz, 3H, CH_2CH_2CH_3) ppm. ^{13}C NMR (126 MHz, CDCl3) δ 141.18, 128.56, 127.85, 127.20 (d, *J* = 10.0 Hz), 95.84 (d, *J* = 182.0 Hz), 83.72 (d, *J* = 19.3 Hz), 52.68 (d, *J* = 12.2 Hz), 31.37, 19.05, 13.87 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): δ = -186.99 ppm; HRMS: m/z calculated for $C_{17}H_{18}F$ $[M - MeO]^+$ = 241.1393; found: 241.1393.

2-Fluoro-1,1-diphenylpentan-1-ol (3.51)

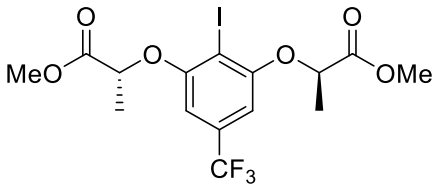
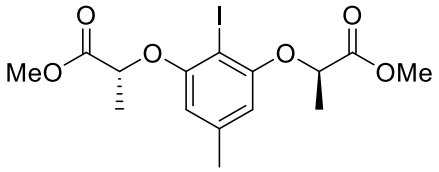
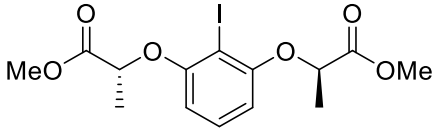
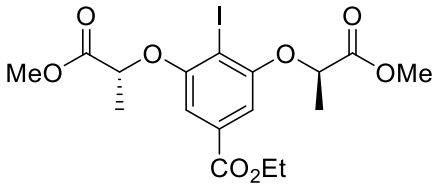
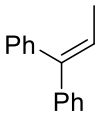


White solid (9.3 mg, 0.036 mmol, 12%).

m.p.:109 -111 ^{O}C; IR (solid) ν/cm^{-1}: 3556, 33028, 2958; ^{1}H NMR (500 MHz, CDCl3) δ 7.47 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.35 – 7.10 (m, 8H, Ar*H*), 5.31 (dd, *J* = 47.4, 10.2 Hz, 1H, C*H*F), 2.52 (s, 1H, OH), 1.82 – 1.50 (m, 1H, C$H_2$$CH_2CH_3$), 1.59 – 1.37 (m, 1H, C$H_2$$CH_2CH_3$), 1.37 – 0.96 (m, 2H, CH_2CH_2CH_3), 0.80 (t, *J* = 7.1 Hz, 3H, CH_2CH_2CH_3) ppm. ^{13}C NMR (126 MHz, CDCl3) δ 144.83, 128.26, 127.22 (d, *J* = 20.6 Hz), 126.78, 125.85, 96.05 (d, *J* = 177.8 Hz), 79.14 (d, *J* = 21.0 Hz), 30.88 (d, *J* = 21.2 Hz), 18.92, 13.83 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): δ = -189.479 ppm; HRMS: m/z calculated for $C_{17}H_{18}F$ $[M- OH]^+$ = 241.1393; found: 241.1393.

6.4. Experimental data for chapter 4: Indirect anodic oxidative rearrangement of alkenes

Cyclic voltammetry

Entry	Compound	E_p^{ox} (V)
1	 **4.27**	2.35
2	 **4.28**	1.86
3	 **4.29**	2.00
4	 **4.30**	2.20
5	 **4.31**	2.15

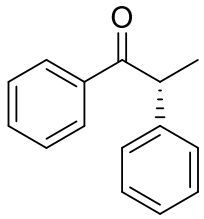
Oxidative cyclic voltammograms of the substrates (2 mM) measured in acetonitrile containing 0.1 M of Bu_4NClO_4 at 100 mV/s scan rate. Working electrode: glassy carbon (3 mm diameter); Platinum wire as a counter electrode and Ag/AgCl in 3M NaCl as a reference electrode.

General procedure C:

A 10 mL three-necked round-bottomed flask was equipped with a magnetic stirrer, two platinum plates (1.0×1.0 cm, each) electrodes and charged with TFE (4 mL). The Alkene (0.1 mmol, 1 equiv.), chiral iodoarene (0.1 mmol, 1 equiv.) and supporting electrolyte, *n*-Bu4NBF4

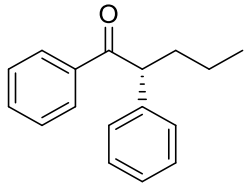
(0.2 mmol, 2 equiv.). The resulting mixture was electrolysed at constant current (7.0 mA) for 63 min at room temperature. The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (Petroleum ether:EtOAc, 9:1) afforded the pure product.

(*R*)-1,2-diphenylpropan-1-one (4.32a)



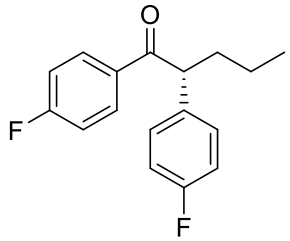
Following the general procedure C. 1,1-Diphenylpropene (19.5 mg, 0.1 mmol), catalyst **4.29** (40.8 mg, 0.1 mmol), electrolyte *n*-Bu_4NBF_4 (66 mg, 0.2 mmol) in TFE (4 mL). The product was obtained as a colourless oil (7.6 mg, 38%, 0.0361 mmol, ee = 55%). Spectroscopic and HPLC data were reported under chapter 3 (see compound **3.47g**).

(*R*)-1,2-diphenylpentan-1-one (4.32b)



Following the general procedure C. 1,1-Diphenylpentene (22.3 mg, 0.1 mmol), catalyst **4.29** (40.8 mg, 0.1 mmol), electrolyte *n*-Bu_4NBF_4 (66 mg, 0.2 mmol) in TFE (4 mL). The product was obtained as a colourless oil (4 mg, 20%, 0.0168 mmol, ee = 12%). Spectroscopic and HPLC data were reported under chapter 3 (see compound **3.47a**).

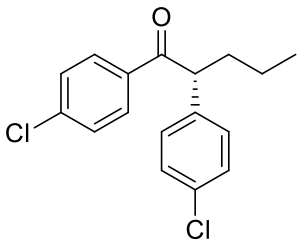
(*R*)-1,2-bis(4-fluorophenyl)pentan-1-one (4.32c)



Following the general procedure C. 1,1-Bis(4-fluorophenyl)pentene (26 mg, 0.1 mmol), catalyst **4.29** (40.8 mg, 0.1 mmol), electrolyte *n*-Bu_4NBF_4 (66 mg, 0.2 mmol) in TFE (4 mL).

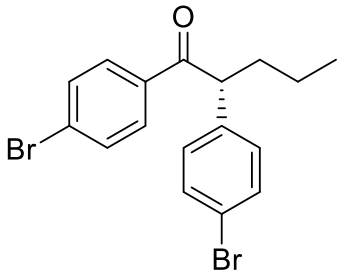
The product was obtained as a colourless oil (8 mg, 30%, 0.0291 mmol, ee = 95%). Spectroscopic and HPLC data were reported under chapter 3 (see compound **3.47b**).

(*R*)-1,2-bis(4-chlorophenyl)pentan-1-one (4.32d)



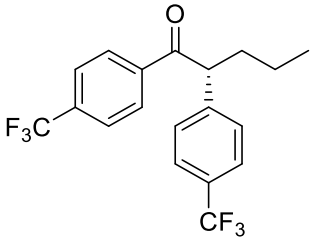
Following the general procedure. 1,1-Bis(4-chlorophenyl)pentene (29 mg, 0.1 mmol), catalyst **4.29** (40.8 mg, 0.1 mmol), electrolyte *n*-Bu4NBF4 (66 mg, 0.2 mmol) in TFE (4 mL). The product was obtained as a colourless oil (9 mg, 30%, 0.0293 mmol, ee = 97%). Spectroscopic and HPLC data were reported under chapter 3 (see compound **3.47c**).

(*R*)-1,2-bis(4-bromophenyl)pentan-1-one (4.32e)



Following the general procedure C. 1,1-Bis(4-bromophenyl)pentene (38 mg, 0.1 mmol), catalyst **4.29** (40.8 mg, 0.1 mmol), electrolyte *n*-Bu4NBF4 (66 mg, 0.2 mmol) in TFE (4 mL). The product was obtained as a colourless oil (5.07 mg, 13%, 0.0128 mmol, ee = 99%). Spectroscopic and HPLC data were reported under chapter 3 (see compound **3.47d**).

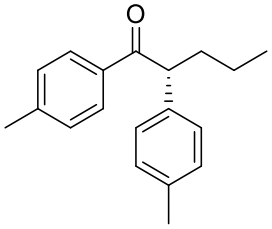
(*R*)-1,2-bis(4-(trifluoromethyl)phenyl)pentan-1-one (4.32f)



Following the general procedure C. 1,1-Bis(3-(trifluoromethyl)phenyl)pentene (35.8 mg, 0.1 mmol), catalyst **4.29** (40.8 mg, 0.1 mmol), electrolyte *n*-Bu4NBF4 (66 mg, 0.2 mmol) in TFE

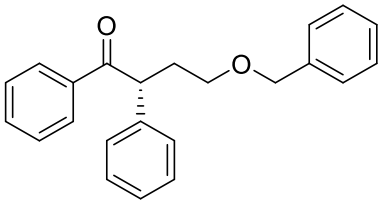
(4 mL). The product was obtained as a colourless oil (7.77 mg, 21%, 0.0208 mmol, ee = 7%). Spectroscopic and HPLC data were reported under chapter 3 (see compound **3.47f**).

(*R*)-1,2-di-*p*-tolylpentan-1-one (4.32g)



Following the general procedure C. 1,1-Bis(4-methylphenyl)pentene (25 mg, 0.1 mmol), catalyst **4.29** (40.8 mg, 0.1 mmol), electrolyte *n*-Bu_4NBF_4 (66 mg, 0.2 mmol) in TFE (4 mL). The product was obtained as a colourless oil (10 mg, 38%, 0.03754 mmol, ee = 71%). Spectroscopic and HPLC data were reported under chapter 3 (see compound **3.47e**).

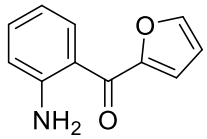
(*R*)-4-(benzyloxy)-1,2-diphenylbutan-1-one (4.32h)



Following the general procedure C. 4-Benzyloxy-1,1-diphenyl-but-1-ene (31.4 mg, 0.1 mmol), catalyst **4.29** (40.8 mg, 0.1 mmol), electrolyte *n*-Bu_4NBF_4 (66 mg, 0.2 mmol) in TFE (4 mL). The product was obtained as a colourless oil (12 mg, 40%, 0.0363 mmol, ee = 65%). Spectroscopic and HPLC data were reported under chapter 3 (see compound **3.47j**).

6.5. Experimental data for chapter 5: Secondary interactions in hypervalent iodine chemistry

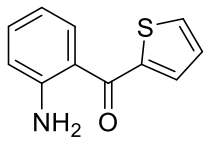
2-Aminophenyl)(furan-2-yl)methanone (5.17)



To a stirred solution of furan (9.0 mL, 114 mmol, 4.5 equiv.) in dry THF (100 mL) at –78 °C *n*-BuLi (2.5 M in hexane, 45 mL, 114 mmol, 4.5 equiv.) was added. The solution left to warm to room temperature overnight, diluted with dry THF. The solution was then added slowly to a cooled (–78°C) stirred solution of 2-cyanoaniline (3.0 g, 25 mmol, 1 equiv.) in dry THF (100 mL). Stirring was continued at room temperature for 12 h. The reaction mixture was then poured into ice and acidified with HCl (4 N) and stirred for 30 min. Solid Na_2CO_3 was then added portion wise with stirring until pH > 10, then extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, the residue was purified by column chromatography (CH_2Cl_2/pentane, 8:2) to afford pure **5.17** as brown oil (3.0 g, 16 mmol, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.66 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.29 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.12 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.76 – 6.65 (m, 2H), 6.55 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.88 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 183.9, 152.7, 150.5, 146.4, 134.1, 132.3, 119.6, 118.3, 117.1, 116.1, 112.0 ppm. Spectroscopic data are in a good agreement with literature.[17]

(2-Aminophenyl)(thiophen-2-yl)methanone (5.18)

