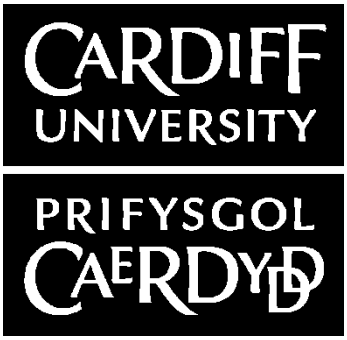
Stereoselective Reactions of Alkenes Mediated by Chiral Hypervalent Iodine Reagents



A Thesis Submitted to Cardiff University

in Fulfilment of the Requirements for the Degree of

Doctor of Philosophy

by **Umar Farid**

PhD Thesis October 2013

Cardiff University

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Umar Farid

Research is the name of patience and hardwork! (Umar Farid)

Dedicated to the Nation of Pakistan, Wishing them Success and Progress in the Field of Sciences

List of Abbreviations

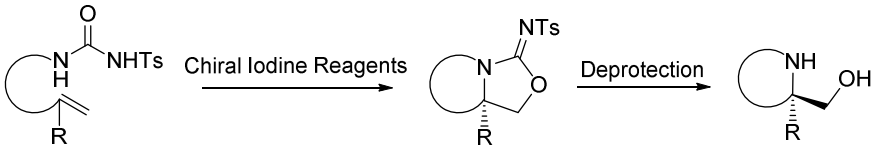
°C	Degree Celsius
Å	Angstrøm
Ac	Acetyl
Ar	Aryl
BuOH	Butanol
d.e.	Diastereomeric excess
d.r.	Diastereomeric ratio
DMF	*N*,*N*-Dimethylformamide
e.e.	Enantiomeric excess
e.r.	Enantiomeric ratio
Et	Ethyl
EtOH	Ethanol
h	Hour/hours
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
HFIP	Hexafluoroisopropanol
i-Pr	*i*-Propyl
LDA	Lithium diisopropylamide
M	Molarity (mol/l)
m-CPBA	3-Chloroperoxybenzoic acid
Me	Methyl
MeOH	Methanol
MHz	Megahertz
min	Minute
mL	Millilitre
mmol	Millimol
m.p.	Melting point
m/z	Mass over charge ratio
n-BuLi	*n*-Butyllithium

NMR	Nuclear magnetic resonance
on	overnight
ppm	Parts per million
Ph	Phenyl
Pr	Propyl
PrOH	Propanol
rt	Room temperature
t-Bu	*t*-Butyl
t-BuOH	*t*-Butanol
THF	Tetrahydrofuran
TBDMSOTf	Tertiarybutyldimethyl silyl triflate
Ts	Tosyl (4-toluenesulfonic)
p-TsCl	4-Toluenesulfonyl chloride
TsOH	*p*-Toluenesulfonic acid
TLC	Thin layer chromatography
TFE	2,2,2-Trifluoroethanol
TMSOTf	Trimethylsilyl triflate
TfOH	Triflic acid
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxy
TMOF	Trimethyl orthoformate

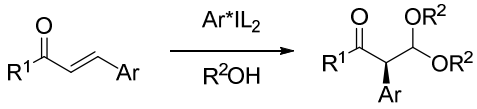
Abstract

Chiral hypervalent iodine compounds are used as environmentally friendly, mild, and selective oxidants for many organic transformations.

In this thesis, enantiomerically pure chiral hypervalent iodine reagents have been synthesized and used in the functionalization of different types of alkenes. A highly enantioselective oxyamination of alkenes with *N*-sulfonyl ureas employing chiral lactic acid-based hypervalent iodine reagents giving a facile synthesis of enantiomerically pure 2-arylproline derivatives is described. This is the first example of stereoselective oxyamination reactions under metal-free conditions.



Then oxidative rearrangement of aryl-substituted ketones induced by lactate acid-based chiral hypervalent iodine reagents via 1,2 migration of the aryl moiety in the presence of alcohol nucleophiles is described leading to the α-arylated and β-oxygenated carbonyl compounds in enantiomerically pure form. This is the first stereoselective rearrangement reaction mediated by chiral hypervalent iodine reagents.



Finally, all experimental details and characterization of the compounds are described.

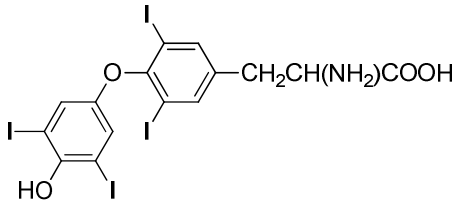
Table of Contents

Chapter 1

Introduction to Chiral Hypervalent Iodine Reagents

1.1 Iodine

Iodine is a chemical element with the symbol **I** and atomic number 53. The lustrous, purple-black metallic sheen of crystalline iodine was firstly observed by the French chemist B. Courtois in 1811. The name is from the Greek word, ἰωδής meaning violet or purple which reflects its most characteristic property. In human biology iodine is a constituent of thyroid hormone named Thyroxine **1**. If the necessary iodine input is insufficient the thyroid gland enlarges in an attempt to acquire more iodine: addition of 0.01% sodium iodide to table salt prevents the condition.



Thyroxine, 1

In addition to its use in medicine, iodine and its compounds have been widely exploited in volumetric analysis (iodometry and iodimetry). Organoiodine compounds have also played a notable part in the development of synthetic organic chemistry like in the A. W. von Hoffman's alkylation of amines, Williamson's synthesis of ethers, Wurtz's coupling reaction, hypervalent iodine reagents for oxidation reactions and Grignard's reagents.[1]

1.2 Introduction to Hypervalent Iodine Reagents

The first organic hypervalent iodine reagent dichloroiodobenzene, $PhICl_2$ was prepared by the German chemist C. Willgerodt in 1886.[2] A growing interest in this field was observed 60 years later. In the mean time a huge expansion occurred in the field of hypervalent iodine chemistry, especially during the last 15 years. Since then hypervalent iodine reagents have been extensively used in organic synthesis as mild and selective oxidants replacing toxic and heavy transition metals.

1.3 Bonding and Structure in Hypervalent Iodine Reagents

Molecules containing elements of Group V-VIII bearing more electrons than the octet in their valence shell are regarded as hypervalent molecules.[3] The term iodane refers to hydrogen iodide (HI). According to IUPAC rules, compounds with nonstandard

bonding numbers are shown by lambda notion; thus H_3I is called λ^3-iodane and H_5I λ^5-iodane. The most common $ArIL_2$ (L: heteroatom ligands) with decet structure is named aryl- λ^3-iodane. The geometry of aryl-λ^3-iodanes ($ArIL_2$) is a pseudotrigonal bipyramid. Commonly, a less electronegative group with an aryl group is bonded to the iodine by a normal covalent bond, lying in the equatorial position of a trigonal bipyramid. The two heteroatom ligands (L) are in the axial positions and each are attached to one of the lobes, of one doubly occupied 5p orbital of the iodine. This is a hypervalent three-center four-electron bond (3c-4e bond) with two electrons from the doubly occupied 5p orbital on iodine and one electron from each of the ligands (L). Molecules of this kind are T-shaped; the electronic structure for a typical member, (dichloroiodo)benzene, is described below.

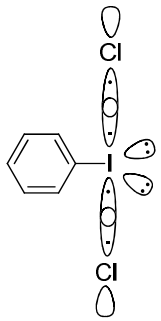


Fig 1.1: The electronic structure of dichloroiodobenzene

Hypervalent iodine compounds show a partial positive charge on the iodine and a partial negative charge on the axial heteroatom ligands. This can be explained by the organisation in the molecular orbitals. The two lower energy molecular orbitals of the three produced for the hypervalent 3c-4e-bond are occupied (Fig. 1.2). They are bonding and non-bonding orbitals. The non-bonding molecular orbital has a node at the central iodine whereby the partial charges are induced. So this highly polarized 3c-4e-bond leads to an electrophilic character of aryl-λ^3-iodanes and the preferred orientation of more electronegative ligands in the axial position. Consequently the presence of more electropositive central atoms is energetically favorable for a hypervalent species. Hence, λ^3-iodanes in general are more stable than analogous λ^3-bromanes and λ^3-chloranes.[4,5]

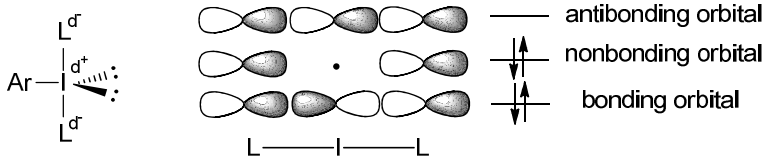


Fig 1.2: Pseudotrigonal bipyramidal structure and molecular orbital of the 3c-4e-bond

1.4 General Reactivities of Hypervalent Iodine Reagents

Traditionally hypervalent iodine reagents were mainly recognized as highly selective oxidants but many other useful synthetic reactions for the construction of carbon-carbon bonds, carbon-heteroatom bonds and rearrangement reactions etc., have also been developed extensively. A brief summary of these reactions and the use of different hypervalent iodine reagents is described below.

1.4.1 Oxidation

The oxidation of alcohols to the corresponding carbonyl compounds under mild reaction conditions is one the prominent feature of hypervalent iodine reagents.[6] Simple oxidation of 2-iodobenzoic acid with oxone gives a quite popular iodine(V) reagent, *ortho*-iodoxybenzoic acid (IBX; **2**).[7] To overcome solubility issues associated with IBX, Dess-Martin periodinane (DMP; **3**) is used in organic syntheses.[8] Other established hypervalent iodine(III) oxidants include (diacetoxyiodo)benzene **4**, [bis(trifluoroacetoxy)iodo]benzene **5** and (hydroxytosyloxyiodo)benzene also known as Koser's reagent **6** (Fig. 1.3).

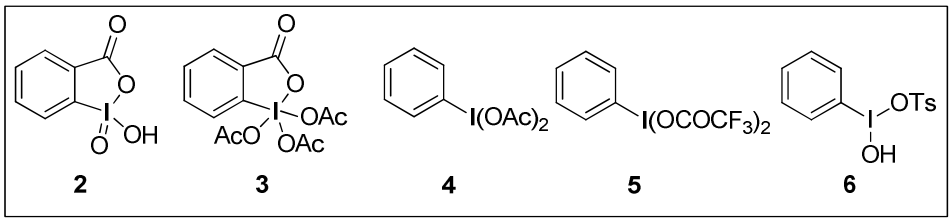
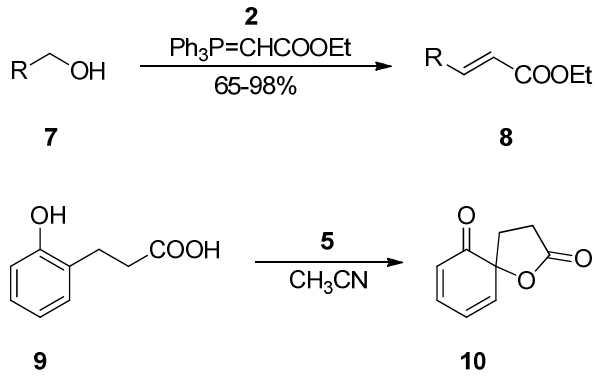


Fig 1.3: Commonly used hypervalent iodine reagents

Benzylic, allylic and propargylic alcohols **7** can be oxidised to the corresponding aldehydes in the presence of stabilized Wittig ylides to generate α,β-unsaturated esters **8** in a one pot procedure by using IBX **2**. This is a useful reaction especially when the intermediate aldehydes are unstable and are difficult to isolate.[9] The dearomatization of phenols **9** with hypervalent iodine reagents has been also used frequently. In the

presence of internal nucleophiles, cyclized products are obtained to give quinone derivatives **10** (Scheme 1.1).[10]

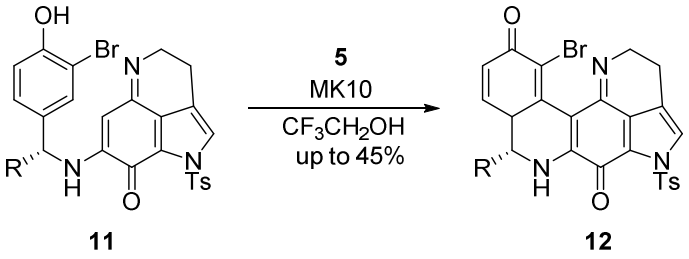


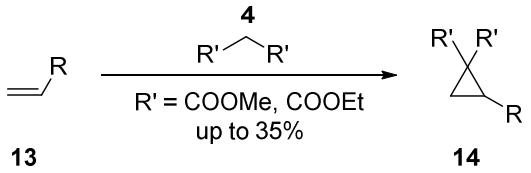
Scheme 1.1: Oxidation of alcohols and phenols with hypervalent iodine reagents

1.4.2 Formation of Carbon-Carbon Bonds

Reactions leading to the formation of carbon-carbon bonds are an important area of practical applications of hypervalent iodine reagents. These reactions proceed either through generation of carbon-centered reactive intermediates such as free radicals, carbocations etc., or by ligand coupling-reactions mediated by tricoordinate iodine intermediates which can be generated by the addition of a carbon nucleophile to an iodonium salt.[11]

Kita and co-workers have efficiently reported oxidative phenol derivative **11** for carbon-carbon coupling reaction to give **12** as a key step in the synthesis of complex natural product mediated by [bis(trifluoroacetoxy)iodo]benzene **5** and MK10 as a solid acid additive.[12] Malonic acid derivatives can be employed to synthesize cyclopropane derivatives **14** from alkenes **13** by *in situ* generation of iodonium ylides from diacetoxy iodobenzene **4** and a carbene precursor (Scheme 1.2).[13]

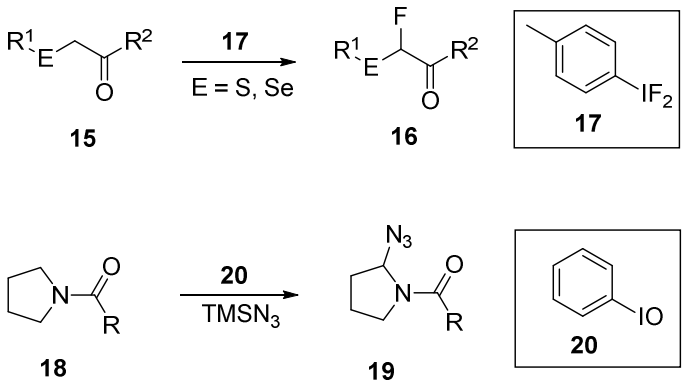




Scheme 1.2: Carbon-carbon bond forming reactions via phenol dearomatization and cyclopropanation of alkenes mediated by hypervalent iodine reagents

1.4.3 Formation of Carbon-Heteroatom Bonds

The use of hypervalent iodine reagents in carbon-heteroatom bond formation is well established and been used successfully for a wide range of substrates. One of the most common example is the halogenation of carbonyl compounds. α-Fluoro sulfides or selenides **16** can be obtained with (difluoroiodo)toluene **17** through a Fluoro-Pummerer reaction in which fluoride is incorporated into the sulfur-containing molecule **15** allowing the synthesis of mono- and difluorides.[14] The treatment of *N*-carbonyl pyrrolidine derivatives **18** with iodosobenzene **20** and trimethylsilyl azide leads to azidonation of the ring **19** with upto 82% yields (Scheme 1.3).[15]

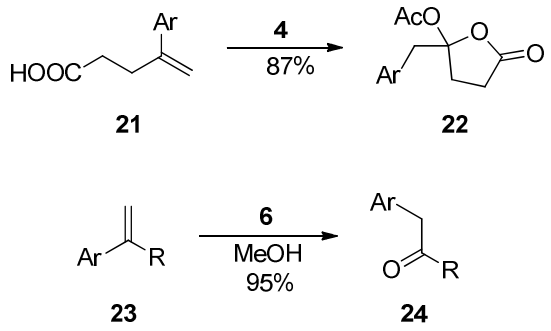


Scheme 1.3: Carbon-heteroatom bond forming reactions via Fluoro-Pummerer reaction and azidonation reaction

1.4.4 Rearrangements

The nature of hypervalent iodine(III) compounds to react as electrophiles and then behave as excellent leaving groups make them highly suitable reagents for generating cationic intermediates which can either directly react with nucleophiles or lead to rearranged products. Treatment of aryl substituted alkenes **21** and **23** with hypervalent iodine(III) reagents **4** and **6** gave rise to the cyclized product **22**[16] when internal

nucleophiles were involved or to the ketones **24** [17] when external nucleophiles were present (Scheme 1.4).



Scheme 1.4: Rearrangement reactions of alkenes mediated by iodine(III) reagents.

1.5 Introduction to Chiral Hypervalent Iodine Reagents

Hypervalent iodine compounds have found broad applications in organic chemistry. They have been frequently used as mild and chemoselective oxidation and oxygenation reagents, replacing toxic and heavy metal containing reagents, thus providing more environmentally friendly reaction conditions. In this context, the use of chiral hypervalent iodine reagents for asymmetric transformations has emerged as an interesting area of research in recent years. Developments and highlights of this chemistry are summarized below, more comprehensive reviews have also appeared in the literature.[18]

Different principles can be used for the synthesis of chiral hypervalent iodine compounds. Iodine(III) derivatives can either have one (**25**) or two (**26**) aryl or alkenyl substituents. Either these substituents or the heteroatom ligands L in these compounds can bear a stereogenic moiety. The same is true for iodine(V) compounds (**27**), although compounds with a stereogenic iodine atom should also be possible. To our knowledge, such compounds have not yet been characterized or employed in asymmetric synthesis. Hypervalent iodate anions can be coordinated to chiral cations allowing the formation of reactive ion-pairs **28** as reagents (Fig. 1.4). Iodine(VII) compounds have not been reported yet for asymmetric synthesis.

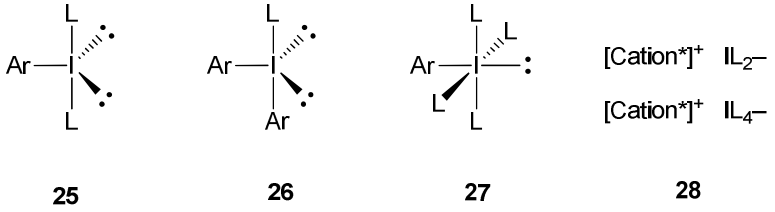


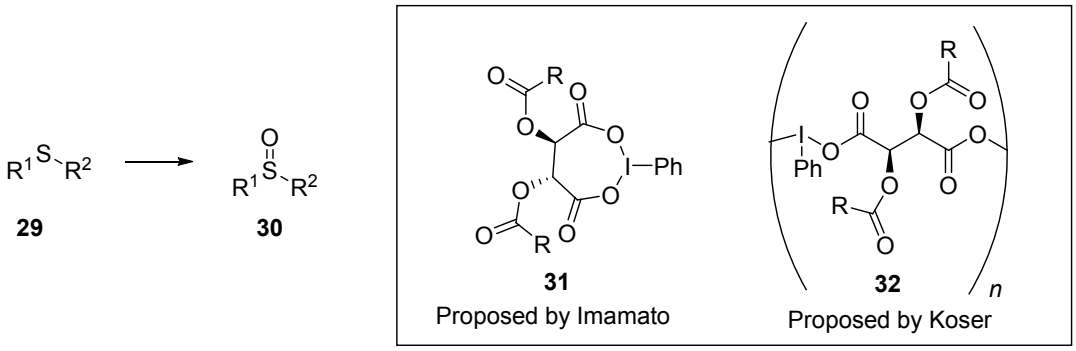
Fig. 1.4: Different types of hypervalent iodine reagents

1.6 General Reactivities of Chiral Hypervalent Iodine Reagents

The use of enantiomerically pure hypervalent iodine reagents in many organic transformations such as the oxidation of sulfides to sulfoxides, α-arylation of carbonyl compounds, the dearomatization of phenols, the dioxygenation, diamination and aminofluorination of alkenes is summarized below.

1.6.1 Oxidation of Sulfides to Sulfoxides

The first optically active hypervalent iodine compound was described in 1907 resulting from the reaction between diphenyliodonium hydroxide and tartaric acid.[19] Similar complexes, although structually not characterized and probably containing oligomeric structures, have been used by Imamoto **31**[20] and later by Koser **32**[21] who performed the oxidation of prochiral sulfides **29** to optically active sulfoxides **30** with selectivities of up to 53% *ee* (Scheme 1.5). The selective sulfide-to-sulfoxide conversion remained for a long time the only reaction to test novel chiral hypervalent iodine compounds.



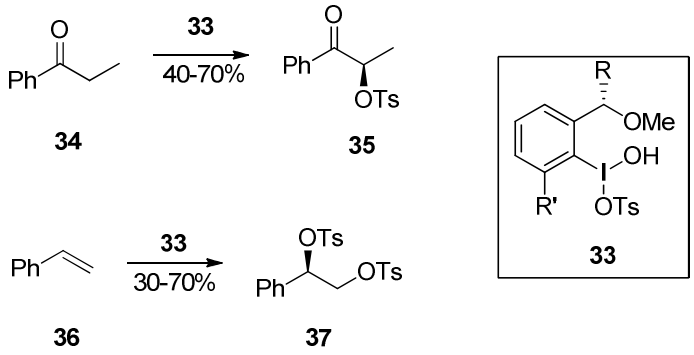
Scheme 1.5: Oxidation of sulfide to sulfoxides by chiral hypervalent iodine reagents

Kita used 10 mol% of a chiral diacyltartaric acid derivative together with iodoxybenzene ($PhIO_2$) and performed the oxidation of sulfides to sulfoxides **30** in the presence of surfactants in excellent yields and enantioselectivities of up to 72% *ee*.[22] Other studies of enantioselective oxidation of sulfides have also been performed by

using camphor-type ligands as stereoselective moieties in iodine(III) compounds of type **25** which resulted in lower selectivities.[23]

1.6.2 Functionaliation of Alkenes and Carbonyl Compounds

In 1997, Wirth reported the first asymmetric functionalizations of alkenes and ketones using chiral iodine(III) dervatives of type **33**. Such compounds **33** (R' = H) were used in the enantioselective oxytosylation of propiophenone **34** and the dioxytosylation of styrene **36**, leading to the selectivities of up to 15% *ee* in **35** and 21% *ee* in **37** respectively.[24] Optimized reagents with second *ortho*-substituents (**33**, R' = Et, OMe) improved these selectivities to up to 65% *ee* in product **37** (Scheme 1.6).[25]



Scheme 1.6: Functionalization of propiophenone and styrene mediated by chiral hypervalent iodine

The development of reactions using hypervalent iodine derivatives in catalytic amounts[26] was the basis for the first enantioselective catalytic reactions involving chiral hypervalent iodine reagents by Wirth.[27] Catalytic reaction involves the utilization of iodine containing molecules together with a stoichiometric oxidant. The oxidant generates the hypervalent iodine reagent *in situ* and after the oxidative transformation mediated by the hypervalent iodine compound; the reduced iodine-containing molecule is re-oxidized (Fig. 1.5).[28]

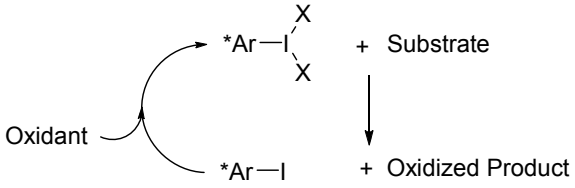
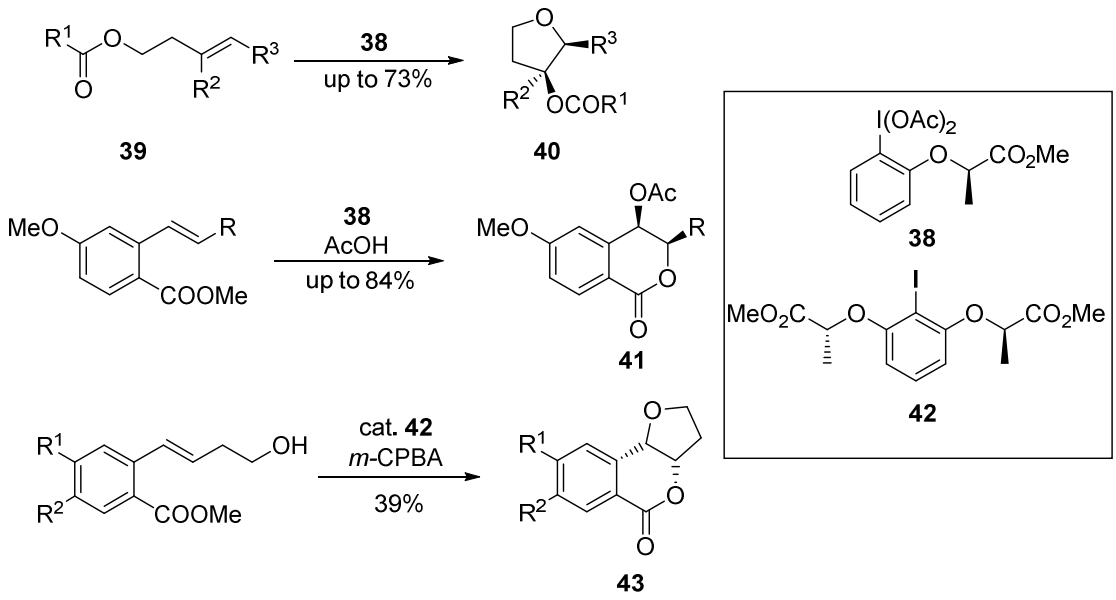


Fig. 1.5: Catalytic cycle for the synthesis of hypervalent iodine reagent.

A range of chiral iodides were investigated together with *m*-CPBA as stoichiometric oxidant in the α-oxytosylation of propiophenone with just 10 mol% chiral aryl iodide and and *para*-toluenesulfonic acid (TsOH) giving the product **35** in selectivities of up to 39% *ee*. When chiral sulfonic acids such as camphorsulfonic acid were used the selectivity was increased to 44% *ee* (Scheme 1.6).[29]

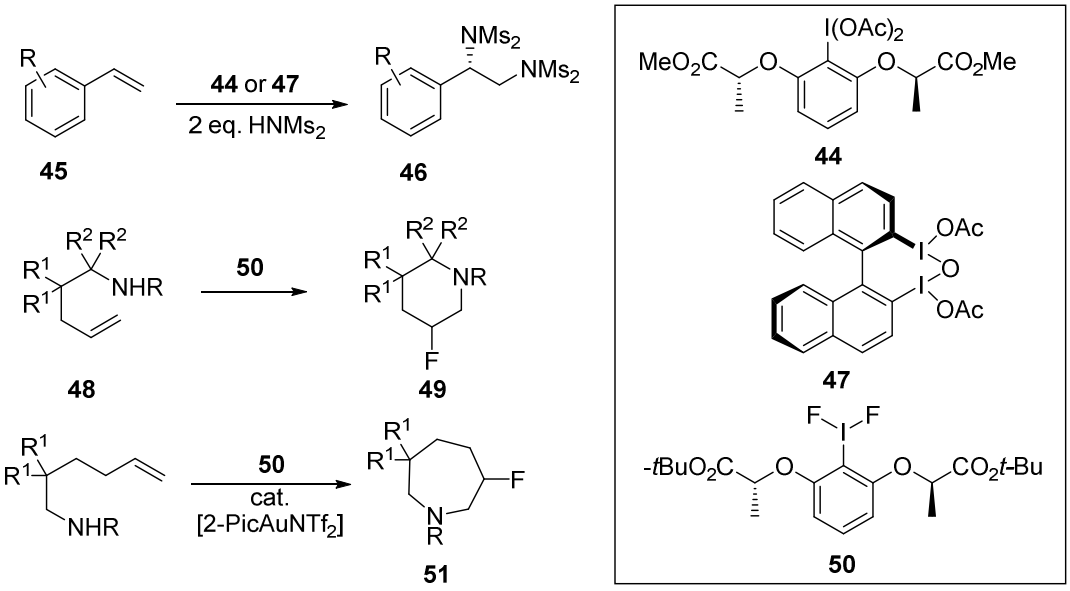
Higher selectivities have been obtained in cyclization reactions. Lactic acid-derived chiral λ^3-iodanes such as **38** were prepared by Fujita and employed in the tetrahydrofuranylation of acyloxybutenes **39** leading to products **40** in up to 64% *ee*.[30] Fujita *et al.* also reported the tosyloxylactonization of 2-ethenylbenzoic acid using stoichiometric amounts of chiral hypervalent iodine reagents of type **38** in the presence of *para*-toluenesulfonic acid (TsOH) or acetic acid. Selectivities of up to 98% *ee* have been obtained which is demonstrated in the synthesis of the natural product **41** (Scheme 1.7).[31]



Scheme 1.7: Lactate-based hypervalent iodine reagents in cyclization reactions

In these reactions *syn* additions to the alkene were observed, this has been already established by previous investigations. A catalytic variant of the oxylactonization was also obtained by using chiral iodine reagent **42** as an organocatalyst along with *m*-CPBA as an oxidant to give dihydrofuran-fused isochromanone **43** with up to 91% *ee*.[32] The same research group also reported enantioselective Prévost and Woodward reactions with lactate derived λ^3-iodanes **38** leading to reaction products with similarly high selectivities (Scheme 1.7).[33]

Hypervalent iodine reagents derived from the lactate-based iodoarene **44** have also been successfully used for the derivatization of alkenes. As shown below, enantioselective diaminations of styrene derivatives **45** have been reported by Muñiz *et al.*[34] These reactions are leading to almost enantiopure diamine **46** (up to 95% *ee*). The utilization of new dinuclear binaphthyl iodine(III) reagent **47** in the similar reaction gave up to 32% *ee*.[35] Nevado *et al.* reported the highly regioselective aminofluorination of alkenes **48** giving the 6-*endo*- cyclized product **49** in 88% *ee* and 79% yield by employing **50** in stoichiometric amounts. The methodology was expanded to give 7-membered *β*-fluorinated azepane scaffolds by employing **50** along with a gold complex in catalytic amounts to give **51** in 77% *ee* and 64% yield (Scheme 1.8).[36]

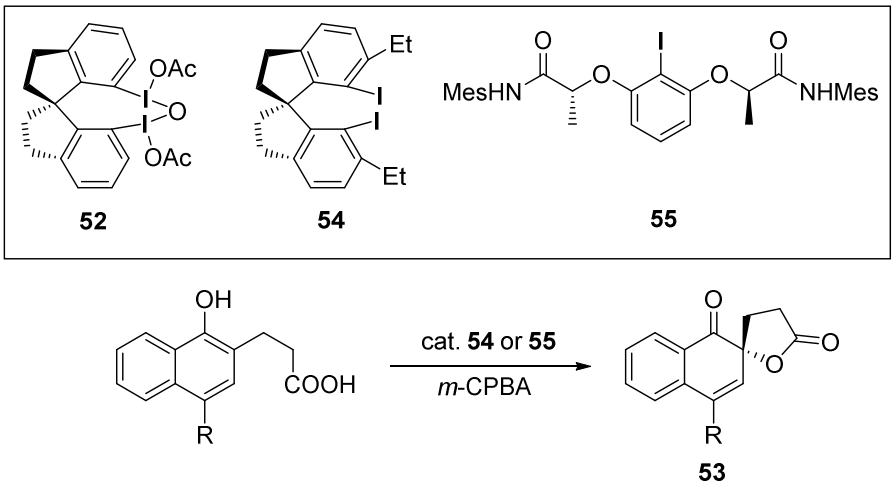


Scheme 1.8: Lactate-based hypervalent iodine reagents in diamination and aminofluorination reactions

1.6.3 Dearomatization of Phenols and *α*-Arylation of Ketones

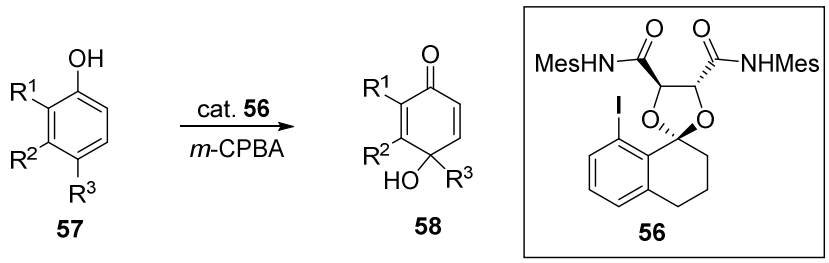
Kita *et al.* introduced hypervalent iodine compounds such as **52** in the enantioselective oxidative spirolactonizations to **53** with selectivities of up to 86% *ee* and 86% yield (92% *ee* and 96% yield in the catalytic reaction by employing **54**).[37,38] Ishihara *et al.* reported a C_2-symmetric chiral iodoarene **55** as a catalyst for spirocyclizations with selectivities of up to 92% *ee* and 94% yields (Scheme 1.9).[39] By using an excess of *m*-CPBA in these reactions (5 equivalents), the product **53** can also be epoxidized. Intramolecular bonding interactions between the amide protons and the iodine ligands

or between the carbonyl oxygen atom and the iodine atom are suggested to directly affect the asymmetric reaction.



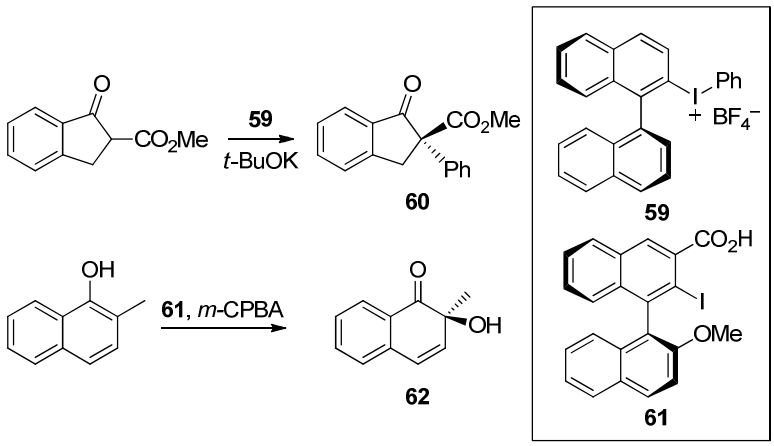
Scheme 1.9: Oxidative spirolactonizations of phenols by chiral hypervalent iodine reagents.

Harned *et al.* synthesized the tricylic chiral iodide **56** derived from 8-iodotetralone and tartaric acid and used them to obtain *para*-quinol derivatives **58** from phenols **57** in up to 60% *ee* and 79% yield (Scheme 1.10).[40]



Scheme 1.10: Tricyclic chiral iodide for *p*-quinol derivatives synthesis

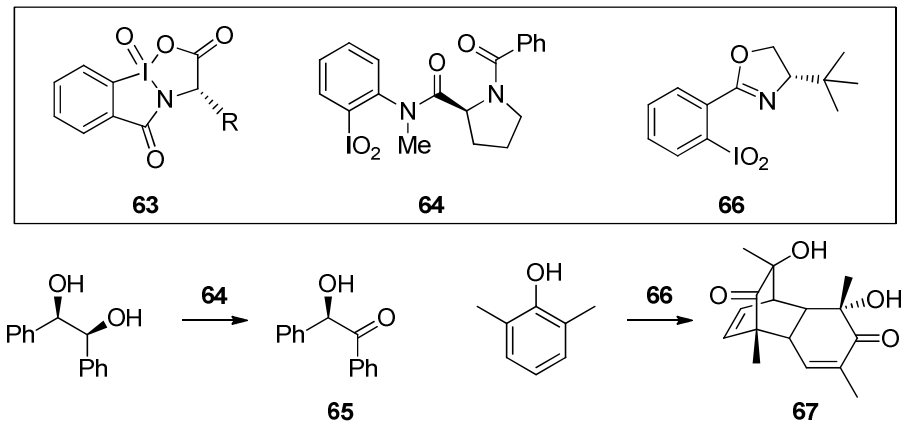
Ochiai *et al.* reported the first iodinanes with a binaphthyl structure.[41] Later his research group used diaryliodonium salts **59** for the phenylation of β-keto esters in the presence of a base to give products **60** with yields of up to 69% and selectivities of up to 53% *ee*.[42] Other chiral iodoarenes based on a binaphthyl system such as **61** have been reported by Quideau *et al.* and used in the asymmetric hydroxylative dearomatization of phenol derivatives. The α-hydroxylated product **62** was obtained with 50% *ee* and in 83% yield (Scheme 1.11).[43]



Scheme 1.11: Utilization of chiral binaphthyl iodoarenes in α-arylation and dearomitization reactions

1.6.4 Stereoselective Oxidation Reactions Mediated by Iodine(V) Reagents

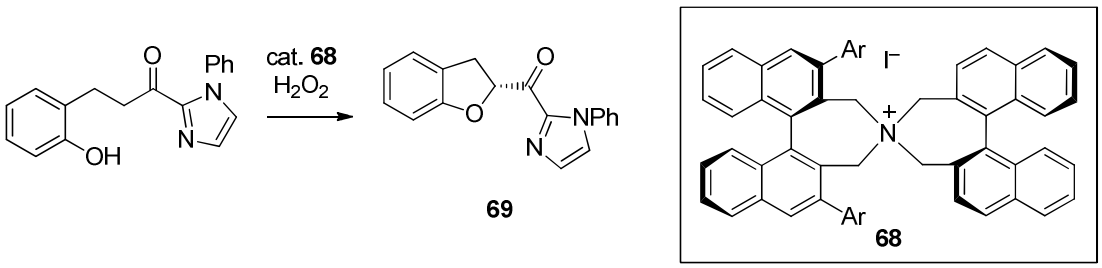
Only very few chiral λ^5-iodanes have been synthesized and used in asymmetric synthesis. Zhdankin *et al.* prepared the series of benziodazoles of type **63** from naturally occurring amino acids and used them for the oxidation of sulfides obtaining sulfoxides **30** in up to 16% *ee*.[44] The same research group also prepared proline containing λ^5-iodanes **64** and investigated their use as stereoselective oxidizing agents for *meso*-diols obtaining selectivities in the products **65** of up to 33% *ee*.[45] Zhdankin *et al.* also prepared different amino acid-based chiral λ^3-iodanes, either with the amino acids as a chiral moiety attached to the iodoarene or as a ligand on the iodine(III) atom.[46] Birman *et al.* introduced a class of chiral iodine(V) aryliodooxazolines such as **66** derived from amino alcohols. They investigated their use for the oxidation of phenols in an oxidative dearomatization followed by a [4+2] dimerization to products **67** with enantioselectivities of up to 77% (Scheme 1.12).[47] Later Wirth and co-workers reported another series of chiral hypervalent iodine(V) compounds as stoichiometric oxidants.[48]



Scheme 1.12: Iodine(V) reagents in oxidation reactions

1.6.5 Cycloetherification of Phenols

Ishihara *et al.* investigated the enantioselective oxidative cycloetherification of ketophenols to 2-acyl-2,3-dihydrobenzofuran derivatives catalyzed by *in situ* generated chiral quaternary ammonium iodide catalysts **68** with hydrogen peroxide as a stoichiometric oxidant. This is a very vital example of asymmetric catalysis using chiral cations paired with inorganic iodine derived oxo acids. In this protocol, the C_2-symmetric chiral binaphthyl-based quaternary ammonium (hypo)iodite reagent was generated *in situ* by reaction with hydrogen peroxide. It was found that ammonium cations bearing bulky and electron deficient substituents gave the best results giving selectivities in **69** of up to 96% *ee* with 99% yield (Scheme 1.13).[49]



Scheme 1.13: Cycloetherification by *in situ* generated chiral quaternary ammonium iodide

1.7 Conclusion

In conclusion, hypervalent iodine reagents have been developed for mild and environmentally friendly reaction protocols leading to synthetically attractive organic molecules. They have been used not only as selective oxidants but also as powerful electrophiles for the activation of carbon-carbon double bonds. The developments and recent advances in the field of chiral hypervalent iodine reagents have led to the synthesis of many biologically important molecules in optically active form.

1.8 References

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Chapter 2

Aminohydroxylations of Alkenes

2.1 Introduction to Aminohydroxylations of Alkenes

The functionalization of an alkene is one of the most popular reaction among synthetic chemists because of their wide occurrence. Many novel methodologies have been developed involving alkenes leading to the synthetically attractive and biologically important molecules. Particularly, the 1,2-difunctionalization of alkenes has always been a challenging target in synthetic chemistry because of regio- and stereochemical issues.[1] The occurrence of 1,2-difunctionalized compounds in natural products and biologically active compounds in the form of 1,2-amino alcohols, 1,2-diamines and 1,2-diols illustrate the importance of the products of such transformations. Given their prominent significance in organic chemistry, it is no surprise that many synthetic routes have been developed to overcome the challenges of their synthesis.

1,2-Amino alcohols are the key functional groups in many bioactive compounds, natural products and chiral reagents for stereoselective synthesis. One of the most common naturally occurring amino alcohols are the hydroxy amino acids like serine and threonine. Other biologically important compounds containing amino alcohol moieties include anisomysin[2] which is a potent inhibitor of protein biosynthesis and have anti cancer activity and bestatin[3] with applications in cancer chemotherapy (Fig. 2.1).

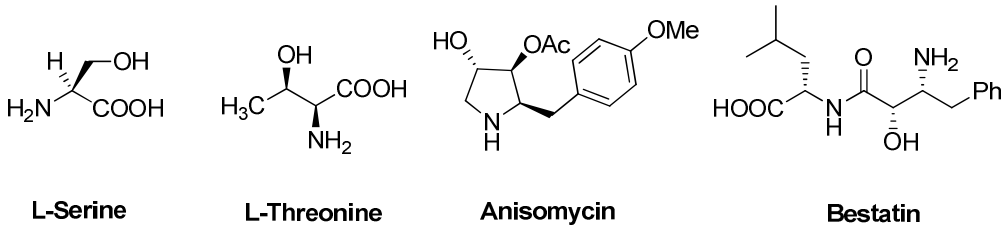
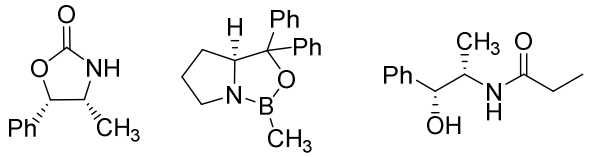


Fig. 2.1: Bioactive compounds with amino alcohol moieties

Vicinal amino alcohol-based chiral reagents have found broad applications in asymmetric synthesis. Most of these amino alcohols are present in cyclic systems for example, Evans' reagents **70**.[4] These enantiopure chiral auxiliaries are used in aldol condensation, alkylation and Diels-Alder reactions. Oxazaborolidine **71** are proline-based systems used in the highly selective catalytic asymmetric reduction of carbonyl compounds.[5] Acyclic amino alcohols are also used in many asymmetric transformations; ephedrine derivative **72** has been used in asymmetric alkylation of amides (Fig. 2.2).[6]



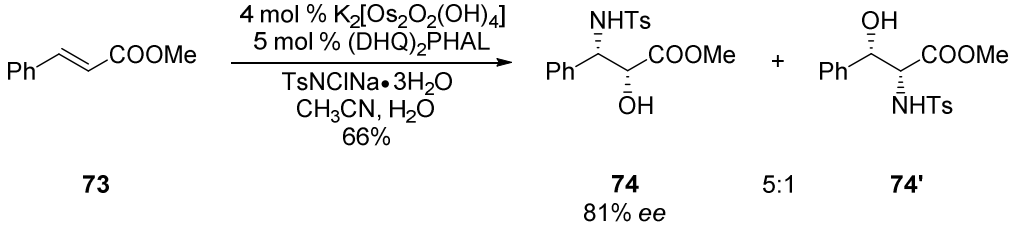
70 **71** **72**

Fig. 2.2: Commonly used chiral amino alcohol reagents in asymmetric transformations

Transition metal-catalyzed oxidative amination reactions are established methods for the synthesis of new carbon-nitrogen and carbon-oxygen bonds through the functionalization of alkenes.[1] Other metal-free protocols are also reported in the literature to overcome the toxicity and cost issues associated with the metal-catalyzed reactions. A brief summary on the background of such reactions is described below.

2.2 Transition Metal-Catalyzed Aminohydroxylations

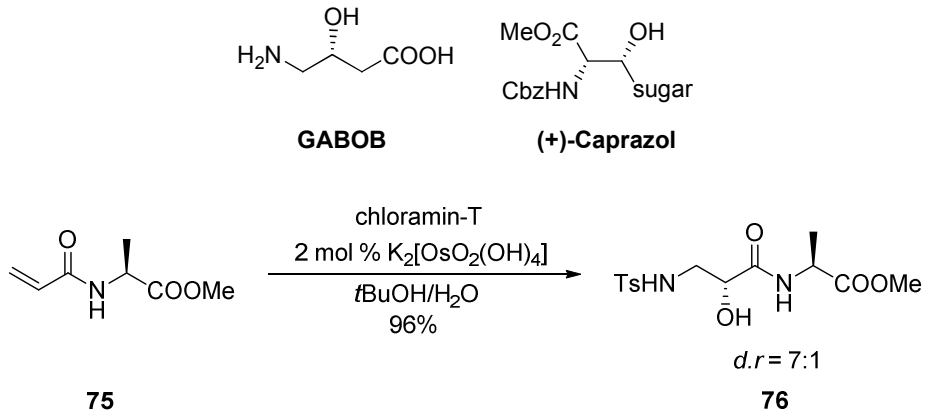
In 1996, Sharpless *et al.* developed the first asymmetric aminohydroxylation (AA) of alkenes. The reaction involves direct enantioselective synthesis of vicinal amino alcohols **74** from the alkenes **73** by loading catalytic amounts of potassium osmate, in the presence of stoichiometric nitrogen source that also acts as a re-oxidant and cinchona alkaloids; hydroquinine 1,4-phthalazinediyl diether $(DHQ)_2PHAL$ to control regio- and stereo-chemistry of the products (Scheme 2.1).[7]



73 **74** 81% *ee* **74'**

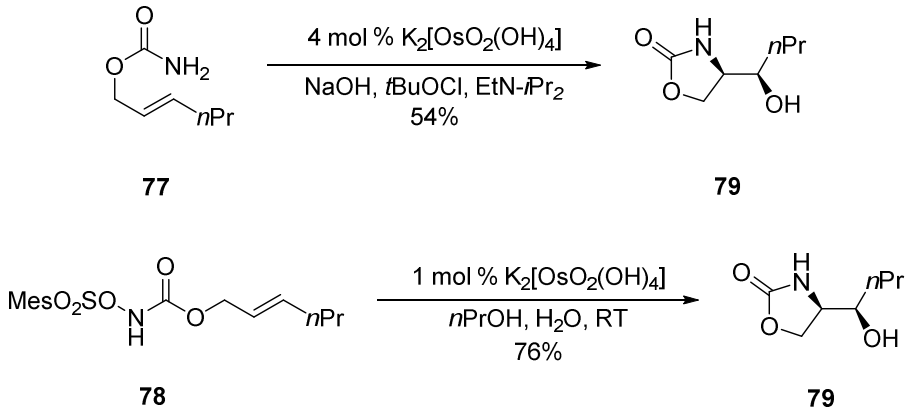
Scheme 2.1: Sharpless asymmetric aminohydroxlation (AA) of alkenes

The Sharpless AA protocol has also been applied in the synthesis of many natural products such as γ-amino-β-hydroxybutyric acid (GABOB)[8] and (+)-caprazol.[9] In 2005 Muñiz *et al*. reported the first osmium catalyzed *substrate-controlled* aminohydroxylation of acrylamides **75** with moderate to excellent yields and diastereoselectivites of amino alcohols **76** (Scheme 2.2).[10]



Scheme 2.2: Natural products synthesized from Sharpless AA and *reagent-controlled* aminohydroxylations

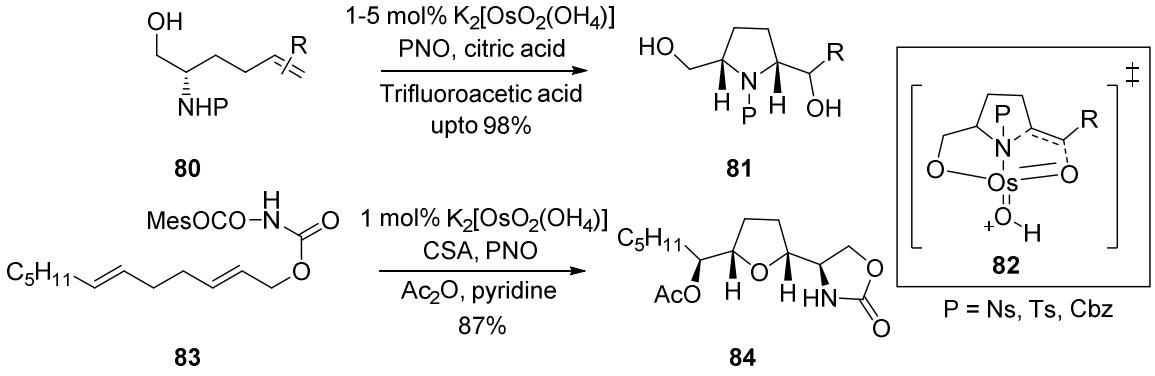
Despite the recent advances in osmium catalyzed aminohydroxylations of alkenes, these reactions are highly dependent on the nature of the substrate and have regiochemical issues. To address these problems, Donohoe *et al*. developed a novel strategy in which the nitrogen source was tethered to the alkene substrates **77** and **78** giving **79** with complete regioselectivity. However, no enantioselectivity was observed when these substrates were exposed to the reaction conditions in the presence of cinchona ligands (Scheme 2.3).[11,12]



Scheme 2.3: Osmium catalyzed tethered aminohydroxylations

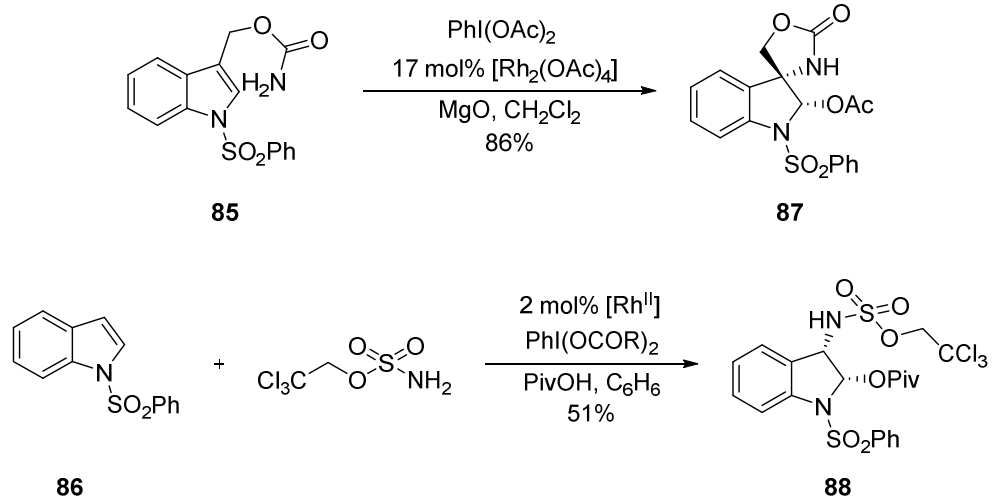
Donohoe *et al*. also reported an osmium catalyzed intramolecular aminohydroxylation of *N*-protected amino alcohols **80** onto tethered alkenes to give corresponding pyrrolidine rings **81** with up to 98% yields. It was proposed that the reaction proceeds via chelation of Os(VI) species and the amino alcohol moiety, followed by the acid promoted *syn*-addition to the alkene **82**. Then the resulting Os(IV) is re-oxidized by using pyridine-*N*-oxide (PNO).[13] By employing similar strategy led to the formation of

a highly substituted tetrahydrofuran derivative as a single diastereomer **84** from the diene **83** (Scheme 2.4).[14]



Scheme 2.4: Osmium catalyzed cyclization reactions

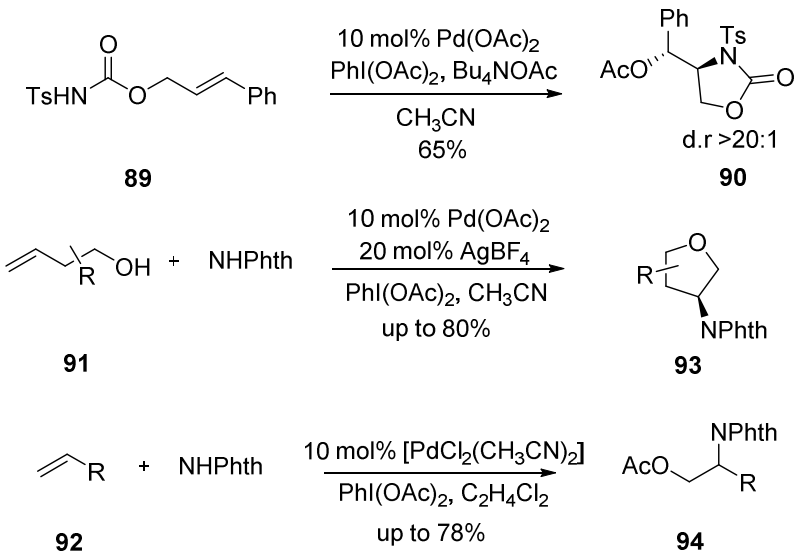
Rhodium(II) catalysts along with hypervalent iodine(III) reagents as stoichiometric oxidants have also been used in the oxyamination of electron rich alkenes. Evidence suggested that the reaction proceeds through the formation of aziridine intermediate via the addition of metallonitrene to the alkene **85** and **86**, followed by the attack of different oxygen nucleophile to give amino alcohol derivatives **87** and **88** in high yields and as single diastereomers (Scheme 2.5).[15,16]



Scheme 2.5: Rhodium(II)-catalyzed intra- and intermolecular oxyamination of alkenes

The direct oxyamination of terminal and internal alkenes was developed by Bäckvall *et al*. in 1975. Stoichiometric amounts of Pd(II) were necessary for the reaction, limiting its scope for further manipulations.[17] However, in 2005 Sorensen *et al.* reported that a catalytic source of Pd(II) in the presence of an iodine(III) re-oxidant could be applied to

the olefin **89** to give oxyaminated product **90** in moderate yields and high diastereoselectivities. The reaction proceeded with *anti*-addition of heteroatoms across the double bonds.[18] An analogous catalytic system was developed further for oxyamination of wide range of alkenes **91** and **92** to give products **93** and **94** with complete regioselectivity and high diastereoselectivity (Scheme 2.6).[19,20]



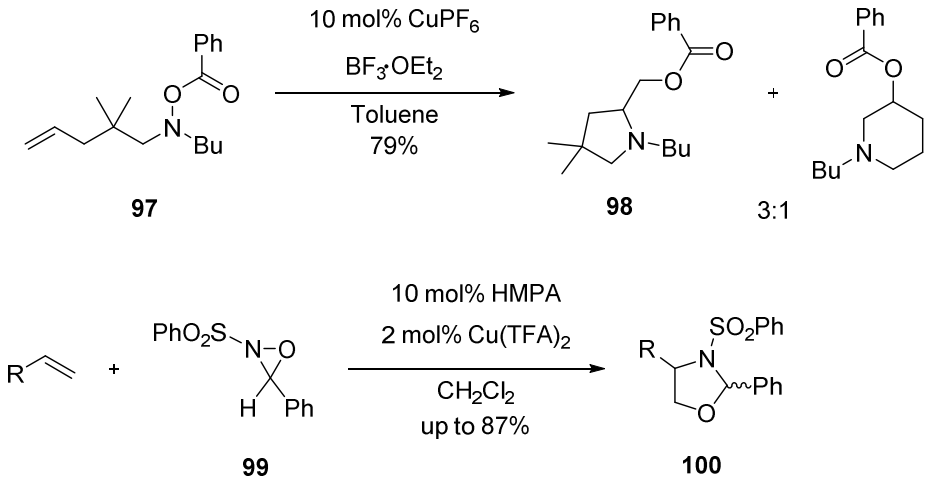
Scheme 2.6: Palladium(II) catalyzed oxyamination of alkenes using iodine(III) reagents as oxidants

Muñiz *et al*. also showed that platinum can also act as a catalyst for intramolecular oxyamination of alkenes in the presence of copper dibromide as co-catalyst. However the reaction was limited to the systems bearing the terminal alkenes **95** to give 5-6 fused ring system **96**. It was observed that the reaction proceeded with high chemo- and diastereoselectivity when a stereocentre was present on the carbon backbone (Scheme 2.7).[21]

Scheme 2.7: Platinum catalyzed oxyaminations.

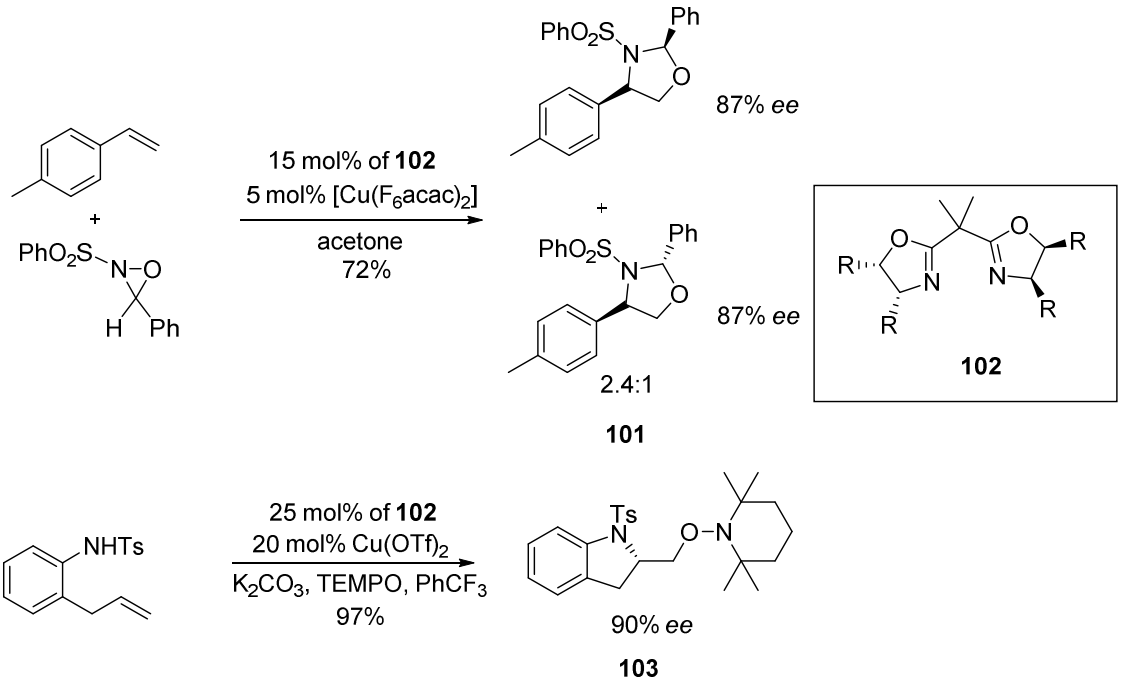
In 2002, Göttlich and Naock reported a copper-catalyzed oxyamintion of alkenes in the presence of Lewis acids. The authors suggested that in this reaction, *N*-benzoyl hydroxylamines **97** with pendant olefins underwent a radical type mechanism followed

by 5-*exo-trig* cyclization onto the tethered alkene to deliver **98** as a major oxyaminated product.[22] The similar strategy was then applied for intermolecular addition of *N-O* bond of an *N*-sulfonyl oxaziridine **99** across a range of alkenes to give a mixture of *cis* and *trans* aminooxygenated products **100** (Scheme 2.8).[23]



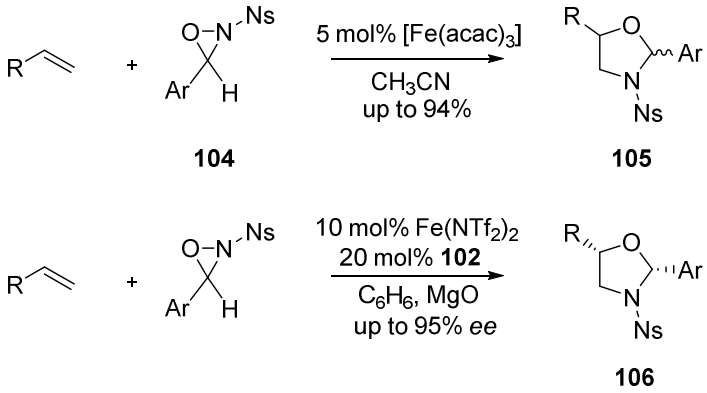
Scheme 2.8: Copper catalyzed oxyamination of alkenes

The use of chiral bisoxazoline copper(II) complexes for enantioselective intermolecular oxyamination of alkenes make them a useful complementary transformation to the Sharpless AA reaction. The reaction proceeded with high regio- and enantioselectivity but the lack of stereospecificity; as illustrated by the formation of mixture of products **101,** was a major drawback.[24] Chemler *et al*. developed the first intramolecular enantioselective oxyamination reaction with high enantio- and regioselectivity by using catalytic amounts of copper in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)-oxyl (TEMPO) which served both as stoichiometric oxidant and the oxygen source. In the presence of asymmetric bisoxazoline ligands of type **102**, chiral indolines and pyrrolidines **103** were obtained. Further kinetic studies indicated that the reaction is first order both in the substrate and the copper complex and zero order in TEMPO (Scheme 2.9).[25,26]



Scheme 2.9: Copper catalyzed enantioselective aminooxygenation of alkenes

First row transition metal catalysts like Fe(III) continue to contribute towards effective intermolecular addition of *N-O* by using *N*-sulfonyl oxaziridine **104** across the range of alkenes giving the oxyaminated products in high yields and selectivities.[27] It is noteworthy that the regioselectivity obtained in Fe(III) catalyzed reaction product **105** is inverted as to that observed with Cu(II) catalyzed product **100** (Scheme 2.8). Iron(III) catalysts have also been used for asymmetric oxyamination reaction of alkenes by using chiral ligands of type **102** to give enantioenriched oxazolidine products **106** that can be easily manipulated to give free amino alcohols (Scheme 2.10).[28]

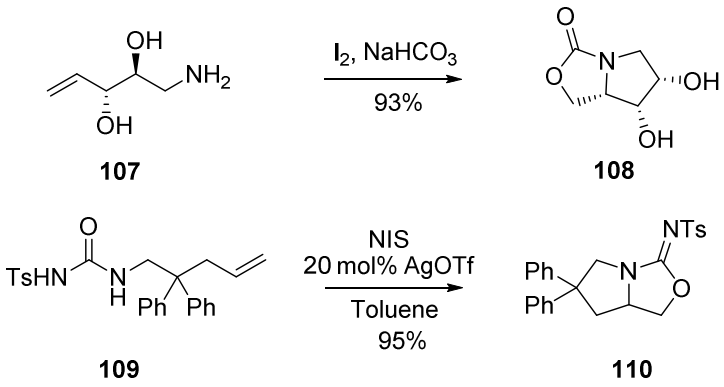


Scheme 2.10: Iron(III) catalyzed oxyamination of alkenes

2.3 Metal-Free Oxyamination Protocols

Transition-metal catalysis though provides an easy access to the broad range of oxyamination products from the wide range of alkenes, however there are several drawbacks of these reagents. As they are expensive, toxic, air sensitive and often difficult to remove in final pharmaceutical products on large scale. As a result, many researchers have been interested to develop metal-free reaction conditions to obtain amino alcohols from alkenes. These are useful synthetic methodologies because of their mild, non-toxic and environmentally friendly reaction conditions.

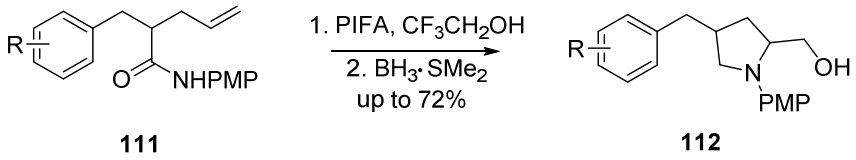
Stoker *et al*. reported the iodine(0) mediated one-pot oxyamination of alkenes. In this paper bishomoallylic amines **107** were cyclized to form hydroxypyrrolidines **108** with high regio- and diastereoselectivity. The reaction proceeded with the activation of the double bond by iodine followed by 5-*exo-tet* cyclization of the primary amine. The resulting haloamine intermediate was substituted by carbon dioxide generated *in situ* from sodium bicarbonate ($NaHCO_3$).[29] *N*-*δ*-alkenyl-*N*′-sulfonyl ureas **109** were also cyclized to give bicyclic isoureas **110** by using *N*-iodosuccinimide (NIS) along with catalytic amounts of silver triflate (AgOTf) (Scheme 2.11).[30]



Scheme 2.11: Iodine(0) mediated oxyamination of alkenes

The use of iodine(III) reagents in oxyamination reactions of alkenes was firstly developed by Dominguez's group. They used [bis(trifluoroacetoxy)iodo]benzene for direct intramolecular oxyamination of terminal alkenes. In the reaction protocol, *N*-*para*-methoxyphenyl amides **111** were transformed into pyrrolidinones **112**. The authors proposed the oxidation of amide group by the PIFA followed by intramolecular addition reaction to the olefin to generate aziridinium cation, as the key step in the reaction.

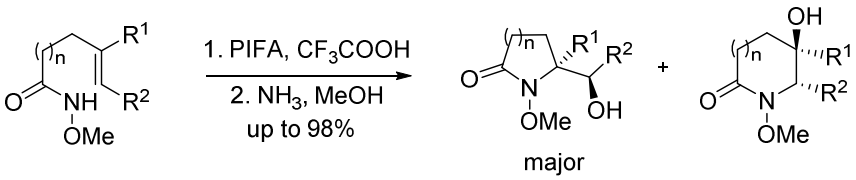
However, the reaction was limited just to the terminal alkenes and to amides bearing the *para*-methoxyphenyl (PMP) protecting group (Scheme 2.12).[31]



111 **112**

Scheme 2.12: PIFA mediated oxyamination of termial alkenes

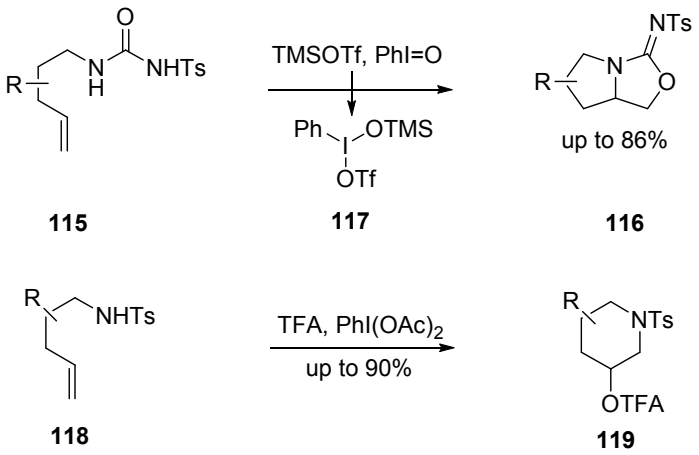
The similar oxidative approach for diastereoselective formation of hydroxylactams **114** from amides **113** which are directly activated by the methoxy group was developed by Wardrop's research group in 2010. This methodology enabled the synthesis of five-eight membered rings in moderate to excellent yields. The main limitation of this protocol was the moderate regioselectivity and the stoichiometric loadings of transition-metal reagents for deprotection of the nitrogen moiety (Scheme 2.13).[32]



113 **114** **114'**

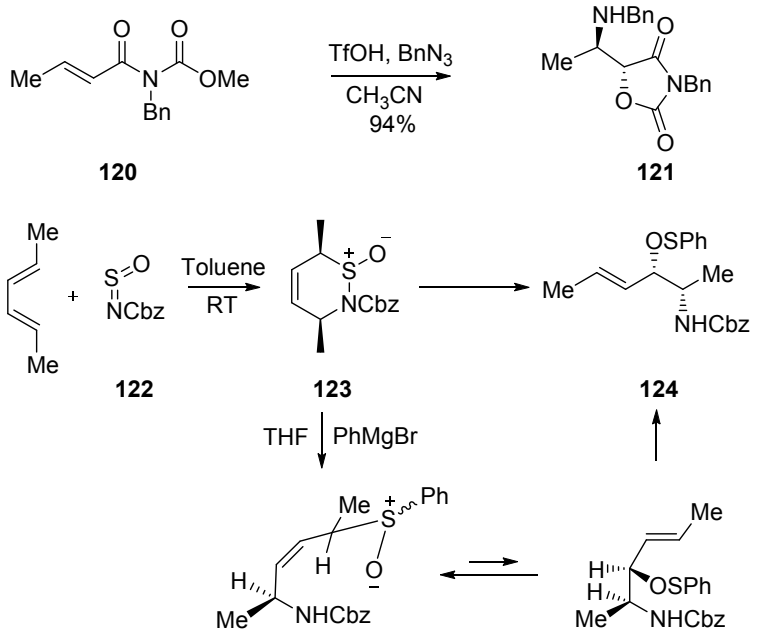
Scheme 2.13: PIFA mediated oxyamidation of alkenes

Michael *et al*. broadened the scope of iodine(III) reagents for intramolecular oxyamination of bis-homoallylic sulfonyl ureas **115**. When these substrates were exposed to iodosyl benzene (PhIO) in the presence of trimethylsilyl triflate (TMSOTf), bicyclic isoureas **116** were obtained in up to 86% yield. An ionic mechanism for this transformation was proposed by the authors which involved the *in situ* generation of a new iodine(III) reagent **117** derived from the PhIO and TMSOTf through ligand exchange reaction on the iodine followed by the activation of the alkene. The resultant cationic intermediate underwent 5-*exo*-*tet*-cyclization through the attack of the nitrogen. Subsequent attack of urea oxygen delivered the isourea **116** with high *syn* selectivity.[33] The same research group also reported the first direct oxyamination of homoallylic amines **118** exhibiting 6-*endo* selectivity to deliver cyclized oxyamination products **119** in the presence of trifluoroacetic acid (TFA) (Scheme 2.14).[34]



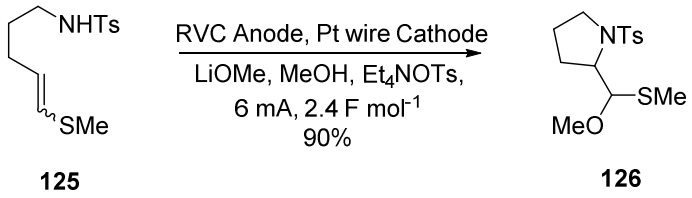
Scheme 2.14: Iodine(III) mediated oxyamination of alkenes

Johnston *et al.* reported the addition of alkyl azides to *α*,*β*-unsaturated amides **120** under acidic conditions to give *β*-amino products **121** in good yields and with *anti* selectivity.[35] This method represents a useful alternative approach to the osmium catalyzed *syn* selective aminohydroxylation reaction (Scheme 2.15). The oxyamination of dienes was reported by Weinreb.[36] In this approach a hetero-Diels-Alder reaction between *N*-sulfinyl carbamate **122** and a range of dienes were used to obtain allylic sulfoxides **123** which underwent a stereospecific [2,3] sigmatropic rearrangement on exposure to phenyl magnesium bromide to deliver the oxyaminated product **124**. However, the limited substrate scope of this methodology has restricted its use in modern synthetic chemistry (Scheme 2.15).



Scheme 2.15: Other metal-free oxyaminations of alkenes

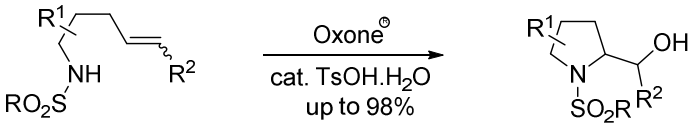
An electrochemical protocol for the synthesis of protected hydroxy-pyrrolidines **126** by the oxidative electrolysis of *N*-sulfonyl amines **125** bearing electron rich alkenes using reticulated vitreous carbon anode (RVC) and platinum wire cathode has been reported by Moeller *et al*. The authors proposed that the reaction proceeds via a radical process in the presence of a nucleophile such as methanol to deliver the oxyamination product in good yield (Scheme 2.16).[37]



125 **126**

Scheme 2.16: Electrochemical oxyamination of electron rich alkenes

Togo *et al*. reported th Bronsted acid-catalyzed intramolecular aminohydroxylation of *N*-alkenylsulfonamides **127** in the presence of oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) to give prolinol derivatives **128** in high yields. The reaction proceeded with an activation of oxone with *p*-toluenesulfonic acid (TsOH) to give a peroxymonosulfate intermediate which reacted with the alkene to give an epoxide. The *exo*-selective intramolecular amination of the epoxide gave rise to the prolinol derivatives (Scheme 2.17).[38]



127 **128**

Scheme 2.17: Acid-catalyzed oxyaminations of alkenes

2.4 Summary

During the past decade, many developments have been made in the field of aminohydroxylation reactions. Metal-catalyzed oxyamination reactions remain the most reliable methods for stereoselective synthesis of amino alcohols. However, not any of these methods are able to offer a complete regio- and stereocontrol aminohydroxylation reaction with all types of olefins. It is also notable that none of the above mentioned metal-free protocols provide an enantioselective route to amino alcohols. Therefore, further advancement in this area of research is necessary to overcome these problems.

2.5 References

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Chapter 3

Results and Discussion of Aminohydroxylation Reactions

3.1 Objectives

The main objective of this work is to develop a stereoselective metal-free protocol for the intramolecular oxyamination of alkenes (Fig. 3.1). Besides the long history of the aminohydroxylation chemistry, it is notable that there is not even a single report of such a reaction under metal-free conditions. In this context, the use of chiral hypervalent iodine reagents for asymmetric transformations can be a suitable replacement because of their environmentally friendly and mild reaction conditions. This avoids the issues of toxicity or the complicated ligands related to many transition metal-based systems. Utilization of chiral hypervalent iodine compounds as electrophilic reagents for alkene functionalization is also a well established research field, as illustrated by the dioxygenation,[1] diamination[2] and aminofluorination[3] reactions of alkenes.

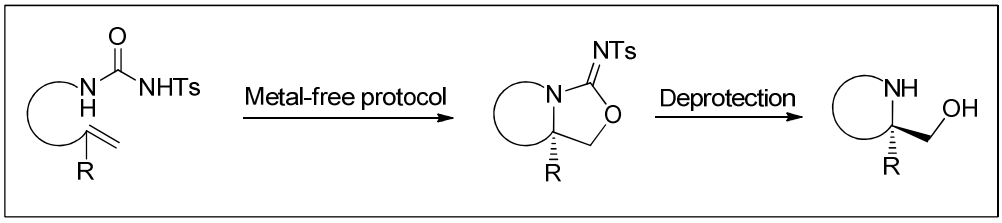
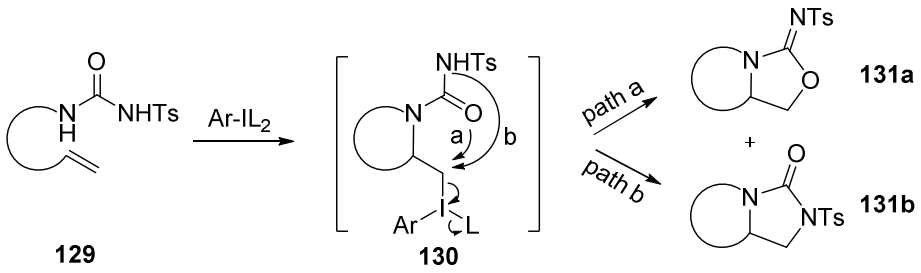


Fig. 3.1: Metal-free aminohydroxylation of alkenes leading to free amino alcohol moiety

3.2 Project Approach

The project approach starts with the synthesis of sulfonyl-substituted homoallylic urea derivatives of type **129**. The use of such bifunctional nucleophiles together with stoichiometric amounts of hypervalent iodine reagents in the addition to alkenes can be used for intramolecular oxyamination reactions. In the reaction protocol, after the activation of the double bond with the hypervalent iodine reagent the first nucleophile reacts to give intermediate **130**. The hypervalent iodine moiety is then attached to a sp^3-hybridized carbon atom and therefore is an excellent leaving group, several orders of magnitude more reactive than triflates or tosylates.[4] The subsequent substitution reaction directly yields bicyclic compounds **131**. It has already been shown in the literature that the strong acidic conditions lead to isoureas **131a** and weak acidic conditions lead to the formation of diamination products **131b** (Scheme 3.1).[5] The deprotection of the nitrogen followed by the cleavage reaction can give rise to the free amino alcohol or diamines derivatives.



Scheme 3.1: Cyclization of urea bisnucleophiles with alkenes using hypervalent iodine reagents (Ar-IL_2) for the synthesis of isoureas **131a** (path a) or of cyclic ureas **131b** (path b)

Based on the reactions mentioned above, we shall also extend this concept towards the enantioselective synthesis of protected amino alcohols from alkenes. As we generate a new stereogenic centre in the reaction, use of chiral hypervalent iodine reagents for stereochemical induction can be interesting which will lead towards the enantiomerically pure amino alcohols. In this perspective, many lactate-based chiral hypervalent iodine reagents of type **132** reported in the literature can be examined (Fig. 3.2).[6,7] The results obtained in these reactions are described below.

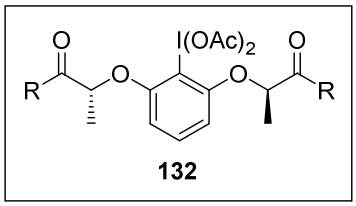
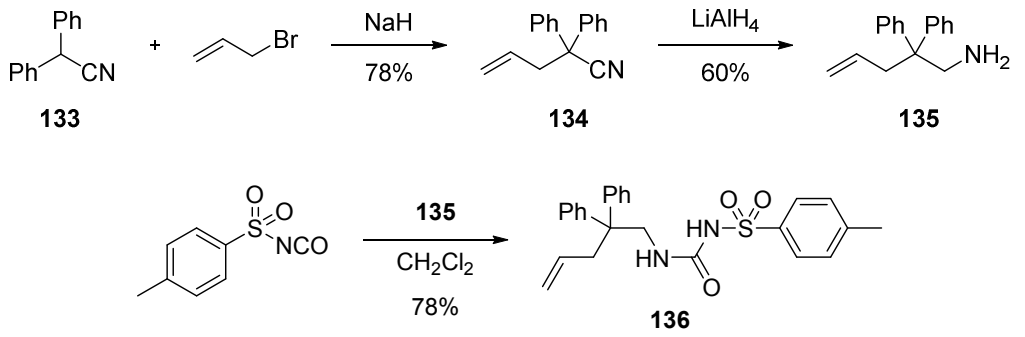


Fig. 3.2: Lactate-based chiral hypervalent iodine reagent

3.3 Initial Oxyamination Cyclizations

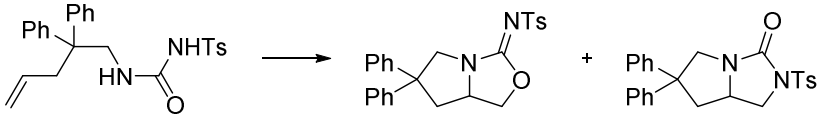
We have investigated sulfonyl-substituted homoallylic urea derivative **136** for the intramolecular oxyamination reaction by using different hypervalent iodine reagent. Substrate **136** was synthesized by a known literature procedure starting from the abstraction of a proton from diphenylacetonitrile **133** by using sodium hydride followed by its reaction with allyl bromide to give 2,2-diphenylpent-4-enenitrile **134** as an oil and then the reduction reaction with $LiAlH_4$ to give 2,2-diphenylpent-4-en-1-amine **135**.[8] The final step was the treatment of **135** with *p*-toluene sulfonylisocyanate (TsNCO) which resulted into the corresponding (2,2-diphenylpent-4-enyl)-3-tosylurea compound **136** as a white solid (Scheme 3.2).



Scheme 3.2: Synthesis of starting material **136** for oxyamination reactions

In the initial experiments for cyclizations, when substrate **136** was exposed to [bis(trifluoroacetoxy)iodo]benzene, a mixture of oxyamination **137a** and diamination **137b** products in almost equimolar ratio with a very slow reaction was observed (Table 3.1, entry 1). The use of catalytic amounts of diphenyl diselenide, a catalyst which was successful in a series of other cyclization-elimination sequences, along with a stoichiometric amounts of hypervalent iodine oxidant did not have a substantial improvement as the reaction time was still long (Table 3.1, entry 2).[9] When *tert*-butyldimethylsilyl triflate (TBDMSOTf, Table 3.1, entries 3 and 4) was added to the reaction mixture along with the hypervalent iodine reagent, complete conversion of the starting material was observed giving the isourea **137a** as a major product. The addition of *tert*-butyldimethylsilyl triflate (TBDMSOTf, Table 3.1, entries 3 and 4) or trimethylsilyl triflate (TMSOTf) to (diacetoxyiodo)benzene generates, as evidenced by NMR investigations (p. 94), *in situ* the more reactive $PhI(OTf)_2$.[10] This led to a mixture

of **137a** and **137b** (approx. 2:1) in a much faster reaction with improved combined yields of 72% (Table 3.1, entry 4).



136 **137a** **137b**

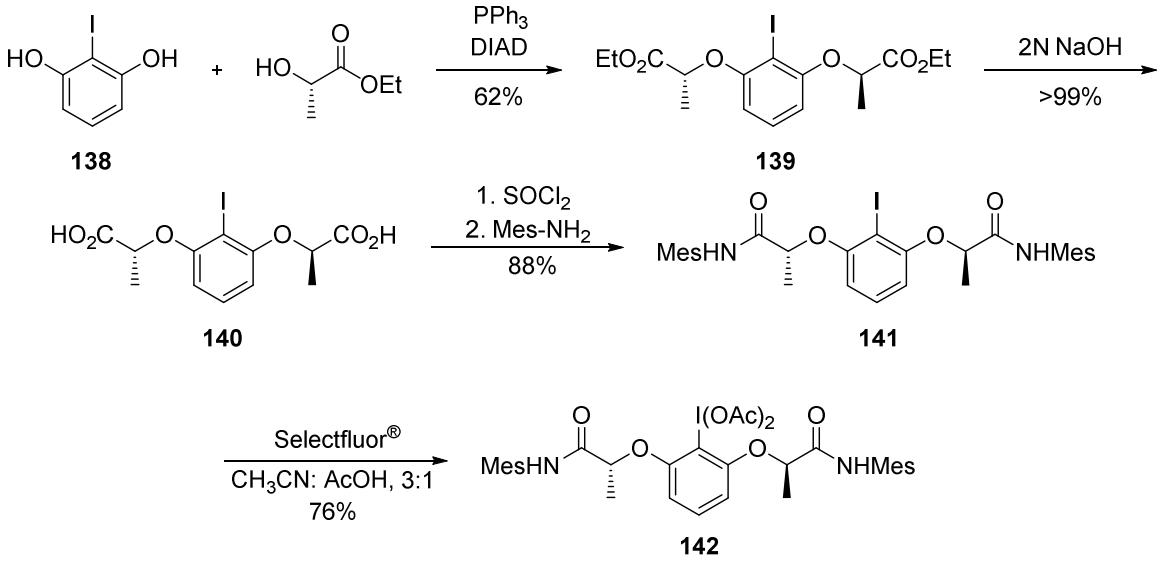
Table 3.1: Different hypervalent iodine reagents for the cyclization of **136**

Entry	Reagents	Solvent, Conditions	**137a** Yield [%]	**137b** Yield [%]
1	$PhI(OCOCF_3)_2$ (1.2 equiv)	CH_2Cl_2, rt, 120 h	26	28
2	$PhI(OCOCF_3)_2$ (1.05 equiv), 5 mol% $(PhSe)_2$	CH_2Cl_2, rt, 72 h	62	6
3	$PhI(OAc)_2$ (1.2 equiv), TBDMSOTf (1.2 equiv)	CH_2Cl_2, –78 ºC to rt, 8 h	48	20
4	$PhI(OCOCF_3)_2$ (1.2 equiv), TBDMSOTf (1.2 equiv)	CH_2Cl_2, –78 ºC to rt, 3 h	50	22

3.4 Synthesis of Chiral Hypervalent Iodine Reagents

As the products **137a** and **137b** contain stereogenic centres, stereoselective synthesis of these cyclized products by using chiral hypervalent iodine reagents was the next step. In this context, many chiral hypervalent iodine reagents were synthesized. Lactate-based hypervalent iodine compounds have been synthesized by Fujita *et al.* and reagent **141** has been introduced by Ishihara *et al.* for a highly enantioselective spirolactonizations.[6,7] These reagents were synthesized by modifying known literature procedures starting from a Mitsunobu reaction between 2-iodoresorcinol **138** and (–)-lactic acid ethyl ester in the presence of diisopropyl azodicarboxylate (DIAD) and triphenyl phophine (PPh_3) to give the ester **139** as a colourless oil. Then the ester **139** was hydrolyzed by NaOH to give the chiral C_2-symmetric acid **140** in quantitative yields. The chiral acid **140** was then converted into the acid chloride *in situ* by using

$SOCl_2$ followed by the addition of excess amount of mesityl amine (Mes-NH_2) to give rise to amide product **141** as a white solid. Now the compound **141** was oxidised by 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) [Selectfluor®] to give the corresponding bisfluoride product *in situ* giving rise to the diacetate hypervalent iodine reagent **142** in the presence of acetic acid (Scheme 3.3).



Scheme 3.3: Synthesis of chiral hypervalent iodine reagent **142**

Other oxidation protocols such as stirring **141** with the mixture of acetic acid in peracetic acid at room temperature[11] or heating a mixture of $NaBO_3.4H_2O$ with acetic acid[12] along with **141** at 40 ^oC to oxidize **141** to **142,** resulted in either partial oxidation or decompositions. Only the oxidation conditions of Selectfluor® with acetic acid were found to be reliable and reproducible.

Hypervalent iodine reagents are known to coordinate with heteroatoms. Therefore, it is quite common to have nitrogen or oxygen in the chiral side chain in many of these reagents. Especially in the reagent **142**, the amide bond in the chiral side chain can coordinate to the iodine centre probably by intramolecular bonding interactions between the carbonyl oxygen atom and the iodine atom **142a** or between the amide protons and the iodine ligands **142b**. These bonding interactions could be responsible to directly affect the asymmetric reaction (Fig. 3.3).[7] Recently, these possible interactions were confirmed by single crystal X-ray diffraction analysis in the chiral hypervalent iodine reagent **143** in which the two intramolecular hydrogen-bonding interactions between the acidic amido protons and the ligands were clearly observed.[13]

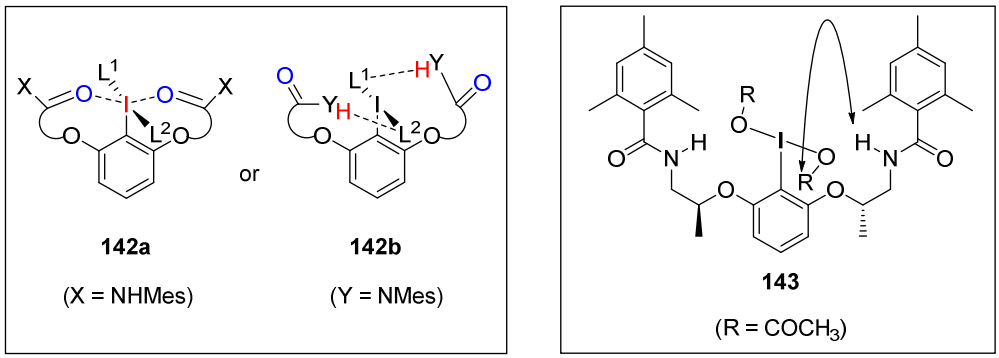
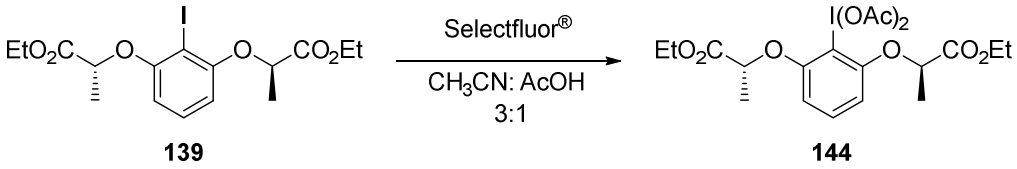


Fig. 3.3: Possible bonding interactions in the chiral hypervalent iodine reagent

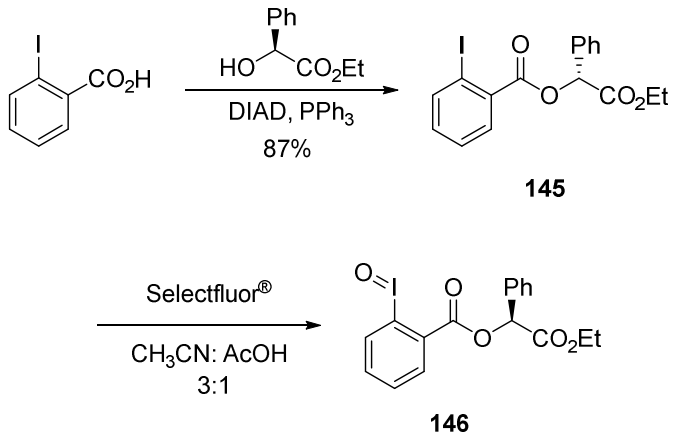
Therefore, the reagent **142** was further modified by varying either the chiral auxiliary in the side; mandelate-derived (**146** and **151**) or by changing the functional groups; esters (**144**) and ethers (**149**) to see the effects on the enantioselectivities.

To avoid long synthetic steps involved in the preparation of reagent **142,** ester **139** was also oxidized by the mixture of Selectfluor® and acetic acid in acetonitrile to give the oxidized product **144** (Scheme 3.4).



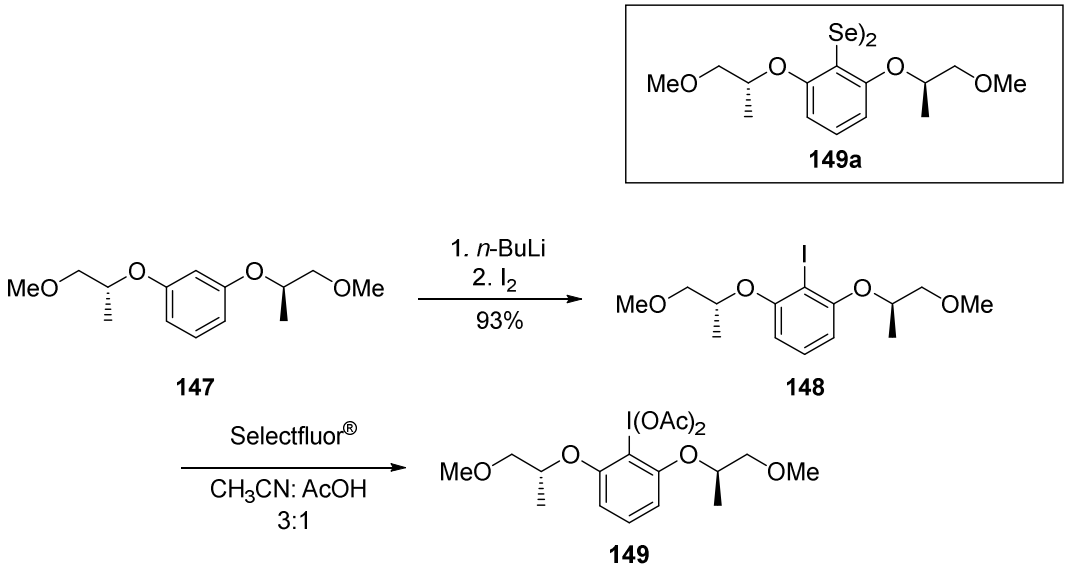
Scheme 3.4: Oxidation of C_2-symmetric chiral ester to give hypervalent iodine(III) reagent **144**

The use of (*R*)-(–)-mandelic acid ethylester in a Mitsunobu reaction with 2-iodophenol led to the synthesis of compound **145** in 87% yield. Oxidation of **145** in the presence of Selectfluor® and acetic acid in acetonitrile gave rise to the chiral hypervalent iodine reagent **146**. Interestingly, corresponding iodoso type iodine(III) oxidized product was obtained rather than bisacetate iodine(III) product. It is noteworthy that the desired chiral iodine(III) reagent **146** was obtained just over two steps, therefore its use in the asymmetric reaction could be interesting (Scheme 3.5).



Scheme 3.5: Synthesis of mandelic acid ethyl ester derived hypervalent iodine(III) reagent **146**

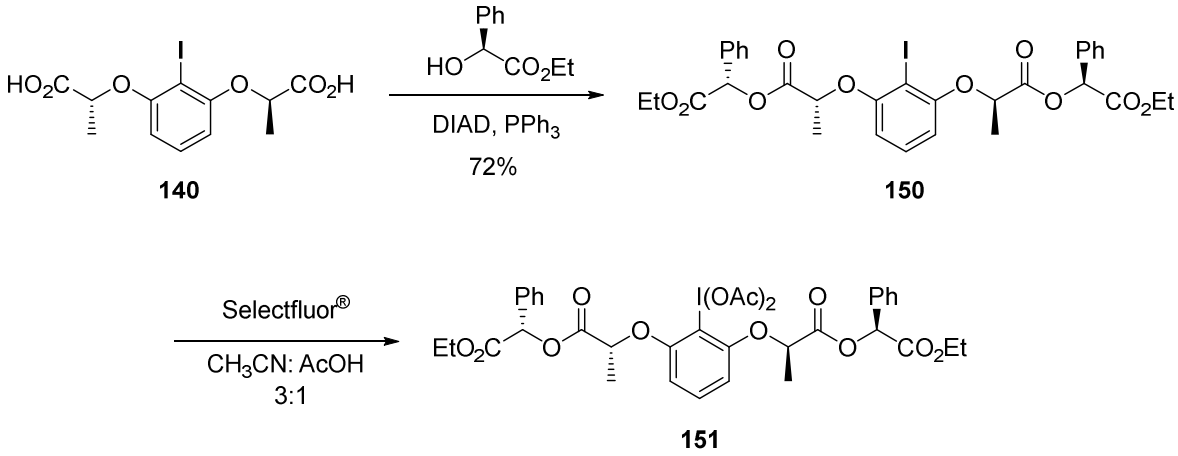
Our research group recently reported the use of C_2-symmetric chiral diselenide **149a** in the methoxyselenylation of styrene derivatives with high selectivities.[14] Therefore, its hypervalent iodine(III) analogue was synthesized and was planned to use in oxyamination cyclization reactions. The synthesis started from the lithiation reaction of **147** which was synthesized from the literature procedure[14] in the presence of *n*-BuLi at 0 ºC followed by slow addition of I_2 to give **148** in 93% yield. The iodine(I) reagent **148** was then oxidized by standard reaction conditions as described above to give the product **149** (Scheme 3.6).



Scheme 3.6: Synthesis of chiral reagent **149** with ether functionality in the side chain

The treatment of chiral C_2-symmetric acid **140** under Mitsunobu reaction conditions with (*R*)-(–)-mandelic acid ethylester led to the synthesis of compound **150** with an

additional chiral center in the novel iodine(I) reagent in 72% yield. The compound **150** was then oxidized to give the desired chiral iodine(III) reagent **151** (Scheme 3.7).



Scheme 3.7: Synthesis of hypervalent iodine(III) reagent **151**

3.5 Stereoselective Oxyamination Reactions

The chiral hypervalent iodine(III) reagents synthesized above were used in the cyclization of substrate **136**. Under various reaction conditions, only isourea compound **137a** was obtained with all chiral hypervalent iodine reagents (Fig. 3.4) and the cyclic urea derivative **137b** could not be detected suggesting that these chiral hypervalent iodine reagents are sterically demanding reagents, therefore in the second cyclization we only observed the smaller oxygen nucleophile reacting to give the bicyclic isourea derivative **137a**.

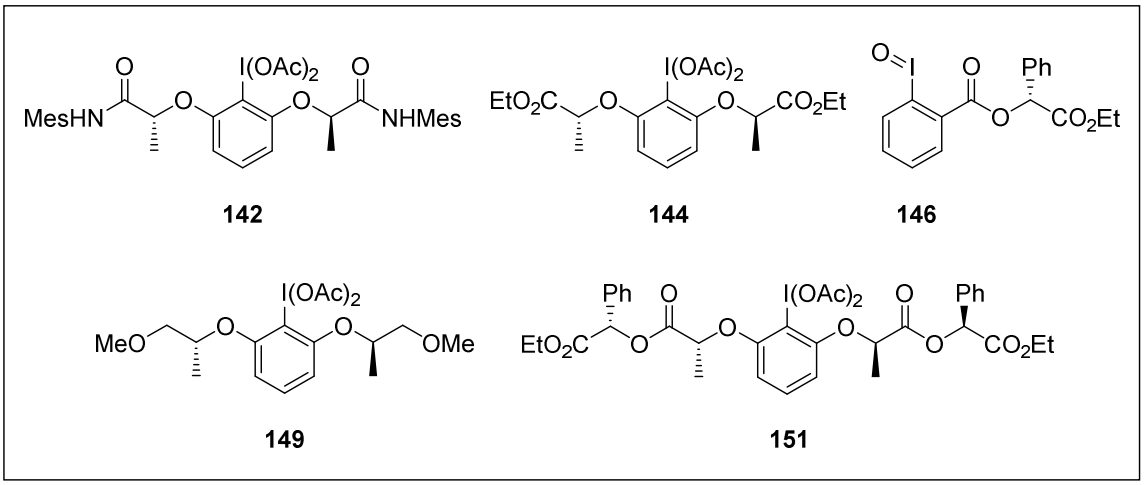
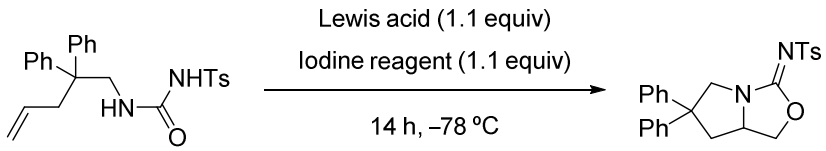


Fig. 3.4: Enantiomerically pure lactate and mandelate-derived hypervalent iodine reagents



136 **137a**

Table 3.2: Conditions for the stereoselective cyclization to **137a**

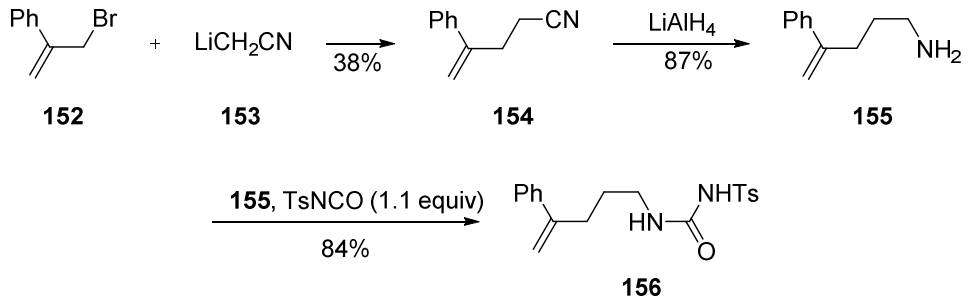
Entry	Reagents[a]	Solvent	**137a** Yield [%]	**137a** *ee* [%]
1	**142**, TBDMSOTf	CH_2Cl_2	50	40
2	**142**, TfOH	CH_2Cl_2	58	40
3	**142**, TMSOTf	CH_2Cl_2	48	61
4	**142**, TMSOTf	CH_2Cl_2	61	57[b]
5	**142**, TMSOTf	toluene	0	-
6	**142**, TMSOTf	THF	34	10
7	**144**, TMSOTf	CH_2Cl_2	30	12
8	**149**, TMSOTf	CH_2Cl_2	50	0

[a] reaction temperature –78 ºC, reaction time 14 h. [b] reaction temperature –78 ºC to rt.

As shown in Table 3.2, the hypervalent iodine reagent **142** has been investigated together with different acids for its activation (Table 3.2, entries 1-3). The highest selectivities have been obtained with trimethylsilyl triflate (TMSOTf) leading to the reaction product **137a** with an enantiomeric excess (*ee*) of 61% (Table 3.2, entry 3). Slightly higher reaction temperatures led to lower selectivities (Table 3.2, entry 4), as did other solvents (Table 3.2, entries 5 and 6). The hypervalent iodine compounds **144** and **149**, which are also derived from lactic acid, were less efficient in the stereoselective cyclization of **137a** (Table 3.2, entries 7 and 8). In these experiments, stoichiometric amounts of the hypervalent iodine reagents have been used. About 80-

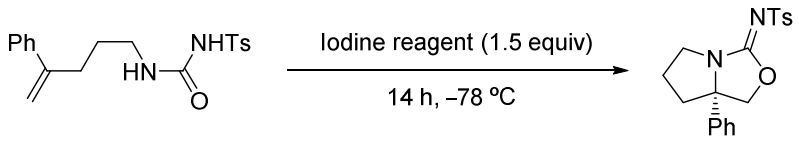
85% of the reduced aryl iodides are recovered after the reaction without any loss of optical purity and were reused by oxidation.

To minimize the chances of racemization and the possibility of generating a chiral quaternary carbon centre led to the development of substrate **156** derived from styrene. Previous research by our group using selenium electrophiles revealed that styrene derivatives are potential substrates for cyclizations with high selectivities.[15] We therefore prepared compound **156** from (3-bromoprop-1-en-2-yl)benzene **152** which was synthesized from α-methylstyrene according to literature procedure[16] and reacted with lithiated acetonitrile **153**.[17] The lithiation reaction was carried out at –78 ºC in the presence of *n*-BuLi for two hours followed by slow addition of **152** and then warming to room temperature to give 4-cyano-2-phenyl-1-butene **154**. Further reduction of **154** with lithium aluminum hydride gave rise to 5-amino-2-phenyl-1-pentene **155**. Amine **155** was reacted with tosyl isocyanate to yield product **156** along with some traces of tosyl amide as a side reaction product which was inseparable by column chromatography (Scheme 3.8).



Scheme 3.8: Synthesis of styrene derived substrate **156**

Stereoselective cyclizations of **156** led to isourea **157** containing a stereogenic tetrasubstituted carbon atom by using different chiral hypervalent iodine reagents. The results are summarized in Table 3.3.



156 **157**

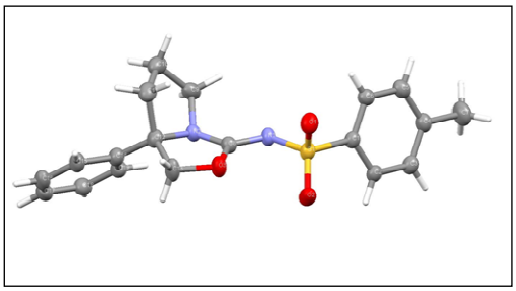
Table 3.3: Stereoselective cyclization of **156** to isourea derivative **157**

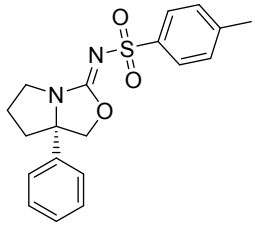
Entry	Reagents[a]	Solvent	**157** Yield [%]	**157** *ee* [%][b]
1	**142**, 1.5 eq. TMSOTf	CH_2Cl_2	40	78
2	**144**, 1.5 eq. TMSOTf	CH_2Cl_2	35	69
3	**146**, 1.5 eq. TMSOTf	CH_2Cl_2	34	50
4	**149**, 1.5 eq. TMSOTf	CH_2Cl_2	20	50
5	**151**, 1.5 eq. TMSOTf	CH_2Cl_2	40	75
6	**142**, 1.5 eq. TMSOTf	CH_2Cl_2:CF_3CH_2OH (1:1)	43	81
7[c,d]	**142**, 2 eq. TMSOTf	CH_2Cl_2:Et_2O (3:1)	48	88
8[c]	**142**, 2 eq. TMSOTf, 0.5 eq. $TsNH_2$	CH_2Cl_2:Et_2O (1:3)	76	90
9[c,e]	**142**, 2 eq. TMSOTf, 0.5 eq. $TsNH_2$	CH_2Cl_2:Et_2O (1:3)	60-71	92-96
10[c,e,f]	**142**, 3 eq. TMSOTf, 0.5 eq. $TsNH_2$	CH_2Cl_2:Et_2O (1:3)	-	>99

[a] **156** with traces of tosyl amide, reaction temperature –78 ºC, reaction time 14–18 h. [b] major enantiomer has (*S*)-configuration. [c] reaction time 3 h. [d] reaction temperature –100 ºC. [e] addition of **156** after reaction of **142** with TMSOTf. [f] reaction performed on analytical scale.

All chiral hypervalent iodine reagents shown in Fig. 3.4 have been used for the cyclization of compound **157** (Table 3.3, entries 1–5). Highest selectivities have been obtained with reagent **142**. Reagent **151** consisting of lactic acid and mandelic acid

moieties, led to a good selectivity in product **157** as well (Table 3.3, entry 5). The addition of 2,2,2-trifluoroethanol, which can strongly influence reactions with hypervalent iodine compounds, did not have a pronounced effect in this case (Table 3.3, entry 6).[18] The use of other solvent mixtures increased selectivities and yields. Experiments with **156** containing small amounts of *para*-toluenesulfonamide ($TsNH_2$) due to the preparation procedure resulted in variable results. Therefore, tosyl amide free starting material was prepared by using small amounts (0.95 equiv) of *p*-tolueneisocyanate (TsNCO). Then the addition of $TsNH_2$ to the reagent **142** together with an excess of TMSOTf, led to reproducible results and to synthetically very attractive selectivities, especially if **142** is allowed to react first with TMSOTf (Table 3.3, entries 9 and 10). To check the role of *para*-toluenesulfonamide ($TsNH_2$) in the reaction and its possible interactions with the electrophilic iodine centre, a NMR experiment was conducted. Due to large signal broadening and decomposition above –40 ºC, the structure of **142** with added TMSOTf and $TsNH_2$ could not be examined using NMR spectroscopy. Compound **157** was obtained enantiomerically pure (>99% *ee*) on an analytical scale reaction (Table 3.3, entry 10) while the selectivity dropped slightly on a larger scale (Table 3.3, entry 9). The absolute configuration of the major isomer of **157** was found to be *S* by anomalous dispersion scattering and the refined Flack parameter[19] was 0.11(11) as determined by X-ray crystallography (Fig. 3.5).[20]



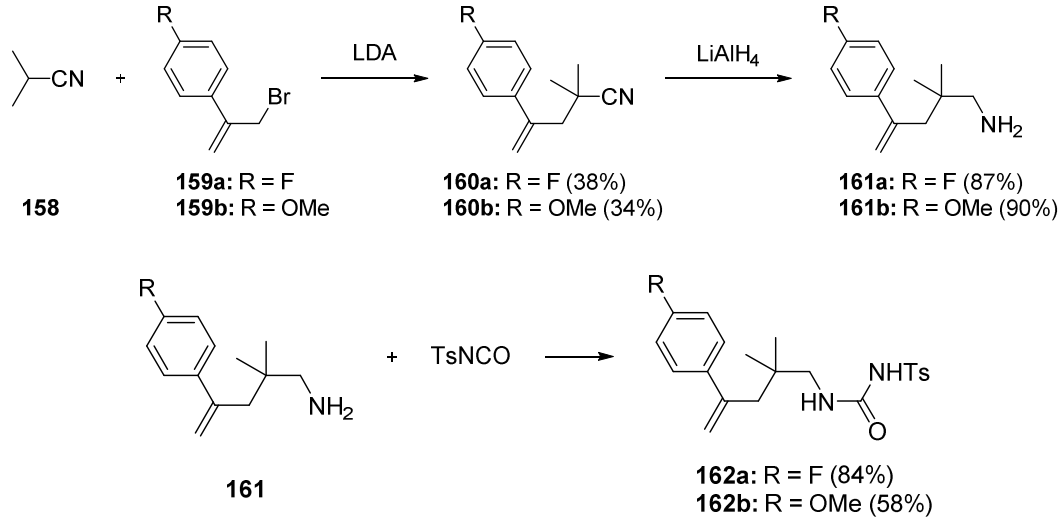


157

Fig. 3.5: X-ray structure of the compound **157**

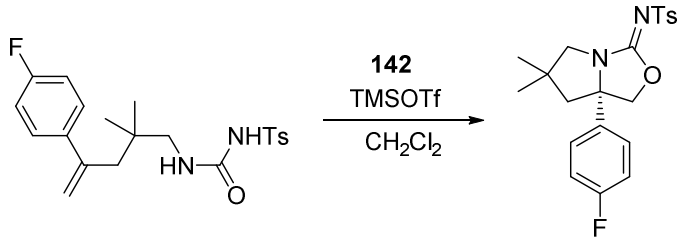
To check the effects of electronically versatile starting materials with different substitutents at the *para*-position of the phenyl ring led to the synthesis of compounds **162 a** and **b**. These compounds were prepared by the abstraction of proton from isobutyronitrile **158** by uing freshly prepared lithium diisopropylamide (LDA)[21] followed by the addition of corresponding styrene derivatives **159** to give the first

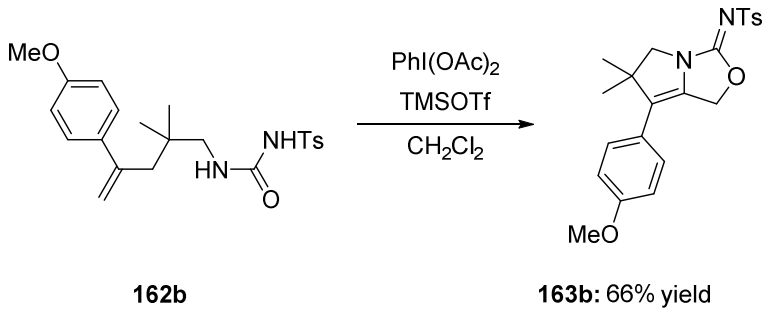
product **160**. Reduction of the nitrile group **160** followed by the reaction with *p*-toluenesulphonylisocyanate (TsNCO) led to the products **162** (Scheme 3.9).



Scheme 3.9: Synthesis of electronically diverse aryl-substituted alkenes for oxyamination reactions

Electronically withdrawing substituents on the aryl moiety in **162a** (R = F) led to the expected aminooxygenated product **163a** with good yields and moderate seletivities. The absolute configuration for the product **163a** was assigned in an analogy to the product **157**. The electron rich derivative **162b** (R = OMe) underwent, after cyclization, further oxidation and rearrangement to give **163b** probably through a reaction between the hypervalent iodine reagent and the methoxy-substituted aryl moiety but the structure of the product based on its NMR data could not be confirmed at this point (Scheme 3.10).

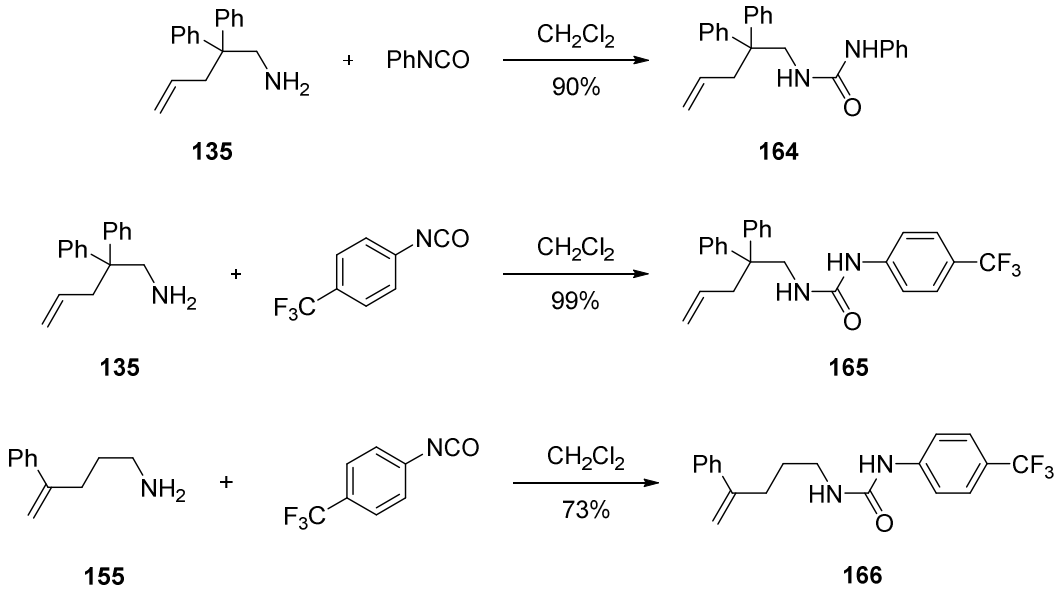




162b **163b:** 66% yield

Scheme 3.10: Effects of substitution on the aryl moiety for oxyamination of alkenes

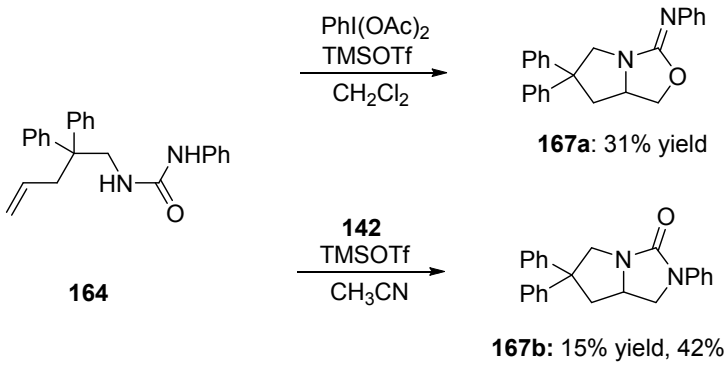
Different protecting groups for the urea moiety have also been tried to see the effects on the yields and enantioselectivities. These substrates were synthesized by reacting the amines **135** and **155** with different protected isocyanates to give products **164**, **165** and **166** in high yields (Scheme 3.11).