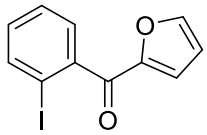


To a stirred solution of thiophene (6.0 mL, 76.5 mmol,4.5 equiv.) in dry THF (50 mL) at –78 °C *n*-BuLi (2.5 M in hexane, 30.6 mL, 76.5 mmol, 4.5 equiv.) was added. The solution left to warm to room temperature overnight, diluted with dry THF. The solution was then added slowly to a cooled (–78°C) stirred solution of 2-cyanoaniline (2.0 g, 17 mmol, 1 equiv.) in dry THF (50 mL). Stirring was continued at room temperature for 12 hours. The reaction mixture was then poured into ice and acidified with HCl (4 N) and stirred for 30 min. Solid Na_2CO_3

was then added portionwise with stirring until pH > 10, then extracted with diethyl ether (3 x 80 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, the residue was purified by column chromatography (CH_2Cl_2) to afford pure **5.18** as brown oil (2.75 g, 13.5 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (dd, *J* = 8.0, 1.6, 1H), 7.65 (dd, *J* = 5.0, 1.1, 1H), 7.57 (dd, *J* = 3.8, 1.1, 1H), 7.29 (ddd, *J* = 14.4, 8.0, 4.4, 1H), 7.13 (dd, *J* = 5.0, 3.8, 1H), 6.77 – 6.65 (m, 2H), 5.55 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 189.6, 150.0, 144.9, 134.0, 133.9, 132.9, 132.9, 127.7, 119.2, 117.1, 116.1 ppm. Spectroscopic data are in a good agreement with literature.[17]

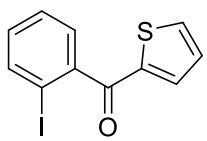
Furan-2-yl(2-iodophenyl)methanone (5.19)



To a cold stirred solution of (2-aminophenyl)(furan-2-yl)methanone(**5.17**) (3.0 g, 16.0 mmol, 1 equiv.) in water (40 mL) and concentrated HCl (2 mL) was added slowly a solution of sodium nitrite (1.13 g, 16.3 mmol, 1 equiv.) in water (2.5 mL). After stirring for additional 5 min, a solution of potassium iodide (2.71 g, 16.3 mmol, 1 equiv.) in water (5 mL) was added. After removing the cooling bath and stirring at room temperature for 5 min, the reaction mixture was heated to 90 °C with stirring for 10 min. After cooling to room temperature, the precipitated solid was filtered off and washed with water. The crude product was purified by column chromatography (hexane/ethyl acetate 9:1) to give pure **5.19** as a pale yellow solid (3.15 g, 10.6 mmol, 66%).

m.p. 75 – 77 °C; IR (solid) ν/cm^{-1}: 3068,1639, 1577; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 – 7.91 (m, 1H), 7.71 (dd, *J* = 1.7, 0.8, 1H), 7.47 – 7.38 (m, 2H), 7.19 (ddd, *J* = 8.0, 7.1, 2.1, 1H), 7.03 (dd, *J* = 3.6, 0.7, 1H), 6.58 (dd, *J* = 3.6, 1.7, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 184.1, 151.1, 148.2, 142.9, 139.9, 131.7, 128.6, 127.8, 122.2, 112.8, 92.5 ppm. HRMS: m/z calcd for $C_{11}H_8IO_2$ $[M+H]^+$ = 298.9563; found: 298.9561.

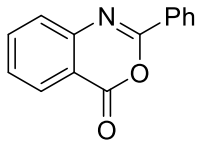
(2-Iodophenyl)(thiophen-2-yl)methanone (5.20)



(2-Aminophenyl)(thiophen-2-yl)methanone (**5.18**) (2.0 g, 9.84 mmol, 1 equiv.) was added to a solution of *p*-TsOH·H_2O (5.6 g, 29.5 mmol, 3 equiv.) in MeCN (7 mL). The reaction mixture was cooled to 10–15 °C, then a solution of $NaNO_2$ (1.357 g, 19.68 mmol, 2 equiv.) and KI (4.0 g, 24.6 mmol, 2.5 equiv.) in H_2O (3 mL) was added slowly. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 4 h. Water (30 mL) was then added followed by $NaHCO_3$ solution (1 M) until pH 9–10 then $Na_2S_2O_3$ solution (2 M, 4 mL). The mixture was extracted with CH_2Cl_2 and purified by flash chromatography (Hexane/Et_2O 9:1) to give pure **5.20** as a brown oil (2.856 g, 9 mmol, 95%).

IR (neat) ν/cm^{-1}: 3089,1633, 1514; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.78 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.44 (td, *J* = 7.4, 1.0 Hz, 1H), 7.39 (dt, *J* = 3.3, 2.1 Hz, 2H), 7.18 (ddd, *J* = 7.9, 7.3, 1.9 Hz, 1H), 7.12 (dd, *J* = 4.9, 3.8 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 189.5, 144.3, 143.1, 140.0, 136.3, 135.9, 131.4, 128.5, 128.3, 127.8, 92.3 ppm. HRMS: m/z calcd for $C_{11}H_8IOS$ $[M+H]^+$ = 314.9335; found: 314.9333.

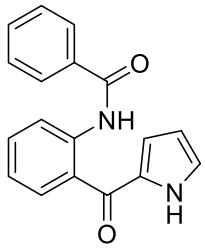
2-Phenyl-4*H*-benzoxazin-4-one (5.22)



Powdered Na_2CO_3 (13.73 g, 129.6 mmol, 2 equiv.) was added to a cooled (ice bath) stirred mixture of anthranilic acid (8.88 g, 64.8 mmol, 1 equiv.) in THF (130 ml), followed by the addition of benzoyl chloride (18.8 ml, 162 mmol, 2.5 equiv.). The cooling bath was removed after 10 min stirring was continued at room temperature overnight. Water (130 ml), was then added, stirring was continued for additional 10. The formed yellow solid was filtered off, washed with water and 50% aqueous methanol. A second crop was obtained from the filtrate upon standing. The combined crops were dried at 50 °C under high vacuum to give **5.22** (13.9 g, 62.3 mmol, 96%) as a pale yellow solid.

m.p. 122 – 125 °C, (lit:[17] 119 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.36 – 8.29 (m, 2H), 8.25 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.71 (dd, *J* = 8.1, 0.6, 1H), 7.60 – 7.49 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.8, 157.3, 147.1, 136.7, 132.8, 130.3, 128.9, 128.8, 128.5, 128.4, 127.4, 117.2 ppm. Spectroscopic data are in a good agreement with literature.[18]

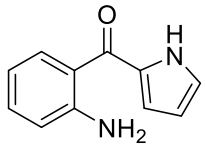
***N*-[2-(1*H*-Pyrrol-2-carbonyl)phenyl]benzamide (5.23)**



A solution of EtMgCl (2.8 M in THF, 9.75 mL, 27.3 mmol, 2.1 equiv.) in dry THF (5 mL) was cooled to 0 °C, then a solution of pyrrole (2.1 mL, 30.3 mmol, 2.3 equiv.) in dry toluene (2 mL) was added dropwise over 20 min. The mixture was then stirred at room temperature for 20 min, then a suspension of **5.22** (2.9 g, 13.0 mmol, 1 equiv.) in THF (3 mL) was added. After stirring for additional 45 min, the reaction mixture was heated under reflux for 3 h. Sat. aq. NH_4Cl solution (3 mL) was then added to the hot mixture over 5 min, stirring was continued for 20 min, then Na_2SO_4 (3 g) was added. The mixture was stirred for additional 20 min then filtered off. The collected solid was washed with THF, and the combined organic filtrate and washes were evaporated under reduced pressure. The residue was suspended in toluene (15 mL), and cooled in an ice bath, the formed solid was collected by filtration and washed with hexane, dried at room temperature overnight under high vacuum to give **5.23** as light green crystals (3.66 g, 12.6 mmol, 97%).

m.p.: 139 – 142 ºC; ^{1}H NMR (400 MHz, DMSO) δ = 12.17 (s, 1H), 11.12 (s, 1H), 8.27 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.90 – 7.86 (m, 2H), 7.84 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.66 – 7.50 (m, 4H), 7.30 (td, *J* = 7.6, 1.1 Hz, 1H), 7.23 (dd, *J* = 2.3, 1.4 Hz, 1H), 6.76 (dd, *J* = 3.8, 1.3 Hz, 1H), 6.27 (dd, *J* = 3.8, 2.4 Hz, 1H) ppm. ^{13}C NMR (101 MHz, DMSO) δ = 184.6, 164.7, 137.8, 134.4, 132.2, 132.0, 131.0, 130.9, 128.8, 127.2, 127.1, 123.7, 122.5, 120.3, 110.7 ppm. Spectroscopic data are in a good agreement with literature.[18]

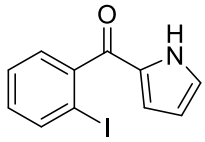
(2-Aminophenyl)(1*H*-pyrrol-2-yl)methanone (5.24)



A mixture of *N*-[2-(1*H*-pyrrol-2-carbonyl)phenyl]benzamide (**5.23**) (3.5 g, 12 mmol), methanol (24 mL) and aqueous NaOH (10 M, 6 mL) was refluxed for 24 h. Water (17 mL) was added to the solution while hot and stirred for 3 h at room temperature. The formed precipitate was filtered and washed with cold water then dried under vacuum and crystallised from toluene to give **5.24** as off-white solid (1.97 g, 10.6 mmol, 99%).

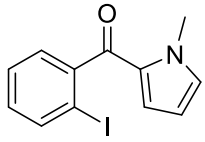
m.p. 125 – 127 °C (lit:[18] 125 – 126 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.55 (s, 1H), 7.86 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.29 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.09 (td, J = 2.7, 1.3 Hz, 1H), 6.85 (ddd, *J* = 3.8, 2.4, 1.3 Hz, 1H), 6.76 – 6.68 (m, 2H), 6.33 (dt, *J* = 3.8, 2.6 Hz, 1H), 5.54 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 186.0, 149.4, 133.3, 132.2, 131.9, 124.4, 119.9, 118.7, 117.0, 116.3, 111.0 ppm. Spectroscopic data are in a good agreement with literature.[18]

(2-Iodophenyl)(1*H*-pyrrol-2-yl)methanone (5.25)



(2-Aminophenyl)(1*H*-pyrrol-2-yl)methanone (**5.24**) (1.22 g, 6.5 mmol, 1 equiv.) was added to a solution of *p*-TsOH·H_2O (3.7 g, 19.6 mmol, 3 equiv.) in MeCN (5 mL). The reaction mixture was cooled to 10–15 °C, then a solution of $NaNO_2$ (0.9 g, 13.7 mmol, 2 equiv.) and KI (2.5 g, 16.3 mmol, 2.5 equiv.) in H_2O (4 mL) was added slowly. The cooling bath was removed, and the reaction mixture was stirred at room temperature overnight. Water (20 mL) was then added followed by $NaHCO_3$ solution (1 M) until pH 9–10 then $Na_2S_2O_3$ solution (2 M, 4 mL). The mixture was extracted with CH_2Cl_2 and purified by flash chromatography (hexane/ethyl acetate 3:2) to give pure **5.25** as a red solid (1.74 g, 5.8 mmol, 92%).
m.p. 105 – 107 °C. IR (solid) ν/cm^{-1}: 3221, 3122, 1602, 1577. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.75 (s, 1H), 7.94 (d, *J* = 7.89 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.22 – 7.13 (m, 2H), 6.57 (ddd, *J* = 3.8, 2.4, 1.4 Hz, 1H), 6.31 (dt, *J* = 3.8, 2.5 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 186.0, 143.7, 140.1, 131.3, 131.0, 128.9, 127.7, 126.8, 121.2, 111.5, 93.0 ppm. HRMS: m/z calcd for $C_{11}H_9INO$ $[M+H]^+$ = 297.9723; found: 297.9727.

(2-Iodophenyl)(1-methyl-1*H*-pyrrol-2-yl)methanone (5.26)

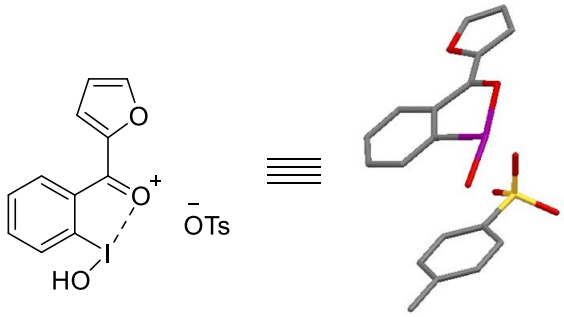


To a solution of the **5.25** (50 mg, 0.168 mmol, 1equiv.) in dry THF (1 mL), NaH (13.5 mg, 0.337 mmol, 2 equiv.) and methyl iodide (59 µL, 0.95 mmol, 5.6 equiv.) were added. The reaction mixture was stirred at room temperature under N_2 atmosphere for 24 h and the solvent removed under reduced pressure. The residue was dissolved in ether (2 mL) and washed with water (2 mL). The aqueous phase was extracted with ether (3 x 2 mL). The combined ether

extracts were washed with 10% $Na_2S_2O_3$ solution (2 mL) and water (2 mL), dried over $MgSO_4$, filtered and the filtrate was evaporated under vacuum to give **5.26** as a red solid (44 mg, 0.14 mmol, 88%).

m.p. 112 – 114 °C. IR (solid) ν/cm^{-1}: 3124, 1624, 1521. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 4.4, 4.0 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.12 (ddd, *J* = 8.0, 6.9, 2.3 Hz, 1H), 6.95 (t, *J* = 2.0 Hz, 1H), 6.42 (dd, *J* = 4.1, 1.7 Hz, 1H), 6.11 (dd, *J* = 4.1, 2.4 Hz, 1H), 4.09 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 186.9, 145.4, 139.6, 132.7, 130.7, 129.9, 128.4, 127.6, 124.3, 108.8, 93.1, 37.7 ppm. HRMS: m/z calcd for $C_{12}H_{11}INO$ $[M+H]^+$ = 311.9880; found: 311.9879.