Scheme 3.11: Synthesis of substrate with versatile protecting groups

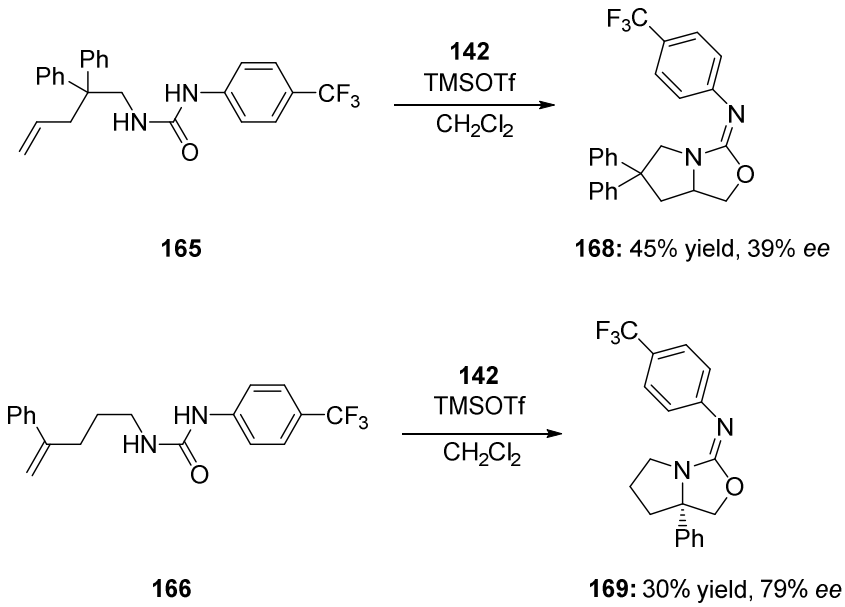
It was found that the variation of protecting groups on the urea moiety led to altered nucleophilicities of the nitrogen moiety. A phenyl substituent substrate **164** resulted in generally lower reactivities as evident through the lower yields in these reactions. Also the solvents used in the reactions had to be adjusted to ensure the solubility of the starting materials. With substrate **164,** the use of $PhI(OTf)_2$ as an achiral reagent led to the expected isourea derivative **167a**, whereas the chiral reagent **142** yielded the cyclic urea **167b** as the product of a diamination reaction (Scheme 3.12). This reaction indicates that the chiral hypervalent iodine reagent **142** is reasonably sterically

demanding. Therefore, it allowed the attack of smaller nitrogen nucleophile with phenyl ring protection in the second cyclization to give diamination product. However, when the relatively bigger tosyl-protected nitrogen nucleophile was reacted under similar conditions, oxyamination was the main reaction pathway as shown above (Table 3.3).



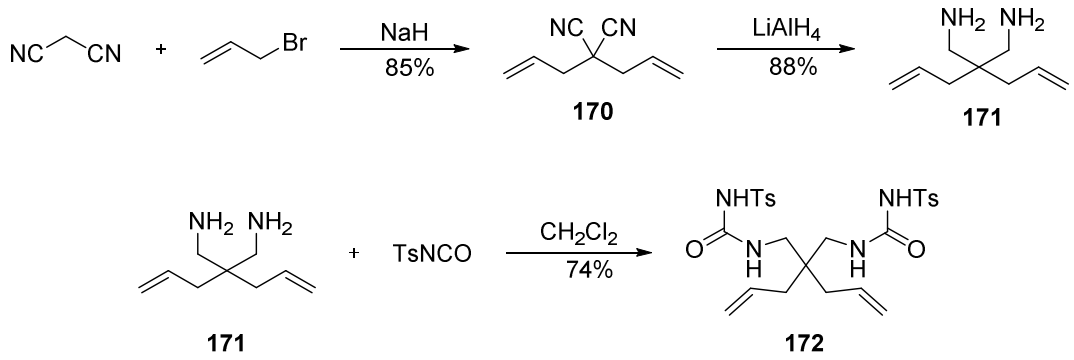
Scheme 3.12: Reactivity alteration by changing protection on the urea moiety

Further variation of the tosyl substituent on the urea moiety gave similarly changed results. A trifluoromethylphenyl substituent on **165** and **166** resulted in oxyaminated products **168** and **169** with generally lower reactivity and selectivities under similar reaction conditions of their analogue products **137a** (48%, 61% *ee*) and **157** (40%, 78% *ee*) (Scheme 3.13).



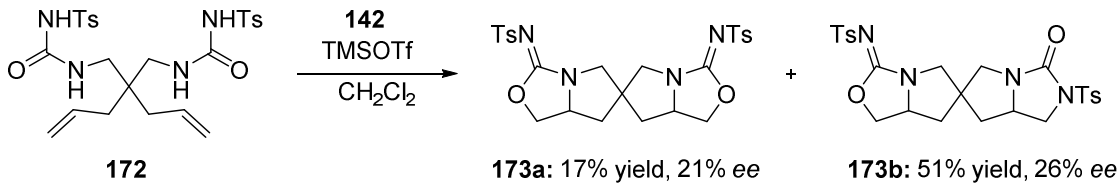
Scheme 3.13: Variation of tosyl-protection on urea moiety for oxyamination reaction

To accomplish results for C_2-symmetric oxyaminated product **173**, substrate **172** was designed. It was synthesized by deprotonation of malononitrile in the excess amount of NaH followed by the addition of allyl bromide to give 2,2-diallylmalononitrile **170** as a yellow oil. Subsequent reduction of **170** gave the corresponding amine[22] **171** which was subjected to tosylisocyanate (TsNCO) to give the product **172** in 74% yield (Scheme 3.14).



Scheme 3.14: Synthesis of substrate **172** for enantioselective aminohydorxylations

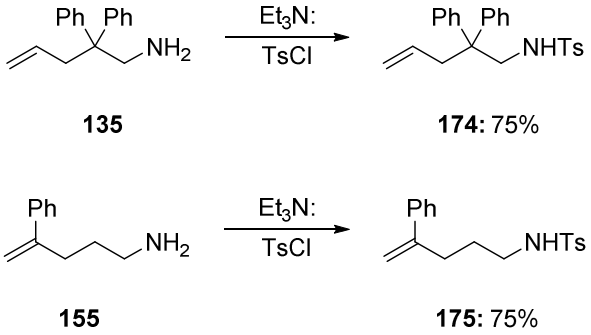
The optimized reaction conditions were then applied to the substrate **172**. The reaction proceeded with the mixture of products. Interestingly, products **173a** and **173b** were isolated as single diastereomers as judged from their NMR spectra but with low selectivities (Scheme 3.15). As lower enantioselectivities were obtained in this reaction along with mixture of products, therefore further investigations on the stereochemistry of these products were not carried out. However, this extension of the methodology with substrates **172** demonstrated that other compounds are also accessible by employing these reaction conditions.



Scheme 3.15: Stereoselective oxyaminations other alkenes

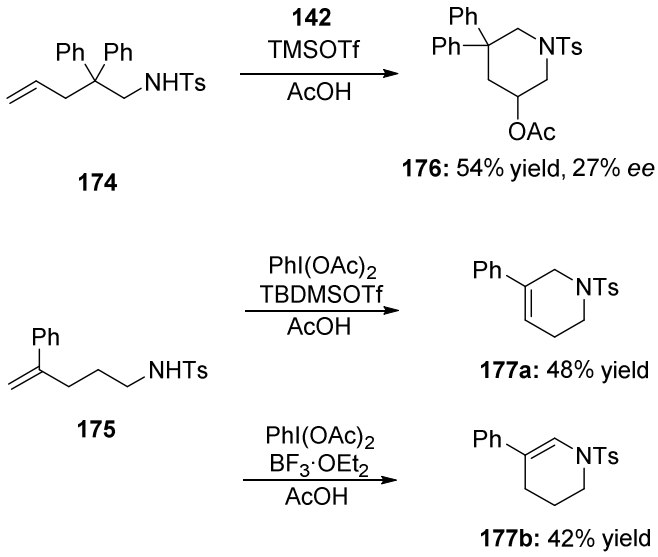
Hypervalent iodine mediated first regioselective aminotrifluoroacetoxylation of alkenes **135** was developed by Michael *et al*.[23] We investigated an enantioselective version of a similar reaction by using acetic acid as a nucleophile. The substrate **174** and **175**

required for such transformation were synthesized by the amines **135** and **155** (Scheme 3.16).



Scheme 3.16: Synthesis of starting materials for aminoacetoxylation of alkenes

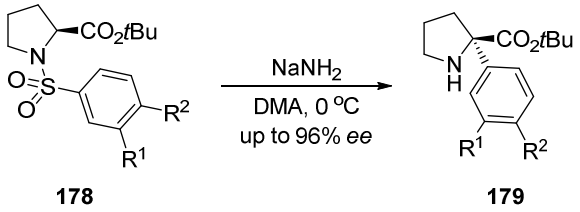
By employing optimized reaction conditions described above, the cyclization of tosylamide **174** resulted in a 6-*endo* cyclized product **176** with the acetate added as an external nucleophile. In this reaction, the use of **142** as a chiral reagent led to an enantiomeric excess of only 27%. It is noteworthy that similar reactions have already been described using gold catalysis.[24] However, the cyclization of tosylamide derivative **175** did not result in the expected oxyaminated product but in the formation of achiral six-membered ring systems with elimination. While the direction of elimination was found to be dependent on the Lewis acid used in the reaction. The addition of TBDMSOTf led to the elimination product **177a** while with $BF_3 \cdot OEt_2$ enamine **177b** was isolated (Scheme 3.17).



Scheme 3.17: Hypervalent iodine mediated aminoacetoxylation of alkenes

3.6 Synthesis of α-Aryl Quaternary Proline Derivatives

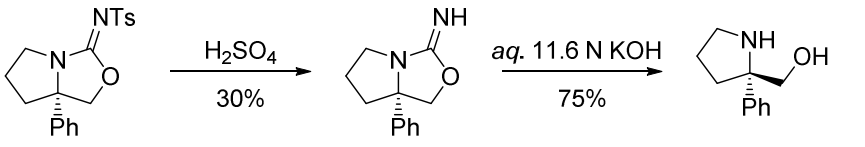
The deprotection of the oxyaminated product **157** may lead to the α-aryl quaternary proline derivative. Despite the importance of proline-based catalysts in organocatalysis, 2-phenylprolinol has not yet been prepared enantiomerically pure because α-aryl proline derivatives are very difficult to synthesize in optically pure form. These reactions require stoichiometric amounts of the chiral proline sulfonamides **178** to give the α-aryl quaternary prolines **179** via rearrangement with partial racemization under anhydrous basic conditions using dimethylacetamide (DMA) as a solvent.[25] This methodology is limited only to electronically withdrawing groups at the 4-position of the aryl ring. (Scheme 3.18).



178 **179**

Scheme 3.18: Rearrangement of proline sulfonamides **178**

The oxyaminated product **157** was exposed to the strong deprotection reaction conditions. This allowed the rapid synthesis of (*S*)-2-phenylprolinol **181** by acidic cleavage of the tosylated derivative **157** to the isourea compound **180** followed by basic cleavage to the amino alcohol **181** (Scheme 3.19). Probably, due to the tetrasubstituted carbon atom in **157** and the related difficult accessibility, all other deprotection attempts were unsuccessful (Table 3.4).



157 **180** **181**

(*S*)-2-Phenylprolinol

Scheme 3.19: Facile route to (*S*)-2-Phenylprolinol **181**

Table 3.4: Deprotection attempts for substrate **157** leading to free amino alcohol moiety

Entry	Reagents for deprotection	Result
1	conc. H_2SO_4:H_2O (1:1) microwave irradiation, 150 ºC, 10 min	Decomposition
2	conc. H_2SO_4:H_2O (1:3) microwave irradiation, 150 ºC, 10 min	Decomposition
3	conc. H_2SO_4:H_2O (1:1) microwave irradiation, 150 ºC, 5 min	Decomposition
4	conc. H_2SO_4:H_2O (1:1) microwave irradiation, 100 ºC, 10 min	Decomposition
5	$LiAlH_4$, rt, on	No reaction
6	$LiAlH_4$, rt, sonication, 1 h	No reaction
7	2N KOH, reflux	No reaction
8	Sodium naphthalide[26]	No reaction

These results demonstrate the large potential of chiral hypervalent iodine reagents in oxyaminations in place of metal-based protocols together with a rapid access to unusual amino acid derivatives **181**. To avoid the stoichiometric amounts of the chiral reagent, developement of the catalytic reaction is still a pormising area of research and more advancement in this field is required.

3.7 References

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Chapter 4

Hypervalent Iodine Mediated Oxidative Rearrangements

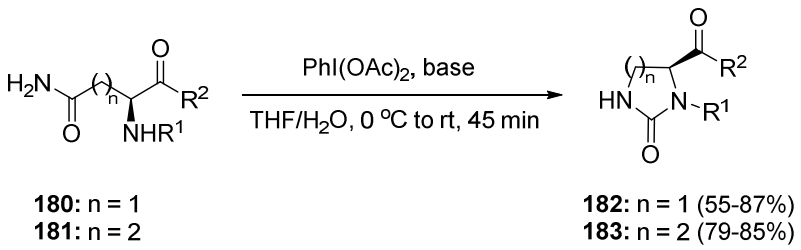
4.1 Introduction to Hypervalent Iodine Mediated Oxidative Rearrangements

Organic molecules bearing hypervalent iodine moieties have stunned chemists over years owing to their mild and environmentally friendly reaction conditions by replacing toxic heavy metals. The plethora of reactions that can be performed with excellent yields and high selectivities has led to their recent renaissance in synthetic organic chemistry. The nature of hypervalent iodine compounds to react as electrophiles and then behave as excellent leaving groups make them highly suitable reagents for generating cationic intermediates which has been successfully exploited in the synthesis of many biologically important molecules. Their use in the Hoffmann-type rearrangement is already well established and the intermediate isocyanate has been used in the synthesis of different heterocycles.[1]

Treatment of styrene derivatives with hypervalent iodine compounds can lead to the formation of intermediates that can be stabilized by aryl substituent via phenonium ions followed by the attack of nucleophiles to give rearranged products. This strategy has been exploited in the efficient synthesis of isoflavones in a one-pot reaction.[2] Ring contractions of cycloalkenes have been a key rearrangement in synthetic organic chemistry. In this context, the role of hypervalent iodine reagents have been remarkable to furnish the biologically important molecules such as (±)indatraline.[3] On the other hand, further developments have been also made in the field of ring expansion reactions mediated by hypervalent iodine reagents giving rise to versatile ketones in high yields. A brief summary on the background of such oxidative rearrangements by hypervalent iodine reagents and the requirement for their stereochemical induction is given below.

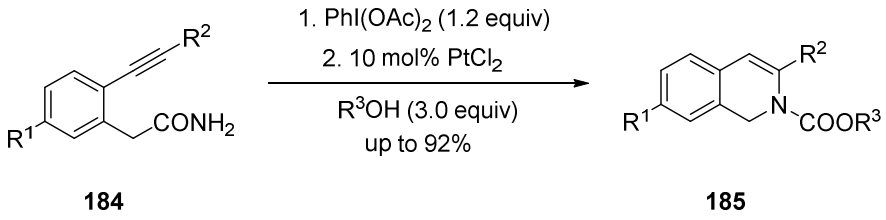
4.2 Hoffmann Rearrangements

The conversion of aliphatic amides into amines with [bis(trifluoroacetoxy)iodo]benzene was the basis for the first Hoffmann rearrangement reported by Loudon and co-workers.[4] Since then, various hypervalent iodine reagents have been applied in the conversion of versatile amides to amines. Tomasini *et al*. reported an efficient route for the transformation of protected asparagines **180** and glutamines **181** to imidazolidin-2-one-4-carboxylates **182** and (tetrahydro)-pyrimidin-2-one-5-carboxylate **183** respectively in good yields by employing (diacetoxyiodo)benzene (Scheme 4.1).[5]



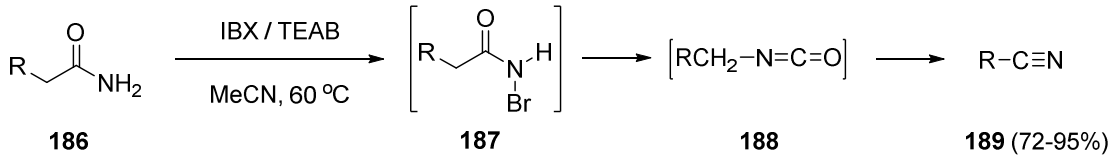
Scheme 4.1: Hofmann rearrangement of asparagine and glutamine derivatives mediated by hypervalent iodine reagents

In 2009 Yanda *et al*. reported the tandem synthesis of functionalized indoles by (diacetoxyiodo)benzene mediated by Hoffmann-type rearrangement of 2-alkynylbenzamides in excellent yields.[6] The reaction for the transformation of alkynylbenzylamides **184** to heteroaromatics **185** was initiated by (diacetoxyiodo)benzene to form an isocyanate intermediate, which cyclized intramolecularly to give **185** in the presence of platinum chloride as a catalyst (Scheme 4.2).



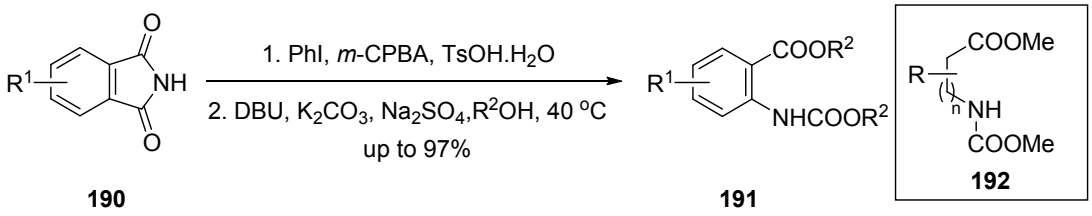
Scheme 4.2: (Diacetoxyiodo)benzene-mediated and Pt-catalyzed transformation of alkynylbenzylamides **184** to benzo-fused nitrogen heteroaromatic systems **185**

In 2007, Akamanchi *et al*. developed the oxidative transformation of primary carboxamides of type **186** to one-carbon dehomologated nitriles **189** via formation of Hoffmann-type isocyanate intermediate **188** in the presence of 2-iodoxybenzoic acid (IBX) and tetraethylammonium bromide (TEAB).[7] It was suggested that the reaction is initiated with the addition of TEAB to IBX followed by the formation of corresponding *N*-bromoamide **187** which on subsequent rearrangement forms the isocyanate intermediate **188**. Further nucleophilic attack of IBA on the isocyanate followed by the decomposition of the intermediate gives rise to an imine, carbon dioxide and *o*-iodobenzoic acid. The imine on further oxidation leads to the nitriles **189** in good yields (Scheme 4.3).



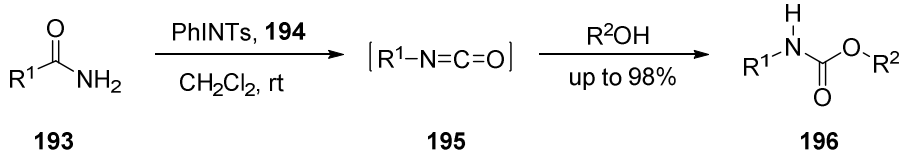
Scheme 4.3: Transformation of primary carboxamides **186** to dehomologated nitriles **189**

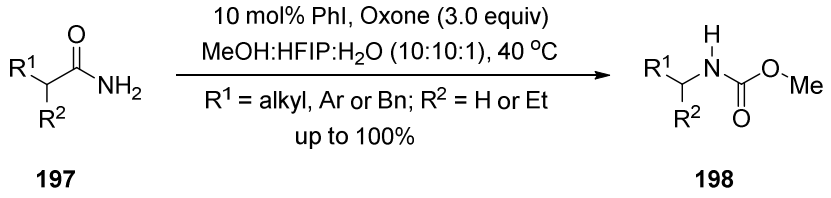
Moriyama *et al*. reported the *in situ* generation of the Koser's reagent from iodobenzene, *p*-toluenesulfonic acid and *m*-CPBA and employed it successfully in the Hofmann-type rearrangement of phthalimide **190** to the corresponding anthranilic acid derivatives **191** in good yields.[8] The same approach was further extended for the synthesis of numerous *β*- and *γ*-amino acids **192** from aliphatic imides (Scheme 4.4).



Scheme 4.4: Hofmann-rearrangement of aryl imides **190** to anthranilic acid derivatives **191**

Zhankdin *et al*. reported the Hofmann rearrangement of aromatic and aliphatic carboxamides **193** using (tosylimino)-phenyl-λ^3-iodane **194** as a hypervalent iodine reagent.[9] Such rearrangements results in complex reaction mixtures if other hypervalent iodine oxidants are used. In these reactions the isocyanate **195** intermediate was trapped by different alcohols to give the corresponding carbamates **196** in good yields. Later on, the same research group was successful in the development of a similar reaction in a catalytic manner in the presence of iodobenzene and a stoichiometric oxidant like oxone by using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) in aqueous methanol as a solvent mixture to give the carbamates of type **198** (Scheme 4.5).[10]

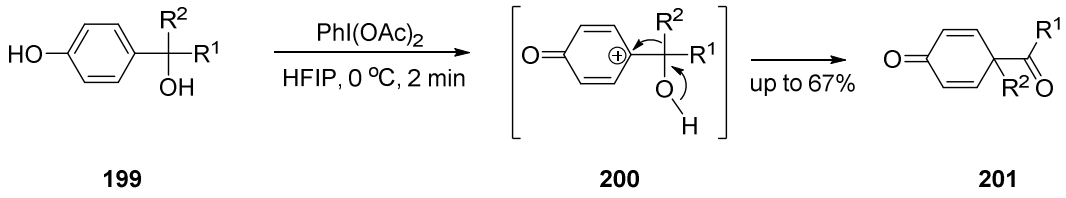




Scheme 4.5: Conversion of carboxamides to carbamates

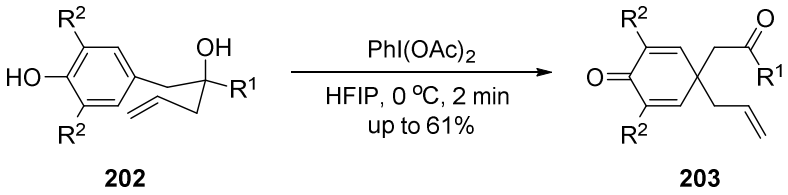
4.3 Wagner-Meerwein Rearrangement

The Wagner-Meerwein rearrangement is an acid catalyzed conversion of alcohols to olefins involving an 1,2-carbocation rearrangement. Recently, hypervalent iodine(III) reagents have been used to induce Wagner-Meewein rearrangements. In 2009, Canesi and co-workers developed an oxidative 1,2-alkyl shift on phenol derivatives **199**. The reaction proceeded by the oxidation of phenols **199**, using (diacetoxyiodo)benzene, to form a carbocation **200** (aromatic ring umpolung) followed by the 1,2-alkyl or aryl group migration. The rearranged products **201** were obtained in moderate yields (Scheme 4.6).[11]



Scheme 4.6: Oxidative 1,2-alkyl shifts for phenolic substrates **199** mediated by (diacetoxyiodo)benzene

A seminal approach was used for the oxidative 1,3-allyl shifts on the aromatic phenols of type **202** in the presence of (diacetoxyiodo)benzene by the same research group. The rearranged products **203** were isolated in good yields (Scheme 4.7). This approach was further extended for the synthesis of tricyclic and tetracyclic systems of alkaloids.[12]

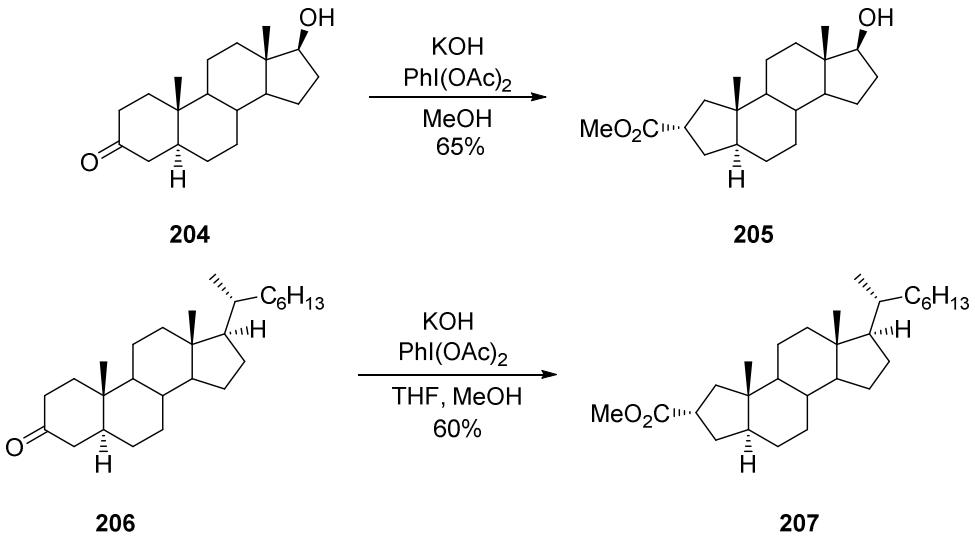


Scheme 4.7: Oxidative 1,3-alkyl shifts on phenolic substrates **202** mediated by (diacetoxyiodo)benzene via aromatic ring umpolung

4.4 Ring Contractions

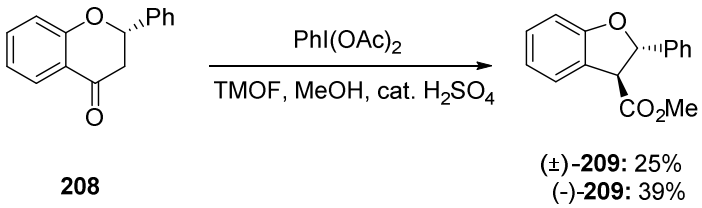
Ring contractions are useful rearrangements in organic chemistry because they provide molecular complexity in a single step with a high level of selectivity to obtain products that are not easily accessible from other approaches. Traditionally, ring contraction reactions are performed by the aid of acids, bases, metal-based oxidizers and photochemically.[13] In this context, various hypervalent iodine(III) reagents have been employed in ring contraction reactions as they provide mild and environmental friendly reaction conditions.

In 1984, Daum *et al.* reported that the reaction of the androstan-3-one **204** with (diacetoxyiodo)benzene lead to a mixture of ring contraction products with **205** as major isomer obtained in 65% yield after recrystallization.[14] In the same year, Moriarty *et al.* developed the ring contraction of 3-cholestanone **206** in the presence of different iodine(III) reagents to give product **207** as a major isomer in 60% yield (Scheme 4.8).[15]



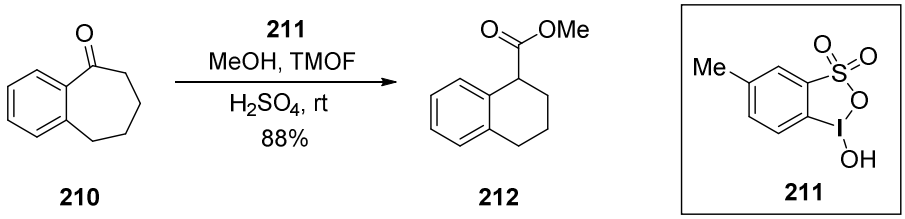
Scheme 4.8: Ring contractions of androstan-3-one **204** and 3-cholestanone **206** mediated by hypervalent iodine(III) reagents

The ring contraction of flavanone **208** was described by Parkash and co-workers to give dihydrobenzofuran derivative **209** in up to 39% yield employing trimethyl orthoformate (TMOF) as a solvent.[16] The similar reaction was reinvestigated by Juhász who also assigned the relative configuration of the products (Scheme 4.9).[17,18]



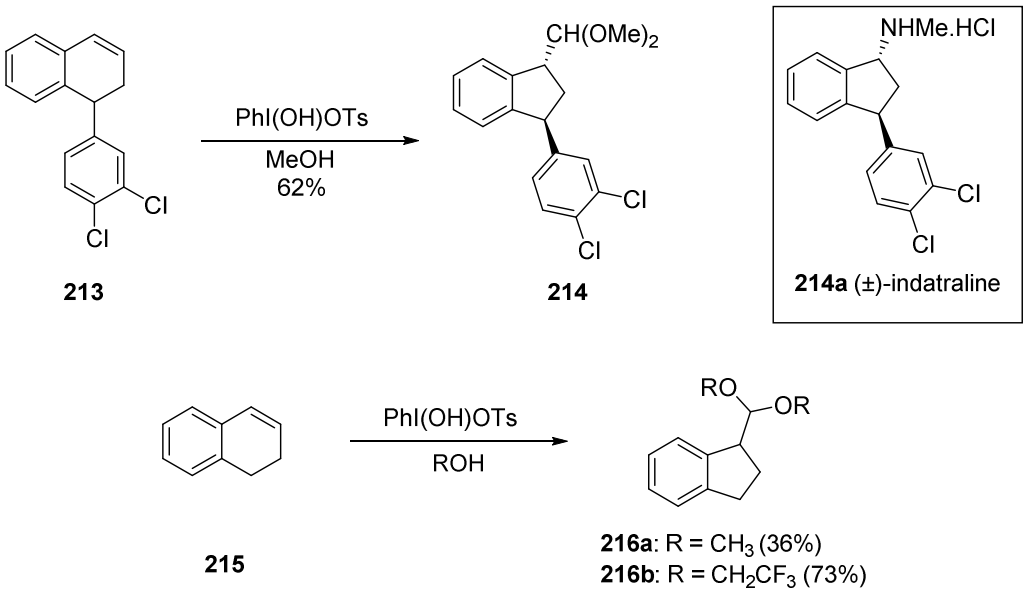
Scheme 4.9: Ring contractions of flavanone **208** mediated by (diacetoxyiodo)benzene

A more detailed discussion on the ring contraction reactions of cycloalkenes and cycloalkanones using iodine(III) reagents until 2006 can be found by the review article written by Silva.[3] Continuing further advancement in the field of ring contraction reactions by Justic *et al*. the conversion of 1-benzosuberone **210** to methyl 1,2,3,4-tetrahydronaphthalene-1-carboxylate **212** was reported in 2007 by using a cyclic hypervalent iodine(III) reagent, *1H*-1-hydroxy-5-methyl-1,2,3-benziodoxathiole 3,3-dioxide **211** (HMBI). The rearranged product **212** was obtained in 88% yield (Scheme 4.10).[19]



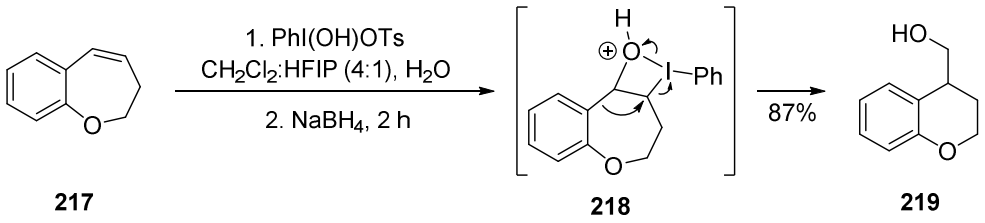
Scheme 4.10: HMBI **211** mediated ring contraction.

In 2007, Silva *et al*. utilized the ring contraction of 1,2-dihydronaphthalenes **213** in the stereoselective synthesis of (±)-indatraline **214a**. The reaction proceeded in the presence of (hydroxytosyloxyiodo)benzene to give the product **214** in 62% yield which after 6 steps of synthesis gave rise to the (±)-indatraline **214a**. In 2011, the same research group developed the modified synthesis of indatraline **214a** and its analogues using similar type of ring contraction approach.[20,21] Furthermore, synthesis of indanes **216** through ring contraction of 1,2-dihydronaphthalenes **215** using Koser's reagent was also developed. Indanes **216** bearing different functional groups were synthesized by using different solvents such as methanol and 2,2,2-trifluoroethanol (TFE) resulting in dimethoxy **216a** and bis-2,2,2-trifluoroethoxyacetals **216b** respectively (Scheme 4.11).[22]



Scheme 4.11: Ring contraction of 1,2-dihydronaphthalenes mediated by the Koser's reagent

Very recently Silva and co-workers reported the Koser reagent-mediated ring contraction of 2,3-dihydrobenzo[*b*]oxepine **217** to hydroxyl functionalized chromane **219** in 87% yield. It was suggested that the reaction proceeded through the formation of an oxonium ion of type **218** followed by an aryl bond migration and deprotonation to give the corresponding ketone which on reduction with sodium borohydride gave rise to the product **219** (Scheme 4.12).[23]

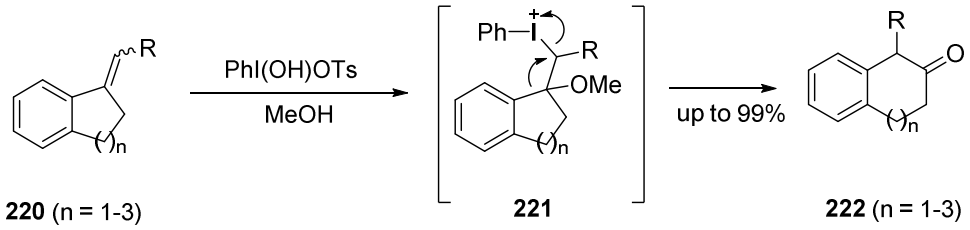


Scheme 4.12: Ring contraction of 2,3-dihydrobenzo[*b*]oxepine mediated by the Koser's reagent

4.5 Ring Expansions

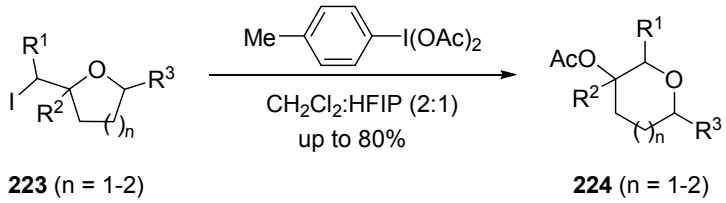
The Koser's reagent has been used in various oxidative rearrangements and fragmentations. One of the oxidative rearrangements induced by the Koser's reagent is a ring expansion reaction. In 2005, Koser and co-workers reported the ring expansion of alkylidenebenzocycloalkenes **220** to *β*-benzocycloalkenones **222** containing six-, seven- and eight-membered rings. A plausible mechanism for such transformations was found to be proceeded by the formation of a cationic intermediate **221** which was stabilised by an aryl bond migration followed by the attack of the methanol to give rise to the

corresponding ketal. Further hydrolysis of the ketal furnished the rearranged product **222** in up to 99% yield (Scheme 4.13).[24]



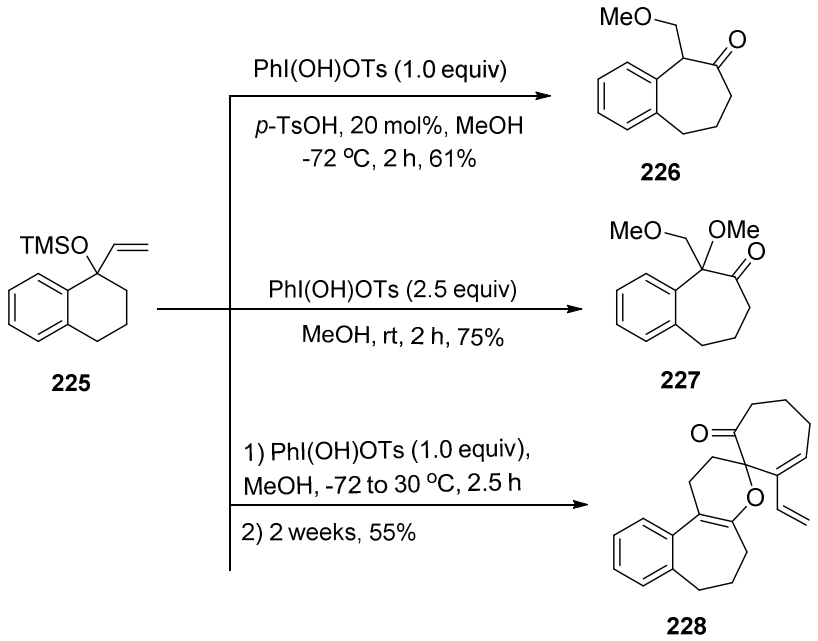
Scheme 4.13: Koser's reagent mediated ring expansion of alkylidenebenzocycloalkenes **220**

Hara and co-workers reported the deiodonative ring expansion of iodoalkyl bearing cyclic ethers **223** using (diacetoxyiodo)toluene. The reaction proceeded by the *in situ* oxidation of the iodine moiety, followed by the decomposition and nucleophilic attack of an acetoxy group to give rise to the ring expansion product **224** in up to 80% yield (Scheme 4.14) .[25]



Scheme 4.14: Deiodonative ring expansion of iodoalkyl cyclic ethers **223**

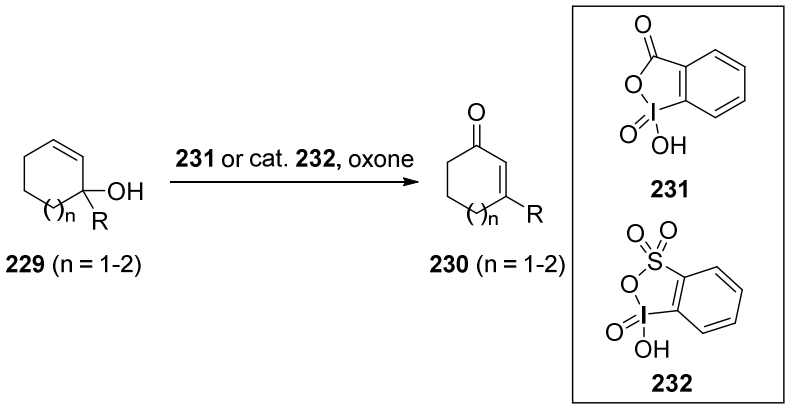
The ring expansion of 1-vinyltetralol derivative **225** using Koser's reagentwas explored by Silva and different rearranged ketones **226**-**228** were isolated under different reaction conditions (Scheme 4.15).[26]



Scheme 4.15: Koser's reagent mediated ring expansion of 1-vinyltetralol derivative **225**.

4.6 Rearrangement of Tertiary Alcohols

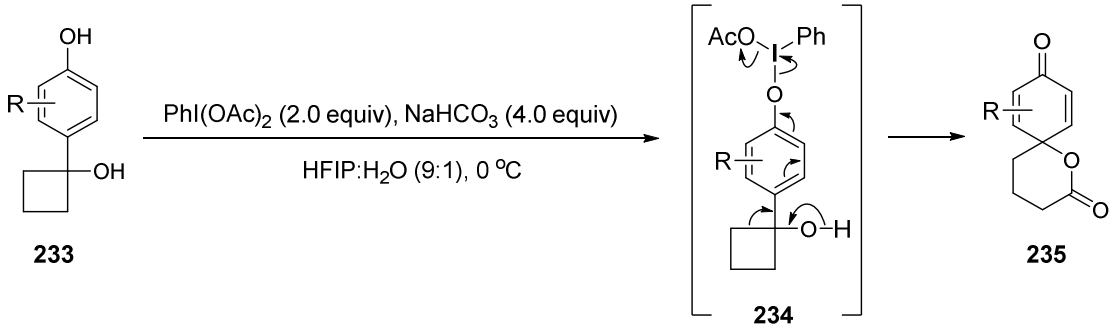
An oxidative rearrangement of tertiary allylic alcohols to the corresponding carbonyl compounds is normally performed using organochromium chemistry. Iwabuchi and co-workers reported the rearrangement of cyclic tertiary allylic alcohols **229** to *β*-disubstituted *α,β*-unsaturated ketones **230** using 2-iodoxybenzoic acid **231** in up to 88% yield.[27] Vatèle *et al*. reported the oxidative rearrangement of acyclic allylic alcohols to *β*-disubstituted enones under Lewis-acidic conditions in the combination with iodosylbenzene and catalytic amounts of TEMPO.[28] Later on, Ishihara developed a 2-iodoxybenzenesulfonic acid **232** catalyzed oxidative rearrangement of tertiary allylic alcohols to enones with up to 85% yield in product **230** using oxone as an oxidant in the presence of potassium carbonate and tetrabutylammonium hydrogen sulfate (Scheme 4.16).[29]



Scheme 4.16: An oxidative rearrangement of tertiary allylic alcohols **229** to enones **230**

4.7 Domino Reactions

In 2010, Kita *et al*. described an unexpected (diacetoxyiodo)benzene-mediated domino reaction of 1-(*p*-hydroxyaryl)cyclobutanols **233** to spiro cyclohexadienone lactones **235** in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and water. It was suggested that the reaction proceeded via oxidation of the phenolic hydroxyl group followed by a rearrangement as shown in intermediate **234** to produce a spirodiene dione compound which on hydrolysis gave rise to the carboxylic phenol derivative. Now, intramolecular cyclization under oxidation conditions gives rise to the final product **235** in up to 77% yield (Scheme 4.17).[30]

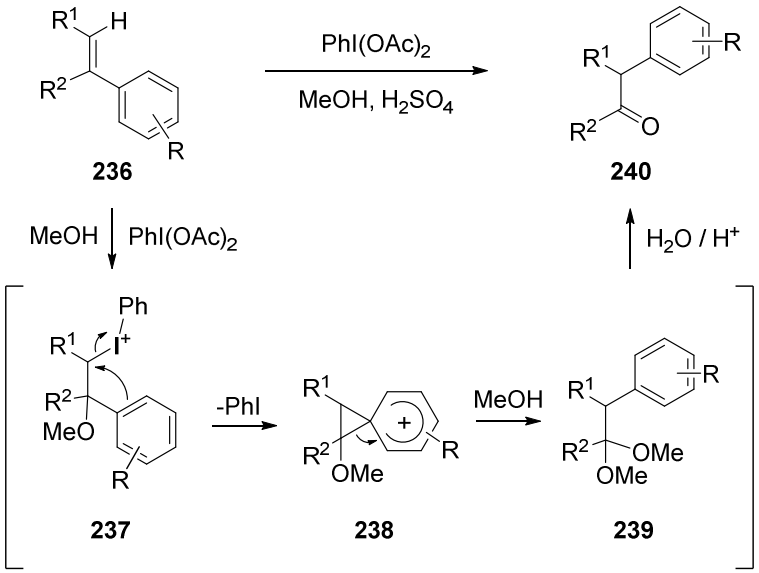


Scheme 4.17: An oxidative 1,3-alkyl shift mediated by (diacetoxyiodo)benzene

4.8 1,2 Aryl Migrations

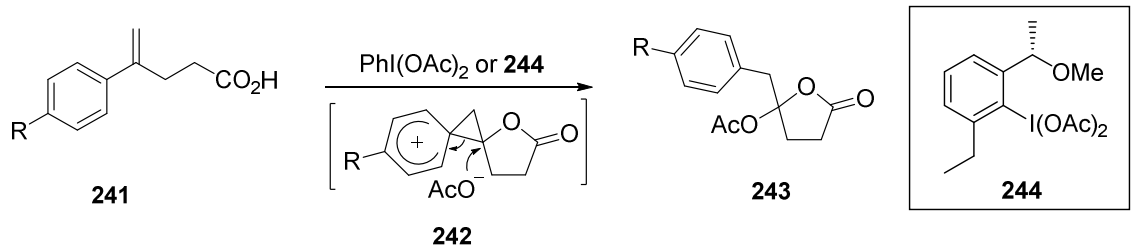
The involvement of aryl moieties in cationic species was proposed by Cram,[31] which was further proven by different experimental, spectroscopic and computational methods.[32] Despite the discovery of phenonium ions a long time ago,[33] these ions have not been widely used in synthetic chemistry. In 2004, Yusubov and co-workers reported the oxidative rearrangement of α-substituted styrenes **236** to the corresponding

arylacetones **240** via migration of aryl functionality involving phenonium ions by using (diacetoxyiodo)benzene. It was suggested that the reaction was initiated with the activation of the double bond of styrene **236** by (diacetoxyiodo)benzene in the presence of methanol to form phenyliodinated intermediate **237**, which was stabilized by the aryl substituent via the formation of phenonium ion intermediate **238**. Furthermore, phenonium ion **238** was attacked by a nucleophile leading to the formation of another intermediate **239** via 1,2-aryl group migration, which on hydrolysis yielded the rearranged product **240** (Scheme 4.18).[34]



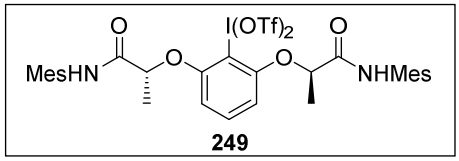
Scheme 4.18: An oxidative 1,2 aryl-migration of styrenes **236** involving phenonium ions

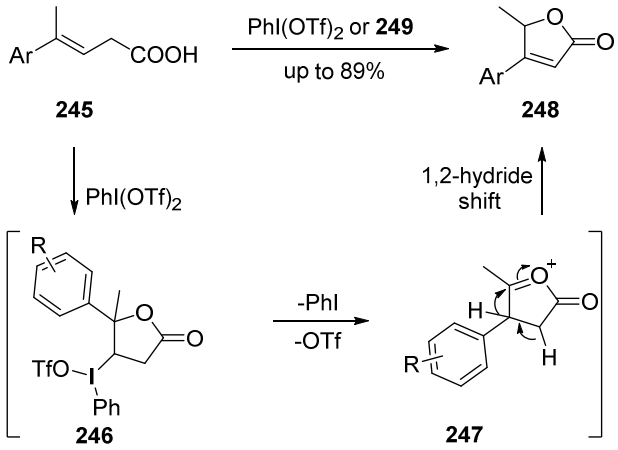
Wirth *et al*. accidently discovered the oxidative cyclization of 4-phenyl-4-pentenoic acid **241** occurring with a 1,2-migration of aryl groups mediated by hypervalent iodine reagents.[35] It was suggested that the reaction proceeded through the formation of phenonium ion intermediate **242** which gave rise to the product **243** on the attack of the acetoxy nucleophile. In this rearrangement reaction the generation of a tetrasubstituted stereogenic centre allowed the use of such substrates in asymmetric synthesis. When chiral hypervalent iodine reagent **244** was used in the rearrangement reaction, the migrated product **243** was obtained in 56% yield but with only 4% *ee* (Scheme 4.19). The authors suggested the reason of low enantioselectivities probably due to a fast reversible first addition step of the chiral iodine electrophile **244** to the alkene **241**.



Scheme 4.19: An oxidative 1,2 aryl-migration mediated by hypervalent iodine(III) reagents.

Later on the same research group reported the oxidative rearrangements of 4-arylbut-3-enoic acids **245** to furanones **248**. It was found that only the hypervalent iodine bistriflates, which were synthesized *in situ* by mixing iodine(III) reagent and trimethylsilyl triflate, had sufficient reactivity for this transformation. Mechanistic investigations and detailed calculations revealed that the migration of the aryl moiety was followed by a 1,2-hydride transfer as shown in intermediate **247** and elimination to yield furanones **248** (Scheme 4.20).[36]

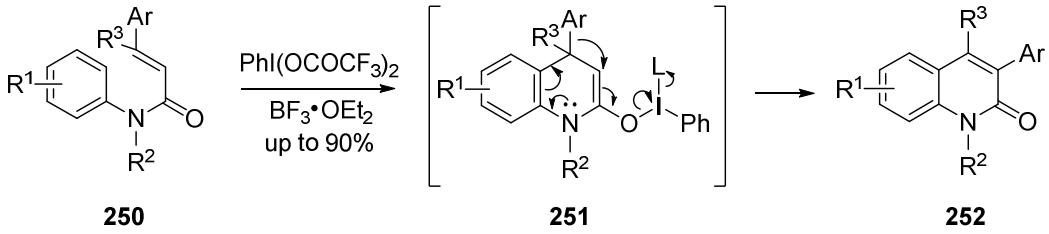




Scheme 4.20: An oxidative rearrangement of unsaturated acids **245** to furanones **248**

By calculations, a phenonium ion intermediate could not be located as a stable intermediate on the mechanistic pathway. This rearrangement did also not lead to any stereoselective product formation using chiral hypervalent iodine reagent **249** (Scheme 4.20).

Recently, Zhao and co-workers reported an 1,2-aryl migration of *N*-methyl-*N*-phenylcinnamides **250** to 3-arylquinolin-2-ones **252** using [bis(trifluoroacetoxy)iodo]-benzene in the presence of a Lewis acid. It was found that the intermediate **251** was obtained after nuclephilic attack of the carbonyl oxygen on the iodine centre followed by ring closure and deprotonation. Then 1,2-aryl migration occurred by a concerted process followed by breakage of the O-I bond and further deprotonation to give rise to the rearranged product **252** in up to 90% (Scheme 4.21).[37]



250 **251** **252**

Scheme 4.21: $PhI(OCOCF_3)_2$-mediated rearrangement of *N*-methyl-*N*-phenylcinnamides **250** to 3-arylquinolin-2-ones **252**

4.9 Summary

The oxidative rearrangement reactions mediated by hypervalent iodine reagents provide mild reaction conditions to obtain important synthetic intermediates and naturally occurring compounds. Alkyl or aryl group migration under Hoffmann rearrangement, ring contraction and ring expansion reactions lead to valuable compounds. Stereoselective rearrangements mediated by chiral hypervalent iodine reagents involving aryl migrations were unsatisfactory. Further advancement in the field of asymmetric migration reactions is still missing in the literature.

4.10 References

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Chapter 5

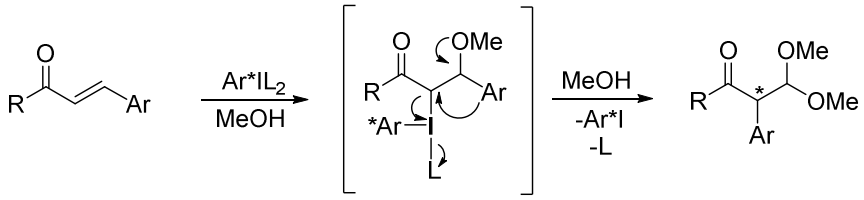
Results and Discussions of Rearrangement Reactions

5.1 Objectives

The main objective of this work is to develop a stereoselective rearrangement reaction mediated by chiral hypervalent iodine reagents. Keeping in mind the long history of oxidative rearrangements induced by hypervalent iodine reagents, no efficient stereoselective method has been developed with chiral hypervalent iodine reagents for rearrangement reactions. Therefore, the use of chiral hypervalent iodine reagents in asymmetric rearrangement reactions seems to be a very promising area of research.

5.2 Project Approach

The project approach starts with the synthesis of aryl-substituted ketones. These chalcones of type **253** can easily be accessible through an aldol condensation between methyl ketones and aryl aldehyde. The oxidative rearrangement of such compounds in the presence of alcohol nucleophiles mediated by hypervalent iodine reagents is already known in the literature and it leads to the α-arylated and β-oxygenated carbonyl compounds.[1] The reaction proceeds through the activation of aryl-substituted alkenes **253** with electrophilic chiral iodine reagents resulting in the formation of phenyliodinated intermediates which are stabilized by the migration of an aryl group followed by the reaction with a second alcohol nucleophile to give the 1,2 migration products **254** with a new stereogenic centre (Scheme 5.1). Stereoselective rearrangement reactions mediated by chiral hypervalent iodine reagents are not known in the literature. Inspired by our previous results, the use of lactate-based chiral hypervalent iodine reagents will be examined in oxidative migration reactions to make this reaction enantioselective.

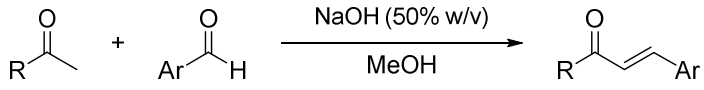


253 **254**

Scheme 5.1: Rearrangement of **253** to **254** via aryl-migration using chiral hypervalent iodine reagents Ar^*IL_2

5.3 Synthesis of Chalcones 253

We have investigated chalcones **253** for the oxidative rearrangement reactions induced by different hypervalent iodine(III) reagents. The chalcones **253** were synthesized effeciently by aldol condensation in the presence of sodium hydroxide between the corresponding aryl ketones and aldehydes.



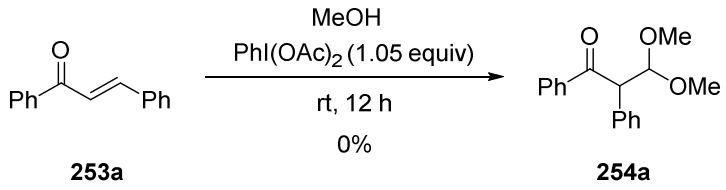
253a-k

Table 5.1: Synthesis of chalcone derivatives **253a-k**

Entry	R	Ar	Product Yield [%]
1	Ph	Ph	**253a**: 51
2	Ph	4-F-C_6H_4	**253b**: 62
3	Ph	4-Cl-C_6H_4	**253c**: 92
4	Ph	4-Br-C_6H_4	**253d**: 61
5	Ph	4-NO_2-C_6H_4	**253e**: 79
6	Ph	4-Me-C_6H_4	**253f**: 82
7	Ph	4-*i*Pr-C_6H_4	**253g**: 82
8	Ph	4-*t*Bu-C_6H_4	**253h**: 69
9	Ph	3-Me-C_6H_4	**253i**: 79
10	Ph	4-OMe-C_6H_4	**253j**: 32
11	2-furyl	Ph	**253k**: 48

5.4 Initial Rearrangement Reactions of 253a

Initially the reaction of (*E*)-1,3-diphenylprop-2-en-1-one **253a** with only (diacetoxyiodo)benzene [$PhI(OAc)_2$] was investigated, but its reactivity was too low and no conversion into the rearranged product **254a** was observed (Scheme 5.2).



Scheme 5.2: (Diacetoxyiodo)benzene induced migration attempt

Traditionally, hypervalent iodine mediated migration reactions are performed in the presence of Brønsted acids. The literature suggests that the activation of the hypervalent iodine(III) reagent by the addition of H_2SO_4 may result into more electrophilic intermediates **A**-**C** *in situ* which can act as better reagents for rearrangement reactions (Fig. 5.1).[1,2]

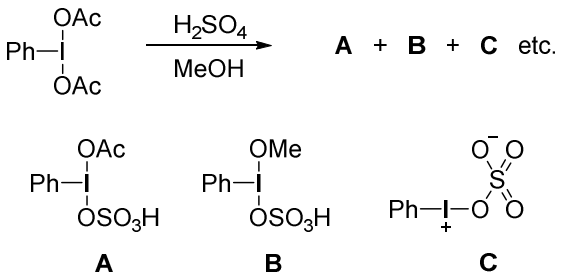
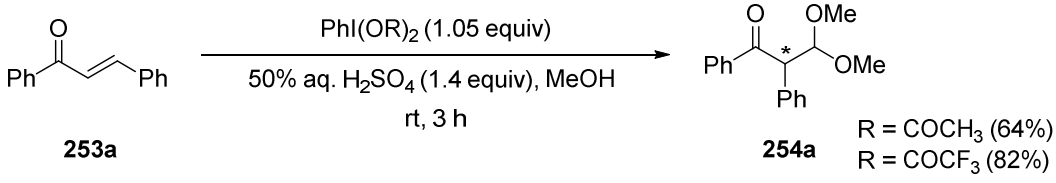


Fig. 5.1: Activation of $PhI(OAc)_2$ with H_2SO_4

When (diacetoxyiodo)benzene was reacted with the chalcone **253a** in combination with 50% aq. H_2SO_4 as an activator, the reaction proceeded well and the rearranged product **254a** was obtained in 64% yield. While using [bis(trifluoroacetoxy)iodo]benzene as iodine(III) source, the yield increased to 82% (Scheme 5.3).



Scheme 5.3: Iodine(III) mediated migration reactions in the presence of H_2SO_4

As a new stereogenic center is established in the product **254a**, lactic acid-based chiral hypervalent iodine compounds **142** and **144** were synthesized according to the known literature method (Fig. 5.2).[3,4]

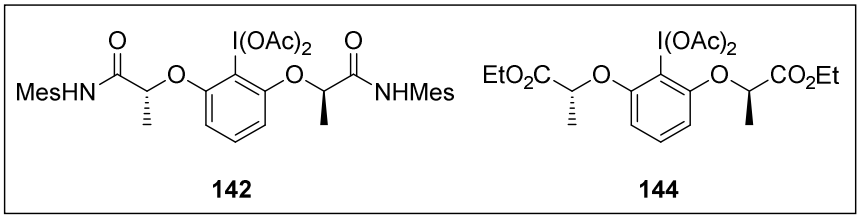


Fig. 5.2: Lactate acid-based chiral hypervalent iodine(III) reagents

These chiral hypervalent iodine reagents were then investigated for the asymmetric migration reaction of **253a** in the presence of 50% aq. H_2SO_4. The reaction proceeded slowly and the rearranged product **254a** was obtained in low yields and with poor enantioselectivities (Table 5.2, entries 1 and 2). Inspired by the successful activation of hypervalent iodine compounds with Lewis acids in the asymmetric aminohydroxylation of alkenes in which NMR studies proved that the addition of *tert*-butyldimethylsilyl triflate (TBDMSOTf) or trimethylsilyl triflate (TMSOTf) to the corresponding (diacetoxyiodo)arenes generates *in situ* the more reactive $ArI(OTf)_2$.[5] Therefore, a similar approach was investigated in these migration reactions. When the reaction was performed with (diacetoxyiodo)benzene in the presence of *tert*-butyldimethylsilyl triflate (TBDMSOTf), the reaction product was obtained in 37% yield (Table 5.2, entry 3). Unfortunately, when chiral reagents **142** was reacted, there was either no reaction at low temperatures or only racemic product after increasing the temperature was obtained by using *tert*-butyldimethylsilyl triflate (TBDMSOTf) in MeOH (Table 5.2, entries 4 and 5).