3-(Furan-2-yl)-1-hydroxy-1*H*-λ^3-benzo[d][1,2]iodaoxol-2-ium 4-methylbenzenesulfonate (5.29)

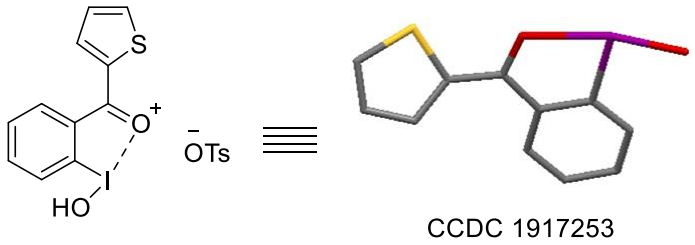


CCDC 1917254

m-Chloroperbenzoic acid (135 mg, 0.6 mmol, 1.2 equiv.) was added to a stirred solution of **5.19** (150 mg, 0.5 mmol, 1 equiv.) in dichloromethane/TFE (1:1 v/v, 5 mL), followed by TsOH•H_2O (96 mg, 0.50 mmol, 1 equiv.). Stirring was continued at room temperature for 30 min. The reaction mixture was then concentrated under a stream of air, diethyl ether (10 mL) was then added to the residue. The resulting precipitate was filtered off and dried to give **5.29** as a yellow solid (211 mg, 0.43 mmol, 86%).

m.p. 130 – 133 °C. IR (solid) ν/cm^{-1}: 3406, 3128, 1716, 1585. ^{1}H NMR (400 MHz, CD_3OD) δ = 9.34 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.37 (dd, *J* = 1.6, 0.7 Hz, 1H), 8.26 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H), 8.22 – 8.16 (m, 2H), 8.03 (ddd, *J* = 8.2, 5.6, 1.2 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.03 (dd, *J* = 3.9, 1.6 Hz, 1H), 2.36 (s, 3H) ppm. ^{13}C NMR (101 MHz, CD_3OD) δ = 182.8, 155.2, 152.1, 143.5, 141.7, 139.6, 137.8, 133.0, 132.2, 130.6, 129.8, 128.6, 127.0, 124.5, 116.4, 21.3 ppm.

1-Hydroxy-3-(thiophen-2-yl)- 1*H*-λ^3-benzo[d][1,2]iodaoxol-2-ium 4-methylbenzenesulfonate (5.30)

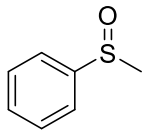


CCDC 1917253

m-Chloroperbenzoic acid (128 mg, 0.57 mmol, 1.2 equiv.) was added to a stirred solution of **5.20** (150 mg, 0.48 mmol, 1 equiv.) in CH_2Cl_2/TFE (1:1 v/v, 5 mL), followed by TsOH•H_2O (91 mg, 0.48 mmol, 1 equiv.). Stirring was continued at room temperature for 30 min. The reaction mixture was then concentrated under a stream of air, diethyl ether (10 mL) was then added to the residue. The resulting precipitate was filtered off and dried to give **5.30** as a red gummy material (204 mg, 0.41 mmol, 85%).

IR (neat) ν/cm^{-1}: 3421, 3088, 2922, 1583. ^{1}H NMR (400 MHz, CD_3OD) δ= 9.02 (dd, *J* = 7.9, 1.3 Hz, 1H), 8.60 (dd, *J* = 4.1, 1.0 Hz, 1H), 8.45 (dd, *J* = 4.9, 1.0 Hz, 1H), 8.29 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 8.22 (dd, *J* = 8.3, 1.1 Hz, 1H), 8.07 – 8.02 (m, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.52 (dd, *J* = 4.9, 4.1 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 2.37 (s, 3H) ppm. ^{13}C NMR (126 MHz, CD_3OD) δ = 190.3, 143.4, 143.2, 141.9, 141.7, 139.6, 138.3, 137.4, 133.0, 132.6, 131.5, 129.9, 128.9, 126.9, 124.5, 21.3 ppm.

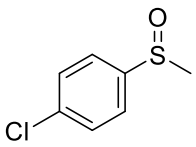
Methyl phenyl sulfoxide (5.31)



To a solution **5.29, 5.30,** or Koser's reagent (0.24 mmol, 1.2 equiv.) in acetonitrile (1 mL) was added thioanisole (25.0 mg, 23.5 µl, 0.2 mmol, 1 equiv.). The mixture was stirred at room temperature for overnight, then 5% aqueous $Na_2S_2O_3$ (5 mL) and saturated $NaHCO_3$ (5 mL) were added, and the mixture was extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification by preparative TLC (hexane/ethyl acetate 3:1) afforded 26 mg (92%) of pure **5.31** as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.63 (m, 2H), 7.57-7.48 (m, 3H), 2.73 (s, 3H) ppm. ^{13}C NMR (126 MHz, CDCl3) δ = 145.94, 131.18, 129.51, 123.65, 44.15 ppm. Spectroscopic data are in a good agreement with literature.[19]

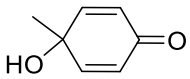
***p*-Chlorophenyl methyl sulfoxide (5.32)**



To a solution **5.29** or **5.30** (0.15 mmol, 1.2 equiv.) in acetonitrile (1 mL) was added *p*-Chlorophenyl methyl sufide (20 mg, 0.125 mmol, 1 equiv..). The mixture was stirred at room temperature for overnight, then 5% aqueous $Na_2S_2O_3$ (5 mL) and saturated $NaHCO_3$ (5 mL) were added, and the mixture was extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification by preparative TLC (hexane/ethyl acetate 3:1) afforded 20 mg (90%) of pure **5.32** as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 2.72 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 144.4, 137.4, 129.8, 125.1, 44.2 ppm. Spectroscopic data are in a good agreement with literature.[19,20]

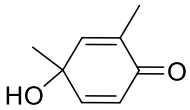
4-Hydroxy-4-methylcyclohexa-2,5-dienone (5.33)



To a solution **5.29** or **5.30** or Koser's reagent (0.15 mmol, 1.2 equiv.) in CH_2Cl_2 (1.5 mL) and water (75 μL) *p*-cresol (14 mg, 0.125 mmol, 1 equiv.) was added. The mixture was stirred at 0 °C to room temperature for 24 h, then 5% aqueous $Na_2S_2O_3$ (5 mL) and saturated $NaHCO_3$ (5 mL) were added, and the mixture was extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification by preparative TLC (hexane/ethyl acetate 3:1) afforded 13 mg (81%) of pure **5.33** as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ =.6.88 (d, *J* = 10 Hz, 2H), 6.15 (d, *J* = 10 Hz, 2H), 1.49 (s, 3H) ppm. Spectroscopic data are in a good agreement with literature.[19]

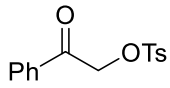
4-Hydroxy-2,4-dimethylcyclohexa-2,5-dien-1-one (5.34)



To a solution **5.29** or **5.30** (0.15 mmol, 1.2 equiv.) in methylene chloride (1.5 mL) and water (75 μL) 2,4-dimethylphenol (15 mg, 0.125 mmol, 1 equiv.) was added. The mixture was stirred at 0 °C to room temperature for 24 h, then 5% aqueous $Na_2S_2O_3$ (5 mL) and saturated $NaHCO_3$ (5 mL) were added, and the mixture was extracted with CH_2Cl_2. The organic phase was dried

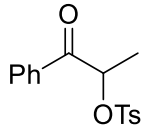
over anhydrous Na_2SO_4 and concentrated under vacuum. Purification by preparative TLC (hexane/ethyl acetate 3:1) afforded 15 mg (83%) of pure **5.34** as a white solid.
^{1}H NMR (500 MHz, $CDCl_3$) 6.84 (dd, *J* = 9.9, 3.1 Hz, 1H), 6.64 (dq, *J* = 3.0, 1.5 Hz, 1H), 6.12 (d, *J* = 9.9 Hz, 1H), 1.87 (d, *J* = 1.5 Hz, 3H), 1.46 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 186.1, 151.8, 147.4, 134.0, 127.2, 67.7, 27.0, 15.7. Spectroscopic data are in a good agreement with literature.[12]

2-Oxo-2-phenylethyl 4-methylbenzenesulfonate (5.35)



To a solution **5.29** or **5.30** (0.165 mmol, 1.5 equiv.) in acetonitrile (1.5 mL) was added acetophenone (13.2 mg, 0.11 mmol, 1 equiv.). The mixture was heated under reflux for 2 h. After cooling down to room temperature then sat. aq. $NaHCO_3$ solution (5 mL) was added, then extracted with CH_2Cl_2 (3 X 5 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure. The residue was purified by preparative TLC (hexane/EtOAc 3:1) to give pure **5.35** as a colourless oil (22.4 mg, 70%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87– 7.81 (m, 4H), 7.60 (t, *J* = 6.9 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.34 (d, *J* = 7.95 Hz, 2H), 5.27 (s, 2H), 2.44 (s, 3H). ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.5, 145.4, 134.3, 133.9, 132.7, 130.0, 129.0, 128.3, 128.1, 70.1, 21.8 ppm. Spectroscopic data are in a good agreement with literature.[21]

1-Oxo-1-phenylpropan-2-yl 4-methylbenzenesulfonate (5.36)



Method A:

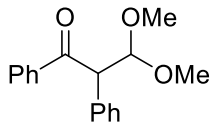
To a solution **5.29** or **5.30** (0.165 mmol, 1.5 equiv.) in acetonitrile (1.5 mL) propiophenone (15 mg, 15 µL, 0.11 mmol, 1 equiv.) was added. The mixture was heated under reflux for 2 h. After cooling down to room temperature then sat. aq. $NaHCO_3$ solution (5 mL) was added, then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure. The residue was purified by preparative TLC (hexane/EtOAc 3:1) to give pure **5.36** as a colourless oil (24 mg, 72%).

Method B:

To a solution of propiophenone (40 mg, 0.3 mmol, 1 equiv.) in MeCN (2 mL) was added the iodoarene catalyst, **5.19**, **5.20**, or **5.26** (10 mmol %) followed by *p*-TsOH·H_2O (0.9 mmol, 3 equiv.) and *m*-Chloroperbenzoic acid (0.9 mmol, 3 equiv.). The reaction mixture was stirred at room temperature for 48 h, then quenched with sat. aq. $Na_2S_2O_3$ solution and neutralized with sat. aq. $NaHCO_3$ solution. The aqueous layer was extracted with AcOEt (3× 10 mL). The combined organic layers were washed brine and dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by preparative TLC (hexane/EtOAc 3:1) to give pure **5.36** as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 – 7.85 (m, 2H), 7.77 – 7.73 (m, 2H), 7.62 – 7.56 (m, 1H), 7.48 – 7.43 (m, 2H), 7.29 – 7.24 (m, 3H), 5.78 (q, *J* = 6.9 Hz, 1H), 2.41 (s, 3H), 1.60 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.0, 145.2, 134.0, 133.8, 133.6, 129.9, 128.9, 128.9, 128.8, 128.1, 77.5, 21.8, 18.9 ppm. Spectroscopic data are in a good agreement with literature.[22]

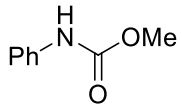
3,3-Dimethoxy-1,2-diphenylpropan-1-one (5.37)



To a stirred solution **5.29** or **5.30** (0.15 mmol, 1.2 equiv.) in methanol (1.5 mL) chalcone (26 mg, 0.125 mmol, 1 equiv.) was added. Stirring was continued for 24 h at room temperature. The reaction was quenched with 5% $Na_2S_2O_3$ solution (5 mL) and sat. $NaHCO_3$ solution (5 mL) then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure. The residue was purified by preparative TLC (hexane/EtOAc 5:1) to give pure **5.37** as a white solid (19 mg, 56%).