253a **254a**

Table 5.2: Different hypervalent iodine reagents for the migration of **253a** to **254a**

Entry	Reagents	Conditions	**254a** Yield [%]	**254a** *ee* [%]
1	1.15 equiv **144**, 1.4 equiv 50% H_2SO_4, MeOH	rt, 2 h	4	17
2	1.15 equiv **142**, 1.4 equiv 50% H_2SO_4, MeOH	rt, 20 h	5	5
3	1.2 equiv $PhI(OAc)_2$, 1.4 equiv TBDMSOTf MeOH	0 ºC to rt, 14 h	37	-
4	1.5 equiv **142**, 3 equiv TBDMSOTf, MeOH	–78 ºC, 12 h	-	-
5	1.5 equiv **142**, 3 equiv TBDMSOTf, MeOH	–78 ºC to rt,12h	50	0

Previous investigations for aminohydroxylation of alkenes indicated that the solvent is crucial in an efficient stereochemical induction mediated by chiral hypervalent iodine(III) reagents. The selection of the appropriate solvent was indispensable for efficient conversions and selectivities. Therefore, a combination of different solvents were investigated in this rearrangement reaction to improve the enantioselectivites. Mixtures of methanol and dichloromethane did not improve the enantiomeric excess in **254a** (Table 5.3, entry 1). However, when the initial synthesis of the highly electrophilic hypervalent iodine reagent $Ar^*I(OTf)_2$ by prior mixing of the chiral hypervalent diacetoxyiodo derivative $Ar^*I(OAc)_2$ with TBDMSOTf in dichloromethane at –78 ^oC is followed by the addition of methanol along with starting material **253a**, the rearranged product **254a** was obtained with improved enantioselectivities (Table 5.3, entry 2). When the reaction temperature was kept at –15 ^oC, the enantioselectivity rose to a promising level of 86% (Table 5.3, entry 3). Also other Lewis acids have been utilized in the migration reaction in combination with different solvents and chiral hypervalent iodine reagents. When boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) was utilized in the migration reaction, the enantioselectivities dropped to 24% *ee* (Table 5.3, entry 4). Other Lewis acids like trimethylsilyl triflate (TMSOTf) and $BF_2OTf{\cdot}OEt_2$ (which is prepared by a 1:1 mixture of TMSOTf and $BF_3{\cdot}OEt_2$ and is known as a more powerful

Lewis acid than its components)[6] also gave a high enantiomeric excess (Table 5.3, entries 5 and 7). When triflic acid was employed in this rearrangement reaction, the selectivities were increased to 92% *ee* in different solvents (Table 5.3, entries 8 and 9). All the results described in Table 5.3 were carried out on a sub-millimolar scale (0.033 mmol) and the product **254a** was purified using preparative TLC.

253a **254a**

Table 5.3: Conditions for the stereoselective rearrangement of **253a** to **254a**

Entry	Reagents[a]	Solvent	**254a** *ee*[%]
1	**142**, TBDMSOTf[b]	CH_2Cl_2:MeOH (1:1)	12
2	**142**, TBDMSOTf[b]	CH_2Cl_2, 10 equiv MeOH	43
3	**142**, TBDMSOTf	CH_2Cl_2, 8 equiv MeOH	86
4	**142**, $BF_3{\cdot}OEt_2$	CH_2Cl_2, 8 equiv MeOH	24
5	**142**, TMSOTf	CH_2Cl_2, 8 equiv MeOH	88
6	**144**, TMSOTf	CH_2Cl_2, 8 equiv MeOH	12
7	**142**, $BF_2OTf{\cdot}OEt_2$[c]	CH_2Cl_2, 8 equiv MeOH	89
8	**142**, TfOH	CH_2Cl_2, 8 equiv MeOH	91
9	**142**, TfOH	CH_3CN, 8 equiv MeOH	92

[a] 1.5 equiv **142** and **144**, 3 equiv Lewis acid, reaction temperature –78 ºC to –15º C, reaction time 14 h. [b] Reaction temperature –78 ºC to rt, reaction time 14 h. [c] Prepared by a 1:1 mixture of TMSOTf and $BF_3{\cdot}OEt_2$.

To check the percentage conversion of the chalcone **253a** into the rearranged product **254a** over time, a ^{1}H NMR experiment was performed. The reaction was executed in the presence of triflic acid as a Lewis acid and dichloromethane and methanol (8 equiv) as solvents. For the close monitoring of the experiment, crude samples were taken after some time over different temperatures and these samples were filtered over silica followed by ^{1}H NMR analysis. Two peaks were analyzed in this experiment, a doublet at 7.82 ppm (J = 15.7 Hz, 1H) corresponds to the H^a in the starting material and a doublet at 5.13 ppm (J = 8.5 Hz, 1H) corresponds to the H^b in the product. From the integration values of these doublets in the ^{1}H NMR spectrum, percentage conversion of the chalcone **253a** into the rearranged product **254a** was calculated. It was revealed from these calculations that the maximum conversion of only 28.5% is obtained over 22 hours (Fig. 5.3). These crude samples were also purified by preparative TLC to check the enantiomeric excess which was found to be constant over the course of the reaction (ca. 85% *ee*), indicating no further interaction of the chiral reagent **142** with the product **254a**.

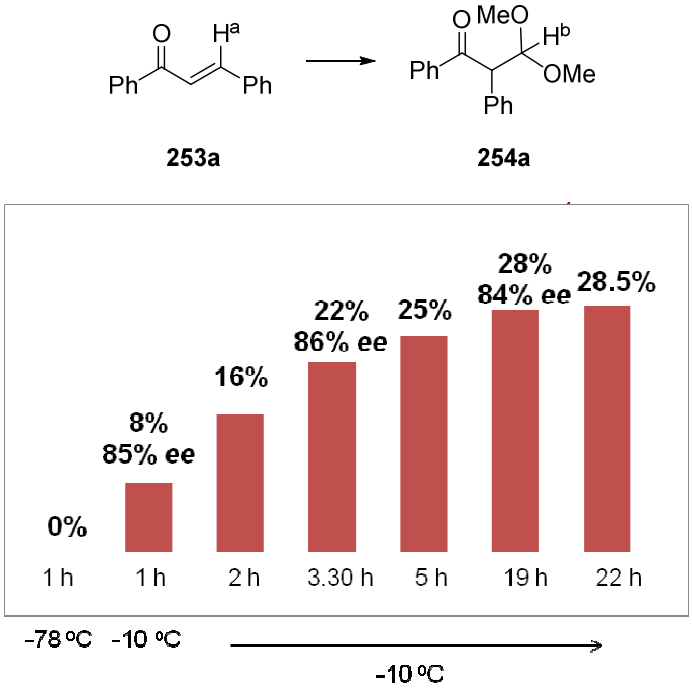
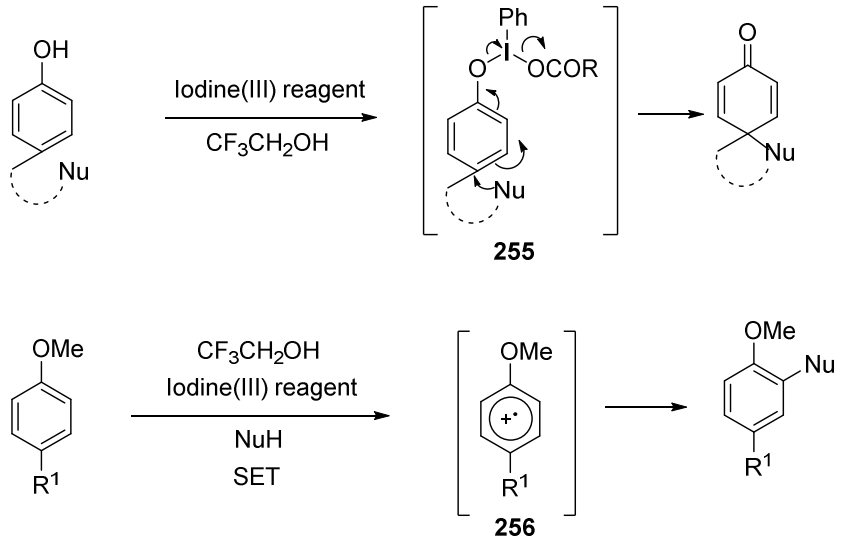


Fig. 5.3: ^{1}H NMR monitoring of the migration reaction over the course of time

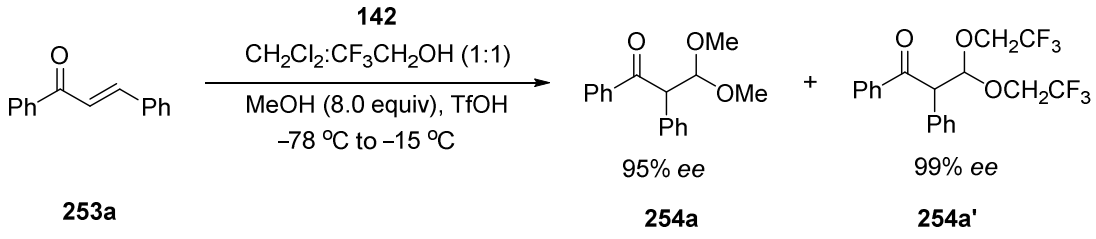
The ^{1}H NMR experiment revealed the poor conversion of the starting material **253a** into the product **254a**. Therefore, further investigation of the reaction conditions to improve the yields and enantioselectvities by changing either the nucleophiles or the solvents

was carried out. The use of 2,2,2- trifluoroethanol (TFE) as a solvent in the oxidation of phenols mediated by hypervalent iodine reagents is quite unique.[7] The high ionizing power, low nucleophilicity and excellent hydrogen-bond donor abilities of this fluoroalcohol dramatically direct the course of reaction in many organic transformations. These properties have been successfully utilized in stabilizing the reactive cationic intermediates such as **255** and **256** generated by iodine(III) reagents in the oxidation of phenolic derivatives and single-electron-transfer (SET) oxidation of aromatic compounds respectively (Scheme 5.4).



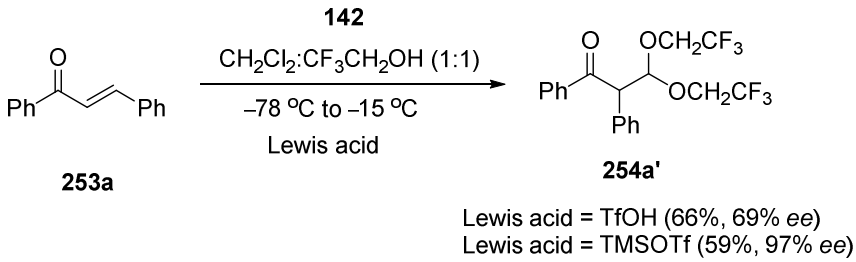
Scheme 5.4: Role of 2,2,2-trifluoroethanol in stabilizing cationic intermediates **255** and **256**

To see the effect of TFE in the migration reaction, an 1:1 mixture of dichloromethane and 2,2,2-trifluoroethanol in the presence of triflic acid together with chiral hypervalent iodine reagent **142** and 8.0 equivalents of methanol was tried over sub-millimolar scale. The reaction resulted in a mixture of the dimethoxy acetal **254a** (95% *ee*) and the bis(trifluoroethoxy)acetal **254a'** (99% *ee*) with very high enantioselectivities (Scheme 5.5).



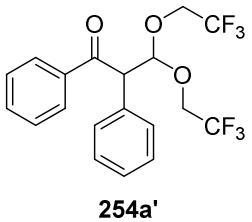
Scheme 5.5: Rearrangement reaction of **253a** in the presence of 2,2,2-trifluoroethanol

When the reaction was performed without the addition of methanol and by using only a 1:1 mixture of dichloromethane and 2,2,2-trifluoroethanol with triflic acid as Lewis acid, a yield of 66% of the product **254a'** with moderate selectivity of 69% *ee*. By employing TMSOTf as the Lewis acid for chiral iodine(III) reagent **142** activation, the asymmetric induction was found to be excellent, giving the product **254a'** in 97% *ee* with 59% yield (Scheme 5.6).



Scheme 5.6: Rearrangement reaction of **253a** in the presence of 2,2,2-trifluoroethanol behaving as a solvent and a nucleophile leading to the product **254a'**

The structure of the rearranged product **254a'** was further confirmed by X-ray crystallography.[13] The absolute stereochemistry of the product **254a'** could not be determined based on the X-ray structure because of the absence of heavy atoms like sulfur, chlorine, bromine etc. in the molecule which are necessary to show the high anomalous dispersion effect (Fig. 5.4).



254a'

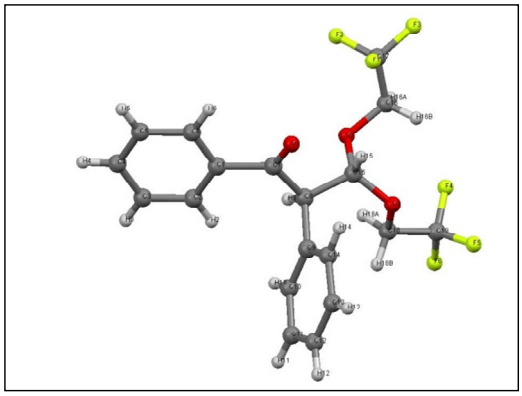
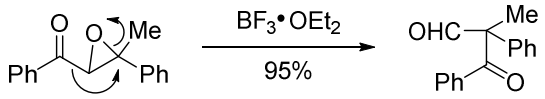


Fig. 5.4: X-ray structure of rearranged product **254a'**

5.5 Mechanistic Insight of the Rearrangement Reaction

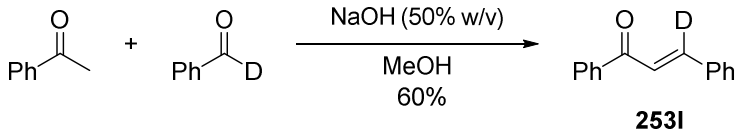
Aryl ketones also have the potential to migrate under Lewis acidic reaction conditions. This was demonstrated in a recent publication that an aryl ketone **257** migrates in a boron trifluoride catalyzed epoxide opening reaction giving the tetrasubstituted aldehyde **258** in optically pure form in 95% yield (Scheme 5.7).[8]



257 **258**

Scheme 5.7: Migration potential for aryl ketones **257** under Lewis acidic conditions

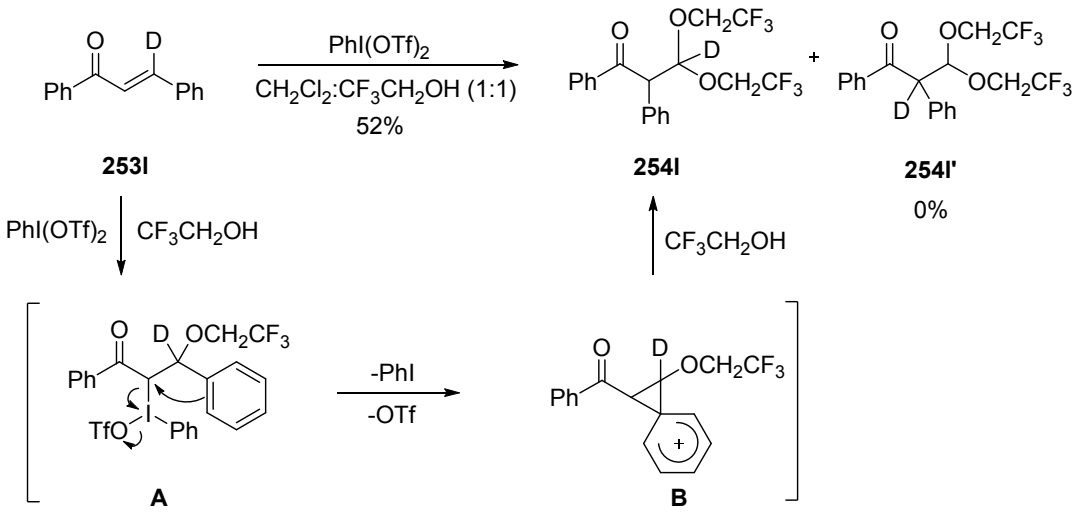
Therefore, to confirm that the reaction mechanism proceeds with aryl ring migration, the deuterium-labelled compound **253l** was synthesized from aldol condensation between acetophenone and the corresponding deuterium-labelled benzaldehyde in 60% yield (Scheme 5.8).



253l

Scheme 5.8: Synthesis of deuterium-labelled chalcone **253l** with aldol condensation reaction

When the compound **253l** was treated with $PhI(OTf)_2$ which was synthesized *in situ* by mixing $PhI(OAc)_2$ together with TfOH, the phenyl ring migrated product **254l** was obtained exclusively alongside unreacted starting material **253l**. The product **254l'**, which would result from an aryl ketone migration was not observed in this reaction. A plausible mechanism is depicted below which starts with the activation of the double bond with electrophilic hypervalent iodine(III) followed by first nucleophilic attack of the CF_3CH_2OH to give rise to the phenyl iodinated intermediate **A**. Now this intermediate **A** can be stabilised by the phenonium ion to give rise to the intermediate **B**.[9] The hyper-leaving ability of the hypervalent iodine moeity in the intermediate **A** is the driving force for this transformation as it is attached to an sp^3-hybridized carbon atom making it an excellent leaving group.[10] Finally the intermediate **B** is further attacked by the other fluoroalcohol nucleophile and it rearranges to give the product **254l** in 52% yield (Scheme 5.9).



Scheme 5.9: Deuterium-labelling to prove the reaction proceedings via phenyl ring migration

5.6 Substrate Scope

To investigate the substrate scope, many different chalcones **253b-k** were exposed to the standardized reaction conditions. When the substrates **253b-e** with electronically withdrawing groups at the 4-position of the aryl moiety were allowed to react under migration reaction conditions, an interesting trend in the yields was observed. The yields decrease with an increase in the Hammett value of the halide substituents from σ_p = 0.06 (F) to σ_p = 0.23 (Br) (Table 5.4, entries 2, 4 and 6). With the 4-nitro substituted chalcone **253e** (σ_p = 0.78), the starting material was completely recovered and no rearrangement took place (Table 5.4, entry 8).[11] The enantioselectivities remained higher with substrates **253b** when TMSOTf was employed as a Lewis acid (Table 5.4, entry 2) but when TfOH was utilized, enantioselevtivities dropped to 69% *ee* (Table 5.4, entry 1). The rearranged products were also synthesized as racemates by using (diacetoxyiodo)benzene [PhI(OAc)$_2$] as an iodine(III) reagent on a small scale to serve as a reference for the determination of enantioselectivity on HPLC (Table 5.4, entries 3, 5 and 7).

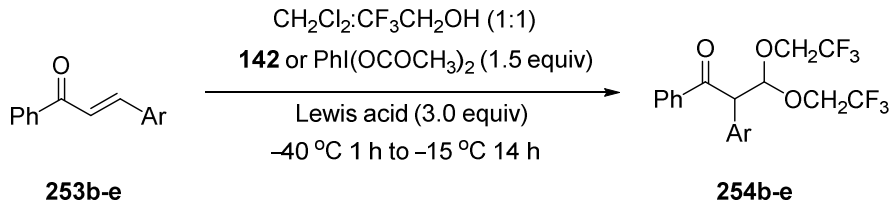
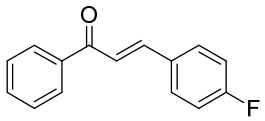
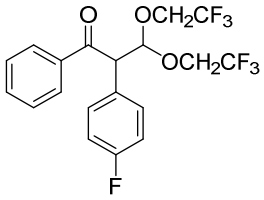
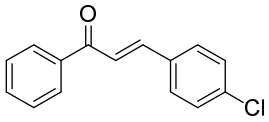
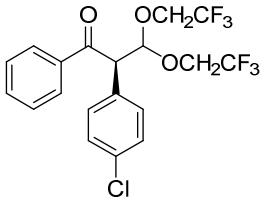
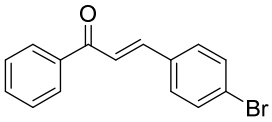
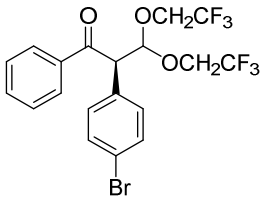
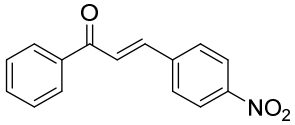
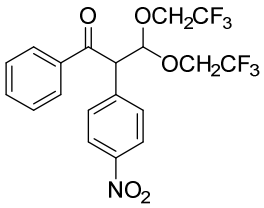


Table 5.4: Electronically withdrawing groups at *para*-position of migrated aryl ring

Entry	Substrate	Product	Reagents	Yield [%]	*ee* [%]
1	 **253b**	 **254b**	**142**, TfOH	60	69
2	**253b**	**254b**	**142**, TMSOTf	50	94
3	**253b**	**254b**	$PhI(OAc)_2$ TMSOTf	30[a]	-
4	 **253c**	 **254c**	**142**, TMSOTf	38	92
5	**253c**	**254c**	$PhI(OAc)_2$ TMSOTf	32[a]	-
6	 **253d**	 **254d**	**142**, TMSOTf	17	91
7	**253d**	**254d**	$PhI(OAc)_2$ TMSOTf	23[a]	-
8	 **253e**	 **254e**	$PhI(OAc)_2$ TMSOTf	0	-

[a] Reaction was performed on sub-millimolar scale at 0 °C for 2 h and purified by preparative TLC.

The absolute configuration of the major isomer of **254c** and **254d** was found to be *R* by anomalous dispersion scattering, and the refined Flack parameters[12] were 0.17(16) and 0.00(4), respectively, as determined by X-ray crystallography.[13] The X-ray structures of these isomers are shown below (Fig. 5.5).

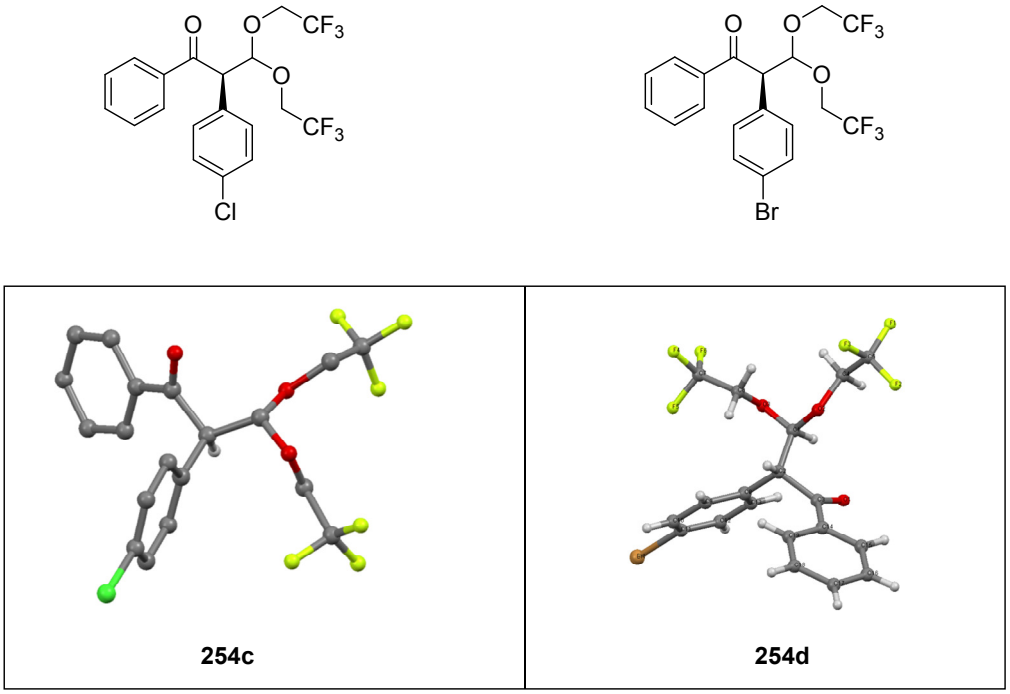


Fig. 5.5: X-ray structure of major enantiomers of rearranged products **254c** and **254d**

The general trend in the yield for the products **254b-e** with electron-withdrawing groups at the 4-position of the aryl moiety demonstrates the reactivity patterns of the substrates **253**. It is evident from the experimental findings that if the alkene is more electron deficient because of electron-withdrawing substituents on the aryl ring **B** (Fig. 5.6), the electrophilic addition of the iodine(III) reagent to the alkene is slower and this results in lower yields of the migrated products. Especially, in the case of substrate **253e**, there was no reactivity even under achiral reaction conditions (Table 5.4, entry 8).

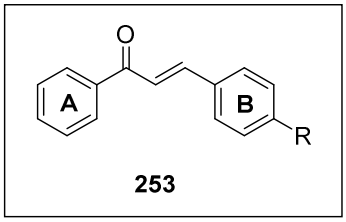
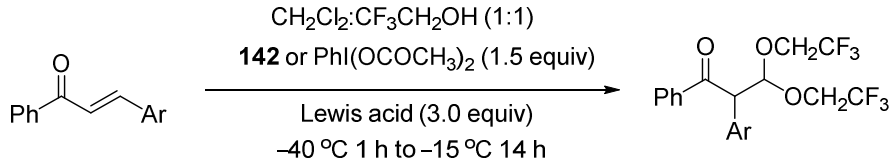


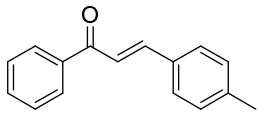
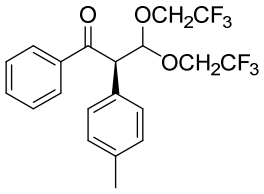
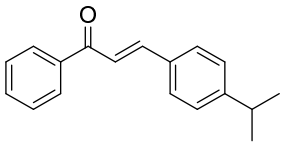
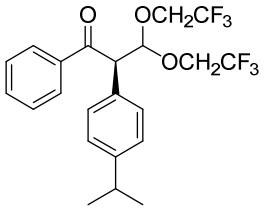
Fig. 5.6: Substituents effects on reactivity of the chalcones **253**

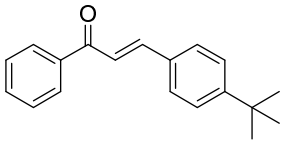
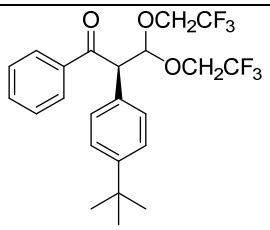
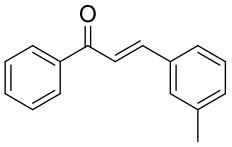
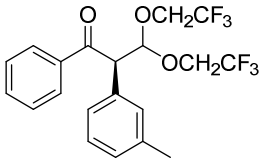
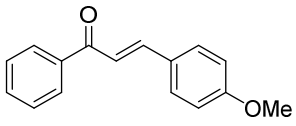
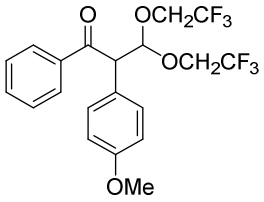
When compounds **253** with electron-donating substituents on the aryl moiety were subjected to the rearrangement reaction conditions, products **254** were obtained in high yields and selectivities (Table 5.5, entries 1 and 4). Unfortunately, compounds **253** with a 4-*tert*-butyl (**253h**) and a 3-methyl substituent (**253i**) resulted in products **254h** and **254i** with only moderate selectivities (Table 5.5, entries 6 and 8). Compound **253j** with a 4-methoxy substituent led to complete decomposition under different reaction conditions (Table 5.5, entry 10). From these results it is obvious that both steric and electronic parameters from substituents in the *para*-position are strongly influencing the yield and selectivity of the reaction.



253f-j **254f-j**

Table 5.5: Electron-donating groups on the migrated aryl ring

Entry	Substrate	Product	Reagents	Yield [%]	*ee* [%]
1	 **253f**	 **254f**	**142** TMSOTf	80	86
2	**253f**	**254f**	**142**, TfOH	92	66
3	**253f**	**254f**	$PhI(OAc)_2$ TMSOTf	80[a]	-
4	 **253g**	 **254g**	**142** TMSOTf	68	89
5	**253g**	**254g**	$PhI(OAc)_2$ TMSOTf	30[b]	-

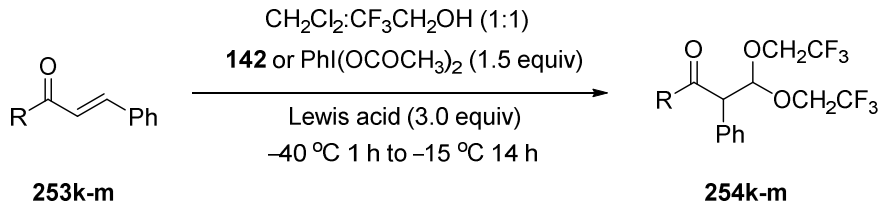
6	 **253h**	 **254h**	**142** TMSOTf	65	52
7	**253h**	**254h**	$PhI(OAc)_2$ TMSOTf	23[b]	-
8	 **253i**	 **254i**	**142** TMSOTf	42	53
9	**253i**	**254i**	$PhI(OAc)_2$ TMSOTf	50[b]	-
10	 **253j**	 **254j**	$PhI(OAc)_2$ TMSOTf	decomposition	-

[a] Reaction was performed on a millimolar scale and column chromatography was performed for purification. [b] Reaction was performed on sub-millimolar scale at 0 °C for 2 h and purified by preparative TLC.

The absolute configuration for the products **254f-i** were assigned in an analogy to the rearranged products **254c** and **254d**. It is evident from the results in the Table 5.5 that electron donating groups on the aryl ring **B** (Fig. 6) make the electrophilic addition of the iodine(III) reagent to the alkene faster resulting in higher yields of the migrated products. Especially, in the case of substrate **253j**, the substrate was so reactive that it resulted in the decomposition and no rearranged product **254j** was isolated (Table 5.5, entry 10).

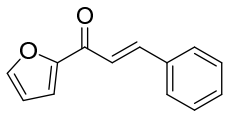
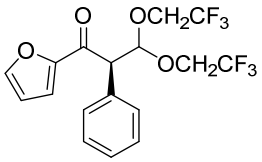
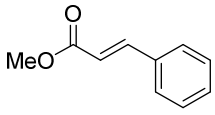
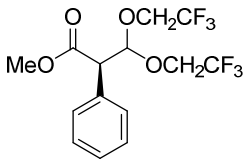
The optimized reaction conditions were then applied to different alkenes. The heteroaromatic compound **253k** was synthesized from the aldol condensation (Table 5.6, entry 1) and the substrates **253m** and **253n** were purchased from commercially available sources. When heteroaromatic compound **253k**, the cinnamyl ester substrate

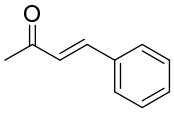
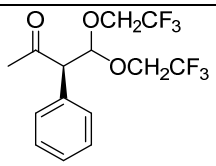
253m and the methyl-substituted ketones **253n** were exposed to the reaction conditions, they underwent the rearrangement reaction with high enantioselectivities, but only gave the reaction products **254** in low yields (Table 5.6, entries 1, 3 and 5). Further optimization of the reaction in the presence of the chiral reagent for these substrates is necessary to increase yields. The reaction resulted in moderate to poor yields while using [$PhI(OAc)_2$] as an electrophillic iodine(III) source (Table 5.6, entry 2, 4 and 6). The absolute configuration for the products **254k, 254m** and **254n** were assigned in an analogy to the rearranged products **254c** and **254d**. The enantiomers of the rearranged product **254n** were inseparable on the chiral HPLC but the product was found to be optically active in the polarimeter analysis suggesting that the reaction proceeded in enantioselective manner (Table 5.6, entry 5).



253k-m **254k-m**

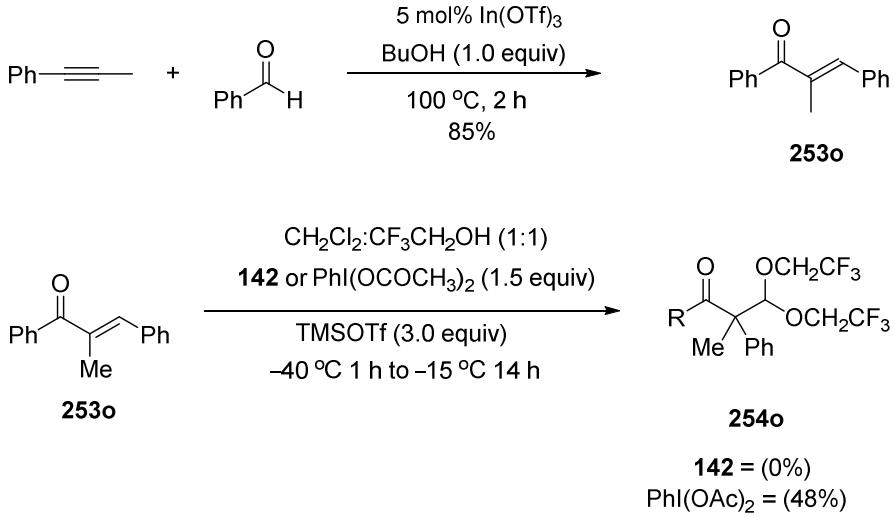
Table 5.6: Different unsaturated carbonyl compounds for the migration reaction

Entry	Substrate	Product	Reagents	Yield [%]	*ee* [%]
1	 **253k**	 **254k**	**142**, TMSOTf	8	83
2	**253k**	**254k**	$PhI(OAc)_2$ TMSOTf	25[a]	-
3	 **253m**	 **254m**	**142**, TMSOTf	12	96
4	**253m**	**254m**	$PhI(OAc)_2$ TMSOTf	52[a]	-

5	 **253n**	 **254n**	**142**, TMSOTf	10	-[b]
6	**253n**	**254n**	$PhI(OAc)_2$ TMSOTf	26[a]	-

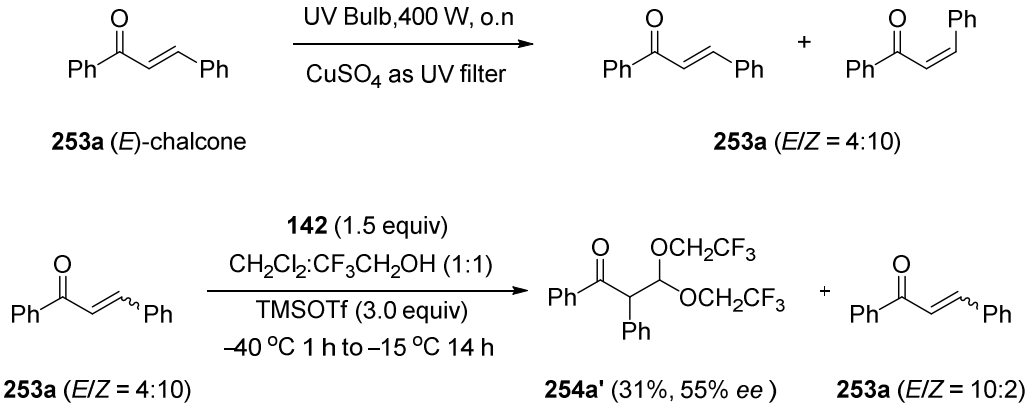
[a] Reaction was performed on sub-millimolar scale at 0 °C for 2 h and purified by preparative TLC. [b] The enantiomers were inseparable on the chiral HPLC.

We also investigated the compound **253o** in an attempt to generate quaternary carbon centers in this process. The compound **253o** was synthesized by indium(III) catalyzed coupling reaction between 1-phenyl-1-propyne and benzaldehyde in 85% yield.[14] When the substrate **253o** was exposed to the asymmetric reaction conditions by employing **142** as a iodine(III) chiral source, no rearranged product was observed, but the reaction proceeded by using (diacetoxyiodo)benzene and TMSOTf as an activating reagent to give the expected rearranged product **254o** in 48% yield. This reactivity pattern could be because of the fact that the chiral reagent $Ar^*I(OTf)_2$, **142** was not reactive enough to activate the methyl-substituted double bond in the substrate **253o** resulting in no reactivity (Scheme 5.10).



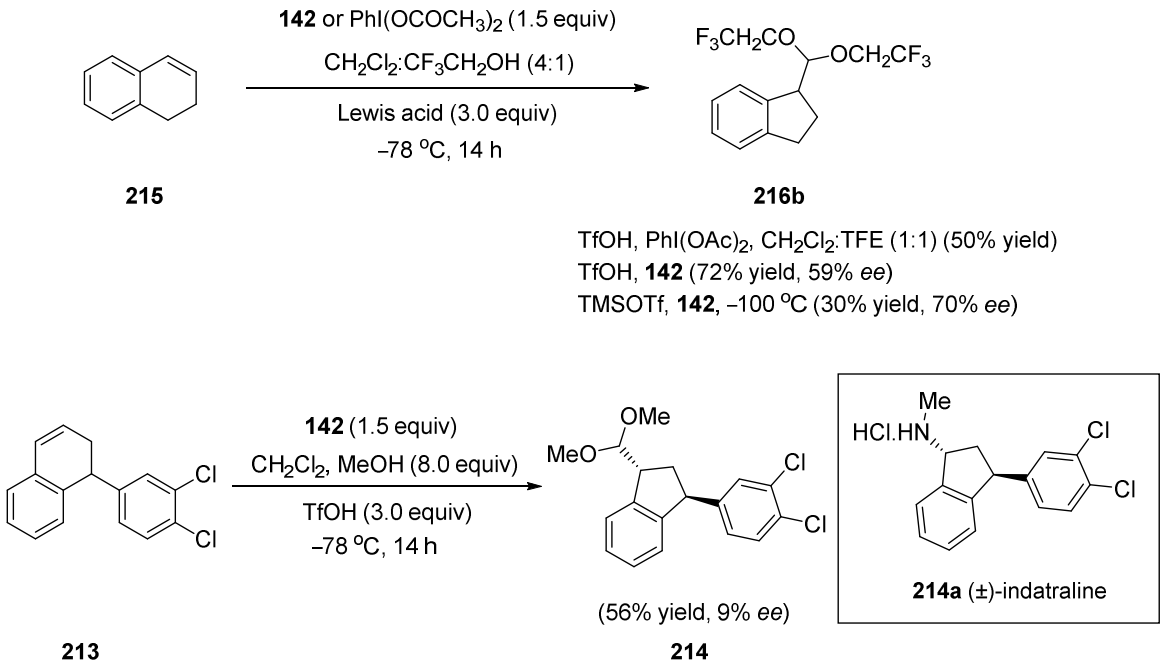
Scheme 5.10: Synthesis and migration of the substrate **253o** to generate a quaternary carbon centre

To investigate the reactivity of (*Z*)-chalcones **253** towards migration reaction, photoisomerization of (*E*)-**253a** was performed leading to an inseparable mixture of (*E*)-**253a** and (*Z*)-**253a** (1:1) isomers, which was further crystallized to obtain a mixture of (*E*)-**253a** and (*Z*)-**253a** (4:10).[15] When this mixture was subjected to the rearrangement reaction conditions using reagent **142**, product **254a'** was obtained in 31% yield and with 55% *ee*. The recovered starting material **253a** showed an altered *E*/*Z* ratio of about 10:2 (determined by ^{1}H NMR studies). This indicates that (*Z*)-**253a** reacts much faster than (*E*)-**253a**, but the enantiomeric excess obtained in the product **254a'** is lower (Scheme 5.11).



Scheme 5.11: Photoisomerization of chalcone **253a** and its reactivity in migration reaction

Hypervalent iodine mediated ring contraction reactions have been known for a while but the enantioselective version of such rearrangements is not yet reported.[16] In 2007, Silva *et al*. reported the ring contraction of 1,2-dihydronaphthalenes **213** induced by the Koser reagent leading to the synthesis of (±)-indatraline **214a** over 6 steps. The synthesis of indanes **216** through ring contraction of 1,2-dihydronaphthalenes **215** using Koser reagent was also developed. Further functionalization of these compound **216** can lead to the synthesis of compounds of biological importance.[17] Therefore, ring contraction reactions of these derivatives in the presence of **142** have also been performed using this method. When compound **215** was subjected to the rearrangement reaction conditions, rearranged product **216b** was obtained in 59% *ee*. The selectivity was improved at lower temperature to 70% *ee* but with decreased yields. Unfortunately, substrate **213** gave a very low selectivity in product **214** when methanol was used as a nucleophile. The use of 2,2,2-trifluoroethanol in this ring contraction reaction resulted in a complex mixture of products (Scheme 5.12).

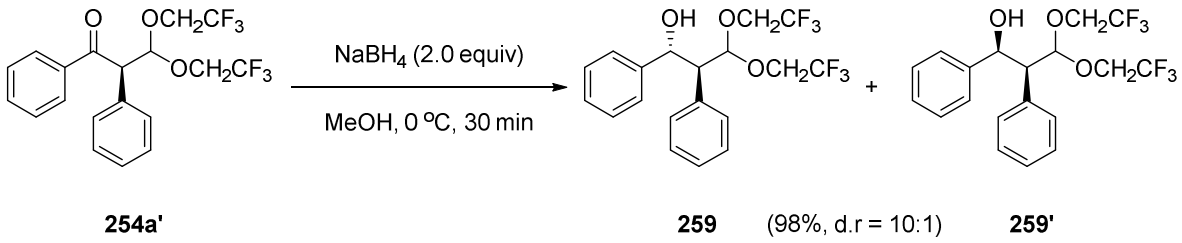


Scheme 5.12: Ring contractions of tetralone derivatives

In conclusion, we have developed an efficient and highly stereoselective method for the α-arylation of a wide range of carbonyl compounds by an oxidative rearrangement procedure. These results are noteworthy as they are the first examples of chiral hypervalent iodine(III) reagents in highly stereoselective rearrangement reactions. Further investigations for developing a catalytic reaction and for the synthesis of enantiomerically enriched building blocks using this approach are currently in progress.

5.7 Further Functionalization of the Rearranged Products

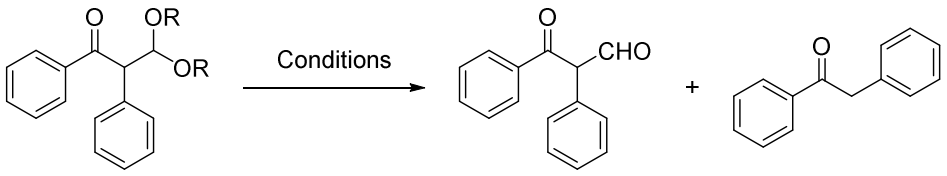
Compound **254a'** was reduced with sodium borohydride to obtain **259** as a major diastereomer as determined by the ^{1}H NMR analysis. The corresponding alcohol was obtained in 98% yield (Scheme 5.13). Products of these type are versatile building blocks for further manipulations. Moreover, this asymmetric method allowed the synthesis of fluorinated acetals, which have many applications in biological chemistry and industry.[18]



254a' **259** (98%, d.r = 10:1) **259'**

Scheme 5.13: Reduction of the carbonyl moiety in **254a'**

The bis(trifluoroethoxy)acetal in **254a'** can also be cleaved to obtain an aldehyde. Indium triflate(III) is known as an efficient catalyst for the deprotection of a wide range of acetals and ketals.[19] Therefore, many different reaction conditions were tried by employing catalytic amounts of indium triflate(III) to cleave the bis(trifluoroethoxy)acetal in **254a'** to give an aldehyde. These reactions (Table 5.7, entries 1, 2, 3 and 4) resulted in no reactivity and no aldehyde **260** was obtained probably because of the fact that bis(trifluoroethoxy)acetals are too electron poor to be coordinated with indium. Acid mediated cleavage of the bis(trifluoroethoxy)acetal in **254a'** was also unsuccessful and it gave the product **261** with full conversion (Table 5.7, entries 7 and 8). However, when iodine was used as a catalyst in the cleavage of dimethoxy acetal of **254a**, the reaction proceeded with a mixture of products along with traces of the aldehyde **260** (Table 5.7, entry 10). Unfortunately compound **254a'** showed no reactivity towards the catalytic use of the iodine for the bis(trifluoroethoxy)acetal cleavage (Table 5.7, entry 11).



254a' (R = OCH_2CF_3)
254a (R = OMe)

260

261

Table 5.7: Reaction conditions for the cleavage of acetals

Entry	Substrate	Conditions	**260**	**261**
1	**254a'**	10 mol % $In(OTf)_3$, MeOH, rt, o.n	0	0
2	**254a'**	10 mol % $In(OTf)_3$, acetone, Microwave (M. W) 100 ^oC, 10 min	0	0
3	**254a'**	10 mol % $In(OTf)_3$, MeOH, M. W. 100 ^oC, 10 min	0	0
4	**254a'**	10 mol % In, acetone, reflux, 6 h	0	0
5	**254a'**	10 mol % In, acetone, conc. HCl, reflux, 6 h	0	0
6	**254a'**	conc. HCl:H_2O (1:1), reflux, 14 h	0	0
7	**254a'**	conc. HCl:MeOH (1:1), M. W. 100 ^oC, 15 min	0	Complete conversion
8	**254a'**	TsOH (1.0 equiv), M. W. 100 ^oC, 15 min	0	Complete conversion
9	**254a**	cat. TsOH, acetone, rt, 6 h	0	Complete conversion
10	**254a**	cat. I_2, acetone, rt, 6 h	Traces, mixture	0

			of products	
11	**254a'**	cat. I_2, acetone, rt, 6 h	0	0

The deprotection of the acetals to obtain the aldehyde **260** remains a challenge in our experiments. These electron poor acetals are not very easy to be cleaved because of their lack of nucleophilicities in the coordination with Lewis acids like indium triflate(III) or their capabilities to be protonated under acidic conditions. Further investigations for developing a catalytic reaction and for the synthesis of enantiomerically enriched building blocks using this approach are still missing.

5.8 References

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Chapter 6

Experimental

6.1 General Methods

The reactions were carried out using standard laboratory equipment. Air and/or moisture sensitive experiments were performed under an inert atmosphere of argon and with flame dried glassware. All reactions were stirred by magnetic stirring and when needed warmed to defined constant temperatures by hotplates with temperature probe control in dry heating blocks or silicon oil baths. Reactions performed at low temperatures were stirred in reaction vessels in a dry ice/diethylether/liquid nitrogen (–100 ^{o}C), dry ice/acetone bath (–78 °C), acetone/liquid nitrogen bath (–50 °C and –40 °C), ice/NaCl bath (–15 °C), or ice/water (0 °C) or a chiller (0 ^{o}C to –40 ^{o}C). Rotary evaporators Büchi B-461, B-481 or B-490 were used for solvent evaporations (reduced pressure to 15 mbar); further drying was undertaken by the use of a high vacuum apparatus. A Büchi GKR-50 Kugelrohr distillation apparatus was employed for Kugelrohr distillations. For inert reactions, freshly over drying agents and under inert atmosphere distilled anhydrous solvents were used. Other chemicals were purchased from Acros, Aldrich, Alfa Aesar or Fluka and were used without further purification, except if indicated otherwise in the experimental procedure.

6.2 Chromatographic Methods

6.2.1 Thin Layer Chromatography

All reactions were monitored by thin-layer chromatography (TLC) which was performed on precoated aluminium sheets of Merck silica gel 60 F254 (0.20 mm) and visualised by UV radiation or by staining with ceric ammonium molybdate solution (235 ml distilled H_2O, 12 g ammonium molybdate, 0.5 g ceric ammonium molybdate, 15 ml concentrated sulfuric acid), potassium permanganate solution (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 ml 10% NaOH, 200 ml distilled H_2O) or iodine.

6.2.2 Column Chromatography

Column chromatography was performed with silica gel 60 (Merck, 230-400 mesh) under increased pressure (Flash Chromatography) or as gravitational column chromatography. The used eluting solvents are indicated in the text.

6.2.3 High Pressure Liquid Chromatography (HPLC)

For HPLC measurements was used an arrangement from Shimadzu. The Shimadzu Class VP consisted of SIL-10ADVP (auto injector), LC-10 ATVP (liquid chromatograph), FCV-10ALVP (pump), DGU-14A (degasser), CTO-10ASVP (column oven), SCL-10AVP (system controller) and a SPD-M10A (diode array detector). The only solvents used were hexane and 2-propanol (both of HPLC grade purity, Fisher Scientific). Analytical chiral columns *Chiracel® OD* (0.46 cm Ø x 25 cm), *Chiracel® OD-H* (0.46 cm Ø x 25 cm), *Chiracel® OB-H* (0.46 cm Ø x 25 cm), *Chiracel® AD* (0.46 cm Ø x 25 cm) were used for separation of enantiomers at solvent flow rates of 0.5 ml/min.

6.3 Physical Data

6.3.1 ^{1}H NMR Spectroscopy

Bruker DPX 600 (600 MHz), Bruker DPX 500 (500 MHz), Bruker DPX 400 (400 MHz), Bruker DPX 250 (250 MHz) or Oxford 300. The chemical shifts δ are given in ppm downfield of tetramethylsilane (δ = 0 ppm). Compounds and crude reaction mixtures are dissolved in either deuterated chloroform, deuterated acetone or deuterated dimethylsulfoxide. Coupling constants (*J*) are given in Hertz. The multiplicity of signals is designated: s = singlet:, d = doublet, t = triplet, q = quartet, quin = quintet, dt = doublet of triplets, td = triplet of doublets, m = multiplet. Residual solvent peaks are assigned as follows: 7.26 ppm for chloroform, 2.54 ppm for dimethylsulfoxide, 2.05 ppm for acetone.

6.3.2 ^{13}C NMR Spectroscopy

Bruker DPX 600 (150 MHz), Bruker DPX 500 (125 MHz), Bruker DPX 400 (100 MHz), Bruker DPX 250 (62.5 MHz) The chemical shifts δ are given in ppm downfield of tetramethylsilane (δ = 0 ppm). Compounds and crude reaction mixtures are dissolved in either deuterated chloroform, deuterated acetone or deuterated dimethylsulfoxide. Residual solvent peaks are assigned as follows: 77.36 ppm for chloroform, 40.45 ppm for dimethylsulfoxide, 29.84 ppm and 206.26 ppm for acetone.

6.3.3 Mass Spectrometry

Swansea: LTQ Orbitrap XL or Cardiff: Water LCR Premier XE-tof.

Mass spectrometric measurements have been performed by the EPSRC Mass Spectrometry Service Centre, Swansea University or by R. Jenkins/R. Hick at Cardiff University. Ions were generated by the atmospheric pressure ionisation techniques voltage applied corana discharge pin (APCI), Electrospray (ES) or Electron Ionisation (EI). Mass fragments usually are in atomic mass units per elementary charges (m/z) with relative abundance of ion in percentage (%). The high resolution mass spectrometry (HRMS) for most of the compounds was carried out at EPSRC Mass Spectrometry Service Centre, Swansea University. The molecular ion peaks values quoted for either molecular ion (M^+), molecular ion plus hydrogen ($M+H^+$) or molecular ion peaks plus ammonium ion ($M+NH_4^+$) or molecular ion plus sodium ($M+Na^+$).

6.3.4 IR Spectroscopy

IR spectra were recorded on either a Perkin Elmer 1600 series FTIR or a PC supported JASCO FT/IR 660 plus with "Spectra Manager for Windows 95/NT", Version 1.53.01 from JASCO Cooperation. Wavenumbers are quoted in cm^{-1}. Crystalline compounds were measured as KBr disk, non-crystalline samples were measured as neat film between NaCl disks.

6.3.5 Melting Points

Melting Points were measured using a Gallenkamp variable heater with samples in open capillary tubes. All melting points are uncorrected.

6.3.6 Optical Rotation

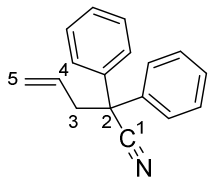
The optical rotation of compounds was measured at 20 °C in cuvettes of 50 mm length with an AA-1000 Polarimeter from Optical Activity LTD.

6.3.7 X-Ray Crystallography

Bruker CCD diffractometer with graphite-monochromatised Mo-K_α radiation (λ = 0.71073 Å). X-Ray crystallographic studies were carried out at the X-Ray Crystallography Service at Cardiff University. The structures were solved by direct methods and refined using the SHELXTL software package. In general, all non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned at idealized locations. The structure was solved by a direct method and refined by a fullmatrix least-squares procedure on F2 for all reflections (SHELXL-97).

6.4 Experimental for Oxyamination Reactions

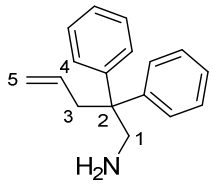
2,2-Diphenylpent-4-enenitrile (**134**)



134

A solution of diphenylacetonitrile (10 g, 51.8 mmol) in dry THF (25 mL) was added slowly to a suspension of NaH (60% dispersion in mineral oil) (3.26 g, 81.5 mmol) in THF (75 mL) which was prewashed with petroleum ether (3 × 10 mL) and the resulting mixture was stirred at room temperature for 1 h. The resulting bright yellow suspension was cooled to 0 °C, treated with allyl bromide (5.29 mL, 67.3 mmol), and warmed to room temperature overnight with stirring. The resulting solution was poured into an ice/water mixture (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined dichloromethane extracts were washed with water (2 × 50 mL), dried over $MgSO_4$, and concentrated to give **134** 2,2-diphenyl-4-pentenenitrile (9.39 g, 78%), which was used in the subsequent step without further purification. The NMR data is in agreement with the literature.[1] Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.07 (dt, *J* = 7.0, 1.1 Hz, 2H, H-3), 5.10 (d, *J* = 10.2, 1H, H-5), 5.14 (d, *J* = 17.0 Hz, 1H, H-5), 5.64 (m, 1H, H-4), 7.27 (m, 10H, Ar-H).

2,2-Diphenylpent-4-en-1-amine (**135**)



135

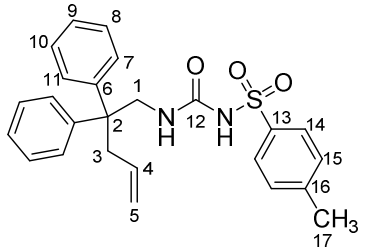
A suspension of $LiAlH_4$ (3.66 g, 96.4 mmol) in dry diethylether (75 mL) was treated with **134** (9.0 g, 38.6 mmol) at 0 °C and then warmed slowly to room temperature and stirred overnight. The resulting suspension was cooled to 0 °C and quenched by slow addition of water dropwise (5.0 mL) and then it was washed with diethylether (3 × 50 mL). The resulting mixture was filtered and the filterate was dried ($MgSO_4$) and concentrated to give 2,2-diphenyl-4-pentenylamine **135** (5.49 g, 60%) as a pale yellow viscous oil. The spectroscopic data are in agreement with the literature.[1] Yellow oil, ^{1}H

NMR (250 MHz, $CDCl_3$): δ = 0.78 (br, 2H, N-H), 2.85 (d, *J* = 7.0 Hz, 2H, H-3), 3.25 (s, 2H, H-1), 4.88-4.96 (m, 2H, H-5), 5.37 (ddt, *J* = 7.0, 9.9, 17.1 Hz, 1H, H-4), 7.07-7.25 (m, 10H, Ar-H) ppm.

General procedure 1 for reactions with isocyanates

To the corresponding amine (1 equiv) in dry CH_2Cl_2 under argon at 0 °C was added the tosyl isocyanate (1.1 equiv). The reaction was warmed to room temperature and stirred while monitoring the consumption of the amine by TLC (12 h). 1 N HCl was added to the reaction, the mixture was stirred, and the layers were separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude products were purified by using flash chromatography on silica gel (ethyl acetate/hexane 0.5:1).