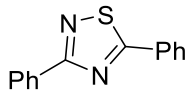
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.98 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.46-7.38 (m, 4H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.25-7.22 (m, 1H), 5.13 (d, *J* = 8.5 Hz, 1H), 4.90 (d, *J* = 8.5 Hz, 1H), 3.44 (s, 3H), 3.21 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 197.9, 137.0, 134.9, 133.3, 129.2, 128.9, 128.8, 128.7, 127.7, 107.0, 57.1, 56.3, 54.6 ppm. Spectroscopic data are in a good agreement with literature.[19]

Methyl phenylcarbamate (5.38)



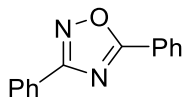
To a stirred solution **5.29** or **5.30** (0.15 mmol, 1.2 equiv.) in methanol (2 mL) benzamide (15 mg, 0.125 mmol, 1 equiv.) was added. The reaction mixture was heated under reflux for 8 h. After cooling down to room temperature then sat. aq. $NaHCO_3$ solution (5 mL) was added, then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure. The residue was purified by preparative TLC (hexane/EtOAc 3:1) to give pure **5.38** as a light-yellow oil (15 mg, 79%).
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.38 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.64 (s, 1H), 3.78 (s, 3H) ppm.^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.1, 138.0, 129.2, 123.6, 118.8, 52.5. ppm. Spectroscopic data are in a good agreement with literature.[23]

3,5-Diphenyl-1,2,4-thiadiazole (5.39)



To a stirred solution **5.29** or **5.30** (0.24 mmol, 1.6 equiv.) in acetonitrile (1 mL) thiobenzamide (21 mg, 0.15 mmol, 1 equiv.) was added. Stirring was continued at r.t. for 1 h. The reaction was quenched with 5% $Na_2S_2O_3$ solution (5 mL) and sat. $NaHCO_3$ solution (5 mL) then extracted with CH_2Cl_2 (3 X 5 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure. The residue was purified by preparative TLC (hexane/EtOAc 3:1) to give pure **5.39** as a white solid (15 mg, 86%).
m.p. 89 – 90 °C (lit.[19], m.p. 87.3 – 88.0 °C). ^{1}H NMR (400 MHz, d^6-acetone) δ 8.44 – 8.37 (m, 2H), 8.20 – 8.13 (m, 2H), 7.66 – 7.53 (m, 6H) ppm. ^{13}C NMR (101 MHz, d^6-acetone) δ = 189.3, 174.4, 133.8, 133.2, 131.4, 130.4, 129.7, 129.0, 128.3. ppm. Spectroscopic data are in a good agreement with literature.[19]

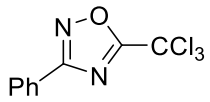
3,5-Diphenyl-1,2,4-oxadiazole (5.40)



To a stirred solution **5.29** or **5.30** (0.15 mmol, 1.2 equiv.) in benzonitrile (1 mL) benzaldoxime (15 mg, 0.125 mmol, 1 equiv.) was added. Stirring was continued at room temperature for 1 h. The reaction was quenched with 5% $Na_2S_2O_3$ solution (5 mL) and sat. $NaHCO_3$ solution (5

mL) then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure. The residue was purified by preparative TLC (hexane/EtOAc 3:1) to give pure **5.40** as a white solid (26 mg, 93%).
m.p. 106 – 107 °C (lit.[19], m.p. 107.3 – 107.6 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (ddd, *J* = 6.8, 1.4, 0.7 Hz, 2H), 8.19 (ddt, *J* = 3.1, 2.2, 1.7 Hz, 2H), 7.64 – 7.59 (m, 1H), 7.59 – 7.46 (m, 5H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.9, 169.1, 132.9, 131.3, 129.2, 129.0, 128.3, 127.7, 127.1, 124.5 ppm. Spectroscopic data are in a good agreement with literature.[19]

3-Phenyl-5-(trichloromethyl)-1,2,4-oxadiazole (5.41)



To a stirred solution **5.29** or **5.30** (0.15 mmol, 1.2 equiv.) in 2,2,2-trichloroacetonitrile (1 mL) benzaldoxime (15 mg, 0.125 mmol, 1 equiv.) was added. Stirring was continued at room temperature for 1 h. The reaction was quenched with 5% $Na_2S_2O_3$ solution (5 mL) and sat. aq. $NaHCO_3$ solution (5 mL) then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and removed under reduced pressure. The residue was purified by preparative TLC (hexane/EtOAc 5:1) to give pure **5.41** as a colourless oil (27 mg, 81%).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16 – 8.09 (m, 2H), 7.60 – 7.49 (m, 3H) ppm. Spectroscopic data are in a good agreement with literature.[19]

6.6. Reference

[1] W. B. Whalley, *J. Chem. Soc.* **1949**, 3016.

[2] M. Fujita, Y. Yoshida, K. Miyata, A. Wakisaka, T. Sugimura, *Angew. Chemie - Int. Ed.* **2010**, *49*, 7068–7071.

[3] F. Malmedy, T. Wirth, *Chem. - A Eur. J.* **2016**, *22*, 16072–16077.

[4] S. Haubenreisser, T. H. Wöste, C. Martínez, K. Ishihara, K. Muñiz, *Angew. Chemie - Int. Ed.* **2016**, *55*, 413–417.

[5] A. Kamal, G. Chouhan, *Tetrahedron Lett.* **2004**, *45*, 8801–8805.

[6] T. Hokamp, L. Mollari, L. C. Wilkins, R. L. Melen, T. Wirth, *Angew. Chemie - Int. Ed.* **2018**, *57*, 8306–8309.

[7] W.-C. Gao, Z.-Y. Xiong, S. Pirhaghani, T. Wirth, *Synthesis (Stuttg).* **2019**, *51*, 276–284.

[8] M. Brown, R. Kumar, J. Rehbein, T. Wirth, *Chem. - A Eur. J.* **2016**, *22*, 4030–4035.

[9] B. Basdevant, C. Y. Legault, *Org. Lett.* **2015**, *17*, 4918–4921.

[10] S. Brenet, F. Berthiol, J. Einhorn, *European J. Org. Chem.* **2013**, *2013*, 8094–8096.

[11] G. Levitre, A. Dumoulin, P. Retailleau, A. Panossian, F. R. Leroux, G. Masson, *J. Org. Chem.* **2017**, *82*, 11877–11883.

[12] T. Yakura, M. Omoto, Y. Yamauchi, Y. Tian, A. Ozono, *Tetrahedron* **2010**, *66*, 5833–5840.

[13] Z.-X. Wang, Y. Shi, *J. Org. Chem.* **1998**, *68*, 3099–3104.

[14] J. Qurban, M. Elsherbini, T. Wirth, *J. Org. Chem.* **2017**, *82*, 11872–11876.

[15] N. Kise, T. Sakurai, *J. Org. Chem.* **2015**, *80*, 3496–3503.

[16] T. E. Hurst, J. A. Deichert, L. Kapeniak, R. Lee, J. Harris, P. G. Jessop, V. Snieckus, *Org. Lett.* **2019**, *21*, 3882–3885.

[17] V.-H. Nguyen, L. Vendier, M. Etienne, E. Despagnet-Ayoub, P.-A. R. Breuil, L. Magna, D. Proriol, H. Olivier-Bourbigou, C. Lorber, *Eur. J. Inorg. Chem.* **2012**, *2012*, 97–111.

[18] G. Rotas, A. Kimbaris, G. Varvounis, *Tetrahedron* **2011**, *67*, 7805–7810.

[19] A. Yoshimura, K. C. Nguyen, S. C. Klasen, A. Saito, V. N. Nemykin, V. V. Zhdankin, *Chem. Commun.* **2015**, *51*, 7835–7838.

[20] P. Hanson, R. A. A. J. Hendrickx, J. R. L. Smith, *Org. Biomol. Chem.* **2008**, *6*, 745.

[21] A. Yoshimura, S. C. Klasen, M. T. Shea, K. C. Nguyen, G. T. Rohde, A. Saito, P. S. Postnikov, M. S. Yusubov, V. N. Nemykin, V. V. Zhdankin, *Chem. - A Eur. J.* **2017**, *23*, 691–695.

[22] O. R. S. John, N. M. Killeen, D. A. Knowles, S. C. Yau, M. C. Bagley, N. C. O. Tomkinson, *Org. Lett.* **2007**, *9*, 4009–4012.

[23] P. Liu, Z. Wang, X. Hu, *European J. Org. Chem.* **2012**, *2012*, 1994–2000.

Appendix

Published work

JOC The Journal of Organic Chemistry

Note

Cite This: J. Org. Chem. 2017, 82, 11872-11876

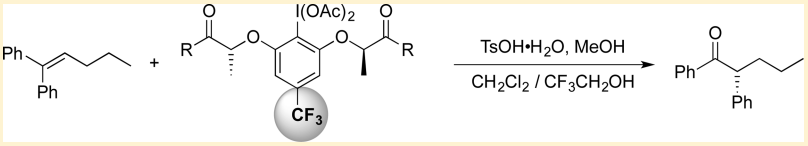
pubs.acs.org/joc

Electron-Deficient Chiral Lactic Acid-Based Hypervalent Iodine Reagents

Jihan Qurban, Mohamed Elsherbini, and Thomas Wirth*

School of Chemistry, Cardiff University, Park Place, Cardiff CF10 3AT, United Kingdom

Supporting Information



ABSTRACT: Novel electron-deficient chiral hypervalent iodine reagents were prepared in good overall yields. The reactivity and stereoselectivity of these reagents in oxidative rearrangements of alkenes to α-aryl ketones were investigated. The results show that the new reagents have good reactivity and generate products with high enantiomeric excess.

The chemistry of hypervalent iodine reagents has witnessed a massive growth and development in the 21st century. The extensive interest in hypervalent iodine reagents is attributed to their powerful oxidizing properties, along with their easy handling, commercial availability, and benign environmental impact. Their synthetic applications include oxidation, halogenation, amination, C−C bond formation, heterocyclization, and rearrangement reactions.[1−3]

Recently, many efforts were devoted to the development of hypervalent iodine-catalyzed chemical transformations.[4] The catalytic cycle relies on the reoxidation of an iodine(I) species, mainly iodoarenes, into the corresponding hypervalent iodine compounds in the presence of a stoichiometric oxidant. Hydrogen peroxide, oxone, *m*-chloroperbenzoic acid, sodium perborate, and Selectfluor are commonly used terminal oxidants in such catalytic transformations. The utilization of chiral iodoarenes as organocatalysts for different enantioselective transformations is a fast-growing research area, and several approaches have been published recently.[5]

Chiral hypervalent iodine(III) reagents have been very successfully used in stereoselective synthesis and received much attention.[6] Fujita[7] and Ishihara[8] initially published the synthesis and use of chiral hypervalent iodine reagents based on lactic acid. Many reactions have been investigated using these chiral reagents, and in some of them very high stereoselectivities have been obtained. We also have contributed to that development and published highly stereoselective oxyaminations[9] and also the first stereoselective rearrangements based on chiral, lactic acid-based iodine(III) reagents.[10] The investigation of more recent rearrangements employing additional orthoesters to generate α-aryl esters as reaction products proved to be less efficient with the known lactic acid-based iodine(III) reagents. We therefore decided to prepare more reactive versions of the reagents **1** by the attachment of an electron-withdrawing group such as a trifluoromethyl substituent (R = CF_3) in the *para*-position to the iodine (Figure 1). This should enhance the electrophilicity of the hypervalent

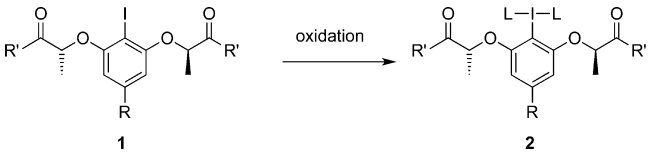


Figure 1. Lactic acid-based hypervalent iodine reagents **2**.

iodine reagents **2** (R = CF_3) as compared to the unsubstituted reagents **2** (R = H). With other hypervalent iodine(III) derivatives, we have already shown that the addition of CF_3 groups in *para* position to the iodine(III) moiety enhances their reactivity.[11]

Such reagents have been prepared by the route shown below starting from the commercially available 3-nitro-5-(trifluoromethyl)phenol **3** (Scheme 1), through which the novel key building block, 2-iodo-5-(trifluoromethyl)benzene-1,3-diol **6**, was accessed. Reduction of the nitro group in **3** to the corresponding amino derivative, 3-amino-5-(trifluoromethyl)phenol **4**, was achieved in 97% yield with disodium sulfide in ethanol. Diazotation of **4** was followed by treatment with a saturated aqueous solution of copper sulfate leading to the formation of 5-(trifluoromethyl)benzene-1,3-diol **5** in 73% yield. The desired iodoarene **6** was obtained in 39% yield via the reaction of diol **5** with elemental iodine.[12]