1-(2,2-Diphenylpent-4-enyl)-3-tosylurea (**136**)



136

The product was obtained in 78% yield. The spectroscopic data are in agreement with the literature.[2]

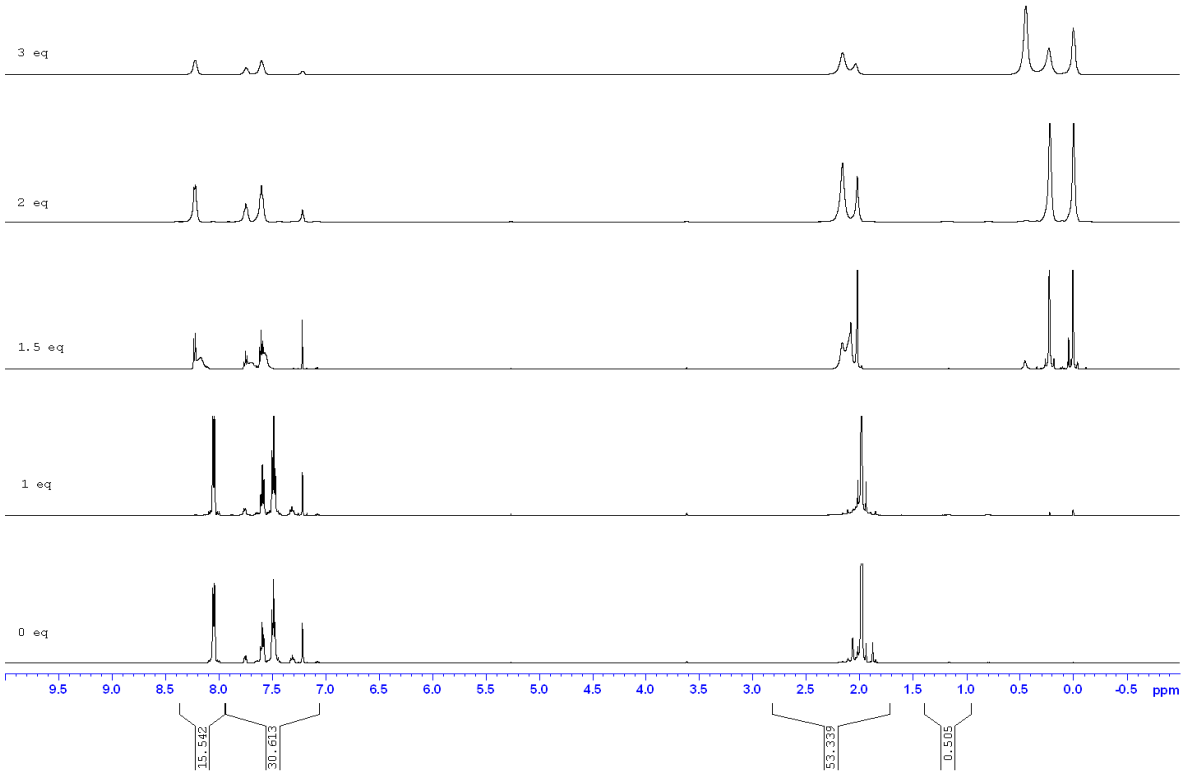
Colourless solid, m.p. 114-115 ºC (Lit. m.p 114-115 ºC)[2] ; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34 (s, 3H, H-17), 2.74 (d, *J* = 7.1 Hz, 2H, H-3), 3.83 (d, *J* = 5.2 Hz, 2H, H-1), 4.84 (d, *J* = 18.0 Hz, 1H, H-5), 4.87 (d, *J* = 10.1 Hz, 1H, H-5), 5.26 (ddt, *J* = 7.1, 10.2, 17.2 Hz, 1H, H-4), 6.21 (br, 1H, N-H), 7.07-7.33 (m, 14H, H-7,8,9,10,11,14 and 15), 8.53 (br, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.6 (C-17), 41.9 (C-3), 47.1 (C-2), 49.6 (C-1), 118.8 (C-5), 126.7 (2C), 126.8 (2C), 127.9 (4C), 128.4 (4C), 129.8 (2C), 133.4 (C-4), 133.6 (C-16), 144.6 (C-13), 144.9 (2C, C-6), 151.6 (C-12) ppm.

Synthesis of [bis(trifluoromethylsulfonyl)iodo]benzene

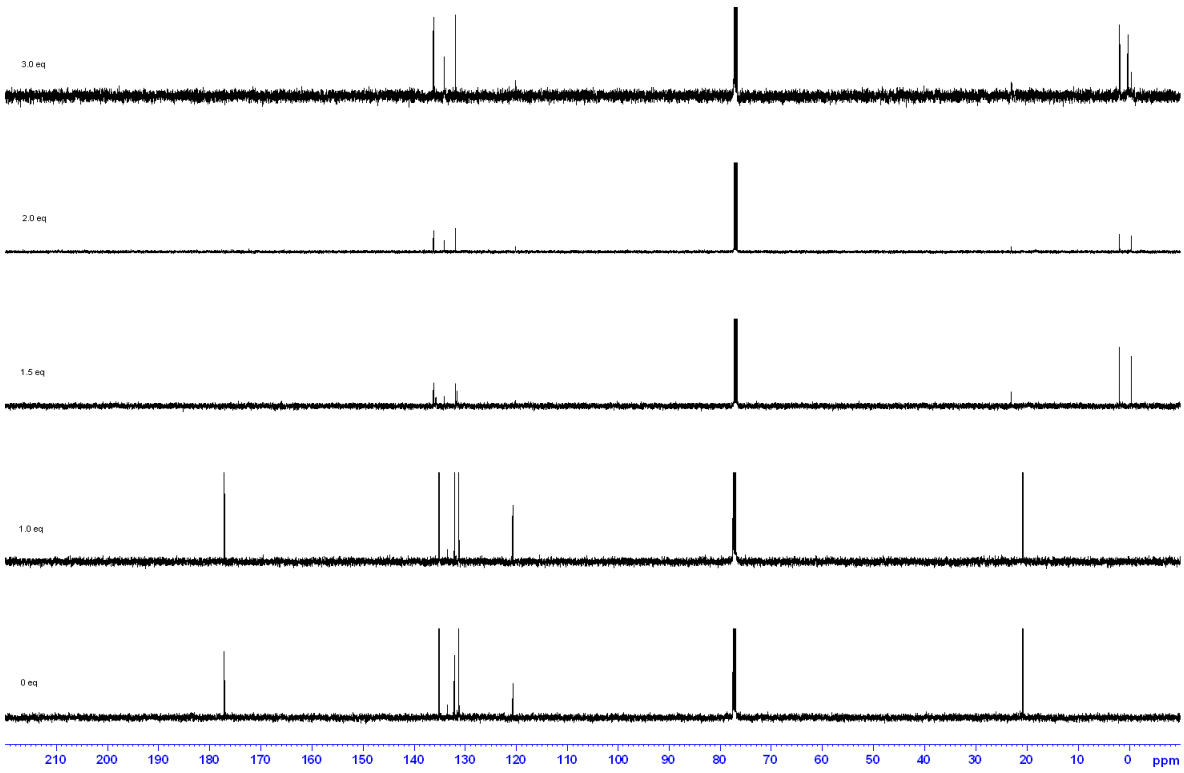
In a NMR tube containing (diacetoxyiodo)benzene (15 mg, 0.047 mmol) in $CDCl_3$ (0.6 mL), a solution of 0.62 M trimethylsilyl triflate (1 equiv., 84 µL, 0.047 mmol in 76 µL $CDCl_3$) was added at –40 ºC. The NMR spectra shown below were also taken at at –40

ºC and clearly indicate the formation of [bis(trifluoromethylsulfonyl)iodo]benzene, $PhI(OTf)_2$, through exchange of both acetate groups with triflate moieties after addition of 2 equivalents (or more) of trimethylsilyl triflate. ^1H NMR (500 MHz, $CDCl_3$, –40 ºC): δ = 7.60 (br s, 2H), 7.74 (br s, 1H), 8.20-8.24 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$, –40 ºC): δ = 118.3, 130.1 (2C), 132.3, 134.4 (2C); CF_3 groups not visible.

^{1}H NMR (500 MHz, $CDCl_3$, –40 ºC): $PhI(OAc)_2$ + n eq. TMSOTf



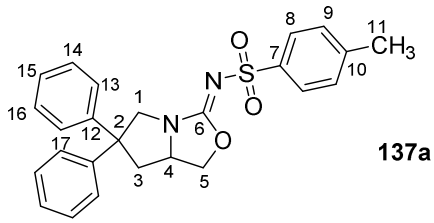
^{13}C NMR (126 MHz, $CDCl_3$, –40 ºC): $PhI(OAc)_2$ + n eq. TMSOTf



General Procedure 2 for initial cyclizations to 137a and 137b (Table 3.1)

To the substrate **136** (50 mg, 0.1 mmol) in dry CH_2Cl_2 (3.0 mL) under argon, added the reagents given in the table 3.1. The mixture was stirred at the given temperature and the progress of reaction was monitored bt using TLC. The reaction was quenched with sat. $NaHCO_3$ (3.0 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated to give the crude products **137a** and **137b** which were isolated by using flash chromatography on silica gel (ethyl acetate/hexane 0.5:1).

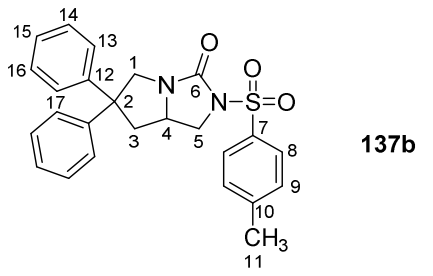
N-(6,6-Diphenyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-ylidene)-4 methylbenzene-sulfonamide (**137a**)



137a

The spectroscopic data are in agreement with the literature.[2] Colourless solid, m.p. 88 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.33 (s, 3H, H-11), 2.32-2.36 (m, 1H, H-3), 2.52 (dd, *J* = 5.2, 11.7 Hz, 1H, H-3), 3.82 (d, *J* = 11.6 Hz, 1H, H-1), 4.05-4.12 (m, 1H, H-4), 4.24 (d, *J* = 11.6 Hz, 1H, H-1), 4.29 (dd, *J* = 7.3, 8.8 Hz, 1H, H-5), 4.64 (t, *J* = 8.8 Hz, 1H, H-5), 7.07-7.23 (m, 12H, Ar-H), 7.78 (d, *J* = 8.2 Hz, 2H, H-8) ppm; HRMS: [M+H$^+$] calcd. for $C_{25}H_{24}N_2O_3S$: 433.1580; found: 433.1573.

6,6-Diphenyl-2-tosyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (**137b**)



137b

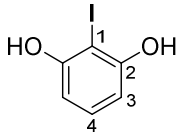
The spectroscopic data are in agreement with the literature.[2] Colourless solid, m.p. 148 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.17 (dd, *J* = 9.9, 11.7 Hz, 1H, H-3), 2.37 (s, 1H, H-11), 2.48 (dd, *J* = 5.2, 11.9 Hz, 1H, H-3), 3.56 (dd, *J* = 5.3, 9.5 Hz, 1H, H-1), 3.78 (d,

J = 12 Hz, 1H, H-1), 3.81-3.87 (m, 1H, H-4), 3.99 (d, *J* = 12 Hz, 1H, H-5), 3.99 (t, *J* = 9 Hz, 1H, H-5), 7.02-7.25 (m, 12H, Ar-H), 7.82 (d, *J* = 8.2 Hz, 2H, H-8) ppm.

Synthesis of chiral hypervalent iodine reagents

The compound **138** was prepared according to literature procedure from resorcinol in the presence of $NaHCO_3$ in 68% yield.[3]

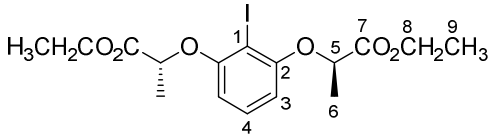
2-Iodobenzene-1,3-diol (**138**)



138

Colourless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.32 (d, *J* = 8.0 Hz, 2H, H-3), 6.91 (t, *J* = 8.0 Hz, 1H, H-4), 10.1 (s, 2H, O-H) ppm.

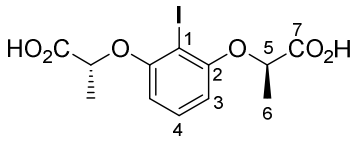
(2*R*,2'*R*)-Diethyl 2,2'-(2-iodo-1,3-phenylene)bis(oxy)dipropanoate (**139**)



139

To a solution of 2-iodoresorcinol **138** (2.36 g, 10.0 mmol), PPh_3 (6.56 g, 25.0 mmol) and (–)-lactic acid ethylester (2.80 mL, 25.0 mmol) in THF (50 mL) was added slowly diisopropyl azodicarboxylate (DIAD, 1.9 M in toluene, 25.0 mmol, 13.2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature. After stirring for overnight, the resulting mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: hexane-EtOAc = 15:1) to give **139** (2.70 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 6H, H-9), 1.68 (d, *J* = 6.8 Hz, 6H, H-6), 4.19 (dq, *J* = 1.7, 7.1 Hz, 4H, H-8), 4.75 (q, *J* = 6.8 Hz, 2H, H-5), 6.38 (d, *J* = 8.3 Hz, 2H, H-3), 7.14 (t, *J* = 8.3 Hz, 1H, H-4) ppm.

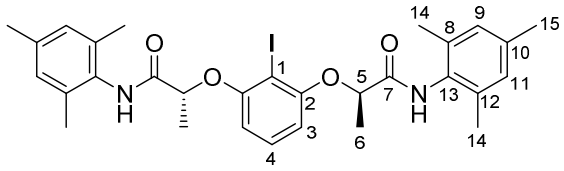
(2*R*,2'*R*)-2,2'-(2-Iodo-1,3-phenylene)bis(oxy)dipropanoic acid (**140**)



140

To a solution of **139** (2.70 g, 6.2 mmol) in THF (20 mL) and MeOH (20 mL) was added 2 N NaOH (20 mL) and stirred overnight at room temperature. The reaction mixture was cooled to 0 °C, quenched with 1N HCl (till it is acidic) and extracted with EtOAc (3 × 25 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed in vacuo to give pure **140** (2.35 g, 6.2 mmol) in 99% yield. White solid ^{1}H NMR (400 MHz, d_6-DMSO): δ = 1.55 (d, *J* = 6.8 Hz, 6H, H-6), 3.33 (s, 2H, COO-H), 4.86 (q, *J* = 6.8 Hz, 2H, H-5), 6.42 (d, *J* = 8.4 Hz, 2H, H-3), 7.22 (t, *J* = 8.3 Hz, 1H, H-4) ppm.

(2*R*,2'*R*)-2,2'-(2-Iodo-1,3-phenylene)bis(oxy)bis(N mesitylpropanamide) (**141**)



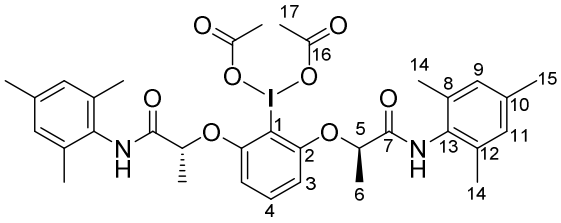
141

A solution of **140** (2.0 g, 5.26 mmol) in $SOCl_2$ (6.0 mL) was refluxed for 1 h. To the resulting mixture was added benzene (2 × 5 mL), and excess reagents were removed in vacuo. The residue was dissolved in dry CH_2Cl_2 (25 mL), and to the resulting mixture was added mesityl aniline (1.26 mL, 11.6 mmol) with cooling (0 °C). The resulting mixture was stirred at 0 °C for 2 h, and gradually warmed to room temperature. After stirring for overnight, the reaction mixture was poured into 1N HCl and extracted with $CHCl_3$ (2 × 25 mL). The organic layers were dried over anhydrous $MgSO_4$ and the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: chloroform-EtOAc = 4:1) to give **141** (2.84 g, 4.62 mmol) in 88% yield. White solid ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (d, *J* = 6.6 Hz, 6H, H-6), 2.15 (s, 12H, H-14), 2.27 (s, 6H, H-15), 5.01 (q, *J* = 6.6 Hz, 2H, H-5), 6.65 (d, *J* = 8.3 Hz, 2H, H-3), 6.90 (s, 4H, H-9 and 11), 7.35 (t, *J* = 8.3 Hz, 1H, H-4), 8.01 (s, 2H, N-H) ppm. HPLC; Chiracel OD-H, hexane:2-propanol (7:3), flow rate: 0.5 ml • min^{-1}, t_r (13.8 min, 232 nm), 99% *ee*.

General procedure 3 for the oxidation of aryl iodides to the hypervalent compounds

A solution of the aryl iodide (0.1 mmol) and 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) [Selectfluor®] (177 mg, 0.5 mmol) in AcOH (1 mL) and CH_3CN (3.2 mL) was stirred overnight at room temperature. The solvent was evaporated in vacuo and water (50 mL) was added to the residue, the resulting solution was extracted with CH_2Cl_2 (3 × 25 mL) and washed with water (25 mL). The combined organic layers were dried over $MgSO_4$. The solvents were removed in vacuo to give the hypervalent compounds.

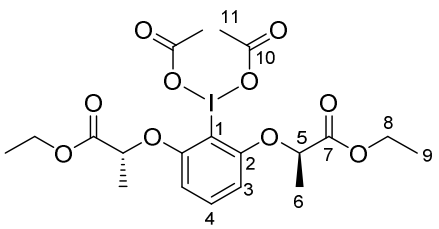
(2*R*,2'*R*)-2,2'-{[2-(Diacetoxy)iodo-1,3-phenylene]bis(oxy)}bis(*N*-mesitylpropanamide) (**142**)



142

Colourless solid, m.p. 119 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 6H, H-17), 1.77 (br, 12H, H-14), 1.81 (d, *J* = 6.7 Hz, 6H, H-6), 2.14 (s, 6H, H-15), 5.06 (q, *J* = 6.7 Hz, 2H, H-5), 6.72 (s, 4H, H-9 and 11), 6.85 (d, *J* = 8.5 Hz, 2H, H-3), 7.50 (t, *J* = 8.4 Hz, 1H, H-4), 8.28 (s, 2H, N-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 16.8 (4C, C-14), 17.1 (2C, C-17), 19.5 (2C, C-6), 19.9 (2C, C-15), 79.5 (2C, C-5), 106.1 (2C, C-3), 128.0, 128.7, 128.9, 129.0, 129.7 (C-13), 134.1, 136.3 (C-4), 156.0 (2C, C-2), 168.8 (C-7), 174.0 (C-16) ppm.

(2*R*,2'*R*)-Diethyl 2,2'-{[2-(diacetoxy)iodo-1,3-phenylene]bis(oxy)}dipropanoate (**144**)

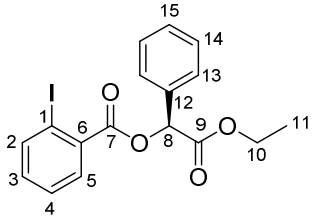


144

$[\alpha]_D^{25}$ = –41.6 (*c* = 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.2 Hz, 6H, H-9), 1.61 (d, *J* = 6.8 Hz, 6H, H-6), 1.91 (s, 6H, H-11), 4.14 (q, *J* = 7.2 Hz, 4H, H-

8), 4.77 (q, *J* = 6.8 Hz, 2H, H-5), 6.50 (d, *J* = 8.4 Hz, 2H, H-3), 7.32 (t, *J* = 8.4 Hz, 1H, H-4) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (2C, C-9), 19.0 (2C, C-6), 20.9 (2C, C-11), 62.0 (2C, C-8), 74.9 (2C, C-5), 106.5 (2C, C-3), 107.3 (C-1), 135.5, 157.1 (2C), 171.3 (2C, C-7), 177.4 (2C, C-10) ppm.

(*S*)-2-Ethoxy-2-oxo-1-phenylethyl 2-iodobenzoate (**145**)

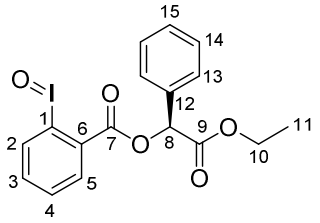


145

To a solution of 2-iodobenzoic acid (1.0 g, 4.03 mmol), PPh_3 (1.32 g, 5.04 mmol) and (*R*)-(–)-mandelic acid ethylester (0.91 g, 5.04 mmol) in THF (50 mL), diisopropyl azodicarboxylate (DIAD, 2 M in toluene, 10 mmol, 5 mL) was added slowly at 0 °C. The reaction mixture was warmed up to room temperature and stirred overnight. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography on silica gel (ethyl acetate/hexane 1:15) to give **145** (1.43 g, 3.49 mmol) in 87% yield.

$[\alpha]_D^{25}$ = 19.5 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 7.2 Hz, 3H, H-11), 4.09-4.20 (m, 2H, H-10), 6.08 (s, 1H, H-8), 7. 09 (ddd, *J* = 7.9, 7.5, 1.7 Hz, 1H, Ar-H), 7.33 (m, 4H, Ar-H), 7.50 (m, 2H, Ar-H), 7.92 (d, *J* = 7.9 Hz, 1H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (C-11), 62.3 (C-10), 74.8 (C-8), 94.9 (C-1), 128.2 (2C, Ar-C), 128.4 (Ar-C), 129.3 (2C, Ar-C), 129.8 (Ar-C), 132.1 (Ar-C), 133.6 (Ar-C), 134.0 (Ar-C), 134.1 (Ar-C), 141.9 (C-2), 166.0 (C-7), 169.0 (C-9) ppm; IR (KBr): 3065, 2981, 1732, 1583, 1465, 1246, 1212, 1099, 1013, 738 cm^{-1}; HRMS: [M+ NH_4^+] calcd. for $C_{17}H_{15}IO_4 \bullet NH_4^+$: 428.0353; found: 428.0352.

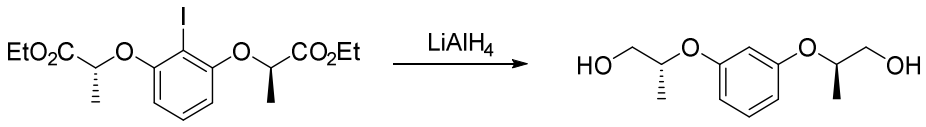
(*S*)-2-Ethoxy-2-oxo-1-phenylethyl 2-iodosylbenzoate (**146**)



146

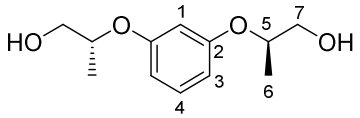
Synthesized from the general procedure of oxidation reaction.[1]H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 3H, H-11), 4.16-4.30 (m, 2H, H-10), 6.26 (s, 1H, H-8), 7.44 (m, 3H, Ar-H), 7.53 (m, 2H, Ar-H), 7.66 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.91 (t, *J* = 7.5 Hz, 1H, Ar-H), 8.21 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.41 (t, *J* = 7.5 Hz, 1H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.0 (C-11), 62.3 (C-10), 125.2 (Ar-C), 125.9 (Ar-C), 127.9 (2C, Ar-C), 129.0 (Ar-C), 129.7 (2C, Ar-C), 131.0 (Ar-C), 132.5 (Ar-C), 133.0 (Ar-C), 135.7 (Ar-C), 149.1 (Ar-C), 167.2 (C-7), 167.6 (C-9) ppm. IR (KBr): 1734, 1685, 1291, 1212, 1098, 1016, 913, 743 cm^{-1}.

(2*R*,2'*R*)-2,2'-(1,3-phenylenebis(oxy))bis(propan-1-ol) (**139a)**



139 **139a**

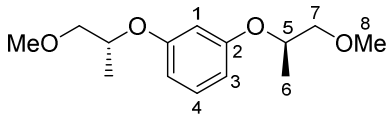
A suspension of $LiAlH_4$ (3.9 g, 10.3 mmol) in dry diethylether (30 mL) was treated with **139** (1.5 g, 3.4 mmol) at 0 °C and then warmed slowly to room temperature and stirred for 30 min. The resulting suspension was cooled to 0 °C and quenched by slow addition of water dropwise (5.0 mL) then it was washed with diethylether (3 × 25 mL). The resulting mixture was filtered and the filterate was dried ($MgSO_4$) and concentrated to give **139a** (0.62 g, 81%) as a viscous oil.



139a

[1]H NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.2 Hz, 6H, H-6), 2.61 (s, 2H, O-H), 3.64-3.68 (m, 4H, H-7), 4.39-4.67 (m, 2H, H-5), 6.50-6.52 (m, 3H, Ar-H), 7.11-7.16 (m, 1H, Ar-H) ppm.

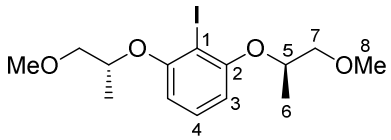
1,3-bis{[(*R*)-1-methoxypropan-2-yl]oxy}benzene (**147**)



147

A solution of **139a** (0.48 g, 2.1mmol) in THF (5 mL) was added slowly to a suspension of NaH (0.17 g, 4.2 mmol) in THF (15 mL) and the resulting mixture was stirred at room temperature for 1 h. The resulting suspension was cooled to 0 °C, treated with methyl iodide (0.26 mL, 4.2 mmol), and warmed to room temperature overnight with stirring. The resulting solution was poured into an ice/water mixture (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined dichloromethane extracts were washed with water (2 × 5 mL), dried ($MgSO_4$), and concentrated to give **147** (0.46 g, 93%), which was used in the subsequent step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30 (d, *J* = 6.3 Hz, 6H, H-6), 3.40 (s, 6H, H-8), 3.47 (dd, *J* = 4.5, 10.1 Hz, 2H, H-7), 3.57 (dd, *J* = 5.7, 10.1 Hz, 2H, H-7), 4.47-4.54 (m, 2H, H-5), 6.51-6.53 (m, 3H, Ar-H), 7.14 (t, *J* = 8.3 Hz, 1H, H-4) ppm.

2-Iodo-1,3-bis{[(*R*)-1-methoxypropan-2-yl]oxy}benzene (**148**)



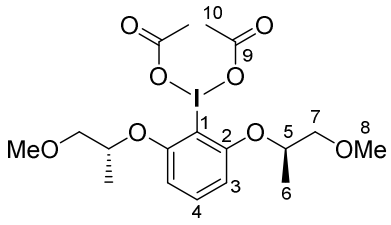
148

To a solution of **147** (660 mg, 2.6 mmol) in dry THF (25 mL), *n*-butyllithium (1.06 mL, 2.5 M solution in hexane, 2.65 mmol) was added slowly at 0 ºC. The mixture was stirred for 30 min at this temperature. At –78 ºC a solution of iodine (762 mg, 3 mmol) in THF (5 mL) was added with stirring. After 10 min at room temperature the mixture was quenched with sat aqueous $Na_2S_2O_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed in vacuo. After column chromatography (hexane/ethyl acetate 10:1) compound **148** was isolated as yellow oil in 93% yield (919 mg, 2.42 mmol).

$[\alpha]_D^{25}$ = –46.5 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.3 Hz, 6H, H-6), 3.46 (s, 6H, H-8), 3.55 (dd, *J* = 4.8, 10.3 Hz, 2H, H-7), 3.68 (dd, *J* = 5.9, 10.3 Hz, 2H, H-7), 4.55 (m, 2H, H-5), 6.56 (d, *J* = 8.3 Hz, 2H, H-3), 7.20 (t, *J* = 8.2 Hz, 1H, H-4) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2 (2C, C-6), 59.6 (2C, C-8), 75.4 (2C,

C-7), 75.9 (2C, C-5), 82.9 (C-1), 107.6 (2C, C-3), 129.4 (C-4), 158.5 (2C, C-2) ppm; HRMS: [M+NH_4^+] calcd. for $C_{14}H_{21}IO_4 \bullet NH_4$: 398.0823; found: 398.0822.

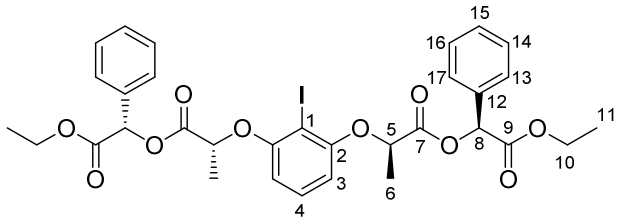
2-(Diacetoxy)iodo-1,3-bis{[(*R*)-1-methoxypropan-2-yl]oxy}benzene (**149**)



149

Synthesized from the general procedure of oxidation reaction. Not complete conversion, some starting material **148** present. $[\alpha]_D^{25}$ = –27.1 (*c* = 1.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.4 Hz, 6H, H-6), 1.88 (s, 6H, H-10), 3.33 (s, 6H, H-8), 3.44 (dd, *J* = 4.7, 10.3 Hz, 2H, H-7), 3.57 (dd, *J* = 6.1, 10.3 Hz, 2H, H-7), 4.61 (m, 2H, H-5), 6.69 (d, *J* = 8.4 Hz, 2H, H-3), 7.37 (t, *J* = 8.4 Hz, 1H, H-4) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (2C, C-6), 19.5 (2C, C-10), 58.5 (2C, C-8), 74.70 (2C, C-7), 74.74 (2C, C-5), 105.5 (2C, C-3), 106.6 (C-1), 134.1 (C-4), 156.1 (2C, C-2), 175.8 (2C, C-9) ppm; IR (KBr): 1635, 1457, 1218, 1110, 772 cm^{-1}.

(2*R*,2'*R*)-Bis[(*S*)-2-ethoxy-2-oxo-1-phenylethyl] 2,2'-{[2-iodo-1,3-phenylene]bis(oxy)} dipropanoate (**150**)

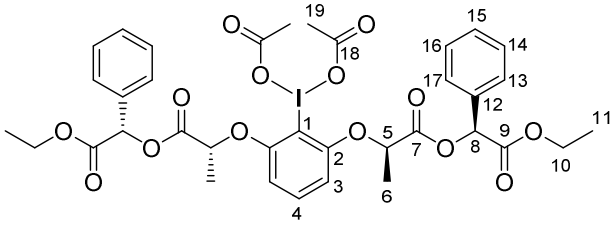


150

To a solution of **140** (500 mg, 1.32 mmol), PPh_3 (863 mg, 3.29 mmol) and (*R*)-(–)-mandelic acid ethyl ester (592 mg, 3.29 mmol) in THF (50 mL), diisopropyl azodicarboxylate (DIAD, 1 M in toluene, 3.3 mmol, 3.3 mL) was added slowly at 0 °C. The reaction mixture was warmed up to room temperature and stirred overnight. The reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane 1:8) to give **150** (670 mg, 0.95 mmol) in 72% yield.

$[\alpha]_D^{25}$ = 26.7 (*c* = 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.0 Hz, 6H, H-11), 1.67 (d, *J* = 7.0 Hz, 6H, H-6), 4.10 (m, 4H, H-10), 4.83 (q, *J* = 6.5 Hz, 2H, H-5), 5.89 (s, 2H, H-8), 6.41 (d, *J* = 8.0 Hz, 2H, H-3), 7.09 (t, *J* = 8.2 Hz, 1H, H-4), 7.30-7.37 (m, 10H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.0 (2C, C-11), 18.5 (2C, C-6), 61.9 (2C, C-10), 73.9 (C-1), 74.9 (2C, C-5), 80.4 (2C, C-8), 107.2 (2C, C-3), 127.5 (4C), 128.7 (4C, Ar-C), 129.2 (2C, Ar-C), 129.7 (Ar-C), 133.4 (2C, Ar-C), 158.1 (2C, C-2), 168.2 (2C, C=O), 170.9 (2C, C=O) ppm; IR (KBr): 2980, 2931, 1744, 1456, 1254, 1180, 1131, 910, 743 cm^{-1}; HRMS: [M+NH_4^+] calcd. for $C_{32}H_{33}IO_{10}$•NH_4: 722.1457; found: 722.1455.

(2*R*,2'*R*)-Bis[(*S*)-2-ethoxy-2-oxo-1-phenylethyl] 2,2'-{[2-(diacetoxy)iodo-1,3phenylene] bis(oxy)} dipropanoate (**151**)



151

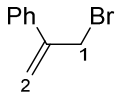
Synthesized from the general procedure of oxidation reaction. $[\alpha]_D^{25}$ = 34.9 (*c* = 1.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.1 Hz, 6H, H-11), 1.65 (d, *J* = 6.9 Hz, 6H, H-6), 1.83 (s, 6H, H-19), 4.06-4.16 (m, 4H, H-10), 4.92 (q, *J* = 6.9 Hz, 2H, H-5), 5.92 (s, 2H, H-8), 6.66 (d, *J* = 6.8 Hz, 2H, H-3), 7.30-7.38 (m, 11H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.0 (C-11), 18.3 (C-6), 20.3 (C-19), 62.0 (C-10), 74.2, 75.0, 106.7 (C-3), 126.5, 127.5, 128.8, 129.3, 133.2, 135.3, 156.4 (C-2), 168.2 (C=O), 170.1 (C=O), 176.9 (C=O) ppm; IR (KBr): 2986, 1746, 1635, 1462, 1255, 1214, 1179, 1132, 1029, 760 cm^{-1}.

General procedure 4 for the stereoselective cyclizations from 136 to 137a (Table 3.2)

To the solution of **136** (50 mg, 0.11 mmol) and chiral hypervalent iodine reagents (0.12 mmol) in the corresponding solvent (3.0 mL), added the Lewis acid (0.12 mmol) at −78 °C. The reaction mixture was stirred at lower temperature for 14 h. The bath was removed and the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL/0.1 mmol alkene), and the layers were separated. The aqueous layer was extracted with

CH_2Cl_2 (2.0 mL/0.1 mmol alkene) and combined with the organic layer, dried over $MgSO_4$, filtered and concentrated in vacuo. The products were purified by chromatography (silica gel, ethyl acetate/hexane 3:5).

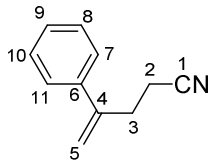
(3-Bromoprop-1-en-2-yl)benzene (**152**)



152

N-Bromosuccinimide (8.90 g, 50.0 mmol) was added to a solution of α-methylstyrene (10.4 mL, 80.0 mmol) in CCl_4 (5 mL), and the mixture was rapidly heated in an oil bath at 170 °C until the solids were dissolved. The reaction mixture was allowed to cool to room temperture and filtered to remove the precipitates. The compound **152** is lachrymator, therefore it was used without purification and isolation.[4] The characteristic peaks for the product **152** using 400 MHz ^{1}H NMR were at 4.38 (s, 2H, H-1), 5.48 (s, 1H, H-2), 5.52 (s, 1H, H-2) ppm.

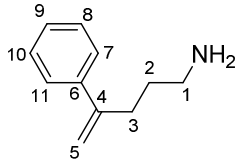
4-Cyano-2-phenyl-1-butene (**154**)



154

α-Lithioacetonitrile,[5] generated by addition of *n*-BuLi (21 mmol, 1.6 M hexane solution) into a solution of acetonitrile (20 mmol) in 30 mL of dry THF at −78 °C followed by stirring at −78 °C for 2 h, was alkylated by treatment with **152** (21 mmol) at −78 °C for 2 h and then was warmed to the room temperature and stirred over night. A mixture of THF-water (5:1, v/v, 4.6 mL) and then 15% aqueous NaOH was added dropwise into the reaction mixture with vigorous stirring and cooling. The aqueous layer was extracted with CH_2Cl_2 (25 mL × 3) and combined with the organic layer, dried over $MgSO_4$, filtered and concentrated in vacuo. The products were purified by chromatography (silica gel, ethyl acetate/hexane 1:15). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.37 (t, *J* = 7.3 Hz, 2H, H-3), 2.77 (t, *J* = 7.3 Hz, 2H, H-2), 5.11 (d, *J* = 0.8 Hz, 1H, H-5), 5.32 (s, 1H, H-5), 7.13-7.28 (m, 5H, Ar-H) ppm.

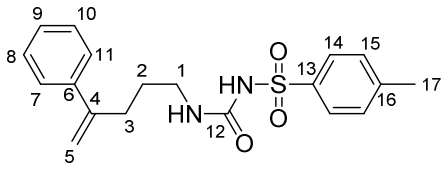
4-Phenylpent-4-en-1-amine (**155**)



155

Synthesized in 87% as a pale yellow viscous oil from **154** by using the reduction procedure for the synthesis of compound **135**. The spectroscopic data are in agreement with the literature. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07-1.15 (m, 2H, N-H), 1.53 (quint, *J* = 7.6 Hz, 2H, H-2), 2.48 (t, *J* = 7.6 Hz, 2H, H-3), 2.64 (t, *J* = 6.8 Hz, 2H, H-1), 5.00 (d, *J* = 1.2 Hz, 1H, H-5), 5.20 (d, *J* = 1.2 Hz, 1H, H-5), 7.19-7.35 (m, 5H, Ar-H) ppm.

4-Methyl-*N*-[(4-phenylpent-4-en-1-yl)carbamoyl]benzenesulfonamide (**156**)

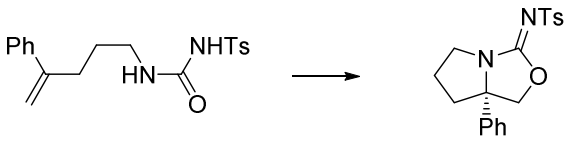


156

Amine **155** was reacted with tosyl isocyanate to yield compound **156** in 84% yield using the general procedure for reactions with isocyanates.

Colourless solid, m.p. 122-124 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (quint, *J* = 7.4 Hz, 2H, H-2), 2.33 (s, 3H, H-17), 2.40 (t, *J* = 7.4 Hz, 2H, H-3), 3.15 (d, *J* = 6.8 Hz, 1H, H-1), 3.18 (d, *J* = 6.8 Hz, 1H, H-1), 4.97 (d, *J* = 1.2 Hz, 1H, H-5), 5.22 (d, *J* = 1.2 Hz, 1H, H-5), 6.52 (m, 1H, N-H), 7.17-7.30 (m, 7H, Ar-H), 7.67 (d, *J* = 8.4 Hz, 2H, H-14), 8.43 (s, 1H, N-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0 (C-17), 28.3 (C-2), 32.7 (C-3), 40.2 (C-1), 113.4 (C-5), 126.5 (2C, Ar-C), 127.3 (2C, Ar-C), 128.0 (Ar-C), 128.8 (2C, Ar-C), 130.4 (2C, Ar-C), 137.0 (C-16), 141.1 (C-13), 145.3 (C-6), 147.6 (C-4), 152.1 (C=O) ppm; IR (KBr): 3328, 2980, 1700, 1657, 1542, 1465, 1347, 1159, 1088, 888 cm^{-1}; HRMS: [M+H$^+$] calcd. for $C_{19}H_{22}N_2O_3S \bullet H^+$: 359.1427; found: 359.1424.

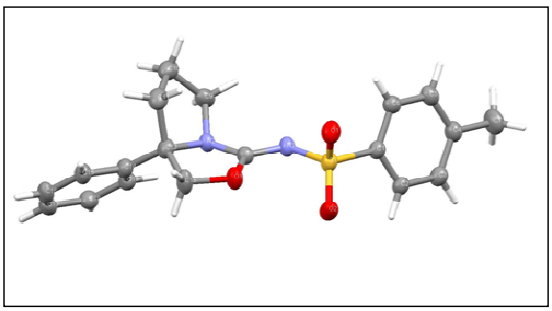
General procedure 5 for cyclizations to 157 (Table 3.3)

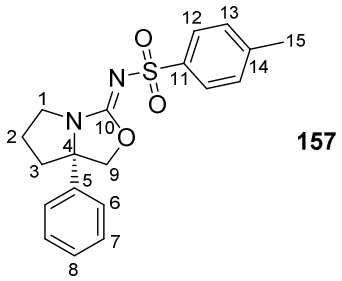


156 **157**

To a solution of the urea-tethered alkene (1 equiv) and the hypervalent iodine compound (1.5 equiv) in the solvent/solvent mixture (2 mL/0.1 mmol alkene) at –78 °C TMSOTf (1.5 or 2.0 equiv) was added slowly. The dry ice/acetone bath was removed and the reaction was allowed to warm to room temperature. The reaction was stirred overnight. The reaction was quenched with sat. aqueous $NaHCO_3$ (2 mL/0.1 mmol alkene), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL/0.1 mmol alkene) and combined with the organic layer, dried over $MgSO_4$, filtered and concentrated in vacuo. The products were purified by chromatography (ethyl acetate/hexane 3:5). Typically, 80-85% of the reduced aryl iodide are isolated without loss of optical purity.

(*S*)-4-Methyl-*N*-(7a-phenyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*) ylidene)benzenesulfonamide (**157**)





157

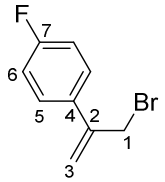
Colourless solid, m.p. 197-199 ºC; $[\alpha]_D^{25}$ = +3.5 (*c* = 1.06, $CHCl_3$) (92% *ee*); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.72 (m, 1H, H-2), 1.90 (dt, *J* = 8.1, 11.8 Hz, 1H, H-2), 2.05 (m, 1H, H-3), 2.33 (s, 3H, H-15), 2.35 (m, 1H, H-3), 3.30 (ddd, *J* = 3.2, 9.6, 11.7 Hz, 1H, H-1), 3.75 (dt, *J* = 8.3, 11.7 Hz, 1H, H-1), 4.35 (d, *J* = 8.9 Hz, 1H, H-9), 4.69 (d, *J* = 8.9 Hz, 1H, H-9), 7.15-7.32 (m, 7H, Ar-H), 7.80 (d, *J* = 8.2 Hz, 2H, H-12) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.5 (C-2), 25.1 (C-15), 37.4 (C-3), 46.8 (C-1), 73.4 (C-4), 79.5 (C-9), 124.6 (2C, Ar-H), 127.0 (2C, Ar-H), 128.3 (Ar-C), 129.1 (2C, Ar-C), 129.2 (2C, Ar-C), 139.9 (C-5), 140.9 (C-14), 142.5 (C-11), 161.6 (C-10) ppm; IR (KBr): 1617,

1420, 1276, 1155, 749 cm^{-1}; HRMS: [M+H^+]; *ee* = 92% ; determined by HPLC analysis: Daicel Chiracel OD-H column (25 cm), hexanes/*i*-PrOH = 50/50, 0.5 mL/min, 232 nm; t_r (major) = 15.1 min, t_r (minor) = 17.2 min.

Procedure for large-scale cyclization of 156 to 157

To a solution of **142** (0.24 mmol, 180 mg) in dry CH_2Cl_2 : Et_2O mixture (1.5 ml : 4.5 mL) TMSOTf (0.49 mmol, 0.088 mL) was added at –78 ºC and stirred for 30 min. Then tosyl amide (0.16 mmol, 28 mg) dissolved in dry CH_2Cl_2 : Et_2O mixture (1.5 ml : 4.5 mL) was added and stirred for 30 min at –78 ºC. The mixture was cooled down to –90 ºC and compound **156** (0.16 mmol, 58 mg), dissolved dry CH_2Cl_2 : Et_2O mixture (1.5 ml : 4.5 mL) was added and stirred for 4 h. After evaporation of the solvents the reaction mixture was subjected (without quenching) to column chromatography (ethyl acetate/hexane 1:2) to obtain compound **157** (0.095 mmol, 34 mg) in 60% yield with 92% *ee*.

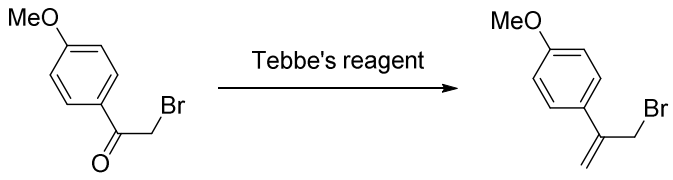
1-(3-Bromoprop-1-en-2-yl)-4-fluorobenzene (**159a**)



159a

It was synthesized similarly as the compound **152** from the bromination of 1-fluoro-4-(prop-1-en-2-yl)benzene. The spectroscopic data are in agreement with the literature.[6] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.25 (s, 2H, H-1), 5.37 (s, 1H, H-3), 5.40 (s, 1H, H-3), 6.90-6.99 (m, 2H, H-5), 7.35-7.39 (m, 2H, H-6) ppm.

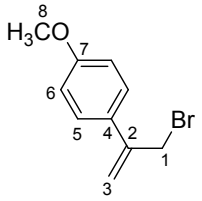
1-(3-Bromoprop-1-en-2-yl)-4-methoxybenzene (**159b**)



159b

It was synthesized from the corresponding ketone by using Tebbe's reagent.[7] The spectroscopic data was in agreement with the literature.[8]

1-(3-Bromoprop-1-en-2-yl)-4-methoxybenzene (**159b**)



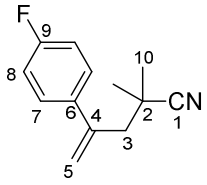
159b

^{1}HNMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3H, H-8), 4.41 (s, 2H, H-1), 5.44 (s, 1H, H-3), 5.52 (s, 1H, H-3), 6.94 (d, *J* = 8.8 Hz, 2H, H-6), 7.48 (d, *J* = 8.8 Hz, 2H, H-5) ppm.

Synthesis of 160a and 160b

To a solution of isobutyronitrile (10mmol) in THF (50 mL) at 0 ºC added freshly prepared LDA (12 mmol)[9] and stirred for 2 hours. Then added the compounds **159a** or **159b** (12 mmol) at 0 ºC and stirred over night at room temperature. Next day the mixture was quenched by using excess amount of water at 0 ºC. After stirring for 10 min, the layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by chromatography (ethyl acetate/hexane 10:1).

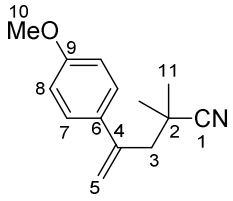
2,2-Dimethyl-4-(4-fluorophenyl)-pent-4-enenitrile (**160a**)



160a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 6H, H-10), 2.76 (s, 2H, H-3), 5.28 (s, 1H, H-5), 5.42 (s, 1H, H-5), 7.05 (t, *J* = 8.6 Hz, 2H, H-8), 7.38 (dd, *J* = 5.6, 8.8 Hz, 2H, H-7) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5 (C-2), 33.4 (2C, C-10), 46.1 (C-3), 115.8 (C-5), 119.1, 124.9, 128.6, 138.0, 143.4 (C-4), 162.9 (d, *J* = 246 Hz, C-9) ppm; IR (KBr): 1979, 1936, 2234, 1602, 1509, 1226, 1161, 842, 748 cm^{-1}; HRMS: [M+H^+] calcd. for $C_{13}H_{14}FN{\bullet}H^+$: 204.1183; found: 204.1182.

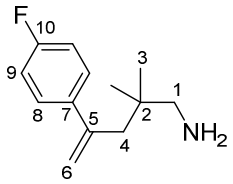
2,2-Dimethyl-4-(4-methoxyphenyl)-pent-4-enenitrile (**160b**)



160b

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s, 6H, H-11), 2.66 (s, 2H, H-3), 3.74 (s, 3H, H-10), 5.12 (s, 1H, H-5), 5.30 (d, *J* = 1.2 Hz, 1H, H-5), 6.80 (d, *J* = 8.7 Hz, 2H, H-8), 7.25 (d, *J* = 8.7 Hz, 2H, H-7) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.1 (C-2), 33.5 (C-11), 45.9 (C-3), 55.8 (C-10), 114.1 (C-5), 117.6, 125.2, 128.0, 134.4, 143.7 (C-4), 159.7 (C-9) ppm; IR (KBr): 2977, 2235, 1680, 1603, 1512, 1466, 1248, 1179, 1032, 835, 772 cm^{-1}; HRMS: [M+H$^+$] calcd. for $C_{14}H_{17}NO•H^+$: 216.1383; found: 216.1385.

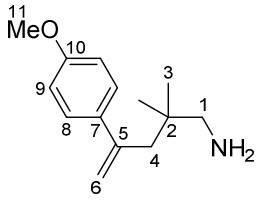
2,2-Dimethyl-4-(4-fluorophenyl)-pent-4-en-1-amine (**161a**)



161a

Synthesized from **160a** using the synthetic procedure as of compound **135**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.73 (s, 6H, H-3), 2.34 (s, 2H, H-4), 2.45 (s, 2H, H-1), 5.02 (s, 1H, H-6), 5.19 (d, *J* = 1.8 Hz, 1H, H-6), 6.98 (t, *J* = 8.6 Hz, 2H, H-9), 7.33 (dd, *J* = 5.4, 8.5 Hz, 2H, H-8) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7 (2C, C-3), 36.4 (C-2), 45.1 (C-4), 53.2 (C-1), 115.5 (t, *J* = 26.1 Hz, 2C, C-9), 117.2 (C-6), 128.4 (2C, C-8), 140.1 (C-7), 146.5 (C-5), 162.5 (d, *J* = 305.5 Hz, C-10) ppm; IR (KBr): 2960, 1624, 1602, 1508, 1224, 841, 749 cm^{-1}; HRMS: [M+H$^+$] calcd. for $C_{13}H_{18}FN•H^+$: 208.1496; found: 208.1493.

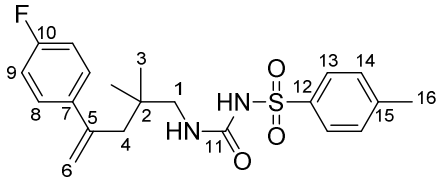
2,2-Dimethyl-4-(4-methoxyphenyl)-pent-4-en-1-amine (**161b**):



161b

Synthesized from **160b** using the synthetic procedure as of compound **135**. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.68 (s, 6H, C-3), 1.25-1.40 (br, 2H, N-H), 2.28 (s, 2H, C-4), 2.37 (s, 2H, C-1), 3.73 (s, 3H, C-11), 4.89 (s, 1H, C-6), 5.11 (d, *J* = 1.9 Hz, 1H, C-6), 6.77 (d, *J* = 8.6 Hz, 2H, H-9), 7.23 (d, *J* = 8.6 Hz, 2H, H-8) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.4 (2C, C-3), 36.0 (C-2), 44.6 (C-4), 52.8 (C-1), 55.2 (C-11), 113.6 (2C, C-9), 115.4 (C-6), 127.5 (2C, C-8), 136.1 (C-7), 146.4 (C-5), 158.9 (C-10) ppm; IR (KBr): 3466, 2957, 1607, 1511, 1465, 1247, 1179, 1034, 835 cm^{-1}; HRMS: [M+H^+] calcd. for $C_{14}H_{21}NO•H^+$: 220.1693; found: 220.1694.

N-{[4-(4-Fluorophenyl)-2,2-dimethylpent-4-en-1-yl]carbamoyl}-4 methylbenzenesulfonamide (**162a**)

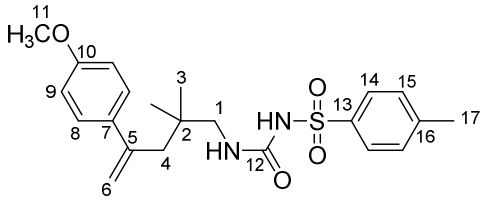


162a

Synthesized from **161a** by using the general procedure **1**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71 (s, 6H, H-3), 2.41 (s, 2H, H-4), 2.44 (s, 3H, H-16), 2.98 (d, *J* = 6.4 Hz, 2H, H-1), 5.01 (s, 1H, H-6), 5.23 (s, 1H, H-6), 6.65 (t, *J* = 6.2 Hz, 1H, N-H), 7.01 (t, *J* = 8.6 Hz, 2H, H-9), 7.27-7.35 (m, 4H, Ar-H), 7.77 (d, *J* = 8.2 Hz, 2H, H-13), 9.37 (s, 1H, N-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.1 (C-16), 25.9 (2C, C-3), 36.1 (C-2), 45.3 (C-4), 50.3 (C-1), 115.7 (d, *J* = 26.4 Hz, 2C, C-9), 117.8 (C-6), 127.2 (2C, Ar-C), 128.4 (d, *J* = 10 Hz, 2C, C-8), 130.4 (2C, Ar-C), 137.2, 139.6, 145.2, 145.6, 152.5 (C=O), 162.6 (d, *J* = 310 Hz, C-10) ppm; IR (KBr): 3446, 1675, 1653, 1507, 1274, 1162, 1091, 764 cm^{-1}; HRMS: [M+H^+] calcd. for $C_{21}H_{25}FN_2O_3S•H^+$: 405.1643; found: 405.1643.

N-{[4-(4-Methoxyphenyl)-2,2-dimethylpent-4-en-1-yl]carbamoyl}-4 methylbenzenesulfonamide (**162b**)

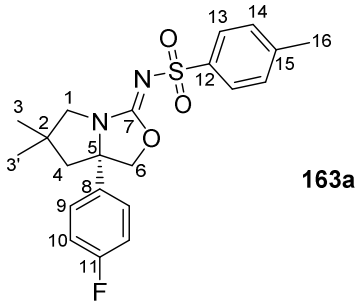


162b

Synthesized from **161b** by using the general procedure **1**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.62 (s, 6H, H-3), 2.31 (s, 2H, H-4), 2.35 (s, 3H, H-17), 2.88 (d, *J* = 6.1 Hz, 2H, H-1), 3.72 (s, 3H, H-11), 4.85 (s, 1H, H-6), 5.12 (d, *J* = 1.2 Hz, 1H, H-6), 6.53 (t, *J* = 5.9 Hz, 1H, N-H), 6.78 (d, *J* = 8.7 Hz, 2H, H-9), 7.21 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.68 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.72 (d, *J* = 8.3 Hz, 2H, H-14), 8.75-8.99 (br, 1H, N-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.7 (C-17), 25.5 (2C, C-3), 35.6 (C-2), 44.8 (C-4), 49.8 (C-1), 55.3 (C-11), 113.8 (2C, C-9), 116.0 (C-6), 126.9 (Ar-C), 127.5 (Ar-C), 129.7 (2C, Ar-C), 130.0 (2C), 135.5, 136.8, 144.8, 145.6, 152.1 (C=O), 159.0 (C-10) ppm; IR (KBr): 3390, 2961, 1668, 1607, 1549, 1511, 1456, 1339, 1247, 1163 cm^{-1}; HRMS: [M+H$^+$] calcd. for $C_{22}H_{29}N_2O_4S•H^+$: 417.1843; found: 417.1842.

(*S*)-*N*-[7a-(4-Fluorophenyl)-6,6-dimethyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-ylidene]-4-methylbenzenesulfonamide (**163a**)

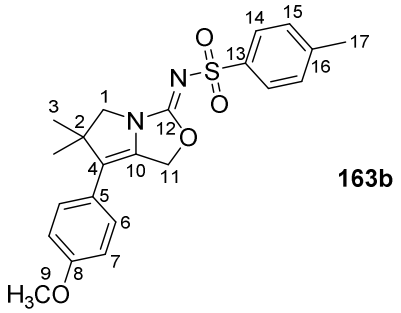


163a

Compound **162a** (0.12 mmol, 50 mg) was cyclized according to the general procedure **5** (Table 3.3, entry 1) to give **163a**. The crude product was purified by chromatography (ethyl acetate/hexane 1:2) to yield **163a** (40 mg, 0.1 mmol, 80%, 61% *ee*) as a colourless solid.

Colorless solid: m.p. 160 ºC (decomp.); $[\alpha]_D^{25}$ = –16.2 (*c* = 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (s, 3H, H-3'), 1.00 (s, 3H, H-3), 2.00 (d, *J* = 13.1 Hz, 1H, H-4), 2.19 (d, *J* = 13.1 Hz, 1H, H-4), 2.34 (s, 3H, H-16), 2.92 (d, *J* = 12.0 Hz, 1H, H-1), 3.69 (d, *J* = 12.0 Hz, 1H, H-1), 4.31 (d, *J* = 8.8 Hz, 1H, H-6), 4.55 (d, *J* = 8.8 Hz, 1H, H-6), 7.00 (t, *J* = 8.6 Hz, 2H, H-9), 7.12-7.20 (m, 4H, Ar-H), 7.81 (d, *J* = 8.3 Hz, 2H, H-13) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (C-16), 27.7 (C-3), 29.1 (C-3'), 42.2 (C-2), 52.8 (C-4), 60.2 (C-1), 72.6 (C-5), 81.5 (C-6), 116.3 (*J* = 21 Hz, 2C, C-10), 126.1 (*J* = 8 Hz, 2C, C-9), 127.0 (2C), 129.1 (2C), 139.6, 142.6, 162.0 (C-11), two carbon missing, ppm; IR (KBr): 2925, 1607, 1508, 1420, 1156, 913, 743 cm^{-1}; HRMS: [M+H^+] calcd. for $C_{21}H_{23}FN_2O_3S•H^+$: 403.1486; found: 403.1486; ee: 61%; determined by HPLC analysis: Chiralcel AD column, hexanes/*i*-PrOH = 90/10, 0.5 mL/min, 232 nm; t_r (minor) = 21.5 min, t_r (major) = 24.4 min.

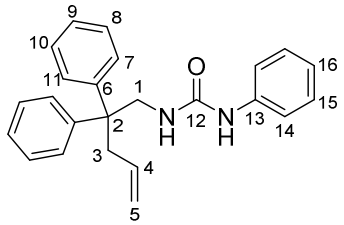
(*Z*)-*N*-(7-(4-Methoxyphenyl)-6,6-dimethyl-5,6-dihydropyrrolo[1,2-c]oxazol-3(1*H*)-ylidene)-4-methylbenzenesulfonamide (**163b**)



163b

To a solution of (diacetoxyiodo)benzene (0.11 mmol, 36 mg) in dry CH_2Cl_2 (2 mL) TBDMSOTf (0.15 mmol, 34 µL) was added at –78 ºC and stirred for 20 min. Then **162b** (0.075 mmol, 31 mg), dissolved in dry CH_2Cl_2 (2 mL) was added, stirred at –78 ºC for 1 h and then subjected to column chromatography (ethyl acetate/hexane 4:3) without quenching to obtain **163b** in 66% yield (0.05 mmol, 21 mg) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 6H, H-3), 2.32 (s, 3H, H-17), 2.65 (s, 2H, H-1), 3.56 (s, 2H, H-11), 3.77 (s, 3H, H-9), 6.85 (d, *J* = 8.9 Hz, 2H, H-7), 7.19-7.24 (m, 4H, Ar-H), 7.81 (d, *J* = 8.3 Hz, 2H, H-6) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.5 (C-17), 27.3 (2C, C-3), 37.4 (C-2), 45.7 (C-1), 55.4 (C-9), 56.5 (C-11), 114.5 (2C, C-7), 119.6 (C-4), 124.9 (2C, Ar-C), 125.5, 127.1 (2C, Ar-C), 129.1 (2C, Ar-C), 136.5 (C-10), 140.0, 142.4, 150.0, 159.4 ppm; IR (KBr): 1623, 1514, 1298, 1252, 1156, 1092, 913 cm^{-1}; HRMS: [M+H^+] calcd. for $C_{22}H_{24}N_2O_4S•H^+$: 413.1530; found: 413.1526.

1-(2,2-Diphenylpent-4-enyl)-3-phenylurea (**164**)

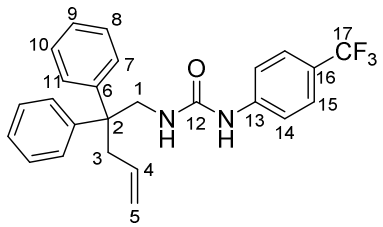


164

The synthesis of **164** was performed by reacting amine **135** (400 mg, 1.7 mmol) with phenyl isocyanate (0.203 ml, 1.87 mmol) similar to the general procedure **1** for reactions with isocyanates. Compound **164** was obtained in 90% yield (545 mg, 1.53 mmol).

The spectroscopic data are in agreement with the literature.[10] Colourless solid, m.p. 148-150 ºC (Lit. 171-172.5 ^{o}C)(10) ; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.79 (d, *J* = 7.05 Hz, 2H, H-3), 3.89 (d, *J* = 5.8 Hz, 2H, H-1), 4.26 (t, *J* = 5.70 Hz, 1H, N-H), 4.88-4.96 (m, 2H, H-5), 5.37 (ddt, *J* = 7.0, 9.9, 17.1 Hz, 1H, H-4), 6.04 (br, 1H, N-H), 7.96-7.25 (m, 15H, Ar-H) ppm.

1-(2,2-Diphenylpent-4-enyl)-3-(4-trifluoromethyl)phenyl)urea (**165**)

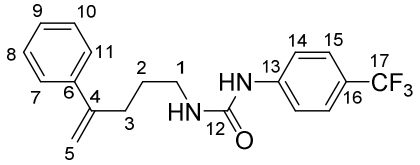


165

The synthesis of **165** was performed by reacting amine **135** (400 mg, 1.7 mmol) with 4-trifluoromethylphenyl isocyanate (0.255 mL, 1.78 mmol) similar to the general procedure **1** for reactions with isocyanates. Compound **165** was obtained in 99% yield (721 mg, 1.7 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.96 (d, *J* = 7.0 Hz, 2H, H-3), 3.98 (d, *J* = 5.7 Hz, 2H, H-1), 4.97-5.05 (m, 2H, H-5), 5.46-5.56 (m, 1H, H-4), 5.75 (t, *J* = 5.7 Hz, N-H), 7.26-7.61 (m, 14H, Ar-H), 9.03 (s, 1H, N-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.3 (C-3), 45.8 (C-2), 50.0 (C-1), 113.4 (C-5), 117.4, 118.6, 123.7, 126.3, 126.4, 126.5, 128.1 (4C), 128.5 (4C), 134.6, 144.4, 146.0 (2C), 155.0 (C=O) ppm.

1-(4-Phenylpent-4-enyl)-3-(4-(trifluoromethyl)phenyl)urea (**166**)

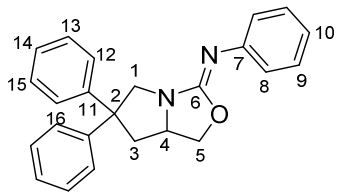


166

The synthesis of **166** was performed by reacting amine **155** (240 mg, 1.48 mmol) with 4-trifluoromethylphenyl isocyanate (0.21 ml, 1.48 mmol) similar to the general procedure **1** for reactions with isocyanates. Compound **166** was obtained in 73% yield (375 mg, 1.07 mmol).

Colourless solid, m.p. 84-86 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55 (quint, *J* = 7.2 Hz, 2H, H-2), 2.42 (t, *J* = 7.4 Hz, 2H, H-3), 3.12 (d, *J* = 6.9 Hz, 1H, H-1), 3.15 (d, *J* = 6.5 Hz, 1H, H-1), 4.92 (s,1H, H-5), 5.17 (s, 1H, H-5), 5.23 (t, *J* = 5.1 Hz, 1H, N-H), 7.17-7.31 (m, 7H, Ar-H), 7.37 (d, *J* = 8.6 Hz, 2H, H-15), 8.21 (s, 1H, N-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7 (C-2), 32.9 (C-3), 40.3 (C-1), 113.4 (C-5), 119.2, 119.4 (2C, Ar-C), 126.7 (2C), 126.8, 128.0, 128.8 (2C), 141.0, 142.3, 147.6 (C-4), 156.1 (C=O); IR (KBr): 3084, 3058, 2941, 1946, 1653, 1603, 1478, 1163, 1067, 1014, 757 cm^{-1}.

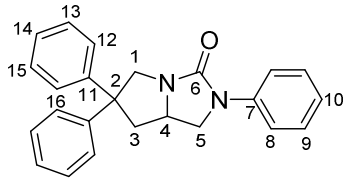
N-(6,6-diphenyltetrahydropyrrolo[1,2-c]oxazol-3(1*H*)-ylidene)aniline **(167a)**



167a

The compound **167a** was synthesized from **164** in the presence of $PhI(OAc)_2$ (1.2 equiv) and TMSOTf (2.0 equiv) in 31% yields. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (dd, *J* = 8.9, 11.9 Hz, 1H, H-3), 2.53 (dd, *J* = 4.8, 11.8 Hz, 1H, H-3), 3.96 (d, *J* = 11.2 Hz, 1H, H-1), 4.0-4.08 (m, 2H, H-5), 4.26 (d, *J* = 11.3 Hz, 1H, H-1), 4.45-4.52 (m, 1H, H-4), 7.00 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.04 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.15-7.26 (m, 9H, Ar-H) ppm.

2,6,6-Triphenyltetrahydro-1*H*-pyrrolo[1,2-c]imidazol-3(2*H*)-one (**167b**)

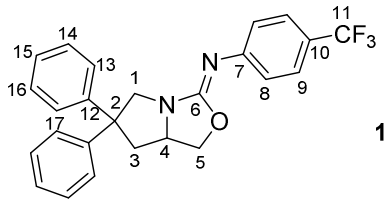


167b

The compound **167b** was synthesized from general procedure **5** for cyclizations of **157** (Table 3.3, entry 1) in 15% yield and 42% *ee* by using CH_3CN as a solvent.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (dd, *J* = 9.1, 11.8 Hz, 1H, H-3), 2.52 (dd, *J* = 4.9, 11.8 Hz, 1H, H-3), 3.98-4.06 (m, 3H), 4.28 (d, *J* = 11.3 Hz, 1H, H-1), 4.42-4.48 (m, 1H, H-4), 6.97 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.15-7.26 (m, 13H, Ar-H) ppm.

N-(6,6-Diphenyltetrahydropyrrolo[1,2-c]oxazol-3(1*H*)-ylidene)aniline (**168**)

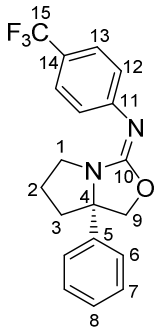


168

The compound **168** was synthesized from general procedure **5** for cyclizations of **157** (Table 3.3, entry 1) in 45% yield and 39% *ee*.

Colourless solid, m.p. 154–156 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.37 (dd, *J* = 9.3, 11.7 Hz, 1H, H-3), 2.53 (dd, *J* = 4.8, 11.8 Hz, 1H, H-3), 3.98-4.10 (m, 3H), 4.27 (d, *J* = 11.1 Hz, 1H, H-1), 4.46-4.50 (m, 1H, H-4), 7.02 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.13-7.27 (m, 10H, Ar-H), 7.40 (d, *J* = 8.1 Hz, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.9 (C-3), 58.7 (C-2), 59.0 (C-1), 59.4 (C-4), 71.5 (C-5), 123.9, 126.1, 127.2 (d, *J* = 3.4 Hz), 127.3 (2C), 127.4 (2C), 129.0 (4C), 129.1 (4C), 145.9 (d, *J* = 33.8 Hz), 151.0 (C-7), 157.5 (C-6). ppm. IR (KBr): 3445, 1674, 1603, 1485, 1395, 1323, 1241, 1159, 1107, 851, 791, 700 cm^{-1}; HRMS: [M+H+] calcd. for $C_{25}H_{21}F_3N_2O$•H+: 423.1679; found: 423.1677.

(*S*)-*N*-(7a-Phenyltetrahydropyrrolo[1,2-c]oxazol-3(1*H*)-ylidene)-4-(trifluoromethyl) aniline (**169**) .

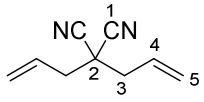


169

The compound **169** was synthesized from procedure **5** for cyclizations of **157** (Table 3.3, entry 1) in 30% yield and 79% *ee*.

Colourless solid, m.p.: 62–64 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65-1.75 (m, 1H, H-2), 1.92 (dd, *J* = 11.4, 19.8 Hz, 1H, H-2), 2.02-2.06 (m, 1H, H-3), 2.33 (dd, *J* = 7.3, 11.3 Hz, 1H, H-3), 3.34-3.36 (m, 1H, H-1), 3.88-3.89 (m, 1H, H-1), 4.22 (d, *J* = 8.5 Hz, 1H, H-9), 4.48 (d, *J* = 8.5 Hz, 1H, H-9), 7.11 (d, *J* = 8.3 Hz, 2H, H-12) 7.25-7.35 (m, 5H, Ar-H), 7.43 (d, *J* = 8.4 Hz, 2H, H-13) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.4 (C-2), 37.3 (C-3), 48.4 (C-1), 77.1 (C-9), 123.6, 124.9, 125.7, 127.8, 129.0, 137.5, 141.0, 142.5, 150.6 (C-10) (2 carbon atoms not appearing due to small amount of compound and coupling to F); IR (KBr): 3465, 1674, 1605, 1322, 1114, 1065, 913, 743 cm–1; HRMS: [M+H+] calcd. for $C_{19}H_{17}F_3N_2O$•H+: 347.1366; found: 347.1368; ee: 79%; determined by HPLC analysis: Chiracel AD column, hexanes/*i*-PrOH = 95/5, 0.5 mL/min, 232 nm; t_r (major) = 3.3 min, t_r (minor) = 4.6 min.

2,2-Diallylmalononitrile (**170**)



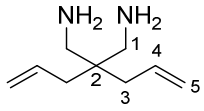
170

In a two neck flask, sodium hydride (5.43 g, 227 mmol) was added and cleaned with petroleum ether under flow of nitrogen. After 10 min, the petroleum ether was removed. Then, dry THF (100 mL) was added and the mixture was stirred vigorously. At 0 °C, malononitrile (3 g, 45.4 mmol) was added and the reaction mixture was stirred for 2 h at room temperature. Then, allyl bromide (9.82 mL, 113.5 mmol) was slowly added at 0 °C and stirring was continued for 4 h at room temperature. The reaction is quenched

with H_2O and extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to provide the crude compound. This compound was made pure by column chromatography on silica gel (Hex:EtOAc/10:1/v:v) to give 3.18 g (21.8 mmol) of the pure product **170** in 85% yield.

Colourless oil, ^{1}H NMR (250MHz, $CDCl_3$): δ = 2.71 (d, *J* = 7.3Hz, 4H, H-3), 5.41-5.50 (m, 4H, H-5), 5.85-6.02 (m, 2H, H-4).

2,2-Diallylpropane-1,3-diamine (**171**)

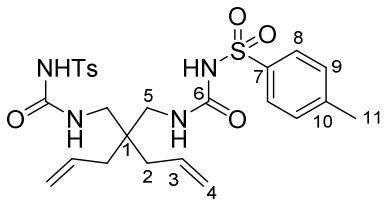


171

Synthesized from general procedure for reduction, using $LiAlH_4$ (4.0 equiv) in 88% yield.

Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (br s, 4H, N-H), 1.96 (d, *J* = 7.5 Hz, 4H, H-3), 2.50 (s, 4H, H-1), 5.03 (m, 4H, H-5), 5.71-5.81 (m, 2H, H-4) ppm.

N,*N*'-{[(2,2-Diallylpropane-1,3-diyl)bis(azanediyl)]bis(carbonyl)}bis(4 methylbenzenesulfonamide) (**172**)



172

To solution of diamine **171** (750 mg, 4.87 mmol) in dry CH_2Cl_2 (8 mL) under argon, tosyl isocyanate (1.77 mL, 10.53 mmol) was added at 0 ºC and the mixture was stirred overnight at room temperature. Then, the reaction mixture was quenched with 1 N HCl (10 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to yield 1.97 g (3.59 mmol, 74%) of the product **172**, which was used without further purification.

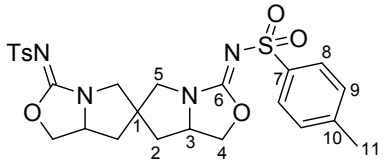
Colourless solid, m.p. = 72-77 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72 (d, *J* = 7.3 Hz, 4H, H-2), 2.32 (s, 6H, H-11), 2.84 (d, *J* = 6.4 Hz, 4H, H-5), 4.98 (m, 4H, H-4), 5.68 (m,

2H, H-3), 6.58 (t, *J* = 6.4 Hz, 2H, N-H), 7.20 (d, *J* = 8.2 Hz, 4H, H-9), 7.72 (d, *J* = 8.3 Hz, 4H, H-8), 9.26 (br, 2H, N-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4 (2C, C-11), 35.7 (C-1), 40.6 (2C, C-2), 42.3 (2C, C-5), 117.6 (2C, C-4), 126.1 (4C, Ar-C), 128.7 (4C, Ar-C), 131.7 (2C), 135.1 (2C), 143.7 (2C, C-7), 151.6 (2C, C-6) ppm; IR (KBr): 3065, 1675, 1539, 1448, 1341, 1162, 1090, 764 cm^{-1}; HRMS: [M+H$^+$] calcd. for $C_{25}H_{32}N_4O_6S_2$•H$^+$: 549.1836; found: 549.1829.

Procedure for the synthesis of racemic 173a and 173b

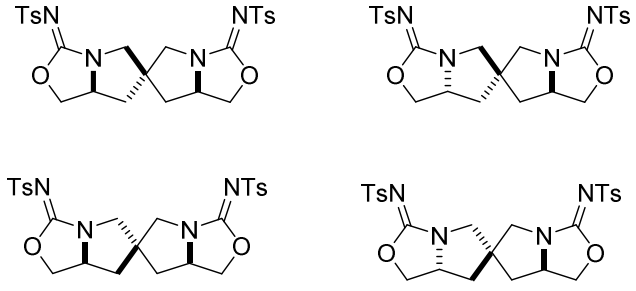
To a solution of **172** (100 mg, 0.18 mmol) and (diacetoxyiodo)benzene (141 mg, 0.44 mmol) in anhydrous CH_2Cl_2 (6 mL) under argon, TMSOTf (79 μL, 0.44 mmol) was added slowly at –78 °C. The mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The reaction mixture was purified by column chromatography on silica gel (hexane:EtOAc:MeOH 3:3:2 v:v:v) to give 8 mg of **173a** (0.015 mmol, 8%), and 32 mg of **173b** (0.059 mmol, 33%).

N,*N*'-(Tetrahydro-1*H*,1'*H*-6,6'-spirobi[pyrrolo[1,2-*c*]oxazol]-3,3'(5*H*,5'*H*)-diylidene)bis(4-methylbenzenesulfonamide) (**173a**)



173a

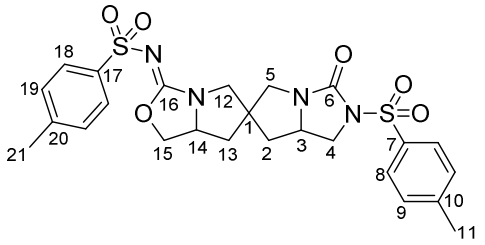
The possible stereoisomers are following,



Colourless solid, m.p. = 96-99 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62 (dd, *J* = 8.6, 13.1 Hz, 2H, H-2), 2.09 (dd, *J* = 6.4, 12.8 Hz, 2H, H-2), 2.34 (s, 6H, H-11), 3.14 (d, *J* = 12 Hz, 2H, H-5), 3.71 (d, *J* = 12 Hz, 2H, H-5), 4.10 (m, 2H, H-3), 4.26 (dd, *J* = 5.9, 9.3

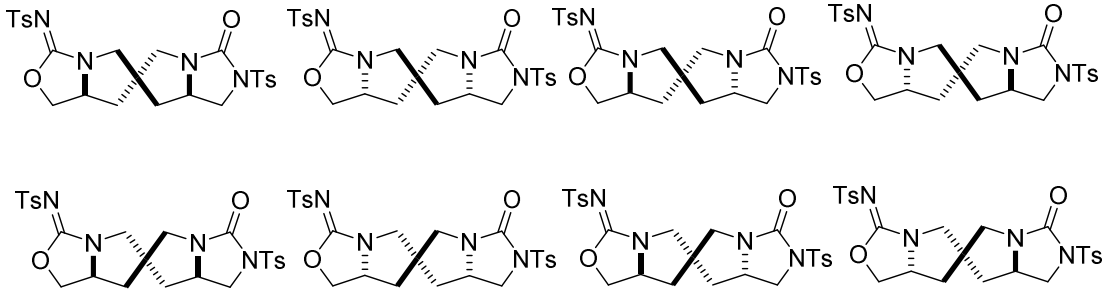
Hz, 2H, H-4), 4.66 (t, *J* = 8.8 Hz, 2H, H-4), 7.19 (d, *J* = 8.2 Hz, 4H, H-9), 7.75 (d, *J* = 8.2 Hz, 4H, H-8) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (2C, C-11), 42.2 (C-1), 57.2 (2C, C-2), 59.1 (2C, C-5), 73.5 (2C, C-3), 77.3 (2C, C-4), 127.1 (4C, Ar-C), 129.2 (4C, Ar-C), 139.1 (2C, C-10), 142.9 (2C, C-7), 161.1 (2C, C-6) ppm; IR (KBr): 2950, 1595, 1436, 1218, 1157, 771 cm^{-1}; HRMS: [M+H$^+$] calcd. for $C_{25}H_{28}N_4O_6S_2$•H$^+$: 545.1523; found: 545.1507.

4-Methyl-*N*-(3-oxo-2-tosyloctahydro-1'*H*-spiro{pyrrolo[1,2-*c*]imidazole-6,6'-pyrrolo[1,2-*c*]oxazol}-3'(5'*H*)-ylidene)benzenesulfonamide (**173b**)



173b

The possible stereoisomers are following,

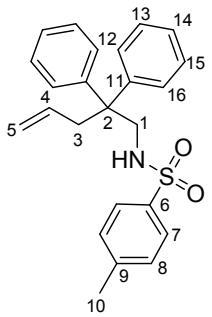


Colourless solid, m.p. = 126-131 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59-1.72 (m, 2H), 1.98 (dd, *J* = 6.0, 12.8 Hz, 1H), 2.11 (dd, *J* = 6.1, 12.5 Hz, 1H), 2.32 (s, 3H), 2.33 (s, 3H), 3.12 (d, *J* = 12.0 Hz, 1H), 3.20 (d, *J* = 11.7 Hz, 1H), 3.53 (t, *J* = 12.1 Hz, 2H), 4.10-4.15 (m, 2H), 4.21-4.23 (m, 1H), 4.33 (dd, *J* = 5.1, 9.2 Hz, 1H), 4.62-4.68 (m, 2H), 7.17-7.19 (m, 4H), 7.72-7.53 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (2C), 29.7, 41.9, 42.6, 54.7, 56.3, 57.4, 59.27, 59.34, 73.2, 73.5, 77.3, 127.0 (4C), 129.25 (2C), 129.28 (2C), 139.2, 139.3, 142.9, 143.0, 160.5, 161.0 ppm; IR (KBr): 2922, 1700, 1594, 1276, 1157, 1082, 749 cm^{-1}; HRMS: [M+H$^+$] calcd. for $C_{25}H_{28}N_4O_6S_2$•H$^+$: 545.1523; found: 545.1514.

Synthesis of **174** and **175**

The compound **174** and **175** were synthesized from known literature procedures from their corresponding amines.[11]

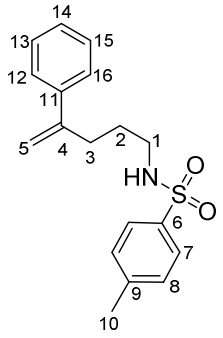
N-(2,2-diphenylpent-4-en-1-yl)-4-methylbenzenesulfonamide (**174**)



174

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3H, H-10), 2.89 (d, *J* = 7.1 Hz, 2H, H-3), 3.51 (d, *J* = 6.4 Hz, 2H, H-1), 3.81 (t, *J* = 6.4 Hz, 1H, N-H), 4.92-4.96 (m, 2H, H-5), 5.20-5.31 (m, 1H, H-4), 7.04-7.06 (m, 4H, Ar-H), 7.19-7.28 (m, 8H, Ar-H), 7.59 (d, *J* = 8.3 Hz, 2H, H-7) ppm.

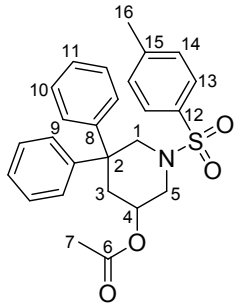
4-Methyl-*N*-(4-phenyl-4-pentenyl)benzenesulfonamide (**175)**



175

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (quint, *J* = 7.2 Hz, 2H, H-2), 2.34 (s, 3H, H-10), 2.42 (t, *J* = 7.2 Hz, 2H, H-3), 2.87 (q, *J* = 6.6 Hz, 2H, H-1), 4.49 (t, *J* = 6.2 Hz, 1H, N-H), 4.92 (d, *J* = 1.2 Hz, 1H, H-5), 5.17 (d, *J* = 1.1 Hz, 1H, H-5), 7.18-7.23 (m, 7H, Ar-H), 7.63 (d, *J* = 8.3 Hz, 2H, H-7) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.5 (C-10), 28.0 (C-2), 32.3 (C-3), 42.8 (C-1), 113.1 (C-5), 126.1 (2C), 127.1 (2C), 127.6, 128.4 (2C), 129.7 (2C), 137.0, 140.6, 143.3, 147.2 (C-4) ppm; HRMS: [M+H^+] calcd. for $C_{18}H_{22}NO_2S•H^+$: 316.1366; found: 316.1367.

3-Acetoxy-5,5-diphenyl-1-tosylpiperidine (**176**)

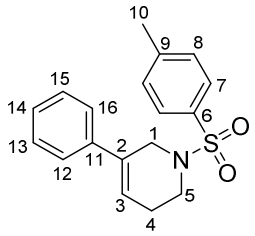


176

Compound **142** (45 mg, 0.061 mmol) and TMSOTf (0.082 mmol, 10 µL) were stirred at –78 ºC for 30 min in dry CH_2Cl_2 (5 mL), before **174** (0.04 mmol, 15 mg) and acetic acid (0.2 mmol, 12 µL) were added. After 20 h at –78 ºC stirring was continued for 4 h at 0 ºC. The reaction mixture was concentrated in vacuo and directly purified by chromatography (ethyl acetate/hexane 2:5). Compound **176** was obtained in 54% yield (0.021 mmol, 10 mg) as colourless solid.

Colourless solid, m.p. 132-133 ºC; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.80 (s, 3H, H-7), 2.09 (dd, *J* = 12.7, 9.9 Hz, 1H, H-3), 2.35 (s, 3H, H-16), 2.41 (t, *J* = 9.3 Hz, 1H, H-3), 2.75 (d, *J* = 12.4 Hz, 2H), 3.62 (dd, *J* = 10.4, 4.3 Hz, 1H), 4.14 (d, *J* = 11.9 Hz, 1H), 4.74 (tt, *J* = 9.4, 4.6 Hz, 1H, H-4), 7.02-7.41 (m, 12H, Ar-H), 7.56 (d, *J* = 8.3 Hz, 2H) ppm; *ee*: 27%; determined by HPLC analysis: Chiracel OD-H column, hexanes/*i*-PrOH = 95/5, 0.5 mL/min, 232 nm; t_r (major) = 37.8 min, t_r (minor) = 41.6 min.

5-Phenyl-1-tosyl-1,2,3,6-tetrahydropyridine (**177a**)



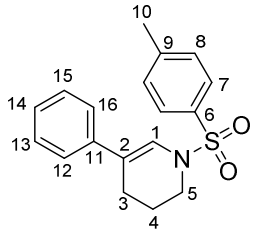
177a

To a solution of (diacetoxyiodo)benzene (0.19 mmol, 61 mg) in dry CH_2Cl_2 (2 mL), TBDMSOTf (0.26 mmol, 0.059 mL) was added at –78 ºC and stirred for 30 min. Then a mixture of **175** (0.13 mmol, 40 mg) and acetic acid (0.37 mmol, 22 µL) in dry CH_2Cl_2 (2 mL) was added and stirred at –78 ºC for 2 h. After warming to room temperature the reaction mixture was subjected to column chromatography (ethyl acetate/hexane 1:10, without any quenching) and the title compound **177a** was obtained in 48% yield (0.063

mmol, 18 mg) as colourless oil. The spectroscopic data are in agreement with the literature.[12]

^{1}HNMR (500 MHz, $CDCl_3$): δ = 2.30-2.33 (m, 2H, H-4), 2.35 (s, 3H, H-10), 3.17 (t, *J* = 5.8 Hz, 2H, H-5), 3.87 (q, *J* = 2.4 Hz, 2H), 5.98-6.01 (m, 1H, H-3), 7.19-7.26 (m, 7H, Ar-H), 7.65 (d, *J* = 8.5 Hz, 2H, H-7) ppm.

5-Phenyl-1-tosyl-1,2,3,4-tetrahydropyridine (**177b**)



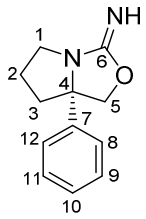
177b

To a solution of (diacetoxyiodo)benzene (0.19 mmol, 61 mg) in dry CH_2Cl_2 (2 mL) BF_3•OEt_2 (0.26 mmol, 0.032 mL) was added at –78 ºC and stirred for 30 min. Then a mixture of **175** (0.13 mmol, 40 mg) and acetic acid (0.64 mmol, 37 µL) in dry CH_2Cl_2 (2 mL) was added and stirred at –78 ºC for 2 h and then at room temperature for another 2 h the reaction mixture was subjected to column chromatography (ethyl acetate/hexane 1:10, without any quenching) and the title compound **177b** was obtained in 42% yield (0.055 mmol, 16 mg) as colourless oil. The spectroscopic data are not described in literature although the synthesis of the compound **177b** has been reported.[13]

^{1}HNMR (500 MHz, $CDCl_3$): δ = 1.70-1.77 (m, 2H, H-4), 2.26 (dt, *J* = 6.3 Hz, 2H, H-3), 2.34 (s, 3H, H-10), 3.34-3.37 (m, 2H, H-5), 7.10 (t, *J* = 1.4 Hz, 1H, H-1), 7.21-7.26 (m, 7H, Ar-H), 7.61 (d, *J* = 8.3 Hz, 2H, H-7) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.0, 21.6, 23.7, 43.5 (C-5), 119.6, 122.2, 124.5 (2C), 126.6, 127.1 (2C), 128.5, 129.9 (2C), 135.0 (2C), 139.7, 143.8 ppm; IR (KBr): 2928, 1636, 1494, 1447, 1343, 1164, 1094, 1027, 767, 697, 666, 562 cm^{-1}; HRMS: [M+H^+] calcd. for $C_{18}H_{20}NO_2S$•H^+: 314.1209; found: 314.1210.

Synthesis of **178**

(*S*)-7a-Phenyltetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-imine (**178**)

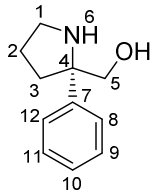


178

Protocol for cleavage is similar to literature procedure. A solution of **157** (0.05 mmol, 18 mg) in a mixture of conc. H_2SO_4/H_2O (1.2 mL, 1:1) was heated to 150 °C while stirring for 4 h. The reaction was cooled to room temperature, CH_2Cl_2 (5 mL) and water (5 mL) were added, the mixture was stirred, and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (2 × 5 mL), then the aqueous layer was cooled in an ice bath and KOH pellets were added until the solution was basic (pH = 14). Precipitated salts were removed by filtration, then the basic aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic phases dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography was performed with $CHCl_3$: MeOH (4:1) to yield compound **178** in 30% yield (0.015 mmol, 3 mg). A similar reaction was performed using ***rac*-157** (0.48 mmol, 171 mg) yielding ***rac*-178** in 36% yield (0.17 mmol, 35 mg).

$[\alpha]_D^{25}$ = +16.6 (*c* = 0.19, $CHCl_3$) (92% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62-1.74 (m, 1H, H-2), 1.87-1.94 (m, 1H, H-2), 1.98-2.06 (m, 1H, H-3), 2.28 (ddd, *J* = 12.0, 6.8, 2.0 Hz, 1H, H-3), 3.31-3.37 (m, 1H, H-1), 3.67-3.74 (m, 1H, H-1), 4.14 (d, *J* = 8.4 Hz, 1H, H-5), 4.44 (d, *J* = 8.4 Hz, 1H, H-5), 4.77-4.87 (br, 1H, N-H), 7.23-7.33 (m, 5H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.6 (C-2), 37.2 (C-3), 48.3 (C-1), 74.3, 76.9, 124.8 (2C), 127.7, 128.9 (2C), 142.6 (C-7), 165.4 (C-6) ppm; IR (KBr): 3466, 2084, 1639, 1585, 1276, 1157, 769 cm^{-1}; HRMS: [M+H$^+$] calcd. for $C_{12}H_{14}N_2O \bullet H^+$: 203.1179; found: 203.1175.

(*S*)-(2-Phenylpyrrolidin-2-yl)methanol (**179**)[14]



179

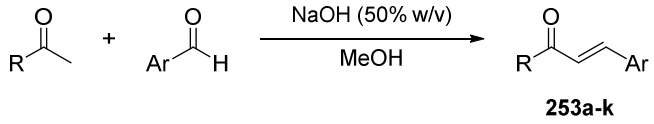
Protocol for cleavage is similar to literature.[15] To compound **178** (0.015 mmol, 3 mg) 11.6N aq. KOH (1.5 mL) was added and heated to reflux for 3 h. The reaction was cooled to room temperature and the basic aqueous layer was extracted with $CHCl_3$ (3 x 5 mL), filtered through a phase separator (Isolute SPE, Biotage) and concentrated to give the product in 75 % yield (0.011 mmol, 2 mg). A similar reaction was performed using ***rac*-178** (0.12 mmol, 25 mg) yielding ***rac*-179** in 80% yield (0.096 mmol, 17 mg).

$[\alpha]_D^{25}$ = +21.4 (*c* = 0.13, $CHCl_3$) (92% ee); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68-1.73 (m, 1H, H-2), 1.74-1.81 (m, 1H, H-2), 1.85-1.95 (m, 1H, H-3), 2.02-2.08 (m, 1H, H-3), 2.23-2.55 (br, 2H, NH and OH), 2.99-3.02 (m, 2H, H-1), 3.43 (d, *J* = 10.6 Hz, 1H, H-5), 3.53 (d, *J* = 10.6 Hz, 1H, H-5), 7.25-7.31 (m, 5H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.5 (C-2), 35.2 (C-3), 45.9 (C-1), 68.3, 69.1, 125.7 (2C), 126.8, 128.4 (2C), 145.8 (C-7) ppm; IR (KBr): 3400, 2959, 1634, 1446, 1054, 913, 760, 701 cm^{-1}; HRMS: [M+H^+] calcd. for $C_{11}H_{15}NO{\bullet}H^+$: 178.1232; found: 178.1239.

6.5 Experimental for Rearrangement Reactions

General procedure 6 for the synthesis of starting materials 253a-k

To a solution of the acetophenone derivative (10 mmol) and the corresponding benzaldehyde (10 mmol) in MeOH (25 mL) an aqueous solution of NaOH (1 mL, 50% w/v) was added dropwise. The reaction mixture was stirred overnight at room temperature. The reaction mixture was then neutralized with a 1 M aqueous solution of HCl. The resulting solution was extracted with EtOAc (3 × 35 mL), the combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo. The chalcone was obtained after crystallization from hexane/EtOAc or by column chromatography (Hexane/EtOAc = 95:5).



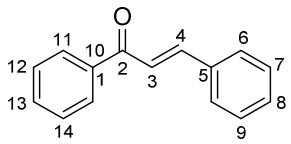
253a-k

Table 5.1: Synthesis of chalcone derivatives **253a-k**

Entry	R	Ar	Product Yield [%]
1	Ph	Ph	**253a**: 51
2	Ph	4-F-C_6H_4	**253b**: 62
3	Ph	4-Cl-C_6H_4	**253c**: 92
4	Ph	4-Br-C_6H_4	**253d**: 61
5	Ph	4-NO_2-C_6H_4	**253e**: 79
6	Ph	4-Me-C_6H_4	**253f**: 82
7	Ph	4-*i*Pr-C_6H_4	**253g**: 82
8	Ph	4-*t*Bu-C_6H_4	**253h**: 69
9	Ph	3-Me-C_6H_4	**253i**: 79

10	Ph	4-OMe-C_6H_4	**253j**: 32
11	2-furyl	Ph	**253k**: 48

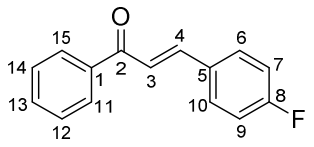
(*E*)-1,3-Diphenyl prop-2-en-1-one (**253a**)



253a

The spectroscopic data are in agreement with literature.[16] Yellow solid, m.p. 59-61 ºC (Lit. 55-57 ºC)[17] ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.44 (m, 3H, Ar-H), 7.50-7.67 (m, 6H, Ar-H), 7.82 (d, *J* = 15.7 Hz, 1H, H-4), 8.02-8.04 (m, 2H, Ar-H) ppm.

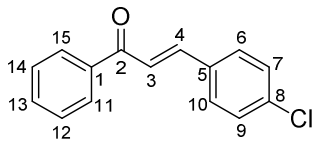
(*E*)-3-(4-Fluorophenyl)-1-phenylprop-2-en-1-one (**253b**)



253b

The spectroscopic data are in agreement literature.[16] Yellow solid, m.p.72-75 ºC (Lit. 75-78 ºC) [18] ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09-7.13 (m, 2H, H-7 and 9), 7.44-7.66 (m, 6H, Ar-H), 7.78 (d, *J* = 15.7 Hz, 1H, H-4), 8.00-8.03 (m, 2H, H-11 and 15) ppm.

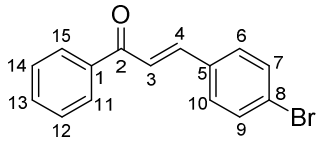
(*E*)-3-(4-Chlorophenyl)-1-phenylprop-2-en-1-one (**253c**)



253c

The spectroscopic data are in agreement with literature.[19] Yellow solid m.p.72-75 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.48-7.63 (m, 6H, Ar-H), 7.76 (d, *J* = 15.8 Hz, 1H, H-4), 8.00-8.04 (m, 2H, H-11 and 15) ppm.

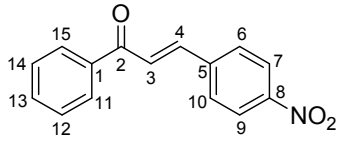
(*E*)-3-(4-Bromophenyl)-1-phenylprop-2-en-1-one (**253d**)



253d

The spectroscopic data are in agreement with literature.[19] Yellow solid, m.p. 116-119 ºC (Lit. 115 ºC)[20] ; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48-7.63 (m, 8H, Ar-H), 7.75 (d, *J* = 15.6 Hz, 1H, H-4), 8.00-8.03 (m, 2H, H-15 and 11) ppm.

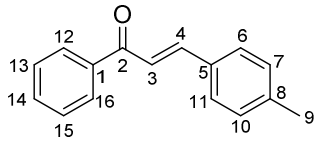
(*E*)-3-(4-Nitrophenyl)-1-phenylprop-2-en-1-one (**253e**)



253e

The spectroscopic data are in agreement with literature.[21] Yellow solid, m.p. 157-158 ºC (Lit. 149-150 ºC)[22] ; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51-7.56 (m, 2H, Ar-H), 7.61-7.68 (m, 2H, Ar-H), 7.77-7.86 (m, 3H, Ar-H), 8.03-8.06 (m, 2H, H-4), 8.26-8.31 (m, 2H, Ar-H) ppm.

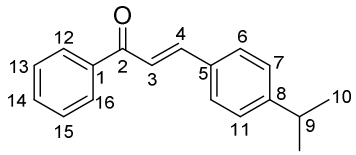
(*E*)-1-Phenyl-3-(*p*-tolyl)prop-2-en-1-one (**253f**)



253f

The spectroscopic data are in agreement with literature.[23] Yellow solid, m.p. 80-84 ºC; (Lit. 92-96 ºC)[21] ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H, H-9), 7.14-7.18 (m, 2H, Ar-H), 7.40-7.53 (m, 6H, Ar-H), 7.72 (d, *J* = 15.7 Hz, 1H, H-4), 7.93-7.95 (m, 2H, Ar-H) ppm.

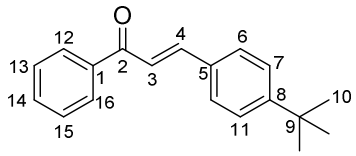
(*E*)-3-(4-Isopropylphenyl)-1-phenylprop-2-en-1-one (**253g**)



253g

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.9 Hz, 6H, H-10), 2.95 (sept, *J* = 6.9 Hz, 1H, H-9), 7.28-7.30 (m, 2H, Ar-H), 7.50-7.53 (m, 3H, Ar-H), 7.56-7.61 (m, 3H, Ar-H), 7.82 (d, *J* = 15.7 Hz, 1H, H-4), 8.01-8.04 (m, 2H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 23.8 (2C, C-10), 34.2 (C-9), 121.2 (C-3), 127.1 (2C), 128.5 (2C), 128.6 (2C), 128.7 (2C), 132.5, 132.7, 138.4 (C-1), 145.0 (C-4), 152.0 (C-8), 190.7 (C-2) ppm; IR (NaCl): 639, 693, 735, 827, 984, 1017, 1033, 1054, 1071, 1143, 1178, 1280, 1332, 1419, 1458, 1577, 1601, 1639, 1661, 1700, 1772 cm^{-1}; HRMS: [M+H^+] calcd. for $C_{18}H_{18}O{\bullet}H^+$: 251.1430; found: 251.1425.

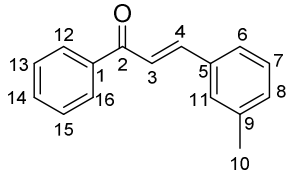
(*E*)-3-(4-(*tert*-Butyl)phenyl)-1-phenylprop-2-en-1-one (**253h**)



253h

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H, H-10), 7.44-7.46 (m, 2H, Ar-H), 7.49-7.53 (m, 3H, Ar-H), 7.57-7.61 (m, 3H, Ar-H), 7.81 (d, *J* = 15.7 Hz, 1H, H-4), 8.01-8.03 (m, 2H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 31.2 (3C, C-10), 35.0 (C-9), 121.3 (C-3), 126.0 (2C), 128.4 (2C), 128.5 (2C), 128.6 (2C), 132.2, 132.7, 138.4 (C-1), 144.9 (C-4), 154.2 (C-8), 190.7 (C-2) ppm; IR (NaCl): 551, 643, 691, 736, 795, 828, 984, 1017, 1033, 1071, 1109, 1178, 1364, 1398, 1447, 1561, 1602, 1640, 1664, 1698, 1772 cm^{-1}; HRMS: [M+ H^+] calcd. for $C_{19}H_{20}O{\bullet}H^+$: 265.1587; found: 265.1580.

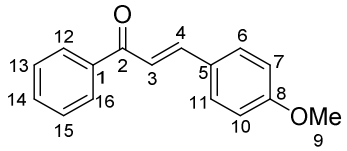
(*E*)-1-Phenyl-3-(*m*-tolyl)prop-2-en-1-one (**253i**)



253i

The spectroscopic data are in agreement with literature.[19] Yellow solid, m.p. 64-65 ºC (Lit. 64 ºC)[24] ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3H, H-10), 7.23-7.25 (m, 1H, Ar-H), 7.32 (t, *J* = 7.9 Hz, 1H, Ar-H), 7.45-7.61 (m, 6H, Ar-H), 7.80 (d, *J* = 15.7 Hz, 1H, H-4), 8.02-8.04 (m, 2H, Ar-H) ppm.

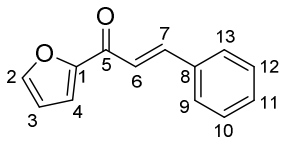
(*E*)-3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one (**253j**)



253j

The spectroscopic data are in agreement with literature. Yellow solid, m.p. 75-77 ºC; (Lit. 70-73 ºC)[21] ; ^{1}H-NMR: (250 MHz, $CDCl_3$): δ = 3.85 (s, 3H, H-9), 6.97-6.91 (m, 2H, Ar-H), 7.42 (d, *J* = 15.6 Hz, 1H, H-3), 7.63-7.50 (m, 5H, Ar-H), 7.79 (d, *J* = 15.6 Hz, 1H, H-4), 8.09-7.93 (m, 2H, Ar-H), ppm.

(*E*)-1-(Furan-2-yl)-3-phenylprop-2-en-1-one (**253k**)



253k

The spectroscopic data are in agreement with literature.[25] Colourless solid, m.p. 79-83 ºC (Lit. 70-73 ºC)[26] ; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.60 (dd, *J* = 1.7 Hz, 3.6 Hz, 1H, Ar-H), 7.33-7.35 (m, 1H, Ar-H), 7.41-7.49 (m, 4H, Ar-H), 7.64-7.68 (m, 3H, Ar-H), 7.89 (d, *J* = 15.8 Hz, 1H, H-7) ppm.

General procedure 7 for synthesis of compound 254a using H_2SO_4

Chalcone **253a** and the hypervalent iodine reagent (1.05 equiv) were dissolved in 3 mL of methanol. Then 0.15 mL of 50% H_2SO_4 (1.4 equiv) is added. Reaction mixture is

stirred for 3 h. The residue is recrystallized in diethylether and hexane (1:20). The crystals are filtered and washed with hexane (2 x 2 ml). The desired compound **254a** is obtained as a colourless solid.

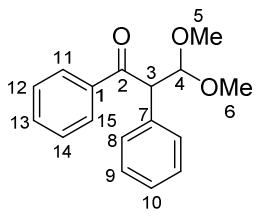
General procedure 8 for synthesis of compound 254a using TBDMSOTf

To the solution of hypervalent iodine reagent (1.5 equiv) in dry solvent (3.0 mL) at 0° C, added TBDMSOTf (3.0 equiv) and was then allowed to stir for 10 min. To this mixture, added the chalcone (0.24 mmol, 1.0 equiv) dissolved in the corresponding solvent (1.0 mL) and 8.0 equiv. of methanol and stirred for further 10 min. Then it was warmed to the room temperature and stirred over night. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo. The migration product was purified by flash column chromatography (Hexane/Ethyl Acetate = 90:10).

General procedure 9 for asymmetric synthesis of compound 254a

To the solution of chiral hypervalent iodine **142** or **144** (0.05 mmol) in dry solvent (1.0 mL) at $^{-}$78 °C, added lewis acid (0.1 mmol) and was then allowed to stir for 10 min. To this mixture, added the chalcone (0.033 mmol) dissolved in the corresponding solvent (0.5 mL) and 8.0 equiv. of methanol and stirred for further 10 min. Then it was warmed to $^{-}$15 °C and stirred over night. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo. The product was purified by preparative TLC (Hexane/Ethyl Acetate = 90:10).

3,3-Dimethoxy-1,2-diphenylpropan-1-one (**254a**)



254a

The spectroscopic data are in agreement with literature.[27] Colourless solid, m.p. 95-96 ºC (Lit. 93-94 ºC)[28]; ^{1}H NMR (400 MHz, $CDCl_3$): 3.21 (s, 3H, H-6), 3.45 (s, 3H, H-5),

4.91 (d, *J* = 8.5 Hz, 1H, H-3), 5.13 (d, *J* = 8.5 Hz, 1H, H-4), 7.22-7.52 (m, 8H, A-H), 7.97-7.99 (m, 2H, Ar-H) ppm.

NMR experiment for monitoring of reaction of 254a

To the solution of chiral hypervalent iodine (0.263 g, 0.36 mmol) in dry solvent (3.0 mL) at ⁻78 °C, added TfOH (0.063 mL, 0.72 mmol) and was then allowed to stir for 10 min. To this mixture, added the chalcone (0.05 g, 0.24 mmol) dissolved in the dichloromethane (0.5 mL) and 8.0 equiv. of methanol and stirred for further 10 min. Then it was warmed to ⁻15 °C and stirred. After regular intervals 0.3 mL of the sample was taken and filtered over silica by using chloroform. Then the solvent was evaporated in the vacuo and measured the NMR yields. The fractions were also purified by using preparative TLC (Hexane/Ethyl Acetate = 90:10) for the HPLC analysis.

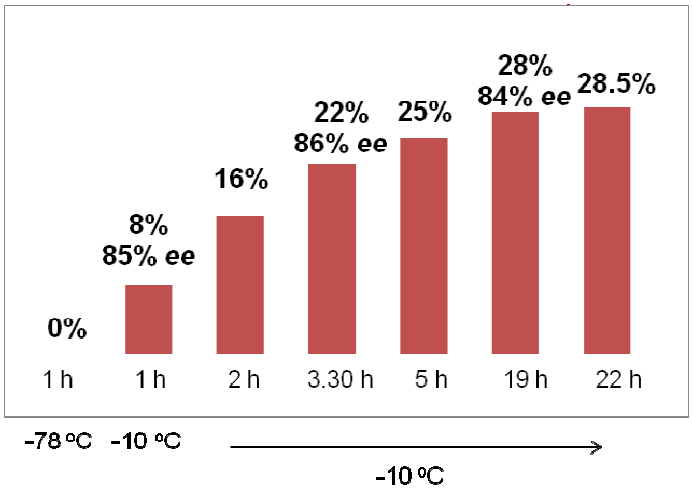


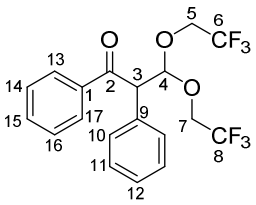
Fig. 1: ^{1}H NMR monitoring of the migration reaction over the course of time

General procedure 10 for asymmetric reactions 254a' to 254m

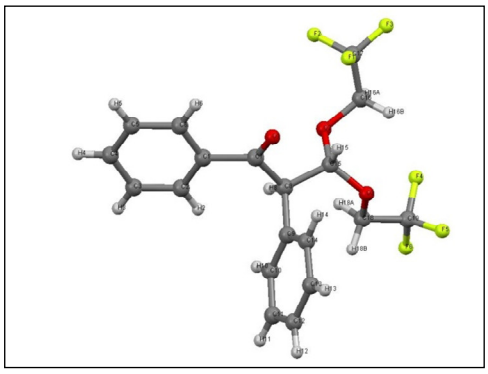
To the solution of chiral hypervalent iodine **142** (0.36 mmol) in dry dichloromethane (1.5 mL) and 2,2,2-trifluoroethanol (1.5 mL) at –40 °C, added TMSOTf or TfOH (0.72 mmol) and was then allowed to stir for 30 min. To this mixture, added the dissolved chalcone (0.24 mmol) in dry dichloromethane (0.5 mL) and 2,2,2-trifluoroethanol (0.5 mL) and stirred for further 30 min. Then it was warmed to –15 °C and stirred overnight. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over

$MgSO_4$ and the solvents were removed in vacuo. The migration product was purified by flash chromatography ($CHCl_3$/Hexane = 1:1).

1,2-Diphenyl-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one (**254a'**):

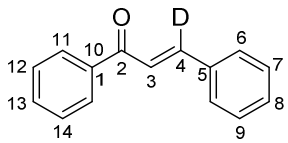


254a'



Colourless solid, m.p. 46-47 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.63-3.74 (m, 2H, H-7), 3.99-4.10 (m, 2H, H-5), 4.89 (d, *J* = 8.4 Hz, 1H, H-3), 5.48 (d, *J* = 8.4 Hz, 1H, H-4), 7.28-7.43 (m, 7H, Ar-H), 7.51-7.54 (m, 1H, Ar-H), 7.93-7.94 (m, 2H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 57.8 (C-3), 64.3 (q, *J* = 34.7 Hz, C-7), 66.1 (q, *J* = 35.0 Hz, C-5), 106.1 (C-4), 123.6 (q, *J* = 276.4 Hz, C-8), 123.7 (q, *J* = 276.0 Hz, C-6), 128.7 (C-12), 129.09 (2C), 129.1 (2C), 129.4 (2C), 129.6 (2C), 133.6, 133.9 (C-9), 136.7 (C-1), 196.8 (C-2) ppm; IR (NaCl): 698, 753, 838, 1012, 1097, 1167, 1281, 1449, 1497, 1598, 1680 cm^{-1}; HRMS: [M+Na^+] calcd. for $C_{19}H_{16}F_6O_3$•Na^+: 429.0896; found: 429.0900; *ee*: 97%, determined by HPLC analysis: Daicel Chiralcel AD column (5 cm), hexanes/*i*-PrOH = 99.8/0.2, 0.5 mL/min, 243 nm; t_r (minor) = 5.3 min, t_r (major) = 7.8 min; $[\alpha]_D^{20}$ = + 70.7 (*c* = 1.41, $CHCl_3$). (Hexane/EtOAc = 90:10).

(*E*)-3-Deuterio-1,3-diphenyl prop-2-en-1-one (**253l**):



253l

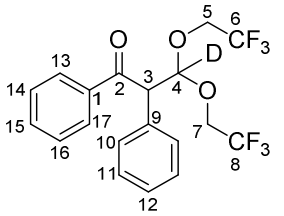
The compound **253l** was synthesised by using general procedure for starting materials in 60% yield. The spectroscopic data are in agreement with literature.[29] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.44 (m, 4H, Ar-H), 7.49-7.54 (m, 3H), 7.64-7.66 (m, 2H, Ar-H), 8.02-8.04 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.4 (C-3), 128.8

(2C), 128.9 (2C), 129.1 (2C), 129.4 (2C), 131.0, 132.2, 135.3 (C-5), 138.7 (C-1), 145.0 (t, *J* = 23.7 Hz, C-4), 191.0 (C-2) ppm.

Procedure for synthesis of deuterated product 254l

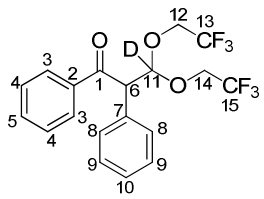
$PhI(OAc)_2$ (0.116g, 0.36 mmol) and the deuterated chalcone **253l** (0.05 g, 0.24 mmol) were dissolved in dry dichloromethane (1.5 mL) and 2,2,2-trifluoroethanol (1.5 mL) and cooled to -40 °C. TfOH (0.06 mL, 0.36 mmol) was then added dropwise and the resulting mixture was allowed to stirred for 3 hours at 0 °C. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo. The product was purified by flash column chromatography in 52% yield.

3-Deuterio-1,2-diphenyl-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one (**254l**)



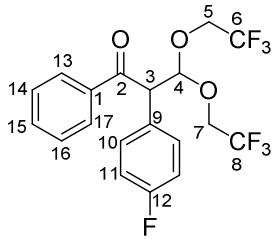
254l

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.65-3.72 (m, 2H, H-7), 4.00-4.08 (m, 2H, H-5), 4.89 (s, 1H, H-1), 7.29-7.43 (m, 7H, Ar-H), 7.51-7.54 (m, 1H, Ar-H), 7.92-7.94 (m, 2H, Ar-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 57.7 (C-3), 64.2 (q, *J* = 35.2 Hz, C-7), 66.1 (q, *J* = 35.1 Hz, C-5), 105.7 (t, *J* = 25.8 Hz. C-4), 123.3 (q, *J* = 276.4 Hz, C-8), 123.7 (q, *J* = 276.3 Hz, C-6), 128.7 (C-12), 129.09 (2C), 129.1 (2C), 129.3 (2C), 129.6 (2C), 133.5, 133.9, 136.6 (C-1), 196.8 (C-2) ppm; IR (NaCl): 426, 668, 699, 750, 769, 835, 966, 1023, 1104, 1164, 1282, 1418, 1448, 1597, 1683, 2342 cm^{-1}; HRMS: [M+ H^+] calcd. for $C_{19}H_{15}{}^2HF_6O_3 \bullet H^+$: 408.1139; found: 408.1132.



Position	^{1}H NMR	^{13}C NMR	HSQC (H → C)	HMBC (H → C)
1	-	196.8	-	-
2	-	136.6	-	-
3, 3’	7.29-7.43 (m, 2H)	129.1	C-3	C-2, C-4
4, 4’	7.92-7.94 (m, 2H)	129.09	C-4	C-3, C-5
5	7.51-7.54 (m, 1H)	133.9	C-5	C-4
6	4.89 (s, 1H)	57.7	C-6	C-1, C-11, C-7, C-8
7	-	133.5	-	-
8, 8’	7.29-7.43 (m, 2H)	129.3	C-8	C-7, C-9
9, 9’	7.29-7.43 (m, 2H)	128.7	C-9	C-8, C-10
10	7.29-7.43 (m, 2H)	129.6	C-10	C-8, C-9
11	-	105.7 (t, J = 25.8 Hz)	-	-
12	3.65 – 3.72 (m, 2H)	64.2 (q, J = 35.2 Hz)	C-12	-
13	-	123.3 (q, J = 276.4 Hz)	-	-
14	4.00 – 4.08 (m, 2H)	66.1 (q, J = 35.1 Hz)	C-14	-
15	-	123.7 (q, J = 276.3 Hz)	-	-

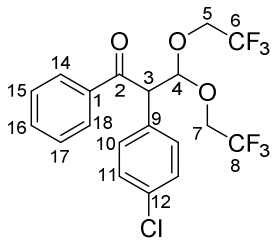
2-(4-Fluorophenyl)-1-phenyl-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one (**254b**)



254b

Colourless solid, m.p. 56-59 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.69-3.78 (m, 2H, H-7), 3.95-4.11 (m, 2H, H-5), 4.89 (d, *J* = 8.5 Hz, 1H, H-3), 5.43 (d, *J* = 8.0 Hz, 1H, H-4), 7.01-7.06 (m, 2H, Ar-H), 7.34-7.38 (m, 2H, Ar-H), 7.41-7.44 (m, 2H, Ar-H), 7.53-7.56 (m, 1H, Ar-H), 7.91-7.92 (m, 2H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.7 (C-3), 64.3 (q, *J* = 35.3 Hz, C-7), 66.0 (q, *J* = 35.3 Hz, C-5), 105.8 (C-4), 116.3 (d, *J* = 21.7 Hz, 2C, C-11), 123.3 (q, *J* = 278.5 Hz, C-8), 123.5 (q, *J* = 278.5 Hz, C-6), 128.8 (2C, Ar-C), 128.9 (2C), 129.2 (d, *J* = 3.3 Hz, C-9), 130.7 (d, *J* = 8.2 Hz, 2C, C-10), 133.8, 136.2 (C-1), 162.6 (d, *J* = 249.5 Hz, C-12), 196.4 (C-2) ppm; IR (NaCl): 581, 723, 762, 821, 968, 1096, 1164, 1228, 1449, 1506, 1598, 1682, 2961 cm^{-1}; HRMS: [M+Na^+] calcd. for $C_{19}H_{15}F_7O_3$•Na^+: 447.0802; found: 447.0805; *ee*: 94%, determined by HPLC analysis: Daicel Chiralcel ODH column (25 cm), hexanes/*i*-PrOH = 99.7/0.3, 0.5 mL/min, 246 nm; t_r (major) = 16.8 min, t_r (minor) = 29.4 min; $[\alpha]_D^{20}$ = + 45.5 (*c* = 1.09, $CHCl_3$).