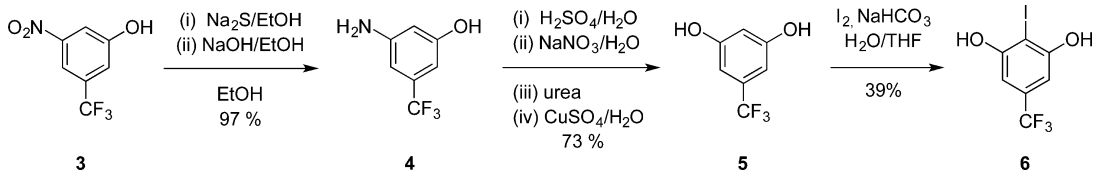
Having the key intermediate **6** in our hands, we could proceed to achieve the synthesis of the target hypervalent iodine reagents of type **2**. Following literature procedures, the iodoarene **6** was transformed into the lactate-based chiral iodoarene derivative **1a** in 98% yield under Mitsunobu reaction conditions. Basic hydrolysis of the diester **1a** afforded the dicarboxylic acid **1b** in 80% yield. Activation of the dicarboxylic acid **1b** followed by the reaction with 2,6-diisopropylaniline and

Special Issue: Hypervalent Iodine Reagents

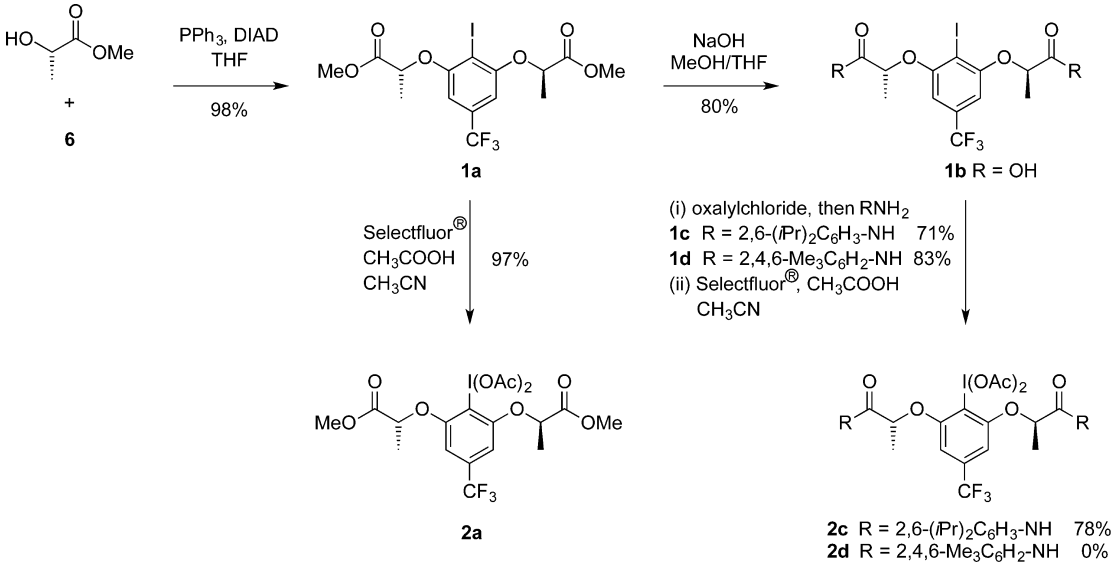
Received: June 25, 2017
Published: July 20, 2017

DOI: 10.1021/acs.joc.7b01571
J. Org. Chem. 2017, 82, 11872−11876

Scheme 1. Synthesis of 2-Iodo-5-(trifluoromethyl)benzene-1,3-diol 6



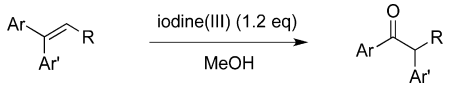
Scheme 2. Synthesis of Chiral Iodine(III) Reagents 2a and 2c



2,4,6-trimethylaniline afforded the amides **1c** in 71% and **1d** in 83% yield, respectively (Scheme 2). Finally, the chiral iodoarenes were oxidized to the corresponding hypervalent iodine reagents **2a** and **2c** using Selectfluor in a mixture of acetonitrile and acetic acid. The iodine compound **2d** could not be isolated despite many attempts.

Several efficient methods for the synthesis of α-aryl substituted carbonyl compounds through metal-catalyzed cross coupling reactions of ketones are known.[13] We have reported an efficient metal-free method for synthesizing α-arylated carbonyl compounds via an enantioselective oxidative rearrangement of alkenes using stoichiometric chiral hypervalent iodine reagents (Scheme 3).[14] Based on this reaction, we have now developed new chiral iodoarenes for accessing α-aryl carbonyl compounds.

Scheme 3. Rearrangement of Alkenes to α-Arylated Ketones



Initially, we explored the oxidative rearrangement of alkene **7** using different chiral iodine(III) reagents as stoichiometric oxidants (1.2 equiv). To evaluate the reactivity of the newly prepared hypervalent iodine reagents **2a** and **2c**, we studied the oxidative rearrangement of the alkene **7** by reagents **2a**, **2c**, and the previously reported reagents **2e**–**2g** (Table 1).[8] Reagent **2a** (Table 1, entry 1) with the trifluoromethyl substituent showed comparable reactivity and similar enantioselectivity to the previously reported reagents with either a methyl substituent **2e** or without substituent **2f** (Table 1, entries 2 and 3). Yields range between 45 and 50%, while the enantiomeric excess is between 87 and 92%. All reagents produce the same enantiomer of **8** (*R*-configuration), but in each reaction, a small amount (5–15%) of ketone **9** is detected as a side product. Reagents **2c** and **2g** with amide functionalities in the side chain showed much lower reactivity (Table 1, entries 4 and 5), while the enantioselectivity is almost identical.

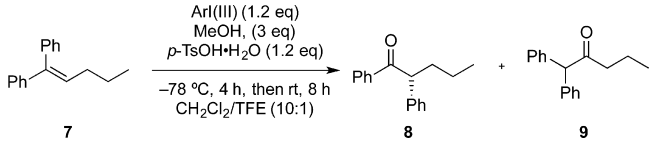
Furthermore, the potential of the oxidative rearrangement of alkene **7** using different iodoarene catalysts (20 mol %) in the presence of a stoichiometric oxidant was investigated. The catalytic reactions had to be performed at a higher reaction temperature, as the oxidation to iodine(III) is too slow at low temperature. Initially, several iodoarenes were screened in the presence of 1 equiv of *m*-chloroperbenzoic acid (*m*CPBA). Substantial amounts of **9** were generated, while the overall yield was very low. Enantioselectivities were also low (45–76% ee, see Supporting Information). Different oxidants were also investigated. Although Selectfluor showed reasonable reactivity, fluorinated byproducts **11a** and **11b** were always produced by direct reaction with the alkene. Some selected reaction conditions are summarized in Scheme 4.

Yields of the rearranged reaction product **8** never exceeded 20%, so no catalytic conversion was achieved. Moreover, if the reaction is performed without iodoarene using 1 equiv *m*CPBA, only compound **9** was formed in 71% yield, indicating a strong background reaction under the reaction conditions. Further details are found in the Supporting Information.

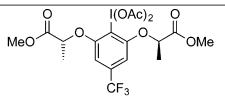
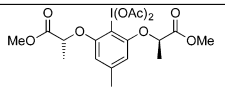
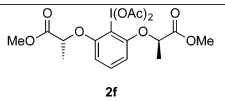
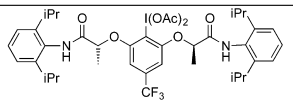
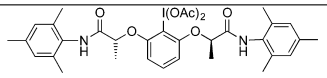
In summary, we have synthesized new trifluoromethyl-substituted lactic acid-based hypervalent iodine derivatives, which showed similar behavior and unfortunately no advantage to the unsubstituted reagents with regards to the stereoselective rearrangement investigated here.

DOI: 10.1021/acs.joc.7b01571
J. Org. Chem. 2017, 82, 11872–11876

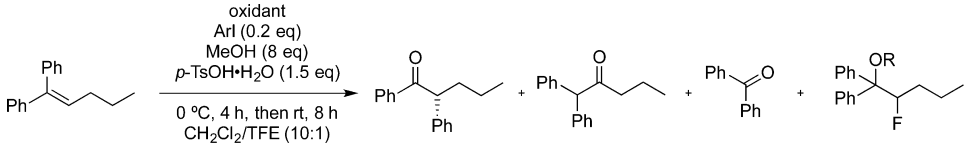
Table 1. Different Iodine(III) Reagents 2 in the Rearrangement of Alkene 7



7 8 9

Entry	ArI(III)	**8** yield [%]	**8** *ee* [%] (absolute configuration)	**9** yield [%]
1	 **2a**	50	91 (*R*)	5
2	 **2e**	45	87 (*R*)	5
3	 **2f**	49	92 (*R*)	10
4	 **2c**	5	78 (*R*)	10
5	 **2g**	15	92 (*R*)	15

Scheme 4. Rearrangement with Chiral Iodoarene Catalysts



7

ArI	oxidant	**8**	**9**	**10**	**11a** R = Me, **11b** R = H
1a	*m*CPBA (1 eq)	6%, 70% *ee*	54%	-	-
1f	*m*CPBA (1 eq)	16%, 70% *ee*	21%	-	-
1f	Selectfluor®(1 eq)	19%, 67% *ee*	2%	-	**11a**: 20%, **11b**: 27%
1f	*m*CPBA (5 eq)	13%, 76% *ee*	62%	3%	-
1f	Selectflour®(5 eq)	19%, 67% *ee*	1%	-	**11a**: 30%, **11b**: 10%

EXPERIMENTAL SECTION

All starting materials were purchased from commercial suppliers and used without further purification, and all solvents used were dried and purified by standard techniques. Reactions requiring the exclusion of moisture were carried out under an atmosphere of argon or nitrogen in oven-dried glassware. Flash chromatography was carried out using Merck silica gel (35−70 μm) or on a Biotage Isolera Four platform using SNAP Ultra (25 μm) cartridges. Melting points were recorded on a Gallenkamp MPD350 apparatus. IR measurements were taken using a PerkinElmer 1600 FTIR spectrometer. NMR spectra were recorded on Bruker DPX 300, Bruker DPX 400, or Bruker DPX 500. ^{1}H NMR spectra were measured at 300, 400, and 500 MHz. ^{13}C {^{1}H} NMR spectra were measured at 75, 100, and 125 MHz using CDCl3 as the solvent and internal reference. Coupling constants *J* are given in Hz. Multiplicity as follows: s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, sept = septet, m = multiplet, br = broad. High-resolution mass spectrometry (HRMS) was carried out using a Waters LCT Premier XE mass spectrometer using electrospray ionization (ESI). Optical rotations were measured with a UniPol L polarimeter. High-performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP.

3-Amino-5-hydroxybenzotrifluoride 4.[11] 3-Nitro-5-hydroxybenzotrifluoride (5 g, 24.1 mmol) dissolved in ethanol (25 mL) was gently refluxed during the gradual addition of a solution of disodium sulfide (25 g, 104 mmol) in alcohol (100 mL). After 1.5 h, hot 10% ethanolic sodium hydroxide solution (12.5 mL) was added, refluxing continued for 1 h, then the alcohol removed under reduced pressure. The residue was acidified with hydrochloric acid (2 M), then neutralized by the addition of sodium hydrogen carbonate solution, and extracted with ether (4 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure affording 3-amino-5-hydroxybenzotrifluoride **4** as a red solid (4.15 g, 97%). Mp: 83−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.49 (s, 1H), 6.45 (s, 1H), 6.29 (s, 1H), 4.98 (br s, 1H), 3.84 (s, 2H) ppm.

3,5-Dihydroxybenzotrifluoride 5.[11] 3-Amino-5-hydroxybenzotrifluoride **4** (3.98 g, 22.47 mmol) was dissolved in a mixture of water (14 mL) and concentrated sulfuric acid (16 mL). After cooling to 0 °C, a solution of sodium nitrite (1.5 g) in water (8 mL) was added slowly, and after 15 min, the excess nitrous acid was destroyed by addition of urea. Then the cooled solution was added to a refluxing

DOI: 10.1021/acs.joc.7b01571
J. Org. Chem. 2017, 82, 11872−11876

saturated solution of copper sulfate (200 mL). Then left to cool down to the room temperature and extracted with ether (4 × 50 mL), the combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure affording 3,5-dihydroxybenzotrifluoride **5** as a red solid (2.93 g, 73%). Mp: 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.66 (s, 2H), 6.50 (s, 1H), 5.32 (br s, 2H) ppm.