2-(4-Chlorophenyl)-1-phenyl-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one (**254c**)

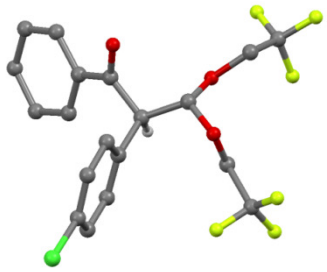


254c

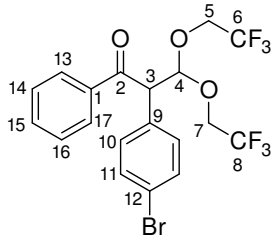
Colourless solid, m.p. 53-55 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.71-3.81 (m, 2H, H-7), 3.99-4.09 (m, 2H, H-5), 4.88 (d, *J* = 8.2 Hz, 1H, H-3), 5.44 (d, *J* = 8.2 Hz, 1H, H-4), 7.32 (m, 4H, Ar-H), 7.41-7.45 (m, 2H, Ar-H), 7.53-7.56 (m, 1H, Ar-H), 7.90-7.91 (m, 2H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.7 (C-3), 64.4 (q, *J* = 35.3 Hz, C-7), 65.8 (q, *J* = 35.3 Hz, C-5), 105.5 (C-4), 123.2 (q, *J* = 278.7 Hz, C-8), 123.3 (q, *J* = 278.6 Hz, C-6), 128.6 (2C, Ar-C), 128.8 (2C), 129.4 (2C), 130.2 (2C), 131.7, 133.7,

134.4, 136.0 (C-1), 196.2 (C-2) ppm; IR (NaCl): 770, 1016, 1093, 1165, 1281, 1492, 1681 cm^{-1}; HRMS: [M+Na^+] calcd. for $C_{19}H_{15}ClF_6O_3$•Na^+: 463.0506; found: 463.0510; *ee*: 92%, determined by HPLC analysis: Daicel Chiralcel ODH column (25 cm), hexanes/*i*-PrOH = 99.5/0.5, 0.5 mL/min, 246 nm; t_r (major, *R* isomer) = 14.8 min, t_r (minor, *S* isomer) = 20.6 min; $[\alpha]_D^{20}$ = + 44.5 (*c* = 0.49, $CHCl_3$).

X-ray Crystallographic structure of **254c**



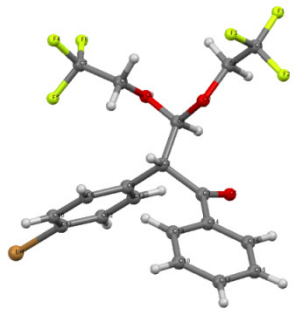
2-(4-Bromophenyl)-1-phenyl-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one (**254d**)



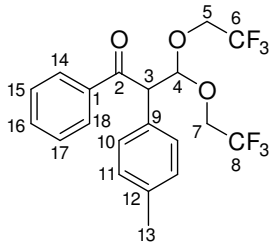
254d

Colourless solid, m.p. 52-55 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.73-3.78 (m, 2H, H-7), 4.01-4.04 (m, 2H, H-5), 4.86 (d, *J* = 8.1 Hz, 1H, H-3), 5.43 (d, *J* = 8.1 Hz, 1H, H-4), 7.24-7.26 (m, 2H, Ar-H), 7.41-7.56 (m, 5H, Ar-H), 7.89-7.91 (m, 2H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 56.8 (C-3), 64.1 (q, *J* = 35.5 Hz, C-7), 65.8 (q, *J* = 35.5 Hz, C-5), 105.4 (C-4), 122.5 (C-12), 123.2 (q, *J* = 278.7 Hz, C-8), 123.3 (q, *J* = 278.8 Hz, C-6), 128.6 (2C, Ar-C), 128.8 (2C), 130.5 (2C), 132.2, 132.3 (2C), 133.7, 135.9 (C-1), 196.1 (C-2) ppm; IR (NaCl): 425, 809, 848, 1012, 1092, 1165, 1280, 1448, 1488, 1596, 1683, 2284 cm^{-1}; HRMS: [M+ Na^+] calcd. for $C_{19}H_{15}BrF_6O_3$•Na^+: 507.0001; found: 507.0004; *ee*: 91%, determined by HPLC analysis: Daicel Chiralcel ODH column (25 cm), hexanes/*i*-PrOH = 99.5/0.5, 0.5 mL/min, 246 nm; t_r (major, *R* isomer) = 13.4 min, t_r (minor, *S* isomer) = 19.5 min; $[\alpha]_D^{20}$ = + 45.5 (*c* = 0.22, $CHCl_3$).

X-ray Crystallographic structure of **254d**



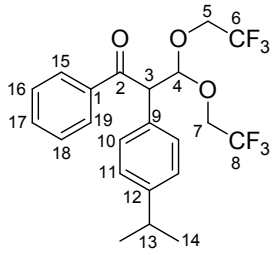
1-Phenyl-2-(*4*-tolyl)-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one (**254f**)



254f

Light yellow solid, m.p. 37-40 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3H, H-13), 3.64-3.74 (m, 2H, H-7), 3.98-4.10 (m, 2H, H-5), 4.86 (d, *J* = 8.4 Hz, 1H, H-3), 5.46 (d, *J* = 8.4 Hz, 1H, H-4), 7.14 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.26-7.28 (m, 2H, Ar-H), 7.39-7.43 (m, 2H, Ar-H), 7.50-7.53 (m, 1H, Ar-H), 7.92-7.94 (m, 2H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.2 (C-13), 56.1 (C-3), 62.8 (q, *J* = 35.1 Hz, C-7), 64.8 (q, *J* = 35.1 Hz, C-5), 104.8 (C-4), 122.3 (q, *J* = 278.7 Hz, C-8), 122.4 (q, *J* = 278.6 Hz, C-6), 127.81 (2C, Ar-C), 127.84 (2C), 127.9 (2C), 129.1 (2C), 129.2, 132.6, 135.3, 137.3, 195.6 (C-2) ppm; IR (NaCl): 689, 759, 804, 968, 1008, 1095, 1166, 1281, 1448, 1513, 1597, 1682 cm^{-1}; HRMS: [M+Na^+] calcd. for $C_{20}H_{18}F_6O_3$•Na^+: 443.1052; found: 443.1055; *ee*: 86%, determined by HPLC analysis: Daicel Chiralcel ODH column (25 cm), hexanes/*i*-PrOH = 99.7/0.3, 0.5 mL/min, 217 nm; t_r (major) = 12.3 min, t_r (minor) = 14.7 min; $[\alpha]_D^{20}$ = + 48.6 (*c* = 1.64, $CHCl_3$).

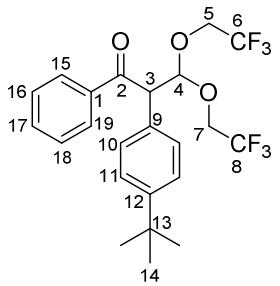
2-(4-Isopropylphenyl)-1-phenyl-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one (**254g**)



254g

Colourless solid, m.p. 42-43 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.5 Hz, 6H, H-14), 2.86 (sept, *J* = 6.5 Hz, 1H, H-13), 3.66-3.70 (m, 2H, H-7), 4.00-4.07 (m, 2H, H-5), 4.87 (d, *J* = 8.3 Hz, 1H, H-3), 5.47 (d, *J* = 8.3 Hz, 1H, H-4), 7.19 (d, *J* = 7.6 Hz, 2H, Ar-H, H-11), 7.30 (d, *J* = 7.7 Hz, 2H, H-10), 7.42 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.52 (t, *J* = 7.0 Hz, 1H, Ar-H), 7.95 (d, *J* = 7.4 Hz, 2H, H-15 and 19) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 23.8 (2C, C-14), 33.7 (C-13), 56.8 (C-3), 63.5 (q, *J* = 35.3 Hz, C-7), 65.6 (q, *J* = 35.0 Hz, C-5), 105.7 (C-4), 123.2 (q, *J* = 277.9 Hz, C-8), 123.3 (q, *J* = 277.8 Hz, C-6), 127.2 (2C, Ar-C), 128.6 (4C), 128.7 (2C), 130.2, 133.4, 136.2 (C-1), 148.9 (C-12), 196.4 (C-2) ppm; IR (NaCl): 688, 818, 1020, 1098, 1164, 1282, 1387, 1448, 1597, 1682, 1718, 2962 cm^{-1}; HRMS: [M+Na^+] calcd. for $C_{22}H_{22}F_6O_3$•Na^+: 471.1365; found: 471.1367; *ee*: 89%, determined by HPLC analysis: Daicel Chiralcel AD column (5 cm), hexanes/*i*-PrOH = 99.8/0.2, 0.5 mL/min, 243 nm; t_r (major) = 12.5 min, t_r (minor) = 16.4 min; $[\alpha]_D^{20}$ = + 25.3 (*c* = 1.42, $CHCl_3$).

2-(4-(*tert*-Butyl)phenyl)-1-phenyl-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one (**254h**)

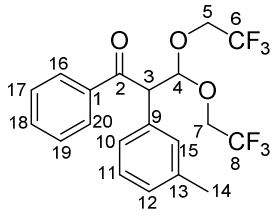


254h

Colourless solid, m.p. 99-103 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (s, 9H, H-14), 3.64-3.74 (m, 2H, H-7), 3.96-4.10 (m, 2H, H-5), 4.88 (d, *J* = 8.4 Hz, 1H, H-3), 5.48 (d, *J* = 8.4 Hz, 1H, H-4), 7.31-7.36 (m, 4H, Ar-H), 7.42 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.52 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.96 (d, *J* = 7.3 Hz, 2H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 30.2 (3C, C-14), 33.5 (C-13), 55.7 (C-3), 62.5 (q, *J* = 35.3 Hz (C-7), 64.6 (q, *J* =

35.3 Hz, C-5), 104.5 (C-4), 122.27 (q, *J* = 278.2 Hz, C-8), 122.3 (q, *J* = 278.1 Hz, C-6), 125.1 (2C, Ar-C), 127.5 (2C), 127.66 (2C), 127.67 (2C), 128.9, 132.4, 135.2 (C-1), 150.3 (C-12), 195.4 (C-2) ppm; IR (NaCl): 684, 721, 773, 816, 838, 998, 1084, 1167, 1418, 1448, 1597, 1673, 2956 cm^{-1}; HRMS: [M+Na^+] calcd. for $C_{23}H_{24}F_6O_3$•Na^+: 485.1522; found: 485.1521; *ee*: 52%, determined by HPLC analysis: Daicel Chiralcel ODH column (25 cm), hexanes/*i*-PrOH = 99.8/0.2, 0.5 mL/min, 243 nm; t_r (major) = 22.1 min, t_r (minor) = 27.6 min; $[\alpha]_D^{20}$ = + 25.1 (*c* = 1.75, $CHCl_3$).

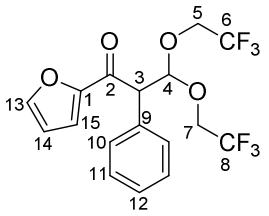
1-Phenyl-2-(*m*-tolyl)-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one (**254i**)



254i

Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.32 (s, 3H, H-14), 3.62-3.74 (m, 2H, H-7), 3.98-4.10 (m, 2H, H-5), 4.85 (d, *J* = 8.4 Hz, 1H, H-3), 5.47 (d, *J* = 8.4 Hz, 1H, H-4), 7.09-7.10 (m, 1H, Ar-H), 7.17-7.24 (m, 3H, Ar-H), 7.40-7.43 (m, 2H, Ar-H), 7.51-7.54 (m, 1H, Ar-H), 7.93-7.95 (m, 2H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.4 (C-14), 57.4 (C-3), 63.9 (q, *J* = 35.0 Hz, C-7), 65.7 (q, *J* = 35.0 Hz, C-5), 105.8 (C-4), 123.0 (q, *J* = 278.7 Hz, C-8) 123.4 (q, *J* = 278.5 Hz, C-6), 126.1 (Ar-C), 128.6 (2C), 128.7 (2C), 129.0, 129.1, 129.4, 132.9, 133.4, 136.3 (C-1), 138.9 (C-13), 196.4 (C-2) ppm; IR (NaCl): 772, 1050, 1098, 1166, 1282, 1679 cm^{-1}; HRMS: [M+NH_4^+] calcd. for $C_{20}H_{18}F_6O_3$•NH_4^+: 438.1498; found: 438.1490; *ee*: 54%, determined by HPLC analysis: Daicel Chiralcel ODH column (25 cm), hexanes/*i*-PrOH = 99.8/0.2, 0.3 mL/min, 245 nm; t_r (major) = 22.2 min, t_r (minor) = 28.6 min.

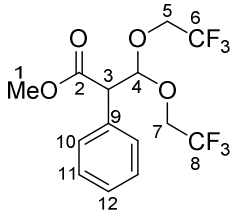
1-(Furan-2-yl)-2-phenyl-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one (**254k**)



254k

Colourless solid, m.p. 43-44 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.64-3.78 (m, 2H, H-7), 3.98-4.09 (m, 2H, H-5), 4.74 (d, *J* = 8.7 Hz, 1H, H-3), 5.52 (d, *J* = 8.7 Hz, 1H, H-4), 6.53 (dd, *J* = 1.7, 3.6 Hz, 1H, Ar-H), 7.23-7.58 (m, 7H, Ar-H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 56.1 (C-3), 62.1 (q, *J* = 35.2 Hz, C-7), 64.5 (q, *J* = 35.2 Hz, C-5), 103.6 (C-4), 111.8 (C-14), 117.8 (C-15), 122.3 (q, *J* = 277.7 Hz, C-8), 122.4 (q, *J* = 277.7 Hz, C-6), 127.4 (Ar-C), 128.0 (2C), 128.1 (2C), 131.9 (C-9), 146.2 (C-13), 150.9 (C-1), 183.8 (C-2) ppm; IR (NaCl): 426, 591, 671, 700, 729, 765, 813, 884, 967, 1022, 1033, 1085, 1164, 1229, 1281, 1395, 1431, 1497, 1568, 1601, 1672, 1732, 2243 cm^{-1}; HRMS: [M+H^+] calcd. for $C_{17}H_{14}F_6O_4$•H^+: 397.0869; found: 397.0862; *ee*: 83%, determined by HPLC analysis: Daicel Chiralcel AD column (5 cm), hexanes/*i*-PrOH = 99.9/0.1, 0.5 mL/min, 273 nm; t_r (minor) = 10.1 min, t_r (major) = 22.6 min; $[\alpha]_D^{20}$ = + 11.6 (*c* = 0.17, $CHCl_3$).

Methyl 2-phenyl-3,3-bis(2,2,2-trifluoroethoxy)propanoate (**254m**)

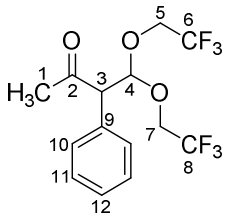


254m

Colourless solid, m.p. 43-44 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.60-3.78 (m, 2H, H-7), 3.70 (s, 3H, H-1), 3.89 (d, *J* = 8.9 Hz, 1H, H-3), 3.98-4.10 (m, 2H, H-5), 5.35 (d, *J* = 8.9 Hz, 1H, H-4), 7.36 (m, 5H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 52.5 (C-3), 55.4 (C-1), 62.7 (q, *J* = 35.3 Hz, C-7), 64.6 (q, *J* = 35.2 Hz, C-5), 103.9 (C-4), 123.2 (q, *J* = 278.0 Hz, C-8), 123.4 (q, *J* = 278.5 Hz, C-6), 128.5 (Ar-C), 128.6 (2C), 128.9 (2C), 132.7, 170.4 (C-2) ppm; IR (NaCl): 771, 1005, 1084, 1165, 1282, 1438, 1739 cm^{-1}; HRMS: [M+NH_4^+] calcd. for $C_{14}H_{14}F_6O_4$•NH_4^+: 378.1135; found: 378.1132; *ee*: 96%, determined by HPLC analysis: Daicel Chiralcel ODH column (25 cm), hexanes/*i*-PrOH

= 99.8/0.2, 0.5 mL/min, 208 nm; t_r (minor) = 14.4 min, t_r (major) = 18.7 min; $[\alpha]_D^{20}$ = + 17.5 (*c* = 0.23, $CHCl_3$).

3-Phenyl-4,4-bis(2,2,2-trifluoroethoxy)butan-2-one (**254n**)



254n

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3H, H-1), 3.53-3.63 (m, 1H, H-7), 3.67-3.75 (m, 1H, H-7), 3.94-4.11 (m, 2H, H-5), 4.02 (d, *J* = 8.4 Hz, 1H, H-3), 5.35 (d, *J* = 8.4 Hz, 1H, H-4), 7.27-7.39 (m, 5H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 29.1 (C-1), 61.3 (C-3), 61.8 (q, *J* = 35.6 Hz, C-7), 64.6 (q, *J* = 35.4 Hz, C-5), 103.1 (C-4), 122.2 (q, *J* = 278.6 Hz, C-8), 122.4 (q, *J* = 278.5 Hz, C-6), 127.4 (Ar-C), 127.8 (2C), 128.2 (2C), 131.5 (C-9), 203.3 (C-2) ppm; IR (NaCl): 427, 652, 693, 735, 778, 983, 1017, 1033, 1097, 1178, 1214, 1294, 1362, 1419, 1511, 1577, 1601, 1639, 1661, 1694, 2283 cm^{-1}; HRMS: $[M+NH_4^+]$ calcd. for $C_{14}H_{14}F_6O_3 \bullet NH_4^+$: 362.1185; found: 362.1187; enantiomers were inseparable by HPLC; $[\alpha]_D^{20}$ = -11.8 (*c* = 0.34, $CHCl_3$).

General procedure 11 for synthesis of racemic products 254

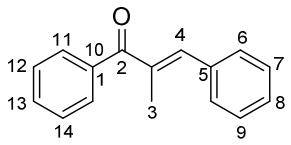
$PhI(OAc)_2$ (0.18 mmol) and the chalcone (0.12 mmol) were dissolved in dry dichloromethane (1.0 mL) and 2,2,2-trifluoroethanol (1.0 mL) and cooled to 0 °C. TMSOTf (0.36 mmol) was then added dropwise and the resulting mixture was allowed to stirred for 2 hours at 0 °C. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo. The product was purified by preparative TLC ($CHCl_3$/Hexane = 3:1).

Procedure for synthesis of 253o

To a solution of the acetophenone derivative (10 mmol) and the benzaldehyde (10mmol) in MeOH (25 mL) was added dropwise an aqueous solution of NaOH (1 mL, 50% w/v). The reaction mixture was stirred overnight at room temperature. The reaction mixture was then neutralized with a 1M aqueous solution of HCl. The resulting solution

was extracted with EtOAc, the combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo. The chalcone **253o** was obtained in 85% yield after purification by column chromatography (Hexane/EtOAc = 95:5).

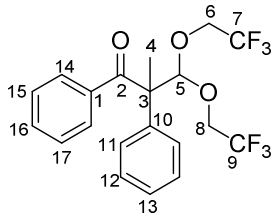
(*E*)-2-Methyl-1,3-diphenylprop-2-en-1-one (**253o**)



253o

The compound **253o** was synthesised by using known literature procedure[30] in 85% yield. The spectroscopic data are in agreement with literature. Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (d, *J* = 1.4 Hz, 3H, H-3), 7.19 (q, *J* = 1.4 Hz, 1H, H-4), 7.34-7.57 (m, 8H, Ar-H), 7.74-7.76 (m, 2H, Ar-H) ppm.

2-Methyl-1,2-diphenyl-3,3-bis(2,2,2-trifluoroethoxy)propan-1-one (**254o**)



254o

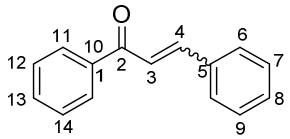
Prepared from general procedure for racemic products in 48% yields. Colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.78 (s, 3H, H-4), 3.27-3.35 (m, 1H, H-8), 3.56-3.64 (m, 1H, H-8), 4.06-4.17 (m, 2H, H-6), 5.25 (s, 1H, H-5), 7.23-7.41 (m, 10H, Ar-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 16.1 (C-4), 59.8 (C-3), 66.7-67.4 (m, 2C, C-6 and 8), 108.9 (C-5), 123.1(q, *J* = 279.3 Hz, C-9), 123.5 (q, *J* = 279.2 Hz, C-7), 127.3 (2C, Ar-C), 128.1 (3C), 129.0 (2C), 129.1 (2C), 132.0, 136.5, 137.7 (C-1), 202.2 (C-2) ppm; IR (NaCl): 671, 730, 768, 848, 970, 1100, 1165, 1281, 1447, 1558, 1675 cm^1; HRMS: [M+NH_4^+] calcd. for $C_{20}H_{18}F_6O_3$•NH_4^+: 438.1498; found: 438.1494.

Photoisomerization of (*E*)-253a

The mixture of isomers were synthesised by modifying literature procedure.[31] After irradiating a solution of (*E*)-chalcone (**253a**, 1.0 g, 4.80 mmol) in acetonitrile (25 mL) with a 400-W mercury lamp with circulated 0.2 M aqueous $CuSO_4$ as a UV filter for 24

h, a (1:1) mixture of the isomers was obtained. The solvent was removed and the oil was crystallized to obtain a 4:10 mixture of *E*/*Z* isomers (0.50 g, 2.40 mmol).

1,3-Diphenyl prop-2-en-1-one (**253a** *E*/*Z* mixture)



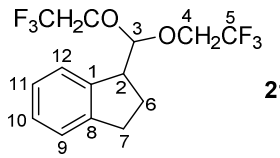
253a E/Z (4:10)

The spectroscopic data are in agreement literature.[16] 4:10 mixture of *E*/*Z* isomers; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (d, *J* = 12.8 Hz, 1H, *Z*-isomer, H-3), 7.04 (d, *J* = 12.8 Hz, 1H, *Z*-isomer, H-4), 7.25-7.69 (m, 17H, *E* and *Z*-isomers, Ar-H), 7.85 (d, *J* = 15.7 Hz, 1H, *E*-isomer, H-4), 7.98-8.00 (m, 2H, *Z*-isomer, Ar-H), 8.04-8.06 (m, 2H, *E*-isomer, Ar-H) ppm.

General procedure 12 for ring contraction reactions of 216b

To the solution of chiral hypervalent iodine (0.36 mmol) in dry dichloromethane (3.0 mL) and 2,2,2-trifluoroethanol (1.0 mL) at –78 °C, added Lewis acid (0.72 mmol) and was then allowed to stir for 30 min. To this mixture, added the dissolved starting material (0.24 mmol) in dry dichloromethane (1.0 mL) and stirred overnight at –78°C. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo. The product was purified by flash chromatography (Hexane/Ethyl Acetate = 90:10).

1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-indene (**216b**)

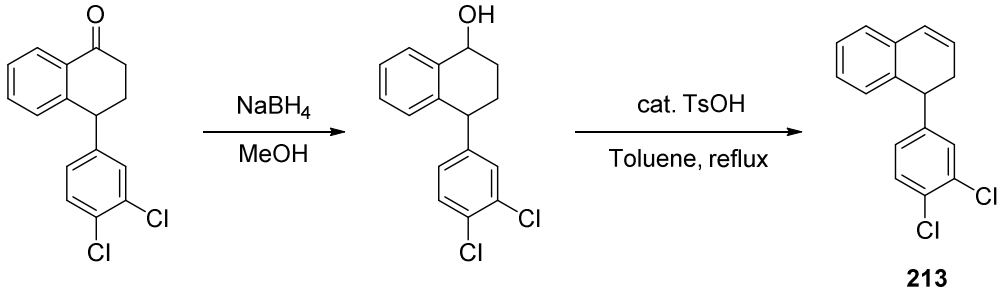


216b

The spectroscopic data is in agreement with the literature.[32] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99-2.07 (m, 1H, H-6), 2.20-2.30 (m, 1H, H-6), 2.85-3.02 (m, 2H, H-7), 3.48 (q, *J* = 7.7 Hz, 1H, H-2), 3.89-4.07 (m, 4H, H-4), 4.71 (d, *J* = 8.2 Hz, 1H, H-3), 7.17-7.24 (m, 3H, Ar-H), 7.39-7.41 (m, 1H, Ar-H) ppm; *ee*: 59%, determined by HPLC analysis: Daicel Chiralcel ODH column (25 cm), hexanes/*i*-PrOH = 99.7/0.3, 0.3

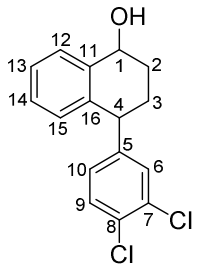
mL/min, 215 nm; t_r (major) = 30.4 min, t_r (minor) = 34.7 min; $[\alpha]_D^{20}$ = +3.7 (*c* = 0.53, $CHCl_3$).

Synthesis of **213**



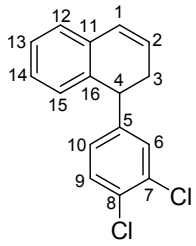
The compound **213** was synthesised by using known literature procedure from the corresponding ketone in overall 75% yield (1.42 g, 5.16 mmol).[33] The spectroscopic data are in agreement with literature.[34]

4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-naphthalen-1-ol



^{1}H NMR (250 MHz, $CDCl_3$): 1.78-1.82 (m, 1H, H-2), 1.90-2.01 (m, 3H, H-2 and 3), 2.23-2.33 (m, 1H, H-4), 3.89-4.01 (m, 1H), 4.78-4.85 (m, 1H, H-1), 6.70-7.49 (m, 7H, Ar-H).

1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene (**213**)



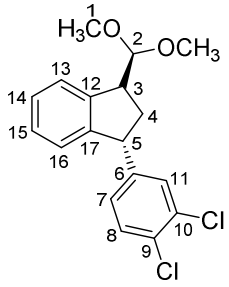
213

^{1}H NMR (300 MHz, $CDCl_3$): 2.49-2.61 (m, 1H, H-3), 2.65-2.75 (m, 1H, H-3), 4.09 (t, *J* = 8.0 Hz, 1H, H-4), 5.92-5.99 (m, 1H, H-2), 6.55 (d, *J* = 9.6 Hz, 1H, H-1), 6.82-7.30 (m, 6H, Ar-H), 7.36 (d, *J* = 8.2 Hz, 1H, Ar-H) ppm.

Procedure for synthesis of compound 214

To the solution of chiral hypervalent iodine (0.36 mmol) in dry dichloromethane (3.0 mL) at ⁻78 °C, added TMSOTf (0.72 mmol) and was then allowed to stir for 30 min. To this mixture, added the starting material **213** (0.24 mmol) dissolved in the dichloromethane (0.5 mL) and 8 equiv. of methanol and stirred for further overnight. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed in vacuo. The migration product was purified by flash chromatography (Hexane/Ethyl Acetate = 90:10).

1-(3,4-Dichlorophenyl)-3-(dimethoxymethyl)-2,3-dihydro-1*H*-indene (**214**)



214

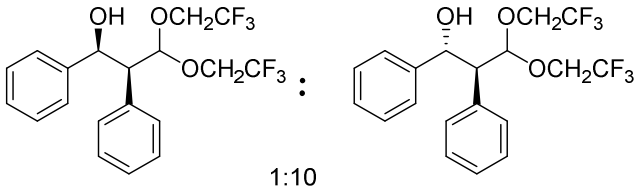
The spectroscopic data are in agreement with literature.[33] Yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.09-2.17 (m, 1H, H-4), 2.54-2.64 (m, 1H, H-4), 3.34 (s, 3H, H-1), 3.43 (s, 3H, 2nd OMe), 3.48-3.60 (m, 1H, H-3), 4.35 (d, *J* = 6.9 Hz, 1H, H-2), 4.40 (t, *J* = 7.8 Hz, 1H, H-5), 6.94-6.99 (m, 2H, Ar-H), 7.17-7.29 (m, 3H, Ar-H), 7.33-7.36 (m, 1H, Ar-H), 7.43-7.47 (m, 1H, Ar-H) ppm; *ee*: 9%, determined by HPLC analysis:

Daicel Chiralcel ODH column (25 cm), hexanes/*i*-PrOH = 99.9/0.1, 0.5 mL/min, 211 nm; t_r (minor) = 17.2 min, t_r (minor) = 18.6 min; $[\alpha]_D^{20}$ = + 2.0 (*c* = 0.98, $CHCl_3$).

Reduction reaction for compound 254a'

To the solution of **254a'** (0.04g, 0.098 mmol) in MeOH (3.0 mL), added $NaBH_4$ (0.007g, 0.196 mmol) at 0 ºC and stirred at room temperature for 30 min. The reaction was quenched with water and extracted with CH_2Cl_2 (3 x 5.0 mL) to give the reduced product **259** in 98% yield (0.039g, 0.0975mmol).

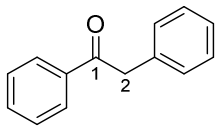
3,3-Bis(2,2,2-trifluoroethoxy)1,2-diphenyl-propan-1-ol (**259**)



259' **259**

Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (d, *J* = 4.4 Hz, 1H, major), 2.68 (d, *J* = 3.1 Hz, 1H, minor), 3.12 (dd, *J* = 4.4, 7.5 Hz, 1H, major), 3.29 (dd, *J* = 5.7, 8.5 Hz, 1H, minor), 3.52-3.61 (m, 1H, major), 3.68-3.79 (m, 1H, major), 3.95-4.05 (m, 2H, major), 5.09 (dd, *J* = 3.1, 8.5 Hz, 1H, minor), 5.23 (d, *J* = 7.5 Hz, 1H, major), 5.26 (t, *J* = 4.4 Hz, 1H, major), 5.33 (d, *J* = 5.7 Hz, 1H, minor), 7.04-7.25 (m, 10H, major), 7.15-7.17 (m, 6H, minor) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.4 (minor), 56.5 (major), 61.9 (q, *J* = 35.1 Hz, major), 64.6 (q, *J* = 34.8 Hz, major), 73.5 (major), 75.3 (minor), 103.5 (major), 104.6 (minor), 123.5 (q, *J* = 277.8 Hz, major), 123.6 (q, *J* = 278.2 Hz, major), 126.0 (2C, major), 126.7 (minor), 127.3 (minor), 127.5 (major), 127.6 (minor), 127.65 (major), 127.7 (minor), 127.8 (minor), 128.0 (minor), 128.09 (2C, major), 128.1 (2C, major), 129.8 (minor), 130.2 (2C, major), 134.0 (major), 135.2 (minor), 141.4 (minor), 141.7 (major) ppm; IR (NaCl): 669,700, 968, 1010, 1085, 1165, 1280, 1456, 2341, 2360, 1852, 2942, 2954 cm^1; HRMS: [M+Na^+] calcd. for $C_{19}H_{18}F_6O_3$•Na^+: 431.1058; found: 431.1053.

1,2-Diphenylethan-1-one (**261**)



261

Compound **261** was synthesized from the reactions in Table 5.7. The data is in agreement with the literature.[35]

Colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.32 (s, 2H, H-2), 7.29-7.59 (m, 8H, Ar-H), 8.03-8.06 (m, 2H, Ar-H), ppm.

6.6 References

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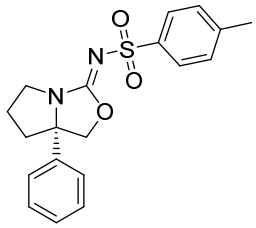
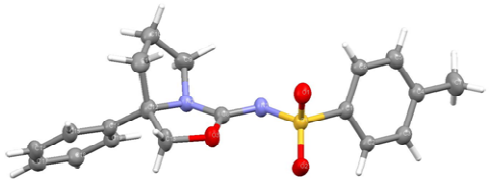
6.7 Appendix

X-Ray crystallographic data of 157 (CCDC 824540)



157

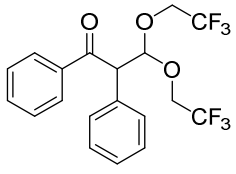


Audit creation method	SHELXL-97
Chemical formula moiety	C_{19} H_{20} N_2 O_3 S
Chemical formula sum	C_{19} H_{20} N_2 O_3 S
Chemical formula weight	356.43
Chemical absolute configuration	ad
celllength_c	13.8565(3)
cell angle alpha	90.00
cell angle beta	90.00
cell angle gamma	90.00
cell volume	1719.40(6)
cell formula units Z	4
cell measurement temperature	150(2)
cell measurement reflns used	3711
cell measurement theta min	2.98
cell measurement theta max	28.69
exptl crystal description	Block
exptl crystal color	Colorless
exptl crystal size max	0.35
exptl crystal size mid	0.35
exptl crystal size min	0.35
exptl crystal density diffrn	1.377
exptl absorpt coefficient mu	0.209
exptl absorpt correction T min	0.9303
exptl absorpt correction T max	0.9303
diffrn ambient temperature	150(2)
diffrn radiation wavelength	0.71073
diffrn radiation monochromator	graphite
symmetry cell setting	'Orthorhombic'
diffrn reflns number	9385
diffrn reflns limit h max	14
diffrn reflns limit k min	-11
diffrn reflns limit k max	15
diffrn reflns limit l max	18
diffrn reflns theta min	2.98

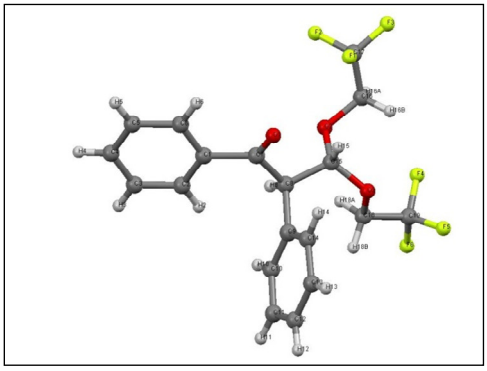
diffrn reflns theta max	28.69
reflns number total	4352
reflns number gt	3711

refine ls matrix type	full
refine ls weighting scheme	calc
refine ls weighting details	
atom sites solution primary	direct
atom sites solution secondary	difmap
atom sites solution hydrogens	geom
refine ls hydrogen treatment	constr
refine ls extinction method	SHELXL
refine ls extinction coef	0.065(5)
refine ls extinction expression	
refine ls abs structure details	
'Flack H D (1983), Acta Cryst. A39, 876-881'	
refine ls abs structure Flack	**-0.11(11)**
refine ls number reflns	4352
refine ls number parameters	228
refine ls number restraints	0
refine ls R factor all	0.0739
refine ls R factor gt	0.0592
refine ls wR factor ref	0.1589
refine ls wR factor gt	0.1429
refine ls goodness of fit ref	1.143
refine ls restrained S all	1.143

X-Ray crystallographic data of 254a'



254a'



audit creation method	SHELXL-97
chemical name systematic	
chemical formula sum	$C_{19}\ H_{16}\ F_6\ O_3$
chemical formula weight	406.32
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'	'C' 'C' 0.0033 0.0016

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'	'H' 'H' 0.0000 0.0000
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'	'F' 'F' 0.0171 0.0103
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'	'O' 'O' 0.0106 0.0060
symmetry cell setting	Triclinic
symmetry space group name H-M	P1
cell length a	5.8865(3)
cell length b	12.0427(7)
cell length c	19.4755(9)
cell angle alpha	81.241(3)
cell angle beta	85.465(3)
cell angle gamma	92.051(2)
cell volume	1358.63(12)
cell formula units Z	3
cell measurement temperature	150(2)
exptl crystal size max	0.35
exptl crystal size mid	0.06
exptl crystal size min	0.04
exptl crystal density diffrn	1.490
exptl crystal density method	'not measured'
exptl crystal F 000	624
exptl absorpt coefficient mu	0.140
exptl absorpt correction T min	0.9526
exptl absorpt correction T max	0.9944
diffrn ambient temperature	150(2)
diffrn radiation wavelength	0.71073
diffrn radiation type	MoK\a
diffrn radiation source	'fine-focus sealed tube'
diffrn radiation monochromator	graphite
diffrn reflns number	5481
diffrn reflns av R equivalents	0.0000
diffrn reflns av sigmaI/netI	0.0607
diffrn reflns limit h min	-5
diffrn reflns limit h max	5
diffrn reflns limit k min	-11
diffrn reflns limit k max	12
diffrn reflns limit l min	-19
diffrn reflns limit l max	19
diffrn reflns theta min	1.06
diffrn reflns theta max	20.83
reflns number total	5481
reflns number gt	4751
reflns threshold expression	>2\s(I)
computing structure refinement	'SHELXL-97 (Sheldrick, 2008)'

refine special details

Refinement of F^2^ against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2^, conventional R-factors R are based on F, with F set to zero

for negative F^2^. The threshold expression of F^2^ > 2\s(F^2^) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2^ are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

refine ls structure factor coef Fsqd
refine ls matrix type fullcycle
refine ls weighting scheme calc
refine ls weighting details
'calc w=1/[\s^2^(Fo^2^)+(0.1885P)^2^+0.7038P] where P=(Fo^2^+2Fc^2^)/3'
atom sites solution primary direct
atom sites solution secondary difmap
atom sites solution hydrogens geom
refine ls hydrogen treatment mixed
refine ls extinction method none
refine ls abs structure details
'Flack H D (1983), Acta Cryst. A39, 876-881'
refine ls abs structure Flack 0.0(14)
refine ls number reflns 5481
refine ls number parameters 757
refine ls number restraints 9
refine ls R factor all 0.1026
refine ls R factor gt 0.0889
refine ls wR factor ref 0.2433
refine ls wR factor gt 0.2225
refine ls goodness of fit ref 1.077
refine ls restrained S all 1.078
refine ls shift/su max 0.009
refine ls shift/su mean 0.002

Atomic coordinates and equivalent isotropic displacement parameters

C1 C -0.0910(14) 0.1452(7) 0.2938(4) 0.0207(19) Uani 1 1 d
C2 C -0.2935(16) 0.1129(7) 0.3312(5) 0.032(2) Uani 1 1 d
H2 H -0.4118 0.0776 0.3106 0.038 Uiso 1 1 calc R
C3 C -0.3262(16) 0.1316(8) 0.3998(5) 0.034(2) Uani 1 1 d
H3 H -0.4655 0.1077 0.4269 0.041 Uiso 1 1 calc R
C4 C -0.1540(18) 0.1852(8) 0.4281(5) 0.037(2) Uani 1 1 d
H4 H -0.1782 0.2003 0.4745 0.044 Uiso 1 1 calc R
C5 C 0.0468(15) 0.2167(7) 0.3918(5) 0.029(2) Uani 1 1 d
H5 H 0.1647 0.2514 0.4129 0.034 Uiso 1 1 calc R
C6 C 0.0823(16) 0.1979(7) 0.3220(4) 0.030(2) Uani 1 1 d
H6 H 0.2225 0.2211 0.2952 0.036 Uiso 1 1 calc R
C7 C -0.0365(16) 0.1231(7) 0.2179(4) 0.0218(19) Uani 1 1 d
C8 C -0.2318(13) 0.0804(7) 0.1791(4) 0.022(2) Uani 1 1 d
H8 H -0.3771 0.1124 0.1954 0.027 Uiso 1 1 calc R
C9 C -0.2546(14) -0.0477(7) 0.1973(4) 0.025(2) Uani 1 1 d
C10 C -0.4499(16) -0.1010(8) 0.2306(4) 0.030(2) Uani 1 1 d

H10 H -0.5744 -0.0576 0.2426 0.036 Uiso 1 1 calc R
C11 C -0.4708(15) -0.2180(8) 0.2476(5) 0.032(2) Uani 1 1 d
H11 H -0.6058 -0.2539 0.2724 0.039 Uiso 1 1 calc R
C12 C -0.2938(17) -0.2801(8) 0.2281(5) 0.036(2) Uani 1 1 d
H12 H -0.3105 -0.3599 0.2373 0.043 Uiso 1 1 calc R
C13 C -0.0902(17) -0.2296(7) 0.1951(5) 0.033(2) Uani 1 1 d
H13 H 0.0327 -0.2735 0.1825 0.040 Uiso 1 1 calc R
C14 C -0.0711(15) -0.1101(8) 0.1807(5) 0.030(2) Uani 1 1 d
H14 H 0.0680 -0.0731 0.1596 0.036 Uiso 1 1 calc R
C15 C -0.1803(17) 0.1219(7) 0.1024(5) 0.034(2) Uani 1 1 d
H15 H -0.0106 0.1239 0.0931 0.041 Uiso 1 1 calc R
C16 C -0.1867(17) 0.2977(8) 0.0249(4) 0.039(2) Uani 1 1 d
H16A H -0.3189 0.3405 0.0095 0.046 Uiso 1 1 calc R
H16B H -0.1498 0.2458 -0.0088 0.046 Uiso 1 1 calc R
C17 C 0.0101(17) 0.3761(9) 0.0255(5) 0.042(3) Uani 1 1 d
C18 C -0.5097(16) 0.0417(9) 0.0644(4) 0.039(2) Uani 1 1 d
H18A H -0.5758 0.1013 0.0885 0.046 Uiso 1 1 calc R
H18B H -0.5586 -0.0322 0.0923 0.046 Uiso 1 1 calc R
C19 C -0.5908(16) 0.0493(9) -0.0072(5) 0.040(3) Uani 1 1 d
C20 C 0.4048(14) 0.4635(7) 0.3256(4) 0.024(2) Uani 1 1 d
C21 C 0.2243(15) 0.4959(7) 0.2865(4) 0.029(2) Uani 1 1 d
H21 H 0.0988 0.5309 0.3065 0.034 Uiso 1 1 calc R
C22 C 0.2284(15) 0.4767(7) 0.2183(4) 0.029(2) Uani 1 1 d
H22 H 0.1066 0.5010 0.1913 0.034 Uiso 1 1 calc R
C23 C 0.4007(18) 0.4244(8) 0.1891(6) 0.041(3) Uani 1 1 d
H23 H 0.3984 0.4108 0.1423 0.050 Uiso 1 1 calc R
C24 C 0.5839(16) 0.3902(7) 0.2279(5) 0.033(2) Uani 1 1 d
H24 H 0.7057 0.3525 0.2081 0.039 Uiso 1 1 calc R
C25 C 0.5843(16) 0.4123(7) 0.2958(5) 0.031(2) Uani 1 1 d
H25 H 0.7100 0.3919 0.3219 0.037 Uiso 1 1 calc R
C26 C 0.4130(16) 0.4876(7) 0.3980(5) 0.029(2) Uani 1 1 d
C27 C 0.2062(14) 0.5233(7) 0.4378(4) 0.025(2) Uani 1 1 d
H27 H 0.0660 0.4885 0.4224 0.030 Uiso 1 1 calc R
C28 C 0.1969(14) 0.6512(7) 0.4230(4) 0.026(2) Uani 1 1 d
C29 C 0.3706(15) 0.7183(7) 0.4419(5) 0.032(2) Uani 1 1 d
H29 H 0.4972 0.6855 0.4631 0.038 Uiso 1 1 calc R
C30 C 0.3555(16) 0.8361(8) 0.4289(5) 0.041(3) Uani 1 1 d
H30 H 0.4761 0.8829 0.4401 0.050 Uiso 1 1 calc R
C31 C 0.1656(17) 0.8857(9) 0.3998(5) 0.045(3) Uani 1 1 d
H31 H 0.1516 0.9648 0.3945 0.054 Uiso 1 1 calc R
C32 C -0.0005(16) 0.8170(7) 0.3789(4) 0.031(2) Uani 1 1 d
H32 H -0.1238 0.8491 0.3555 0.037 Uiso 1 1 calc R
C33 C 0.0137(15) 0.6988(7) 0.3925(5) 0.033(2) Uani 1 1 d
H33 H -0.1048 0.6518 0.3803 0.040 Uiso 1 1 calc R
C34 C 0.223(2) 0.4800(8) 0.5163(5) 0.043(3) Uani 1 1 d
H34 H 0.3883 0.4843 0.5243 0.052 Uiso 1 1 calc R
C35 C 0.185(3) 0.3052(10) 0.5912(6) 0.075(4) Uani 1 1 d
H35A H 0.2516 0.3575 0.6196 0.090 Uiso 1 1 calc R
H35B H 0.0331 0.2778 0.6142 0.090 Uiso 1 1 calc R
C36 C 0.320(3) 0.2162(12) 0.5907(7) 0.074(4) Uani 1 1 d

C37 C -0.107(2) 0.5361(12) 0.5570(6) 0.081(5) Uani 1 1 d
H37A H -0.1527 0.4695 0.5363 0.097 Uiso 1 1 calc R
H37B H -0.1488 0.6048 0.5268 0.097 Uiso 1 1 calc R
C38 C -0.229(2) 0.5289(12) 0.6377(6) 0.053(3) Uani 1 1 d
C39 C 0.3844(13) 0.5013(7) 0.8149(4) 0.021(2) Uani 1 1 d
C40 C 0.2215(15) 0.4363(8) 0.7892(5) 0.033(2) Uani 1 1 d
H40 H 0.0837 0.4681 0.7755 0.040 Uiso 1 1 calc R
C41 C 0.2593(16) 0.3244(8) 0.7836(5) 0.036(2) Uani 1 1 d
H41 H 0.1510 0.2811 0.7638 0.043 Uiso 1 1 calc R
C42 C 0.4515(16) 0.2774(8) 0.8063(4) 0.034(2) Uani 1 1 d
H42 H 0.4715 0.2000 0.8045 0.041 Uiso 1 1 calc R
C43 C 0.6186(17) 0.3391(8) 0.8320(5) 0.039(2) Uani 1 1 d
H43 H 0.7539 0.3054 0.8465 0.046 Uiso 1 1 calc R
C44 C 0.5833(15) 0.4545(7) 0.8362(5) 0.029(2) Uani 1 1 d
H44 H 0.6956 0.4990 0.8536 0.035 Uiso 1 1 calc R
C45 C 0.3336(16) 0.6235(7) 0.8199(4) 0.028(2) Uani 1 1 d
C46 C 0.5189(14) 0.6997(7) 0.8381(4) 0.025(2) Uani 1 1 d
H46 H 0.6708 0.6704 0.8254 0.030 Uiso 1 1 calc R
C47 C 0.4915(15) 0.7019(7) 0.9154(5) 0.033(2) Uani 1 1 d
C48 C 0.6622(17) 0.6648(9) 0.9572(5) 0.044(3) Uani 1 1 d
H48 H 0.7981 0.6385 0.9369 0.053 Uiso 1 1 calc R
C49 C 0.6350(19) 0.6658(9) 1.0298(5) 0.045(3) Uani 1 1 d
H49 H 0.7528 0.6418 1.0585 0.054 Uiso 1 1 calc R
C50 C 0.4415(19) 0.7010(9) 1.0574(6) 0.049(3) Uani 1 1 d
H50 H 0.4252 0.7009 1.1063 0.059 Uiso 1 1 calc R
C51 C 0.2644(18) 0.7373(9) 1.0195(5) 0.043(2) Uani 1 1 d
H51 H 0.1276 0.7605 1.0411 0.051 Uiso 1 1 calc R
C52 C 0.2959(17) 0.7385(8) 0.9451(5) 0.043(3) Uani 1 1 d
H52 H 0.1795 0.7651 0.9166 0.052 Uiso 1 1 calc R
C53 C 0.4933(15) 0.8143(7) 0.7926(5) 0.031(2) Uani 1 1 d
H53 H 0.3271 0.8287 0.7920 0.038 Uiso 1 1 calc R
C54 C 0.522(2) 0.8923(10) 0.6735(5) 0.059(3) Uani 1 1 d
H54A H 0.5364 0.9651 0.6908 0.071 Uiso 1 1 calc R
H54B H 0.3629 0.8806 0.6622 0.071 Uiso 1 1 calc R
C55 C 0.683(2) 0.8934(10) 0.6096(6) 0.064(3) Uani 1 1 d
C56 C 0.8426(15) 0.8998(7) 0.8208(6) 0.040(3) Uani 1 1 d
H56A H 0.9087 0.8536 0.7870 0.048 Uiso 1 1 calc R
H56B H 0.8738 0.8649 0.8683 0.048 Uiso 1 1 calc R
C57 C 0.9452(16) 1.0177(7) 0.8048(5) 0.039(2) Uani 1 1 d U
F1 F 0.2002(10) 0.3236(5) 0.0427(4) 0.0620(17) Uani 1 1 d
F2 F -0.0257(11) 0.4468(5) 0.0710(3) 0.0605(17) Uani 1 1 d
F3 F 0.0606(12) 0.4388(5) -0.0368(3) 0.0643(18) Uani 1 1 d
F4 F -0.5736(15) 0.1579(6) -0.0391(4) 0.089(2) Uani 1 1 d
F5 F -0.4910(12) -0.0125(7) -0.0482(3) 0.078(2) Uani 1 1 d
F6 F -0.8131(10) 0.0201(6) -0.0013(3) 0.0663(19) Uani 1 1 d
F7 F 0.5475(17) 0.2716(9) 0.5655(4) 0.114(3) Uani 1 1 d
F8 F 0.3001(15) 0.1488(5) 0.5459(3) 0.080(2) Uani 1 1 d
F9 F 0.3652(14) 0.1560(5) 0.6510(3) 0.075(2) Uani 1 1 d
F10 F -0.1973(13) 0.4258(6) 0.6685(3) 0.078(2) Uani 1 1 d
F11 F -0.4460(12) 0.5435(7) 0.6348(3) 0.077(2) Uani 1 1 d

F12 F -0.1557(11) 0.5956(7) 0.6779(4) 0.074(2) Uani 1 1 d
F13 F 0.9043 0.8994 0.6225 0.105 Uani 1 1 d
F14 F 0.6387 0.9772 0.5603 0.097 Uani 1 1 d
F15 F 0.6596 0.7994 0.5826 0.119 Uani 1 1 d
F16 F 1.1673 1.0218 0.8029 0.076 Uani 1 1 d
F17 F 0.8639 1.0846 0.8466 0.072 Uani 1 1 d
F18 F 0.8995 1.0697 0.7417 0.098 Uani 1 1 d
O1 O 0.1545(11) 0.1328(5) 0.1921(3) 0.0352(15) Uani 1 1 d
O2 O -0.2443(11) 0.2351(5) 0.0916(3) 0.0401(16) Uani 1 1 d
O3 O -0.2694 0.0549 0.0577 0.042 Uani 1 1 d
O4 O 0.5960(12) 0.4791(5) 0.4245(3) 0.0385(16) Uani 1 1 d
O5 O 0.1559(14) 0.3650(5) 0.5250(3) 0.053(2) Uani 1 1 d
O6 O 0.1096(15) 0.5389(6) 0.5643(4) 0.063(2) Uani 1 1 d
O7 O 0.1458(12) 0.6524(5) 0.8113(4) 0.0448(17) Uani 1 1 d
O8 O 0.5786(12) 0.8029(5) 0.7256(3) 0.0391(16) Uani 1 1 d
O9 O 0.6052(10) 0.9064(4) 0.8159(3) 0.0303(14) Uani 1 1 d

Anisotropic displacement parameters

C1 0.021(5) 0.015(5) 0.024(5) -0.004(4) 0.011(4) 0.002(4)
C2 0.043(6) 0.019(5) 0.037(6) -0.014(4) -0.002(5) 0.004(4)
C3 0.033(6) 0.035(6) 0.030(6) 0.002(5) 0.007(4) -0.006(4)
C4 0.060(7) 0.025(5) 0.026(5) -0.011(4) 0.006(5) 0.005(5)
C5 0.034(6) 0.024(5) 0.031(5) -0.016(4) 0.002(4) 0.003(4)
C6 0.039(6) 0.021(5) 0.026(5) 0.011(4) -0.002(4) -0.003(4)
C7 0.027(6) 0.012(5) 0.027(5) -0.003(4) -0.003(4) 0.001(4)
C8 0.022(5) 0.021(5) 0.019(5) 0.011(4) -0.001(4) 0.001(4)
C9 0.022(5) 0.029(5) 0.024(5) -0.005(4) 0.004(4) 0.006(4)
C10 0.041(6) 0.029(6) 0.024(5) -0.011(4) -0.011(4) 0.007(4)
C11 0.031(6) 0.032(7) 0.031(5) 0.004(4) -0.006(4) -0.015(5)
C12 0.053(7) 0.029(6) 0.028(5) -0.006(4) -0.011(5) 0.014(5)
C13 0.044(6) 0.021(6) 0.034(5) -0.005(4) -0.002(5) -0.006(4)
C14 0.022(5) 0.033(6) 0.032(5) 0.003(4) 0.005(4) -0.006(4)
C15 0.055(6) 0.014(5) 0.040(6) -0.017(4) -0.021(5) 0.008(4)
C16 0.059(7) 0.029(6) 0.020(5) 0.017(4) 0.004(4) -0.001(5)
C17 0.041(7) 0.057(7) 0.023(6) 0.008(5) 0.004(4) -0.009(6)
C18 0.040(6) 0.053(7) 0.019(5) 0.003(4) 0.007(4) 0.002(5)
C19 0.031(6) 0.047(7) 0.041(6) -0.012(6) 0.004(5) -0.009(5)
C20 0.018(5) 0.023(5) 0.032(5) -0.007(4) 0.002(4) 0.006(4)
C21 0.032(5) 0.031(5) 0.021(5) -0.002(4) -0.002(4) -0.006(4)
C22 0.039(6) 0.020(5) 0.022(5) 0.010(4) -0.006(4) -0.004(4)
C23 0.062(7) 0.024(6) 0.041(6) -0.012(5) -0.010(6) 0.009(5)
C24 0.044(6) 0.012(5) 0.042(6) -0.013(4) 0.016(5) 0.001(4)
C25 0.036(6) 0.024(5) 0.032(6) 0.000(4) -0.009(4) -0.008(4)
C26 0.034(6) 0.014(5) 0.041(6) 0.003(4) -0.026(5) -0.003(4)
C27 0.024(5) 0.028(5) 0.023(5) -0.002(4) 0.004(4) 0.014(4)
C28 0.026(5) 0.027(5) 0.021(5) 0.003(4) 0.000(4) -0.001(4)
C29 0.031(5) 0.026(6) 0.037(6) -0.003(4) 0.000(4) 0.002(4)
C30 0.042(6) 0.031(6) 0.048(6) 0.000(5) -0.002(5) -0.011(5)

C31 0.050(7) 0.038(6) 0.046(6) 0.000(5) 0.001(5) 0.012(6)
C32 0.044(6) 0.023(6) 0.024(5) 0.010(4) -0.009(4) 0.010(4)
C33 0.036(6) 0.026(6) 0.039(6) -0.009(4) -0.003(5) 0.006(4)
C34 0.078(7) 0.021(6) 0.031(6) -0.010(5) 0.014(5) 0.017(5)
C35 0.134(12) 0.034(7) 0.053(8) 0.009(6) -0.006(7) 0.028(8)
C36 0.111(12) 0.064(10) 0.047(8) -0.006(8) 0.002(7) 0.026(9)
C37 0.070(9) 0.092(10) 0.065(8) 0.048(7) -0.048(7) -0.063(7)
C38 0.037(8) 0.081(10) 0.031(6) 0.022(7) 0.006(5) -0.001(6)
C39 0.025(5) 0.023(5) 0.014(4) -0.003(4) 0.000(4) -0.005(4)
C40 0.030(5) 0.030(6) 0.038(5) 0.005(4) -0.010(4) 0.002(4)
C41 0.035(6) 0.036(6) 0.042(6) -0.022(5) -0.007(4) 0.004(5)
C42 0.044(6) 0.034(6) 0.024(5) -0.009(4) 0.000(4) -0.009(5)
C43 0.046(6) 0.025(6) 0.042(6) 0.003(5) -0.005(5) 0.008(5)
C44 0.030(5) 0.016(5) 0.040(5) -0.006(4) -0.002(4) -0.002(4)
C45 0.025(6) 0.031(6) 0.031(5) -0.003(4) -0.019(4) 0.003(4)
C46 0.028(5) 0.024(5) 0.022(5) 0.006(4) -0.010(4) 0.001(4)
C47 0.024(5) 0.020(5) 0.053(6) -0.004(4) -0.007(5) -0.006(4)
C48 0.038(6) 0.050(7) 0.047(7) -0.011(5) -0.007(5) 0.003(5)
C49 0.053(7) 0.049(7) 0.033(6) -0.001(5) -0.013(5) 0.000(5)
C50 0.054(8) 0.051(7) 0.038(6) -0.002(5) 0.002(6) -0.003(6)
C51 0.051(7) 0.049(7) 0.031(6) -0.016(5) -0.004(5) 0.001(5)
C52 0.043(7) 0.037(6) 0.046(7) 0.006(5) -0.002(5) 0.006(5)
C53 0.032(5) 0.026(6) 0.039(6) -0.010(4) -0.004(4) 0.012(4)
C54 0.081(8) 0.062(8) 0.036(6) -0.003(6) -0.010(6) 0.029(6)
C55 0.099(9) 0.052(8) 0.041(7) 0.002(6) -0.010(6) 0.019(6)
C56 0.038(6) 0.004(5) 0.079(7) -0.001(4) -0.016(5) 0.006(4)
C57 0.046(5) 0.005(4) 0.067(6) -0.011(4) -0.001(4) 0.002(4)
F1 0.046(4) 0.059(4) 0.077(4) -0.001(3) 0.002(3) 0.004(3)
F2 0.098(5) 0.030(3) 0.054(4) -0.010(3) -0.002(3) -0.007(3)
F3 0.099(5) 0.049(4) 0.035(4) 0.011(3) 0.012(3) -0.016(3)
F4 0.141(7) 0.066(5) 0.057(4) 0.012(4) -0.043(4) -0.002(4)
F5 0.084(5) 0.102(6) 0.052(4) -0.041(4) 0.026(4) -0.010(4)
F6 0.045(4) 0.114(6) 0.048(4) -0.041(4) -0.005(3) -0.001(3)
F7 0.115(7) 0.143(8) 0.078(6) 0.004(5) 0.003(5) 0.043(6)
F8 0.165(7) 0.035(4) 0.046(4) -0.018(3) -0.014(4) 0.034(4)
F9 0.143(6) 0.051(4) 0.031(3) 0.010(3) -0.012(4) 0.044(4)
F10 0.113(6) 0.074(5) 0.034(3) 0.017(4) 0.014(3) -0.010(4)
F11 0.060(5) 0.131(7) 0.038(4) -0.009(4) 0.000(3) 0.009(4)
F12 0.060(4) 0.089(5) 0.069(5) 0.008(4) -0.020(4) 0.001(4)
F13 0.100 0.144 0.054 0.029 0.004 -0.007
F14 0.177 0.066 0.037 0.027 0.006 0.037
F15 0.253 0.074 0.038 -0.015 -0.015 0.071
F16 0.030 0.031 0.167 -0.020 0.000 -0.010
F17 0.064 0.031 0.120 -0.020 0.014 -0.012
F18 0.109 0.072 0.098 0.015 0.001 -0.045
O1 0.022(4) 0.046(4) 0.038(4) -0.012(3) 0.008(3) -0.002(3)
O2 0.063(4) 0.026(4) 0.026(4) 0.009(3) 0.004(3) 0.009(3)
O3 0.062 0.040 0.023 -0.004 0.001 0.003
O4 0.049(4) 0.032(4) 0.035(4) -0.006(3) -0.009(3) -0.001(3)
O5 0.117(6) 0.016(4) 0.024(4) 0.007(3) -0.015(4) 0.007(4)