2-Iodo-5-(trifluoromethyl)benzene-1,3-diol 6.[15] 3,5-Dihydroxybenzotrifluoride **5** (2.14 g, 12 mmol) was dissolved in H_2O/THF (1:1) (250 mL). After cooling to 0 °C, iodine (3.12 g, 12.6 mmol) was added followed by slow addition of $NaHCO_3$ (1.108 g, 13.2 mmol). The resulting reaction mixture was stirred for 10 min at 0 °C and then allowed to warm to room temperature and stirred for 40 min. The reaction was then quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution (10 mL). After extraction with EtOAc (4 × 40 mL), the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (8:2 Hex/EtOAc) afforded the pure product **6** as a yellow solid (1.37 g, 39%). Mp: 91−92 °C; IR (solid) υ/cm^{-1}: 3277, 1250, 1010; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.80 (s, 2H), 5.55 (s, 2H) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 156.2, 133.2 (q, J = 33.3 Hz), 123.4 (q, J = 272.5 Hz), 104.4, 81.6 ppm; ^{19}F-NMR (471 MHz, $CDCl_3$): δ = −63.32 ppm; HRMS (ESI-TOF) m/z: [M − H] calcd for $C_7H_3F_3IO_2$ = 302.9130; found: 302.9134.

Dimethyl 2,2′-((2-Iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))(2*R*,2′*R*)-dipropionate 1a.[14] 2-Iodo-5-(trifluoromethyl)-benzene-1,3-diol **6** (1.3 g, 4.27 mmol) was dissolved in dry THF (25 mL) under an argon atmosphere. After addition of methyl (*S*)-lactate (0.897 g, 9.4 mmol), triphenylphosphine (2.6 g, 9.83 mmol), and diisopropyl azodicarboxylate (2 g, 10.26 mmol), the reaction mixture was stirred for 16 h at room temperature and then concentrated under reduced pressure. Purification by flash column chromatography (8:2 Hexane/EtOAc) afforded the pure product **1a** as a colorless solid (1.96 g, 98%). Mp: 69−71 °C; $[\alpha]_D^{20}$: −90.5° (c = 0.243, $CHCl_3$); IR (solid) υ/cm^{-1}: 1739, 1244, 1109; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.58 (s, 2H), 4.83 (q, J = 6.8 Hz, 2H), 3.77 (s, 6H), 1.73 (d, J = 6.8 Hz, 6H) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 171.6, 158.7, 132.3 (q, J = 33.6 Hz), 123.6 (q, J = 273.2 Hz), 103.6, 85.3, 74.5, 52.7, 18.6 ppm; ^{19}F-NMR (471 MHz, $CDCl_3$): δ −62.94 ppm; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{15}H_{16}F_3IO_6Na$ = 498.9841; found: 498.9847.

(2*R*,2′*R*)-2,2′-((2-Iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))dipropionic acid 1b.[14] Dimethyl 2,2′-((2-iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))(2*R*,2′*R*)-dipropionate **1a** (1.683 g, 3.534 mmol) was dissolved in THF/MeOH (1:1) (20 mL). After addition of aqueous NaOH (2 M, 10 mL, 20 mmol, 5.6 equiv), the reaction mixture was stirred for 6 h at room temperature and then acidified with aqueous HCl (3 M). After extraction with EtOAc (4 × 40 mL), the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure, affording product **1b** as a colorless solid (1.265 g, 80%). Mp: 127−128 °C; IR (solid) υ/cm^{-1}: 2991, 1705, 1242, 1110; ^{1}H NMR (500 MHz, DMSO): δ = 13.18 (s, 2H), 6.74 (s, 2H), 5.11 (q, J = 6.7 Hz, 2H), 1.57 (d, J = 6.7 Hz, 6H) ppm; ^{13}C {^{1}H} NMR (126 MHz, CD_3OD): δ = 174.6, 160.3, 132.8 (q, J = 32.8 Hz), 125.2 (q, J = 271.2 Hz), 103.9, 85.4, 75.2, 18.8 ppm; ^{19}F NMR (471 MHz, DMSO): δ = −61.34 ppm; HRMS (ESI-TOF) m/z: [M − H] calcd for $C_{13}H_{11}F_3IO_6$ = 446.9553; found: 446.9569.

(2*R*,2′*R*)-2,2′-((2-Iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))bis(*N*-(2,6-diisopropylphenyl)propanamide) 1c.[14] (2*R*,2′*R*)-2,2′-((2-Iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))-dipropionic acid **1b** (1.344 g, 3 mmol) was suspended in dry CH_2Cl_2 (30 mL) under an argon atmosphere. After addition of oxalyl chloride (1.33 g, 10.5 mmol, 3.5 equiv) and a catalytic amount of DMF, the reaction mixture was stirred for 3 h at room temperature and then concentrated in vacuum. The crude product was redissolved in dry CH_2Cl_2 (16 mL) under an argon atmosphere, and 2,6-diisopropylaniline (2.632 g, 15 mmol, 5 equiv) as well as pyridine (0.95 g, 12 mmol) were added. The reaction mixture was stirred for 16 h at room temperature and quenched by the addition of aqueous HCl (3 M). After extraction with CH_2Cl_2, the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (8:2 → 2:2 Hex/EtOAc) afforded **1c** as a yellow solid (1.639 g, 71%). Mp: 230−233 °C; $[\alpha]_D^{20}$: −503 (c = 0.286, $CHCl_3$); IR (solid) υ/cm^{-1}: 3203, 1660, 1249, 1101; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (s, 2H), 7.32 (t, J = 7.7 Hz, 2H), 7.18 (d, J = 7.7 Hz, 4H), 6.92 (s, 2H), 5.10 (q, J = 6.6 Hz, 2H), 3.0−2.85 (m, 4H), 1.82 (d, J = 6.5 Hz, 6H), 1.20 (d, J = 6.8 Hz, 12H), 1.15−1.0 (m, 12H) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 169.9, 157.4, 146.1, 133.3 (q, J = 33 Hz), 129.9, 128.9, 123.6, 123.0, 103.6, 84.6, 76.6, 28.8, 22.5, 18.7 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): δ = −62.9 ppm; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{37}H_{47}F_3IN_2O_4$ = 767.2527; found: 767.2521.

(2*R*,2′*R*)-2,2′-((2-Iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))bis(*N*-mesitylpropanamide) 1d.[14] (2*R*,2′*R*)-2,2′-((2-Iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))dipropionic acid **1c** (1.286 g, 2.87 mmol) was suspended in dry CH_2Cl_2 (29 mL) under an argon atmosphere. After addition of oxalyl chloride (1.276 g, 10 mmol) and a catalytic amount of DMF, the reaction mixture was stirred for 3 h at room temperature and then concentrated in vacuo. The crude product was redissolved in dry CH_2Cl_2 (4 mL) under an argon atmosphere, and 2,4,6-trimethylaniline (1.54 g, 11.39 mmol, 5 equiv) as well as pyridine (0.882 g, 11.16 mmol) were added. The reaction mixture was stirred for 16 h at room temperature and quenched by addition of aqueous HCl (3 M, 10 mL). After extraction with CH_2Cl_2, the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (8:2 → 2:2 Hex/EtOAc) afforded pure **1d** as a yellow solid (1.621 g, 83%). Mp: 293−297 °C; $[\alpha]_D^{20}$: −740 (c = 1.0, $CHCl_3$); IR (solid) υ/cm^{-1}: 3257,1670, 1250, 1150; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (s, 2H), 6.91 (s, 4H), 6.87 (s, 2H), 5.05 (q, J = 6.7 Hz, 2H), 2.27 (s, 6H), 2.16 (s, 12H), 1.82 (d, J = 6.7 Hz, 6H) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 168.9, 157.5, 137.4, 135.1, 129.9, 129.1, 128.8, 122.0, 103.9, 85.0, 76.7, 20.9, 18.8, 18.3 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): δ = −63.00 ppm; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{31}H_{35}F_3IN_2O_4$ = 683.1588; found: 683.1594.

Dimethyl 2,2′-((2-(Diacetoxy-λ^3-iodanyl)-5-(trifluoromethyl)-1,3-phenylene)bis(oxy)) (2*R*,2′*R*)-dipropionate 2a.[8] Dimethyl 2,2′-((2-iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))(2*R*,2′*R*)-dipropionate **1a** (0.238 g, 0.5 mmol) and Selectfluor (0.885 g, 2.5 mmol) were dissolved in CH_3CN (16 mL) and glacial acetic acid (5 mL) under N_2. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum, then water (25 mL) was added to the residue, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure, to give **2a** as a yellowish solid (0.288 g, 97%). Mp: 195−197 °C; $[\alpha]_D^{20}$: −65 (c = 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.78 (s, 2H), 4.93 (q, J = 6.8 Hz, 2H), 3.77 (s, 6H), 1.98 (s, 6H), 1.70 (d, J = 6.8 Hz, 6H); ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 177.25, 170.76, 157.08, 137.08 (q, J = 33.2 Hz), 122.91 (q, J = 273.6 Hz), 110.43, 103.41, 74.90, 52.84, 20.46, 18.35 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): δ = −63.7 ppm.

(2*R*,2′*R*)-2,2′-((2-(Diacetoxy-λ^3-iodanyl)-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))bis(*N*-(2,6-diisopropylphenyl)-propanamide) 2c.[8] (2*R*,2′*R*)-2,2′-((2-Iodo-5-(trifluoromethyl)-1,3-phenylene)bis(oxy))bis(*N*-(2,6-diisopropylphenyl) propanamide) **1c** (191.7 mg, 0.25 mmol) and Selectfluor (885 mg, 2.5 mmol) were dissolved in CH_3CN (16 mL) and glacial acetic acid (5 mL) under N_2. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum, then water (25 mL) was added to the residue, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure, to give **2c** (yield 78%). Mp: 220−222 °C; $[\alpha]_D^{20}$: −60 (c = 0.167, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (s, 2H), 7.33−7.2 (m, 2H), 7.18 (s, 2H), 7.11 (s_{br}, 4H), 5.21 (q, J = 6.7 Hz, 2H), 2.98 (m, 4H), 1.91 (d, J = 6.6 Hz, 6H), 1.44 (s, 6H), 1.3−0.8 (m, 24H) ppm; ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ = 176.8, 169.7, 156.4, 146.1, 129.7, 129.0, 123.6, 103.0, 77.2, 76.9, 28.6, 23.4, 19.5, 19.3 ppm (2 signals (C−CF_3) did

DOI: 10.1021/acs.joc.7b01571
J. Org. Chem. 2017, 82, 11872−11876

not appear in the NMR spectrum). ^{19}F NMR (471 MHz, $CDCl_3$): δ = −63.05 ppm.

Compounds **2e**, **2f**, and **2g** were prepared following the same procedure as compounds **2a** and **2c**. Their spectral data are in agreement with literature.[8]

Dimethyl 2,2′-((2-(Diacetoxy-λ^3-iodanyl)-5-methyl-1,3-phenylene)bis(oxy))(2*R*,2′*R*)-dipropionate 2e.[8] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (s, 2H), 4.86 (q, J = 6.8 Hz, 2H), 3.77 (s, 6H), 2.36 (s, 3H), 1.98 (s, 6H), 1.68 (d, J = 6.8 Hz, 6H) ppm.

Dimethyl 2,2′-((2-(Diacetoxy-λ^3-iodanyl)-5-methyl-1,3-phenylene)bis(oxy))(2*R*,2′*R*)-dipropionate 2f.[8] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (t, J = 8.4 Hz, 1H), 6.57 (d, J = 8.4 Hz, 2H), 4.87 (q, J = 6.8 Hz, 2H), 3.75 (s, 6H), 1.98 (s, 6H), 1.68 (d, J = 6.8 Hz, 6H) ppm.

(2,6-Bis(((*R*)-1-(mesitylamino)-1-oxopropan-2-yl)oxy)-phenyl)- λ^3-iodanediyl diacetate 2g.[8] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 2H), 7.58 (t, J = 8.4 Hz, 1H), 6.93 (d, J = 8.4, 2H), 6.8 (s, 4H), 5.15 (q, J = 6.6 Hz, 2H), 2.20 (s, 6H), 1.95−1.78 (m, 12H), 1.89 (d, J = 6.6 Hz, 6H), 1.49 (s, 6H) ppm.

General Procedure for Catalytic Oxidative Rearrangement for 1,1-Diphenyl-1-pentene by Chiral Iodine Reagents. To the solution of 1,1-diphenyl-1-pentene (1.0 equiv), iodine reagent (0.2 equiv), *m*CPBA (1.0 equiv), methanol (8.0 equiv) in CH_2Cl_2/TFE (10:1), TsOH·H_2O (1.5 equiv) were added. The reaction mixture was stirred for 4 h at 0 °C and then 16 h at room temperature. Quenched with a (1:1) mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (0.5 mL). Then water (4 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were filtered through a TELOS phase separator and concentrated under vacuum to give the crude product. The product 1,2-diphenyl-1-pentanone **8** was isolated by TLC (hexane/ethyl acetate 9:1).