O6 0.078(6) 0.048(5) 0.059(5) 0.008(4) -0.018(4) 0.000(4)
O7 0.043(5) 0.029(4) 0.066(5) -0.014(3) -0.019(3) 0.003(3)
O8 0.073(5) 0.017(3) 0.026(4) 0.002(3) 0.001(3) 0.015(3)
O9 0.039(4) 0.002(3) 0.050(4) -0.006(3) -0.002(3) 0.001(2)

Geom special details

All s.u.'s (except the s.u. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell s.u.'s are taken into account individually in the estimation of s.u.'s in distances, angles and torsion angles; correlations between s.u.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic)

treatment of cell s.u.'s is used for estimating s.u.'s involving l.s. planes.

geom bond atom site label 1

geom bond atom site label 2

geom bond distance

geom bond site symmetry 2

geom bond publ flag

C1 C2 1.358(12)	C20 C26 1.486(13)	C40 H40 0.9500
C1 C6 1.376(12)	C21 C22 1.380(12)	C41 C42 1.358(13)
C1 C7 1.552(12)	C21 H21 0.9500	C41 H41 0.9500
C2 C3 1.388(13)	C22 C23 1.347(13)	C42 C43 1.382(13)
C2 H2 0.9500	C22 H22 0.9500	C42 H42 0.9500
C3 C4 1.377(13)	C23 C24 1.404(14)	C43 C44 1.426(12)
C3 H3 0.9500	C23 H23 0.9500	C43 H43 0.9500
C4 C5 1.339(13)	C24 C25 1.387(13)	C44 H44 0.9500
C4 H4 0.9500	C24 H24 0.9500	C45 O7 1.188(10)
C5 C6 1.411(13)	C25 H25 0.9500	C45 C46 1.498(12)
C5 H5 0.9500	C26 O4 1.232(10)	C46 C47 1.507(13)
C6 H6 0.9500	C26 C27 1.503(13)	C46 C53 1.542(12)
C7 O1 1.189(10)	C27 C28 1.527(12)	C46 H46 1.0000
C7 C8 1.540(12)	C27 C34 1.549(13)	C47 C52 1.365(13)
C8 C15 1.503(12)	C27 H27 1.0000	C47 C48 1.387(13)
C8 C9 1.528(12)	C28 C33 1.374(12)	C48 C49 1.412(14)
C8 H8 1.0000	C28 C29 1.387(12)	C48 H48 0.9500
C9 C10 1.363(13)	C29 C30 1.410(13)	C49 C50 1.331(14)
C9 C14 1.383(12)	C29 H29 0.9500	C49 H49 0.9500
C10 C11 1.396(12)	C30 C31 1.405(14)	C50 C51 1.371(14)
C10 H10 0.9500	C30 H30 0.9500	C50 H50 0.9500
C11 C12 1.367(13)	C31 C32 1.383(14)	C51 C52 1.444(14)
C11 H11 0.9500	C31 H31 0.9500	C51 H51 0.9500
C12 C13 1.388(14)	C32 C33 1.414(12)	C52 H52 0.9500
C12 H12 0.9500	C32 H32 0.9500	C53 O8 1.389(11)
C13 C14 1.422(13)	C33 H33 0.9500	C53 O9 1.420(10)
C13 H13 0.9500	C34 O6 1.400(12)	C53 H53 1.0000

C14 H14 0.9500	C34 O5 1.407(12)	C54 O8 1.430(12)
C15 O3 1.394(8)	C34 H34 1.0000	C54 C55 1.498(17)
C15 O2 1.417(10)	C35 C36 1.356(17)	C54 H54A 0.9900
C15 H15 1.0000	C35 O5 1.403(13)	C54 H54B 0.9900
C16 O2 1.409(11)	C35 H35A 0.9900	C55 F15 1.326(12)
C16 C17 1.470(14)	C35 H35B 0.9900	C55 F14 1.330(11)
C16 H16A 0.9900	C36 F8 1.288(14)	C55 F13 1.349(13)
C16 H16B 0.9900	C36 F9 1.335(14)	C56 O9 1.413(10)
C17 F2 1.329(12)	C36 F7 1.489(18)	C56 C57 1.500(13)
C17 F3 1.334(11)	C37 O6 1.292(13)	C56 H56A 0.9900
C17 F1 1.345(11)	C37 C38 1.665(18)	C56 H56B 0.9900
C18 O3 1.411(9)	C37 H37A 0.9900	C57 F16 1.304(9)
C18 C19 1.501(14)	C37 H37B 0.9900	C57 F17 1.306(9)
C18 H18A 0.9900	C38 F12 1.289(14)	C57 F18 1.343(10)
C18 H18B 0.9900	C38 F11 1.303(12)	
C19 F5 1.294(12)	C38 F10 1.319(13)	
C19 F6 1.334(11)	C39 C44 1.383(12)	
C19 F4 1.357(12)	C39 C40 1.387(12)	
C20 C25 1.376(12)	C39 C45 1.528(12)	
C20 C21 1.390(12)	C40 C41 1.392(13)	

geom angle atom site label 1

geom angle atom site label 2

geom angle atom site label 3

geom angle

geom angle site symmetry 1

geom angle site symmetry 3

geom angle publ flag

C2 C1 C6 121.5(8)	C25 C20 C21 119.3(8)	C44 C39 C45 122.1(7)
C2 C1 C7 122.9(7)	C25 C20 C26 119.3(7)	C40 C39 C45 117.9(7)
C6 C1 C7 115.5(7)	C21 C20 C26 121.4(8)	C39 C40 C41 120.2(8)
C1 C2 C3 119.5(8)	C22 C21 C20 119.6(8)	C39 C40 H40 119.9
C1 C2 H2 120.2	C22 C21 H21 120.2	C41 C40 H40 119.9
C3 C2 H2 120.2	C20 C21 H21 120.2	C42 C41 C40 119.8(8)
C4 C3 C2 119.1(8)	C23 C22 C21 121.6(8)	C42 C41 H41 120.1
C4 C3 H3 120.4	C23 C22 H22 119.2	C40 C41 H41 120.1
C2 C3 H3 120.4	C21 C22 H22 119.2	C41 C42 C43 121.9(9)
C5 C4 C3 121.7(8)	C22 C23 C24 119.7(9)	C41 C42 H42 119.1
C5 C4 H4 119.1	C22 C23 H23 120.2	C43 C42 H42 119.1
C3 C4 H4 119.1	C24 C23 H23 120.2	C42 C43 C44 118.4(9)
C4 C5 C6 119.7(8)	C25 C24 C23 119.0(8)	C42 C43 H43 120.8
C4 C5 H5 120.2	C25 C24 H24 120.5	C44 C43 H43 120.8
C6 C5 H5 120.2	C23 C24 H24 120.5	C39 C44 C43 119.6(8)
C1 C6 C5 118.4(8)	C20 C25 C24 120.8(8)	C39 C44 H44 120.2
C1 C6 H6 120.8	C20 C25 H25 119.6	C43 C44 H44 120.2

C5 C6 H6 120.8	C24 C25 H25 119.6	O7 C45 C46 123.1(8)
O1 C7 C8 120.9(7)	O4 C26 C20 118.1(8)	O7 C45 C39 118.0(7)
O1 C7 C1 120.4(7)	O4 C26 C27 120.5(8)	C46 C45 C39 118.8(7)
C8 C7 C1 118.6(7)	C20 C26 C27 121.5(7)	C45 C46 C47 108.7(7)
C15 C8 C9 113.6(7)	C26 C27 C28 109.4(7)	C45 C46 C53 105.3(6)
C15 C8 C7 108.3(7)	C26 C27 C34 107.9(7)	C47 C46 C53 114.4(7)
C9 C8 C7 108.3(6)	C28 C27 C34 111.9(7)	C45 C46 H46 109.4
C15 C8 H8 108.8	C26 C27 H27 109.2	C47 C46 H46 109.4
C9 C8 H8 108.8	C28 C27 H27 109.2	C53 C46 H46 109.4
C7 C8 H8 108.8	C34 C27 H27 109.2	C52 C47 C48 119.5(9)
C10 C9 C14 119.7(8)	C33 C28 C29 120.6(8)	C52 C47 C46 120.1(8)
C10 C9 C8 121.3(7)	C33 C28 C27 119.6(7)	C48 C47 C46 120.4(8)
C14 C9 C8 119.0(7)	C29 C28 C27 119.8(7)	C47 C48 C49 120.3(10)
C9 C10 C11 121.4(8)	C28 C29 C30 118.7(8)	C47 C48 H48 119.8
C9 C10 H10 119.3	C28 C29 H29 120.7	C49 C48 H48 119.8
C11 C10 H10 119.3	C30 C29 H29 120.7	C50 C49 C48 118.8(9)
C12 C11 C10 118.9(8)	C31 C30 C29 121.3(8)	C50 C49 H49 120.6
C12 C11 H11 120.5	C31 C30 H30 119.3	C48 C49 H49 120.6
C10 C11 H11 120.5	C29 C30 H30 119.3	C49 C50 C51 124.1(10)
C11 C12 C13 121.7(9)	C32 C31 C30 118.7(9)	C49 C50 H50 118.0
C11 C12 H12 119.2	C32 C31 H31 120.7	C51 C50 H50 118.0
C13 C12 H12 119.2	C30 C31 H31 120.7	C50 C51 C52 116.7(9)
C12 C13 C14 118.0(8)	C31 C32 C33 119.8(8)	C50 C51 H51 121.7
C12 C13 H13 121.0	C31 C32 H32 120.1	C52 C51 H51 121.7
C14 C13 H13 121.0	C33 C32 H32 120.1	C47 C52 C51 120.6(9)
C9 C14 C13 120.1(8)	C28 C33 C32 120.8(8)	C47 C52 H52 119.7
C9 C14 H14 119.9	C28 C33 H33 119.6	C51 C52 H52 119.7
C13 C14 H14 119.9	C32 C33 H33 119.6	O8 C53 O9 111.1(7)
O3 C15 O2 114.7(6)	O6 C34 O5 114.0(8)	O8 C53 C46 106.0(6)
O3 C15 C8 115.9(7)	O6 C34 C27 117.4(8)	O9 C53 C46 114.2(7)
O2 C15 C8 106.0(7)	O5 C34 C27 104.9(7)	O8 C53 H53 108.5
O3 C15 H15 106.5	O6 C34 H34 106.6	O9 C53 H53 108.5
O2 C15 H15 106.5	O5 C34 H34 106.6	C46 C53 H53 108.5
C8 C15 H15 106.5	C27 C34 H34 106.6	O8 C54 C55 108.5(8)
O2 C16 C17 111.0(8)	C36 C35 O5 114.7(11)	O8 C54 H54A 110.0
O2 C16 H16A 109.4	C36 C35 H35A 108.6	C55 C54 H54A 110.0
C17 C16 H16A 109.4	O5 C35 H35A 108.6	O8 C54 H54B 110.0
O2 C16 H16B 109.4	C36 C35 H35B 108.6	C55 C54 H54B 110.0
C17 C16 H16B 109.4	O5 C35 H35B 108.6	H54A C54 H54B 108.4
H16A C16 H16B 108.0	H35A C35 H35B 107.6	F15 C55 F14 106.5(8)
F2 C17 F3 106.8(8)	F8 C36 F9 108.3(11)	F15 C55 F13 104.3(8)
F2 C17 F1 105.8(8)	F8 C36 C35 120.8(12)	F14 C55 F13 110.5(9)
F3 C17 F1 106.8(8)	F9 C36 C35 119.5(11)	F15 C55 C54 111.8(10)
F2 C17 C16 112.6(8)	F8 C36 F7 100.2(10)	F14 C55 C54 110.3(9)
F3 C17 C16 111.4(8)	F9 C36 F7 101.2(11)	F13 C55 C54 113.2(9)
F1 C17 C16 112.9(9)	C35 C36 F7 102.4(12)	O9 C56 C57 107.2(6)
O3 C18 C19 108.3(7)	O6 C37 C38 104.3(9)	O9 C56 H56A 110.3
O3 C18 H18A 110.0	O6 C37 H37A 110.9	C57 C56 H56A 110.3
C19 C18 H18A 110.0	C38 C37 H37A 110.9	O9 C56 H56B 110.3
O3 C18 H18B 110.0	O6 C37 H37B 110.9	C57 C56 H56B 110.3

C19 C18 H18B 110.0 H18A C18 H18B 108.4 F5 C19 F6 107.1(8) F5 C19 F4 108.9(9) F6 C19 F4 105.4(8) F5 C19 C18 116.4(9) F6 C19 C18 108.8(8) F4 C19 C18 109.7(8)	C38 C37 H37B 110.9 H37A C37 H37B 108.9 F12 C38 F11 106.8(10) F12 C38 F10 106.4(9) F11 C38 F10 109.7(10) F12 C38 C37 119.8(10) F11 C38 C37 108.9(9) F10 C38 C37 105.0(10) C44 C39 C40 120.0(7)	H56A C56 H56B 108.5 F16 C57 F17 109.4(6) F16 C57 F18 104.6(7) F17 C57 F18 102.9(6) F16 C57 C56 112.9(7) F17 C57 C56 114.0(8) F18 C57 C56 112.2(7) C16 O2 C15 117.0(7) C15 O3 C18 114.3(6) C35 O5 C34 114.6(8) C37 O6 C34 109.8(10) C53 O8 C54 113.5(7) C56 O9 C53 116.3(6)

diffrn measured fraction theta max 0.998

diffrn reflns theta full 20.83

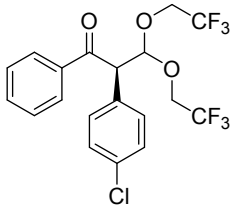
diffrn measured fraction theta full 0.998

refine diff density max 0.725

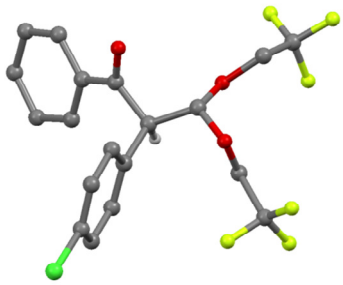
refine diff density min -0.337

refine diff density rms 0.122

X-ray Crystallographic data for 254c (CCDC-929704)



254c



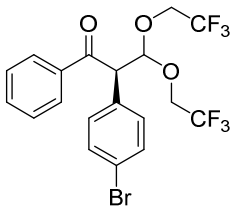
audit creation method	SHELXL-97
chemical formula moiety	C_{19} H_{15} Cl F_6 O_3
chemical formula sum	C_{19} H_{15} Cl F_6 O_3
chemical formula weight	440.76
atom type scat source 'C' 'C' 0.0033 0.0016	
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4' 'H' 'H' 0.0000 0.0000	
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4' 'Cl' 'Cl' 0.1484 0.1585	
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4' 'F' 'F' 0.0171 0.0103	
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4' 'O' 'O' 0.0106 0.0060	

symmetry cell setting	Monoclinic
cell length a	5.8641(3)
cell length b	33.384(2)
cell angle alpha	90.00
cell angle beta	90.00
cell angle gamma	90.00
cell volume	3855.5(4)
cell formula units Z	8
cell measurement temperature	293(2)
cell measurement reflns used	3462
cell measurement theta min	2.44
cell measurement theta max	23.63
exptl crystal description	needle
exptl crystal colour	colourless
exptl crystal size max	0.50
exptl crystal size mid	0.10
exptl crystal size min	0.03
exptl crystal density meas	
exptl crystal density diffrn	1.519
exptl crystal F 000	1792
exptl absorpt coefficient mu	0.272
exptl absorpt correction T min	0.8759
exptl absorpt correction T max	0.9919
diffrn ambient temperature	293(2)
diffrn radiation wavelength	0.71073
diffrn radiation source	'fine-focus sealed tube'
diffrn radiation monochromator	graphite
diffrn reflns number	12356
diffrn reflns av R equivalents	0.0677
diffrn reflns av sigmaI/netI	0.0898
diffrn reflns limit h min	-6
diffrn reflns limit h max	5
diffrn reflns limit k min	-31
diffrn reflns limit k max	37
diffrn reflns limit l min	-21
diffrn reflns limit l max	21
diffrn reflns theta min	2.44
diffrn reflns theta max	23.63
reflns number total	5271
reflns number gt	3462

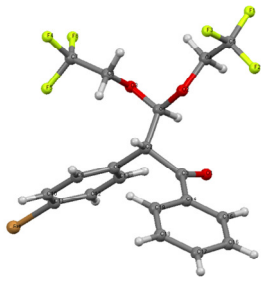
refine ls matrix type	full
refine ls weighting scheme	calc
refine ls weighting details	
atom sites solution primary	direct
atom sites solution secondary	difmap
atom sites solution hydrogens	geom
refine ls hydrogen treatment	constr

refine ls extinction method	none
refine ls extinction coef	
refine ls abs structure details	
refine ls abs structure Flack	**0.17(16)**
refine ls number reflns	5271
refine ls number parameters	578
refine ls number restraints	255
refine ls R factor all	0.1430
refine ls R factor gt	0.0876
refine ls wR factor ref	0.1955
refine ls wR factor gt	0.1696
refine ls goodness of fit ref	1.088
refine ls restrained S all	1.101
refine ls shift/su max	0.013
refine ls shift/su mean	0.001

X-Ray crystallographic data of 254d (CCDC-929705)



254d



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Chapter 7

Research Publications

Stereoselective Synthesis

DOI: 10.1002/anie.201107703

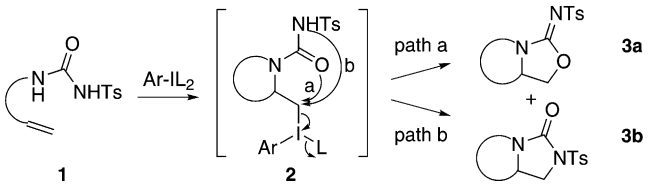
Highly Stereoselective Metal-Free Oxyaminations Using Chiral Hypervalent Iodine Reagents**

*Umar Farid and Thomas Wirth**

Hypervalent iodine reagents are frequently used and have found wide applications in synthesis.[1,2] They are used in a wide range of transformations as environmentally friendly, mild and highly selective oxidants because they avoid the issues of toxicity or the complicated ligands of many transition-metal-based systems. They can also be employed as electrophilic reagents for the functionalization of alkenes in halolactonizations[3] and dioxytosylations,[4] for the oxidative dearomatization of phenols,[5] and the α-functionalization of ketones.[6,7] In this context, the use of chiral hypervalent iodine reagents for asymmetric transformations has emerged as an interesting area of research in recent years.[8] Only recently the catalytic use of iodine compounds in synthesis has been developed.[9] We reported the first catalytic use of enantiomerically pure iodoarenes in asymmetric reactions,[10] which opened the possibility to employ a wide range of such compounds with various structural features as catalysts.[11]

The 1,2-difunctionalization of alkenes is a very important transformation as is illustrated by the occurrence of the 1,2-amino alcohol moiety in a huge range of bioactive compounds, natural products, and chiral reagents for stereoselective synthesis. Transition-metal-catalyzed oxidative amination reactions are established methods for the synthesis of new carbon–nitrogen and carbon–oxygen bonds through the functionalization of alkenes.[12] The osmium-based catalytic aminohydroxylation is an early efficient route developed by Sharpless et al.,[13] but other metal catalysts, such as palladium and platinum, have also been used for intramolecular aminations.[14] The use of bifunctional nucleophiles together with hypervalent iodine reagents in additions to alkenes can lead to versatile building blocks as shown in the aminohydroxylations of alkenes.[15]

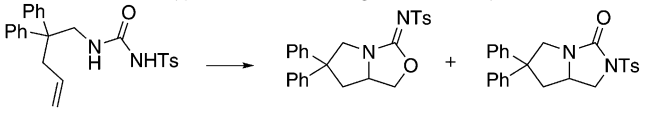
Herein we describe the first efficient stereoselective oxyaminations using chiral hypervalent iodine compounds. For these reactions we have investigated sulfonyl-substituted homoallylic urea derivatives of type **1** (Scheme 1). After the activation of the double bond with the hypervalent iodine reagent, the first nucleophile reacts to give intermediate **2**. The hypervalent iodine moiety is then attached to an sp^3-hybridized carbon atom and is therefore an excellent leaving group, several orders of magnitude more reactive than triflates or tosylates.[16] The subsequent substitution reaction directly yields bicyclic compounds **3**. It has already been shown that, depending on the reaction conditions, such cyclizations can lead either to isoureas **3a** or to the formation of diamination products **3b** (Scheme 1).[15c,17]



Scheme 1. Cyclization of urea bisnucleophiles with alkenes using hypervalent iodine reagents (Ar-IL_2) for the synthesis of isoureas **3a** (path a) or of cyclic ureas **3b** (path b).

Initial cyclizations of substrate **4** were performed by modifying literature procedures.[15c] [Bis(trifluoroacetoxy)iodo]benzene led to the reaction products **5a** and **5b** in low yields in a very slow reaction (Table 1, entry 1). Also the addition of catalytic amounts of diphenyl diselenide, a catalyst which was successful in a series of other cyclization–elimination sequences,[18] did not provide a substantial improvement as reaction time is still long (entry 2). The addition of *tert*-butyldimethylsilyl triflate (TBDMSOTf, Table 1, entries 3 and 4) or trimethylsilyl triflate (TMSOTf) to (diacetoxyiodo)benzene generates in situ, as evidenced by NMR spectroscopic investigations (see the Supporting Infor-

Table 1: Different hypervalent iodine reagents for the cyclization of **4**.



4 **5a** **5b**

Entry	Reagents	Solvent, Conditions	Yield [%] 5a	5b
1	$PhI(OCOCF_3)_2$	CH_2Cl_2, RT, 120 h	26	28
2	$PhI(OCOCF_3)_2$, 5 mol% $(PhSe)_2$	CH_2Cl_2, RT, 72 h	62	6
3	$PhI(OAc)_2$, TBDMSOTf	CH_2Cl_2, −78 to RT, 8 h	48	20
4	$PhI(OCOCF_3)_2$, TBDMSOTf	CH_2Cl_2, −78 to RT, 3 h	50	22

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[**] We thank Dr. Benson Kariuki (Cardiff University) for the X-ray analysis of **8**, Grégory Bonnamain (University of Nantes, France) and Pierre-Henri Belin, (ESCOM, France) for assistance in the synthesis of some starting materials, and the EPSRC National Mass Spectrometry Service Centre, Swansea, for mass spectrometric data. We thank The Charles Wallace Pakistan Trust (U.F.) and Cardiff University for financial support.

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mation), the more reactive $PhI(OTf)_2$.[19] This step leads to a mixture of **5a** and **5b** (ratio approx. 2:1) in a much faster reaction with improved combined yields of 72% (Table 1, entry 4).

Lactate-based hypervalent iodine compounds have been synthesized by Fujita et al.[20] and reagent **6a** has been introduced by Ishihara et al. for a highly enantioselective spirolactonizations.[21] As the products **5a** and **5b** contain stereogenic centers, substrate **4** was cyclized using the different chiral hypervalent iodine reagents **6** (Figure 1). Under various reaction conditions, only isourea compound **5a** was obtained with all reagents **6** and the cyclic urea derivative **5b** could not be detected.

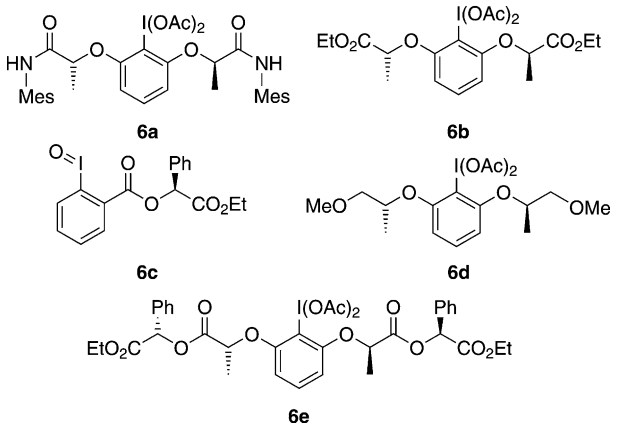


Figure 1. Enantiomerically pure lactate- and mandelate-derived hypervalent iodine reagents **6**.

As shown in Table 2, the hypervalent iodine reagent **6a** has been investigated together with different acids for its activation (Table 2, entries 1–3). The highest selectivities are obtained with trimethylsilyl triflate (TMSOTf) leading to the reaction product **5a** with an enantiomeric excess of 61% *ee* (Table 2, entry 3).[22] Slightly higher reaction temperatures led to lower selectivities (Table 2, entry 4), as did other solvents (Table 2, entries 5 and 6). The hypervalent iodine compounds **6b** and **6d**, which are also derived from lactic acid, were less efficient in the stereoselective cyclization of **4** (Table 2, entries 7 and 8). In these experiments, stoichiometric amounts of the hypervalent iodine reagents **6** are being used. About 80–85% of the reduced aryl iodides are recovered after the reaction without loss of optical purity and can be reused by oxidation. Previous research by our group using selenium electrophiles revealed that styrene derivatives are potential substrates for cyclizations with high selectivities.[23] We therefore prepared and investigated compound **7** in stereoselective cyclizations leading to isourea **8** containing a stereogenic tetrasubstituted carbon atom.

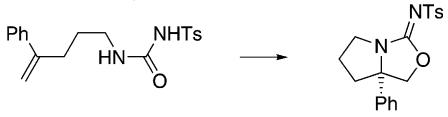
All the chiral hypervalent iodine reagents **6** shown in Figure 1 have been used for the cyclization of compound **7** (Table 3, entries 1–5). Highest selectivities have been obtained with reagent **6a**, probably because of its ability to coordinate through the amide nitrogen atoms to the iodine atom.[21] Also reagent **6e**, containing lactic acid and mandelic acid moieties, led to a good selectivity for product **8** (Table 3, entry 5). The addition of trifluoroethanol, which can strongly influence reactions with hypervalent iodine compounds,[24] did not have a pronounced effect in this case (Table 3, entry 6). The use of other solvent mixtures increased selectivities and yields. Experiments with **7** containing small amounts of *para*-toluenesulfonamide ($TsNH_2$) as a result of the preparation procedure gave variable results. Addition of $TsNH_2$ to the reagent **6a** together with an excess of TMSOTf, led to reproducible results and to synthetically very attractive selectivities, especially if **6a** is allowed to react first with TMSOTf (Table 3, entries 9 and 10).

Table 2: Conditions for the stereoselective cyclization to **5a**.

Entry	Reagents[a]	Solvent	Yield [%]	*ee* [%]
1	**6a**, TBDMSOTf	CH_2Cl_2	50	40
2	**6a**, TfOH	CH_2Cl_2	58	40
3	**6a**, TMSOTf	CH_2Cl_2	48	61
4	**6a**, TMSOTf	CH_2Cl_2	61	57[b]
5	**6a**, TMSOTf	toluene	0	–
6	**6a**, TMSOTf	THF	34	10
7	**6b**, TMSOTf	CH_2Cl_2	30	12
8	**6d**, TMSOTf	CH_2Cl_2	50	0

[a] Reaction temperature −78 °C, reaction time 14 h. [b] Reaction temperature −78 °C to room temperature.

Table 3: Stereoselective cyclization of **7** to isourea derivative **8**.



7 **8**

Entry	Reagents[a]	Solvent	Yield [%]	*ee* [%][b]
1	**6a**, 1.5 equiv TMSOTf	CH_2Cl_2	40	78
2	**6b**, 1.5 equiv TMSOTf	CH_2Cl_2	35	69
3	**6c**, 1.5 equiv TMSOTf	CH_2Cl_2	34	50
4	**6d**, 1.5 equiv TMSOTf	CH_2Cl_2	20	50
5	**6e**, 1.5 equiv TMSOTf	CH_2Cl_2	40	75
6	**6a**, 1.5 equiv TMSOTf	CH_2Cl_2/CF_3CH_2OH (1:1)	43	81
7[c,d]	**6a**, 2 equiv TMSOTf	CH_2Cl_2/Et_2O (3:1)	48	88
8[c]	**6a**, 2 equiv TMSOTf, 0.5 equiv $TsNH_2$	CH_2Cl_2/Et_2O (1:3)	76	90
9[c,e]	**6a**, 2 equiv TMSOTf, 0.5 equiv $TsNH_2$	CH_2Cl_2/Et_2O (1:3)	60–71	92–96
10[c,e,f]	**6a**, 3 equiv TMSOTf, 0.5 equiv $TsNH_2$	CH_2Cl_2:Et_2O (1:3)	–	>99

[a] Reaction temperature −78 °C, reaction time 14–18 h. [b] The major enantiomer has *S* configuration. [c] Reaction time 3 h. [d] Reaction temperature −100 °C. [e] Addition of **7** after reaction of **6a** with TMSOTf. [f] Reaction performed on analytical scale.

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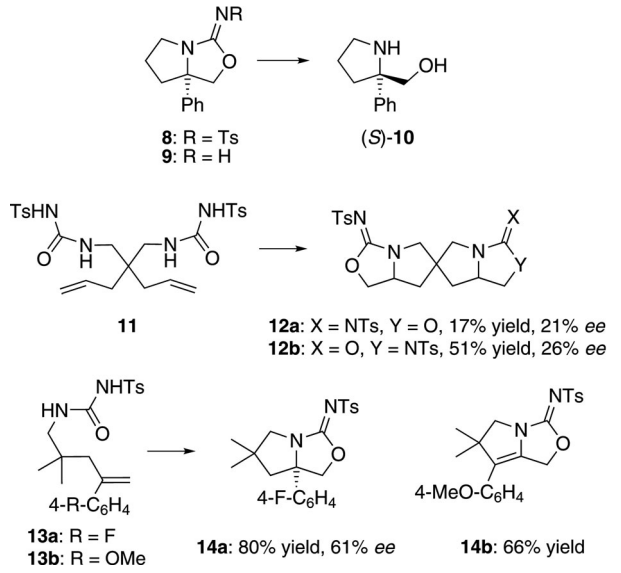
Owing to large signal broadening and decomposition above −40 °C, the structure of **6a** after the addition of TMSOTf and $TsNH_2$ could not be examined by NMR spectroscopy. Compound **8** was obtained enantiomerically pure (> 99 % *ee*) on an analytical-scale reaction (Table 3, entry 10), however, the selectivity dropped slightly on larger scale (Table 3, entry 9). The absolute configuration of the major isomer of **8** was found to be *S* by anomalous dispersion scattering by X-ray crystallography[25] and the refined Flack parameter[26] was 0.11(11). This allowed the rapid synthesis of (*S*)-2-phenylprolinol [(*S*)-**10**] by acidic cleavage of the tosylated derivative **8** to give the isourea compound **9** and subsequent basic cleavage to form the amino alcohol **10**.[15c] As a result of the tetrasubstituted carbon atom in **8**, all one-step deprotection attempts were unsuccessful. Despite the importance of proline-based catalysts in organocatalysis, 2-phenylprolinol **10** has not yet been prepared enantiomerically pure because α-aryl proline derivatives are very difficult to synthesize in optically pure form.[27]

This method was then also applied to substrates **11** and **13** demonstrating that other compounds are also accessible in good enantioselectivities (Scheme 2). Products **12a** and **12b** are formed as single diastereomers as judged from their NMR spectra but with low selectivities. Electron-withdrawing substituents on the aryl moiety in **13a** (R = F) led to the expected amino oxygenated product **14a**, whereas the electron-rich derivative **13b** (R = OMe) undergoes, after cyclization, further oxidation and rearrangement, probably through a reaction between the hypervalent iodine reagent and the methoxy-substituted aryl moiety.

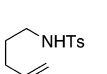
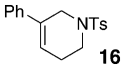
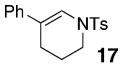
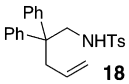
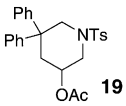
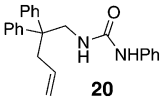
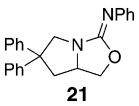
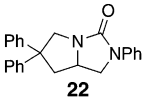
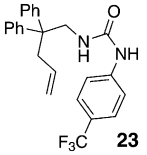
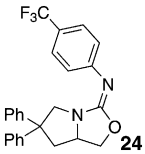
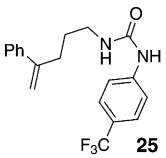
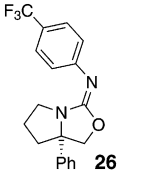
Apart from the N-tosylated urea derivatives shown above, substrates with other substituents on the nitrogen atom were investigated. The cyclization of tosylamide derivative **15** did result in the formation of achiral six-membered ring systems with elimination whereas the direction of elimination was found to be dependent on the Lewis acid used in the reaction (Table 4, entries 1 and 2). The addition of TBDMSOTf led to the elimination product **16** while with $BF_3{\cdot}OEt_2$ enamine **17** was isolated. The cyclization of tosylamide **18** also resulted in a 6-*endo* cyclization product with the acetate added as an external nucleophile. In this reaction the use of **6a** as chiral reagent led to an enantiomeric excess of only 27 % in product **19** (Table 4, entry 3). Similar reactions have already been described using gold catalysis.[28] The variation of the tosyl substituent on the urea moiety leads to altered nucleophilicities of the nitrogen moiety. A phenyl (Table 4, entries 4 and 5) or trifluoromethylphenyl substituent (entries 6 and 7) resulted in substrates with generally lower reactivity as seen by the lower yields in these reactions. Also the solvents used in the reactions had to be adjusted to ensure the solubility of the starting materials. With substrate **20** the use of $PhI(OTf)_2$ as the achiral reagent led to the expected isourea derivative **21**, whereas the chiral reagent **6a** yielded the cyclic urea **22** as the product of a diamination reaction. Good enantioselectivity (79 % *ee*) was obtained in product **26** (Table 4, Entry 7) and the absolute configuration was assigned in analogy to the results shown above.

The addition of nitrogen nucleophiles to alkenes using hypervalent iodine reagents is known and we have inves-



Scheme 2. Application of the hypervalent-iodine-mediated oxyamination of alkenes: Synthesis of (*S*)-2-phenylprolinol **10** and other oxyaminations.

Table 4: Other substrates in stereoselective cyclization reactions using **6a** and TMSOTf.

Entry	Substrate	Product	Yield [%]	*ee* [%][b]
1	 **15**	 **16**	48[a]	–
2		 **17**	42[b]	–
3	 **18**	 **19**	54	27
4	 **20**	 **21**	31[c]	0
5		 **22**	15[d]	42
6	 **23**	 **24**	45	39
7	 **25**	 **26**	30	79

[a] $PhI(OAc)_2$, TBDMSOTf, AcOH. [b] $PhI(OAc)_2$, $BF_3{\cdot}OEt_2$, AcOH. [c] $PhI(OAc)_2$, TMSOTf. [d] solvent: CH_3CN, no reaction occurred in CH_2Cl_2.

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tigated aziridinations in detail, but stoichiometric amounts of the reagents were always necessary.[29] The requirement for a catalytic reaction is an oxidant that can convert iodoarenes into the iodine(III) reagents but that does not oxidize the alkene substrates. We are still investigating if such an oxidant exists for the aminohydroxylation described herein which would allow a catalytic asymmetric, metal-free aminohydroxylation.

These results demonstrate the large potential of chiral hypervalent iodine reagents in oxyaminations in place of metal-based methods together with a rapid access to unusual amino acid derivatives.

Experimental Section

General procedure for cyclizations: TMSOTf was added slowly to a solution of the urea-tethered alkene (1 equiv) and the hypervalent iodine compound **6** (1.2 equiv) in the solvent/solvent mixture (2 mL/0.1 mmol alkene) at −78 °C. The dry ice/acetone bath was removed and the reaction was allowed to warm to room temperature. The reaction was stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL/0.1 mmol alkene), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL/0.1 mmol alkene) and combined with the organic layer, dried over $MgSO_4$, filtered and concentrated in vacuo. The products were purified by chromatography (silica gel, ethyl acetate/hexane 3:5). Product yields are given in Tables 1–4 and Scheme 2. Typically, 80–85 % of the reduced aryl iodide are isolated without loss of optical purity.

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Stereoselective Rearrangement

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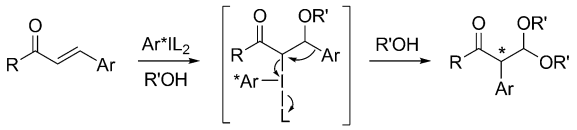
Stereoselective Rearrangements with Chiral Hypervalent Iodine Reagents**

*Umar Farid, Florence Malmedy, Romain Claveau, Lena Albers, and Thomas Wirth**

Organic molecules bearing hypervalent iodine moieties have fascinated chemists over the years. Mild reaction conditions and environmentally friendly behavior through replacement of toxic heavy metals have led to their recent renaissance in organic synthesis.[1] Their use not only as selective oxidants[2] but also as enantiomerically pure reagents[3] make them versatile reagents for many organic transformations, such as the oxidation of sulfides to sulfoxides,[4] the α-oxygenation[5] and α-arylation of carbonyl compounds,[6] the dearomatization of phenols,[7] and the dioxygenation,[8] diamination,[9] aminohydroxylation,[10] and aminofluorination[11] of alkenes. The nature of hypervalent iodine(III) compounds to react as electrophiles and then act as excellent leaving groups make them highly suitable reagents for generating cationic intermediates, which can either directly react with nucleophiles or lead to rearranged products[12] under ring expansion,[13] ring contraction,[14] or aryl migration.[8d,15] Similar rearrangements have been performed with much more toxic thallium reagents.[16]

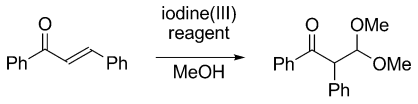
We recently reported a novel oxidative rearrangement of aryl substituted unsaturated carboxylic acids for the facile access of furanones.[17] Calculations were conducted to investigate the interplay of various cationic intermediates. Other studies have also confirmed the involvement of aryl moieties in cationic intermediates of rearrangement reactions.[18] The use of chiral hypervalent iodine reagents in asymmetric rearrangement reactions seems to be a very promising area of research and, to our knowledge, no reactions of this type have been reported to date. Herein, we describe the first stereoselective rearrangements of aryl substituted alkenes with high enantioselectivites mediated by chiral hypervalent iodine reagents. We have investigated chalcones of type **1**, which are easily accessible through an aldol condensation between methyl ketones RCOMe and aryl aldehydes ArCHO. Oxidative rearrangements of such compounds to α-arylated carbonyl compounds have been known for some time.[19] The reaction of aryl-substituted alkenes **1** with electrophilic chiral iodine reagents results in the formation of phenyliodinated intermediates **2**, which can be stabilized by the formation of phenonium ions[20] followed by the reaction with a second alcohol nucleophile to give the 1,2-migration products **3** (Scheme 1).



Scheme 1. Rearrangement of **1** to **3** via phenyliodinated intermediate **2** using hypervalent iodine reagents Ar^*IL_2.

Initially the reaction of (*E*)-1,3-diphenyl prop-2-en-1-one **1a** with only (diacetoxyiodo)benzene [$PhI(OAc)_2$] was investigated, but its reactivity with **1a** is too low and no conversion was observed (Table 1, entry 1). As already described,[19] an activation of the hypervalent iodine(III) reagent is necessary, and addition of 50% aqueous H_2SO_4 as a Brønsted acid to the reaction mixture[21] resulted in the rearranged product in 64% yield. When using [bis(trifluoroacetoxy)iodo]benzene as an iodine(III) source, the yield increased to 82% (Table 1, entries 2 and 3).

Table 1: Different hypervalent iodine reagents for the migration of **1a**.



Entry	Reagents	Reaction Conditions[a]	3a Yield [%]	3a *ee* [%][b]
1	1.05 equiv $PhI(OAc)_2$	RT, 12 h	0	–
2	1.05 equiv $PhI(OAc)_2$ 1.4 equiv 50% H_2SO_4	RT, 3 h	64	–
3	1.05 equiv $PhI(OCOCF_3)_2$ 1.4 equiv 50% H_2SO_4	RT, 3 h	82	–
4	1.2 equiv $PhI(OAc)_2$ 1.4 equiv TBDMSOTf	0°C to RT, 14 h	37	–
5	1.15 equiv **4a** 1.4 equiv 50% H_2SO_4	RT, 2 h	4	17
6	1.15 equiv **4b** 1.4 equiv 50% H_2SO_4	RT, 20 h	5	5
7	1.5 equiv **4a** 3 equiv TBDMSOTf	−78°C, 12 h	–	–
8	1.5 equiv **4a** 3 equiv TBDMSOTf	−78°C to RT, 12 h	50	0

[a] Solvent: MeOH. [b] Determined by HPLC on chiral stationary phase.

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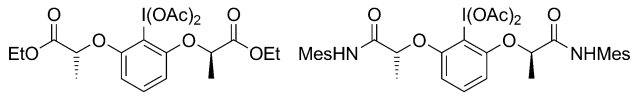
As a new stereogenic center is established in the product, lactic acid based chiral hypervalent iodine compounds, synthesized initially by Fujita et al.[8f,h,22] and further explored by various research groups[7d,9,10] in asymmetric reactions, were investigated. The reagents **4a** and **4b** (Figure 1) are diacetoxyiodo arenes and not reactive enough to induce the



4a **4b**

Figure 1. Lactate-based chiral hypervalent iodine reagents **4a** and **4b**.

rearrangement (see also Table 1, entry 1), but after addition of sulfuric acid the reaction proceeded slowly and the rearranged product was obtained in low yields and with poor enantioselectivities (Table 1, entries 5 and 6). Inspired by the successful activation of hypervalent iodine compounds with Lewis acids in asymmetric functionalizations of alkenes,[8h,10] a similar approach was investigated in these migration reactions. Unfortunately, there was either no reaction at low temperatures or only racemic product was obtained by using *tert*-butyldimethylsilyl triflate (TBDMSOTf) in MeOH (Table 1, entries 7 and 8).

Previous investigations also indicated that the solvent composition is crucial in stereoselective reactions with iodine(III) reagents.[10] Mixtures of methanol and dichloromethane did not improve the enantiomeric excess in **3a** (Table 2, entry 1). However, when the initial synthesis of the highly electrophilic hypervalent iodine reagent Ar*I(OTf)$_2$ by prior mixing of the chiral hypervalent diacetoxyiodo derivative Ar*I(OAc)$_2$ with TBDMSOTf in dichloromethane at −78 °C as evidenced by NMR studies[10,23] is followed by addition of methanol along with starting material **1a**, the product **3a** was obtained with improved enantioselectivities (Table 2, entry 2). When the reaction temperature was kept at −15 °C, the enantioselectivity rose to a promising level of 86 % (Table 2, entry 3). Also other Lewis acids have been utilized in the migration reaction in combination with different solvents and chiral hypervalent iodine reagents, as shown by entries 4–8 in Table 2.

Table 2: Conditions for the stereoselective rearrangement of **1a** to **3a**.

Entry	Reagents[a]	Solvent	**3a** *ee* [%]
1	**4b**, TBDMSOTf[b]	CH_2Cl_2/MeOH (1:1)	12
2	**4b**, TBDMSOTf[b]	CH_2Cl_2, 10 equiv MeOH	43
3	**4b**, TBDMSOTf	CH_2Cl_2, 8 equiv MeOH	86
4	**4b**, $BF_3{\cdot}OEt_2$	CH_2Cl_2, 8 equiv MeOH	24
5	**4b**, TMSOTf	CH_2Cl_2, 8 equiv MeOH	88
6	**4a**, TMSOTf	CH_2Cl_2, 8 equiv MeOH	12
7	**4b**, $BF_2OTf{\cdot}OEt_2$[c]	CH_2Cl_2, 8 equiv MeOH	89
8	**4b**, TfOH	CH_2Cl_2, 8 equiv MeOH	91
9	**4b**, TfOH	CH_2Cl_2/2,2,2-trifluoroethanol (1:1), 8 equiv MeOH	95[d] 99[e]
10	**4b**, TfOH	CH_3CN, 8 equiv MeOH	92

[a] 1.5 equiv **4**, 3 equiv Lewis acid, reaction temperature −78 °C to −15 °C, reaction time 14 h. [b] Reaction temperature −78 °C to RT, reaction time 14 h. [c] Prepared by a 1:1 mixture of TMSOTf and $BF_3{\cdot}OEt_2$.[24] [d] **3a**. [e] **3a′**: Bis-2,2,2-trifluoroethoxy acetal.

When triflic acid was used together with hypervalent iodine reagent **4b** in a 1:1 mixture of dichloromethane and 2,2,2-trifluoroethanol, a mixture of the dimethoxy acetal **3a** (95 % *ee*) and the bis(trifluoroethoxy)acetal **3a′** (99 % *ee*) was obtained (Table 2, entry 9). A close monitoring of the reaction by ^{1}H NMR revealed only a 28 % conversion into the product **3a** by employing triflic acid as Lewis acid and dichloromethane and methanol (8 equiv) as solvents (see the Supporting Information). The enantiomeric excess was found to be constant over the course of the reaction (ca. 85 % *ee*), indicating no further interaction of the chiral reagent with the product. This reaction and all the results described in Table 2 have been carried out on a sub-millimolar scale without isolation of the reaction products.

When the reaction was performed without the addition of methanol using only a 1:1 mixture of dichloromethane and 2,2,2-trifluoroethanol with triflic acid as Lewis acid, a higher yield (66 %) of the product **3a'** with moderate selectivity (69 % *ee*) was obtained. By using TMSOTf as the Lewis acid for iodine(III) activation, the asymmetric induction was found to be excellent, giving the product in 97 % *ee* (Table 3, entry 2). When TMSOTf is used as the activating Lewis acid, the same significant increase in selectivity is observed with the 4-fluorophenyl substituted chalcone **1b** (Table 3, entries 3 and 4). These reaction conditions were then applied to a wide range of substrates. Electronically withdrawing substituents on the aryl moiety at position 4 led to the expected rearranged products **3** with high selectivities, but the yields decrease with an increase in the Hammett value[25] of the halide substituents from $\sigma_p = 0.06$ (F) to $\sigma_p = 0.23$ (Br) (Table 3, entries 4 to 6). With the 4-nitro substituted chalcone **1e** ($\sigma_p = 0.78$), the starting material was completely recovered and no rearrangement took place (Table 3, entry 7). The absolute configuration of the major isomer of **3c** and **3d** was found to be *R* by anomalous dispersion scattering, and the refined Flack parameters[26] were 0.17(16) and 0.00(4), respectively, as determined by X-ray crystallography.[27]

When compounds **1** with electron-donating substituents on the aryl moiety were subjected to the rearrangement reaction conditions, products **3** were obtained in high yields and selectivities (Table 3, entries 9 and 10). Unfortunately, compounds **1** with a 4-*tert*-butyl (**1h**) and a 3-methyl substituent (**1i**) resulted in products **3h** and **3i** with only moderate selectivities (Table 3, entries 11 and 12). Compound **1j** with a 4-methoxy substituent only led to complete decomposition under different reaction conditions (Table 3, entry 13). From these results it is obvious that both steric and electronic parameters from substituents in the *para* position are strongly influencing the yield and selectivity of the reaction.

Heteroaromatic compound **1k** as well as other unsaturated carbonyl compounds such as the cinnamyl ester **1l** and the methyl-substituted ketones **1m** also underwent the rearrangement reaction with high selectivities, but only gave the reaction products **3** in low yields (Table 3, entries 14–16).

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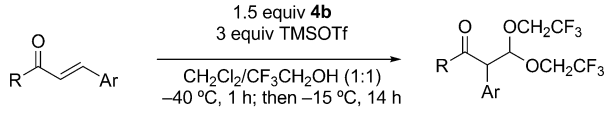
Table 3: Other substrates for the stereoselective rearrangement.[a]



1 3

Entry	Substrate	R	Ar	Product	Yield [%]	*ee* [%]
1	**1a**	Ph	Ph	**3a′**	66[b]	69
2	**1a**	Ph	Ph	**3a′**	59	97
3	**1b**	Ph	4-F-C_6H_4	**3b**	60[b]	69
4	**1b**	Ph	4-F-C_6H_4	**3b**	50	94
5	**1c**	Ph	4-Cl-C_6H_4	(*R*)-**3c**	38	92
6	**1d**	Ph	4-Br-C_6H_4	(*R*)-**3d**	17	91
7	**1e**	Ph	4-NO_2-C_6H_4	**3e**	0[c]	–
8	**1f**	Ph	4-Me-C_6H_4	**3f**	92[b]	66
9	**1f**	Ph	4-Me-C_6H_4	**3f**	80	86
10	**1g**	Ph	4-*i*Pr-C_6H_4	**3g**	68	89
11	**1h**	Ph	4-*t*Bu-C_6H_4	**3h**	65	52
12	**1i**	Ph	3-Me-C_6H_4	**3i**	42	53
13	**1j**	Ph	4-OMe-C_6H_4	**3j**	0[c]	–
14	**1k**	2-furyl	Ph	**3k**	8	83
15	**1l**	OMe	Ph	**3l**	12	96
16	**1m**	Me	Ph	**3m**	10	–[d]

[a] Reaction conditions: CH_2Cl_2/CF_3CH_2OH (1:1), 1.5 equiv **4b**, 3 equiv TMSOTf, −40 °C, 1 h; then −15 °C, 14 h. [b] Lewis acid: TfOH. [c] Hypervalent iodine reagent: $PhI(OAc)_2$, reaction temperature: 0 °C. [d] The enantiomers were inseparable on a HPLC column.

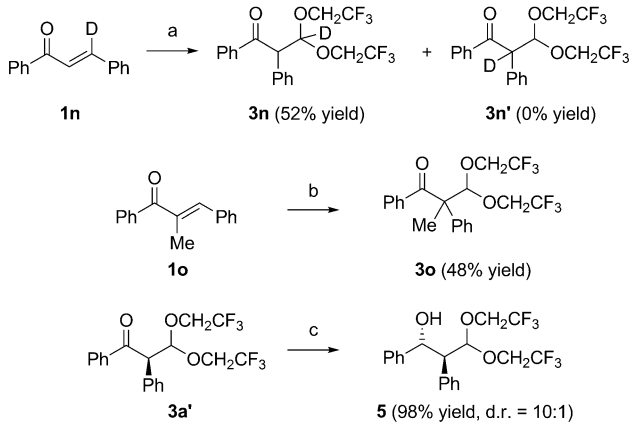
In these experiments, an excess of the hypervalent iodine reagent **4b** (1.5 equiv) is being used. About 80–85 % of the reduced aryl iodide can be recovered after the reaction without loss of optical purity and can be reoxidized.

A recent publication showed the potential of an aryl ketone to migrate in boron trifluoride catalyzed epoxide opening reactions.[28] To confirm that the reaction mechanism proceeds with aryl ring migration, the deuterium-labeled compound **1n** was treated with $PhI(OAc)_2$ together with TfOH. The phenyl ring migrated product **3n** was obtained exclusively alongside unreacted starting material. The product **3n′**, which would result from an aryl ketone migration, was not observed in this reaction. We also investigated compound **1o** in an attempt to generate quaternary carbon centers in this process. No reaction was observed in attempted stereoselective rearrangement with **4b**, but the reaction proceeded by using (diacetoxyiodo)benzene and TMSOTf as activating reagent to give the expected rearranged product **3o** in 48 % yield. Photoisomerization of (*E*)-**1a**[29] led to an inseparable mixture of (*E*)-**1a** and (*Z*)-**1a** (4:10), which was subjected to the rearrangement conditions using reagent **4b**. Product **3a′** was obtained in 31 % yield and with 55 % *ee*; the recovered starting material **1a** showed an altered *E*/*Z* ratio of about 10:2. This indicates that (*Z*)-**1a** reacts much faster than (*E*)-**1a**, but the enantiomeric excess obtained in the product **3a′** is lower.

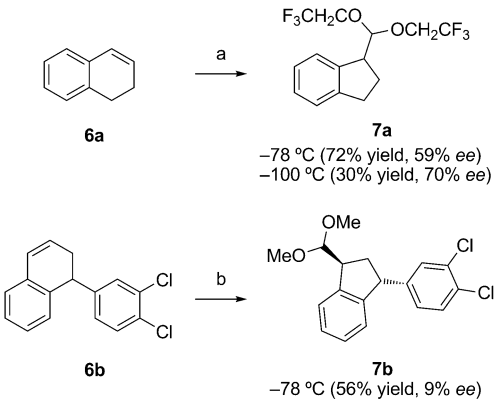
Compound **3a′** was reduced with sodium borohydride to obtain the corresponding alcohol **4** with good diastereoselectivity (Scheme 2). Products of type **4** are versatile building blocks for further manipulations. Moreover, this asymmetric method allowed the synthesis of fluorinated acetals, which have many applications in biological chemistry and industry.[30]

Ring contraction reactions of tetralone derivatives have also been performed using this method.[14] When compound **6a** was subjected to the rearrangement reaction conditions, rearranged product **7a** was obtained in 59 % *ee*. The selectivity was improved at lower temperature to 70 % *ee* but with decreased yields. Further functionalization of compound **7a** can lead to the synthesis of compounds of biological importance.[31] Unfortunately, substrate **6b** gave a very low selectivity in product **7b** when methanol was used as nucleophile. The use of 2,2,2-trifluoroethanol in this ring-contraction reaction resulted in a complex mixture of products (Scheme 3).

In conclusion, we have developed an efficient and highly stereoselective method for the α-arylation of a wide range of



Scheme 2. Isotope labeling and generation of quaternary centers. Reaction conditions: a) 1.5 equiv $PhI(OAc)_2$, 3 equiv TfOH, CH_2Cl_2/CF_3CH_2OH (1:1), −40 °C, 1 h; then 0 °C, 3 h. b) 1.5 equiv $PhI(OAc)_2$, 3 equiv TMSOTf, CH_2Cl_2/CF_3CH_2OH (1:1), −40 °C, 1 h; then −15 °C, 14 h. c) 2 equiv $NaBH_4$, MeOH, 0 °C, 30 min.



Scheme 3. Ring-contraction reactions of tetralone derivatives **6**. Reaction conditions: a) −78 °C: 1.5 equiv **4b**, 3 equiv TfOH, CH_2Cl_2/CF_3CH_2OH (4:1), 14 h; −100 °C: 1.5 equiv **4b**, 3 equiv TMSOTf, $CH_2Cl_2/CF_3CH_2OH/Et_2O$ (3:1:4), 3 h. b) 1.5 equiv **4b**, 3 equiv TfOH, 8 equiv MeOH, CH_2Cl_2, −78 °C, 14 h.

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carbonyl compounds by an oxidative rearrangement procedure. These results are noteworthy as they are the first examples of chiral hypervalent iodine(III) reagents in highly stereoselective rearrangement reactions. Further investigations for developing a catalytic reaction and for the synthesis of enantiomerically enriched building blocks using this approach are currently in progress.

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