General Procedure for the Stochiometric Oxidative Rearrangement of Aryl Alkene Derivative Using Chiral Hypervalent Iodine Reagents.[13] To a solution of alkene (0.09 mmol), iodine(III) reagent (0.11 mmol, 1.2 equiv), and methanol (0.26 mmol, 3 equiv) in CH_2Cl_2:TFE (10:1 v/v) (1.5 mL) at −78 °C was added TsOH·H_2O (21 mg, 0.11 mmol, 1.2 equiv). The reaction was stirred for 4 h at −78 °C and 16 h at room temperature and then quenched with a 1:1 mixture of aqueous sat. $NaHCO_3$ and sat. $Na_2S_2O_3$ (0.5 mL). Water (4 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were filtered through a TELOS phase separator and concentrated under vacuum to give the crude product. The product 1,2-diphenyl-1-pentanone **8** was isolated by TLC (hexane/ethyl acetate 9:1).

(2*R*)-1,2-Diphenyl-1-pentanone 8.[13] 1,1-Diphenylpentene (20 mg, 0.09 mmol), iodine(III) reagent **1** (65.4 mg, 0.11 mmol), TsOH·H_2O (20 mg, 0.11 mmol), and methanol (11 μL, 0.27 mmol) were reacted according to the general procedure to give the product as a colorless (10 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.6 Hz, 2H), 7.44 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.7 Hz, 2H), 7.29−7.20 (m, 4H), 7.18−7.12 (m, 1H), 4.52 (t, J = 7.3 Hz, 1H), 2.17−2.06 (m, 1H), 1.84−1.71 (m, 1H), 1.36−1.14 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H) ppm.

(2-Fluoro-1-methoxypentane-1,1-diyl)dibenzene 11a. Colorless oil (48 mg, 30%); IR (neat) υ/cm^{-1}: 3024, 2958, 1076; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50−6.99 (m, 10H), 5.39−5.17 (m, 1H), 3.12 (s, 3H), 1.54−1.40 (m, 2H), 1.40−1.22 (m, 2H), 0.80 (t, J = 7.0 Hz, 3H) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 141.2, 128.6, 127.9, 127.2 (d, J = 10.0 Hz), 95.8 (d, J = 182.0 Hz), 83.7 (d, J = 19.3 Hz), 52.7 (d, J = 12.2 Hz), 31.4, 19.1, 13.9 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): δ = −186.99 ppm; HRMS (ESI-TOF) m/z: [M − MeOH + H]$^+$ calcd for $C_{17}H_{18}F$ = 241.1393; found: 241.1393.

2-Fluoro-1,1-diphenylpentan-1-ol 11b. Colorless solid (15 mg, 10%); m.p.: 109−111 °C; IR (solid) υ/cm^{-1}: 3556, 33028, 2958; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47 (d, J = 7.5 Hz, 2H), 7.35−7.10 (m, 8H), 5.31 (dd, J = 47.4, 10.2 Hz, 1H), 2.52 (s, 1H), 1.82−1.50 (m, 1H), 1.59−1.37 (m, 1H), 1.37−0.96 (m, 2H), 0.80 (t, J = 7.1 Hz, 3H) ppm; ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 144.8, 128.3, 127.2 (d, J = 20.6 Hz), 126.8, 125.9, 96.1 (d, J = 177.8 Hz), 79.1 (d, J = 21.0 Hz), 30.9 (d, J = 21.2 Hz), 18.9, 13.8 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): δ = −189.48 ppm; HRMS (ESI-TOF) m/z: [M − H_2O + H]$^+$ calcd for $C_{17}H_{18}F$ = 241.1393; found: 241.1390.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01571.

Catalyst screening, oxidant screening, ^{1}H and ^{13}C NMR spectral data of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wirth@cf.ac.uk.

ORCID

Thomas Wirth: 0000-0002-8990-0667

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Chemistry Department, Umm Al-Qura University, Makkah, Saudi Arabia, for the financial support and scholarship to J.Q. and a private sponsor for the fellowship to M.E. We thank the EPSRC National Mass Spectrometry Facility, Swansea, for mass spectrometric data.

■ REFERENCES

(1) Hypervalent Iodine Chemistry. In *Topics in Current Chemistry*; Wirth, T., Ed.; Springer: Berlin, 2016; Vol. *373*.

(2) Zhdankin, V. V. Hypervalent Iodine Chemistry: Preparation. *Structure and Synthetic Application of Polyvalent Iodine Compounds*; John Wiley & Sons: New York, 2014.

(3) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328−3435.

(4) Richardson, R. D.; Wirth, T. *Angew. Chem.* **2006**, *118*, 4510−4512; *Angew. Chem., Int. Ed.* **2006**, *45*, 4402−4404.

(5) Singh, F. V.; Wirth, T. *Chem. - Asian J.* **2014**, *9*, 950−971.

(6) For reviews, see: (a) Kumar, R.; Wirth, T. *Top. Curr. Chem.* **2015**, *373*, 243−261. (b) Berthiol, F. *Synthesis* **2015**, *47*, 587−603. (c) Parra, A.; Reboredo, S. *Chem. - Eur. J.* **2013**, *19*, 17244−17260. (d) Liang, H.; Ciufolini, M. *Angew. Chem.* **2011**, *123*, 12051−12053; *Angew. Chem., Int. Ed.* **2011**, *50*, 11849−11851.

(7) Fujita, M.; Okuno, S.; Lee, H. J.; Sugimura, T.; Okuyama, T. *Tetrahedron Lett.* **2007**, *48*, 8691−8694.

(8) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem.* **2010**, *122*, 2221−2223; *Angew. Chem., Int. Ed.* **2010**, *49*, 2175−2177.

(9) Farid, U.; Wirth, T. *Angew. Chem.* **2012**, *124*, 3518−3522; *Angew. Chem., Int. Ed.* **2012**, *51*, 3462−3465.

(10) Farid, U.; Malmedy, F.; Claveau, R.; Albers, L.; Wirth, T. *Angew. Chem.* **2013**, *125*, 7156−7160; *Angew. Chem., Int. Ed.* **2013**, *52*, 7018−7022.

(11) Schäfer, S.; Wirth, T. *Angew. Chem.* **2010**, *122*, 2846−2850; *Angew. Chem., Int. Ed.* **2010**, *49*, 2786−2789.

(12) Whalley, W. B. *J. Chem. Soc.* **1949**, 3016.

(13) (a) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264−1266. (b) Marelli, E.; Renault, Y.; Sharma, S. V.; Nolan, S. P.; Goss, R. J. M. *Chem. - Eur. J.* **2017**, *23*, 3832−3836.

(14) Brown, M.; Kumar, R.; Rehbein, J.; Wirth, T. *Chem. - Eur. J.* **2016**, *22*, 4030−4035.

(15) Haubenreisser, S.; Wöste, T. H.; Martínez, C.; Ishihara, K.; Muñiz, K. *Angew. Chem.* **2016**, *128*, 422−426; *Angew. Chem., Int. Ed.* **2016**, *55*, 413−417.

DOI: 10.1021/acs.joc.7b01571
J. Org. Chem. 2017, 82, 11872−11876

ChemComm

COMMUNICATION

Cite this: *Chem. Commun.*, 2019, **55**, 7998

Received 20th May 2019,
Accepted 17th June 2019

DOI: 10.1039/c9cc03905h

rsc.li/chemcomm

Synthesis, characterisation, and reactivity of novel pseudocyclic hypervalent iodine reagents with heteroaryl carbonyl substituents†

Jihan Qurban,‡ Mohamed Elsherbini, ‡ Haifa Alharbi and Thomas Wirth *

Two new hypervalent iodine reagents containing furan and thiophene moieties in addition to a carbonyl group in the vicinity of the iodine atom were synthesised and characterised. The X-ray analysis of both compounds revealed a strong intramolecular contact between the carbonyl oxygen and the hypervalent iodine atom with tosylate as a counter ion. The two reagents showed a broad range of synthetic applications and proved to be versatile oxidizing agents.

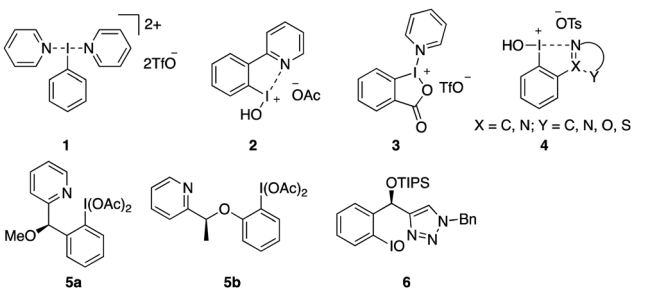
The chemistry of hypervalent iodine compounds has expanded largely during the last two decades. Due to their ready availability, easy handling and diversity, organic hypervalent iodine reagents are widely used in modern synthetic organic chemistry. Their electrophilic nature, in addition to their superior leaving group ability ($\sim 10^6$ times triflate) are the key features behind their unique reactivity.[1,2] Hence, hypervalent iodine reagents found a wide range of synthetic applications, especially selective oxidative transformations including, but not limited to, oxidative C–C, C–heteroatom and heteroatom–heteroatom couplings,[3–6] oxidative rearrangements,[7–10] difunctionalisation of alkenes,[11–13] and dearomatisation of phenols.[14–18] Moreover, hypervalent iodine compounds are environmentally friendly alternatives to heavy metal oxidants as a result of their low toxicity and mild reaction conditions. As hypervalent iodine reagents are electrophilic in nature, heteroatoms in the vicinity of the electrophilic iodine centre affect the structural features, reactivity and selectivity of hypervalent iodine reagents.[19–21] Various reagents incorporating nitrogen-containing heterocyclic units of various classes have been reported in literature (Fig. 1).[20–26]

Herein, we report the synthesis of new hypervalent iodine reagents containing 5-membered heterocyclic moieties. The aromatic iodoketone precursors **10** and **11** were prepared in 44% and 77% yield, respectively, over two steps starting from 2-aminobenzonitrile (**7**) as shown in Scheme 1.[27]

On the other hand, the pyrrole analogue **16** was prepared following a different synthetic route (Scheme 2).[28,29] Iodoketone **16** was obtained in 85% overall yield starting from anthranilic acid over four steps. *N*-Methylation of **16** afforded the iodoketone **17** in 88% yield.

Having the iodoketones **10**, **11** and **17** in hand, their oxidation to the corresponding hypervalent iodine reagents was investigated. Although the oxidation of simple iodoarenes usually proceeds smoothly, the oxidation of **10**, **11** and **17** was cumbersome. A wide range of oxidants and oxidation protocols were investigated, but either there was no reaction at all, or the reaction mixture was very complex to isolate the oxidized products in a pure form, although the ^{1}H NMR of the crude reaction mixture showed an evidence of the formation of the corresponding iodine(III) species in many attempts.

Only the oxidation of iodoarenes **10** and **11** using *m*-chloroperbenzoic acid (*m*CPBA)[30] in the presence of *p*-toluenesulfonic acid monohydrate was successful and the products **18** and **19** were isolated in a pure form in 86% and 85% yield, respectively (Scheme 3). The oxidation products of **10** and **11** were recrystallised from hexane–dichloromethane and characterised by single crystal X-ray crystallography. The solid-state structure of the products ruled out the initially expected Koser's[31] type structures with a close tosylate–iodine distance and confirmed



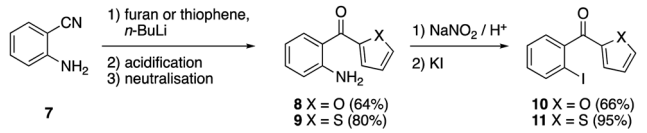
1 2 3 4 5a 5b 6

Fig. 1 Some hypervalent iodine reagents containing heterocycles.

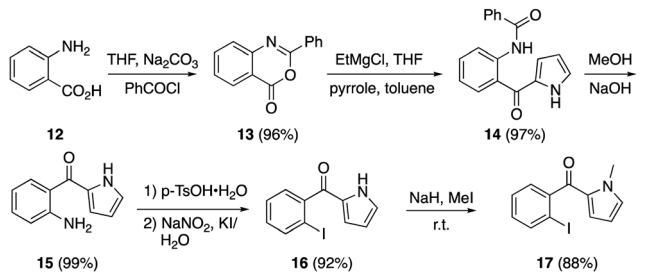
School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, UK. E-mail: wirth@cf.ac.uk

† Electronic supplementary information (ESI) available. CCDC 1917253 and 1917254. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc03905h

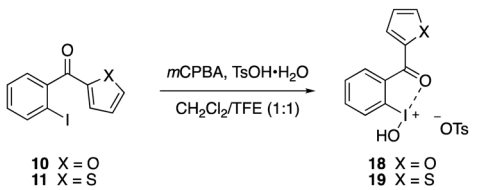
‡ These two authors contributed equally to this work.



Scheme 1 Synthesis of iodoketones bearing furan and thiophene moieties.



Scheme 2 Synthesis of iodoketones bearing a pyrrole moiety.



Scheme 3 Oxidation of iodoketones **10** and **11**.

the pseudocyclic[32,33] forms **18** and **19** manifesting the Lewis-base assisted activation[21,32] of the iodine centre.

Analysis of the X-ray data of tosylate **18** (Fig. 2A) showed the presence of a strong intramolecular interaction of 2.342 Å between the carbonyl oxygen and the hypervalent iodine atom besides one short iodine–oxygen covalent bond [I(1)–O(1) = 1.945 Å] and the iodine–carbon covalent bond [I(1)–C(1) = 2.080 Å]. The observed angle [O(1)–I(1)–O(2)] of the iodonium ion fragment of **18** (167.7°) is in good agreement with the distorted T-shaped geometry characteristic to hypervalent iodine(III) compounds.[21,34,35]

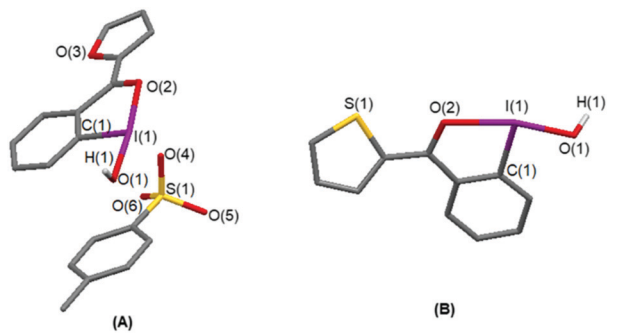


Fig. 2 X-ray crystal structure of compound **18** (A) and the cationic fragment of compound **19** (B). Hydrogen atoms bound to carbon atoms were removed for clarity. Selected bond lengths and angles: **18**: I(1)–O(1) 1.945 Å, I(1)–O(2) 2.342 Å, I(1)–C(1) 2.080 Å, O(1)–I(1)–O(2) 167.7°; **19**: I(1)–O(1) 1.943 Å, I(1)–O(2) 2.326 Å, I(1)–C(1) 2.155 Å, O(1)–I(1)–O(2) 166.7°.

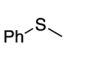
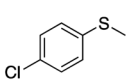
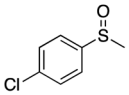
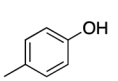
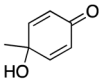
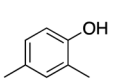
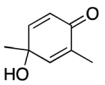
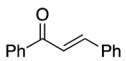
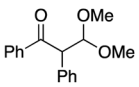
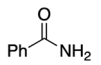
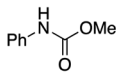
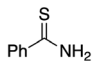
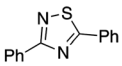
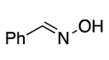
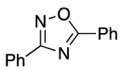
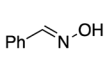
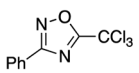
Although a single crystal of high quality of product **19** could not be obtained, a crystal structure showing only the cationic fragment of product **19** was obtained (Fig. 2B). Similar to product **18**, the analysis of the X-ray data of product **19** showed the presence of a strong intramolecular interaction of 2.326 Å between the carbonyl oxygen and the hypervalent iodine atom besides one short iodine–oxygen covalent bond [I(1)–O(1) = 1.943 Å] and iodine–carbon covalent bond [I(1)–C(1) = 2.155 Å] with an observed angle [O(1)–I(1)–O(2)] of 166.7° indicating a distorted T-shaped geometry characteristic to hypervalent iodine(III) compounds.[21,34,35] The iodonium ion of **19** showed a secondary interaction (2.830 Å) between the coordinated carbonyl oxygen (O(2)) and the sulfur atom (S(1)) of the thiophene ring which is not observed in the case of its furan analogue **18**.

A broad range of potential synthetic applications of hypervalent iodine reagents **18** and **19** as versatile oxidizing reagents is demonstrated (Table 1). Generally, all the reactions with both reagents lead to the formation of the expected products in moderate to excellent yields. The furan-derived reagent **18** proved to be more reactive than its thiophene analogue **19** which might be attributed to the presence of additional secondary interaction in the case of compound **19** (*vide supra*) rendering it more stable and hence less reactive.

Sulfoxides **20** and **21** were obtained in excellent yields (90–92%) *via* the oxidation of the corresponding sulfides using **18** and **19**. Oxidizing thioanisole under the same conditions with Koser's reagent led to the isolation of **20** in 80% yield. Phenol dearomatisation of *p*-cresol and 2,4-dimethylphenol led to the corresponding ketones **22** and **23** in 79–87% yield. When Koser's reagent was used as the oxidant for the oxidative dearomatisation of *p*-cresol, the corresponding ketone **22** was obtained in 74% yield. Both compounds **18** and **19** affected the α-tosyloxylation of acetophenone and propiophenone in good yields. Performing the α-tosyloxylation of propiophenone in a catalytic manner using 10 mol% of **10**, **11**, and **17** as organocatalysts in the presence of *m*CPBA as the terminal oxidant led to the formation of product **25** albeit in low yields, 21%, 10%, and 13%, respectively. In addition, the oxidative rearrangement of benzalacetophenone mediated by **18** and **19** in methanol afforded the corresponding α-aryl ketone **26** in 56% and 53% yield, respectively. Moreover, Hofmann rearrangement[9] of benzamide in methanol led to the corresponding carbamate **27** in good yield. Reagents **18** and **19** are efficient oxidants for oxidative heterocyclisations. 3,5-Diphenyl-1,2,4-thiadiazole (**28**) was obtained in 86% and 83% yield *via* oxidative dimerization of thiobenzamide using reagents **18** and **19**, respectively. In the same context, the reaction of benzaldehyde oxime with **18** and **19** in acetonitrile and 2,2,2-trichloroacetonitrile proceeded smoothly to afford 1,2,4-oxadiazoles **29** and **30** in high yields.

In conclusion, the synthesis and structural elucidation of two new hypervalent iodine reagents **18** and **19** is reported. The X-ray analysis of **18** and **19** showed the presence of strong intramolecular interaction (2.342 and 2.326 Å) between the carbonyl oxygen and the hypervalent iodine atom of compounds **18** and **19**. Reagents **18** and **19** are versatile reagents for a wide range of oxidative transformations such as oxidation of sulfides,

Table 1 Synthetic applications of reagents **18** and **19**

Substrate	**18 / 19** (1.2 - 1.6 equiv.)	Product	Yield[a]
	MeCN, r.t., 12 h		**20** (92%, 90%)[b]
	MeCN, r.t., 12 h		**21** (90%, 90%)
	MeCN / H_2O (20:1) 0 °C to r.t., 24 h		**22** (87%, 80%)[c]
	MeCN / H_2O (20:1) 0 °C to r.t., 24 h		**23** (83%, 79%)
	MeCN, reflux, 2 h		**24** (70%, 67%)
	MeCN, reflux, 2 h		**25** (70%, 65%)
	MeCN, r.t., 24 h		**26** (56%, 53%)
	MeCN, reflux, 8 h		**27** (79%, 72%)
	MeCN, r.t., 1 h		**28** (86%, 83%)
	PhCN, r.t., 1 h		**29** (93%, 86%)
	Cl_3CCN, r.t., 1 h		**30** (81%, 75%)

[a] Using **18** and **19**, respectively. [b] 80% using Koser's reagent. [c] 74% using Koser's reagent.

phenol dearomatisation, oxidative rearrangements and heterocyclisations. In general, both reagents lead to the formation of the products in moderate to excellent yields. Moreover, the furan derived reagent **18** shows higher reactivity than its thiophene analogue **19** in most cases.

Conflicts of interest

The authors declare no conflicts of interests.

Notes and references

1 V. V. Zhdankin, *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*, Wiley, 2013.
2 *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis*, ed. T. Wirth, Topics in Current Chemistry, Springer-Verlag, 2016, vol. 373.
3 S. Ghosh, S. Pradhan and I. Chatterjee, *Beilstein J. Org. Chem.*, 2018, **14**, 1244–1262.
4 G.-L. Gao and Q. Chen, *Curr. Organocatal.*, 2017, **4**, 33–47.
5 A. Yoshimura and V. V. Zhdankin, *Chem. Rev.*, 2016, **116**, 3328–3435.
6 C. Martínez, A. E. Bosnidou, S. Allmendinger and K. Muñiz, *Chem. – Eur. J.*, 2016, **22**, 9929–9932.
7 M. Brown, R. Kumar, J. Rehbein and T. Wirth, *Chem. – Eur. J.*, 2016, **22**, 4030–4035.
8 Z. Zhao, Z. Peng, Y. Zhao, H. Liu, C. Li and J. Zhao, *J. Org. Chem.*, 2017, **82**, 11848–11853.
9 F. V. Singh and T. Wirth, *Synthesis*, 2013, **45**, 2499–2511.
10 J. Qurban, M. Elsherbini and T. Wirth, *J. Org. Chem.*, 2017, **82**, 11872–11876.
11 X. Li, P. Chen and G. Liu, *Beilstein J. Org. Chem.*, 2018, **14**, 1813–1825.
12 K. Muñiz, L. Barreiro, R. M. Romero and C. Martínez, *J. Am. Chem. Soc.*, 2017, **139**, 4354–4357.
13 C. Martínez, E. G. Pérez, Á. Iglesias, E. C. Escudero-Adán and K. Muñiz, *Org. Lett.*, 2016, **18**, 2998–3001.
14 T. Dohi, N. Takenaga, T. Nakae, Y. Toyoda, M. Yamasaki, M. Shiro, H. Fujioka, A. Maruyama and Y. Kita, *J. Am. Chem. Soc.*, 2013, **135**, 4558–4566.
15 D. C. Smith, E. Vitaku and J. T. Njardarson, *Org. Lett.*, 2017, **19**, 3508–3511.
16 S. J. Murray and H. Ibrahim, *Chem. Commun.*, 2015, **51**, 2376–2379.
17 A. M. Harned, *Tetrahedron Lett.*, 2014, **55**, 4681–4689.
18 C. Bosset, R. Coffinier, P. A. Peixoto, M. El Assal, K. Miqueu, M. Sotiropoulos, L. Pouységu and S. Quideau, *Angew. Chem., Int. Ed.*, 2014, **53**, 9860–9864.
19 S. Haubenreisser, T. H. Wöste, C. Martínez, K. Ishihara and K. Muñiz, *Angew. Chem., Int. Ed.*, 2016, **55**, 413–417.
20 P. Mizar, A. Laverny, M. El-Sherbini, U. Farid, M. Brown, F. Malmedy and T. Wirth, *Chem. – Eur. J.*, 2014, **20**, 9910–9913.
21 K. Aertker, R. J. Rama, J. Opalach and K. Muñiz, *Adv. Synth. Catal.*, 2017, **359**, 1290–1294.
22 R. Weiss and J. Seubert, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 891–893.
23 V. V. Zhdankin, A. Y. Koposov and N. V. Yashin, *Tetrahedron Lett.*, 2002, **43**, 5735–5737.
24 A. Boelke, E. Lork and B. J. Nachtsheim, *Chem. – Eur. J.*, 2018, **24**, 18653–18657.
25 F. Malmedy and T. Wirth, *Chem. – Eur. J.*, 2016, **22**, 16072–16077.
26 C. Hempel, C. Maichle-Mössmer, M. A. Pericàs and B. J. Nachtsheim, *Adv. Synth. Catal.*, 2017, **359**, 2931–2941.
27 V.-H. Nguyen, L. Vendier, M. Etienne, E. Despagnet-Ayoub, P.-A. R. Breuil, L. Magna, D. Proriol, H. Olivier-Bourbigou and C. Lorber, *Eur. J. Inorg. Chem.*, 2012, 97–111.
28 C. C. Llopart and J. A. Joule, *ARKIVOC*, 2004, **x**, 20–38.
29 G. Rotas, A. Kimbaris and G. Varvounis, *Tetrahedron*, 2011, **67**, 7805–7810.
30 E. A. Merritt, V. M. T. Carneiro, L. F. Silva and B. Olofsson, *J. Org. Chem.*, 2010, **75**, 7416–7419.
31 G. F. Koser and R. H. Wettach, *J. Org. Chem.*, 1977, **42**, 1476–1478.
32 A. Yoshimura, M. S. Yusubov and V. V. Zhdankin, *Org. Biomol. Chem.*, 2016, **14**, 4771–4781.
33 V. V. Zhdankin, *Adv. Heterocycl. Chem.*, 2015, **115**, 1–91.
34 A. Yoshimura, S. C. Klasen, M. T. Shea, K. C. Nguyen, G. T. Rohde, A. Saito, P. S. Postnikov, M. S. Yusubov, V. N. Nemykin and V. V. Zhdankin, *Chem. – Eur. J.*, 2017, **23**, 691–695.
35 A. Yoshimura, K. C. Nguyen, S. C. Klasen, A. Saito, V. N. Nemykin and V. V. Zhdankin, *Chem. Commun.*, 2015, **51**, 7835–7838.