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Synthesis and Reactivity of Chiral *N*-Heterocyclic Iodanes

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Contribution of the candidate in % of the total work load (up to 100% for each of the following categories):

Experimental concept and design: ca. 80%

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Chapter: 4.2 An Enantioconvergent Benzylic Hydroxylation Using a Chiral Aryl Iodide in a Dual Activation Mode

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Chapter: 4.4 Application of Chiral Triazole-Substituted Iodoarenes in the Enantioselective Construction of Spirooxazolines

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“Where there is a will, there is a way. If there is a chance in a million that you can do something, anything, to keep what you want from ending, do it.”

Pauline Kael

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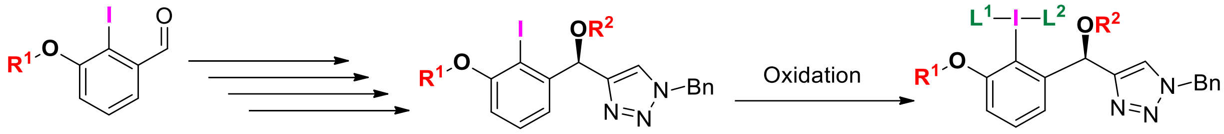
List of Schemes

List of abbreviations

Ts	Tosylate
AcO	Acetoxy
PIDA	(Diacetoxyiodo)benzene
PIFA	[Bis-(trifluoracetoxy)-iod]-benzol
TMSBr	Bromotrimethylsilane
IBX	2-Iodoxybenzoic acid
$BF_3.Et_2O$	Bortrifluorid-diethyletherat
DCM	Dichloromethane
$TMSN_3$	Trimethylsilylazid
HFIP	Hexafluoro-2-propanol
HN_3	Hydrazoic acid
$HNTs_2$	Bistosylimide
CTAB	Hexadecyltrimethylammonium bromide
m-CPBA	3-Chloroperbenzoic acid
MeCN	Acetonitrile
$TsOH.\ H_2O$	p-Toluolsulfonsäure Monohydrat
$CHCl_3$	Chloroform
TMSOTf	Trimethylsilyltrifluormethansulfonat
TFE	2,2,2-Trifluoroethanol
MeOH	Methanol
TfOH	Trifluoromethanesulfonic acid
TFA	Trifluoroacetic acid
AcOH	Acetic acid
DCE	1,2-Dichloroethane
HF.py	Hydrogen fluoride pyridine
EtOAc	Ethyl acetate
BnOH	Benzyl alcohol
CSA	Camphor sulfonate
Mes	Mesitylene

Abstract

Hypervalent iodine compounds, in particular aryl-Λ^3-iodanes, have found widespread applications for many organic transformations. Their reactivities are comparable to highly oxidized period-6 metals, in particular Hg(II), Tl(III), and Pb(IV), with less toxicity. All these merits make hypervalent iodine compounds suitable reagents to perform a wide range of oxidative transformation reactions.



1 **2** **3**

Scheme 1. Synthesis of novel chiral iodine(III) reagents.

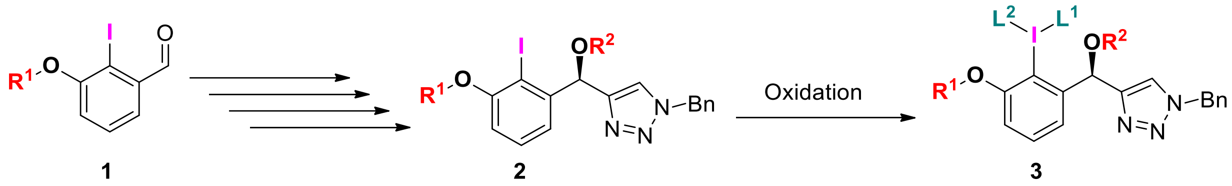
The first part of this thesis describes the efficient synthesis of novel triazole substituted chiral hypervalent iodine catalysts (Scheme 1). It also describes the reactivity and selectivity of these new catalysts in different stereoselective oxidative transformations, such as Kita-spirocyclizations, the α-tosyloxylation of propiophenone, oxidative lactonizations, oxidative dearomtization of phenols and the oxidative rearrangement of allyl alcohols.

The second part of the thesis describes the development of a novel enantioconvergent benzylic hydroxylation by employing a chiral iodine catalyst that fulfills a dual purpose as both oxidant and chiral ligand for a Cu co-oxidant.

Finally, the enantioselective cyclization of unsaturated amides using chiral aryl iodides has been described, which has the facility to synthesize oxazoline derivatives. This method can be used to prepare natural products and biologically active compounds efficiently. Also, the asymmetric oxidative cyclization of naphthol compounds for the synthesis of chiral spirooxazolines has been described. These compounds have many applications in drugs and industrial applications.

Zusammenfassung

Hypervalente Iodverbindungen, insbesondere Aryl-λ^3-iodane, haben weit verbreitete Anwendungen für viele organische Umsetzungen gefunden. Ihre Reaktivitäten sind vergleichbar mit stark oxidierten Metallen der Periode 6, insbesondere Hg (II), Tl (III) und Pb (IV), bieten aber den Vorteil einer geringeren Toxizität. All diese Vorzüge machen hypervalente Iodverbindungen zu geeigneten Reagenzien, um eine Reihe von oxidativen Transformationsreaktionen durchzuführen.



Schema 1. Synthese neuartiger chiraler Iod(III)-reagenzien

Der erste Teil dieser Arbeit beschreibt die effiziente Synthese neuer chiraler hypervalenter Iodkatalysatoren (Schema. 1) der Reaktivität und Selektivität dieser neuen Katalysatoren in verschiedenen stereoselektiven oxidativen Umwandlungen wie der Kita-Spirocyclisierung, der α-Tosyloxylierung von Propiophenon, oxidativen Lactonisierungen und oxidativen Umlagerungen von Allylalkoholen.

Der zweite Teil dieser Arbeit beschreibt eine enantiokonvergente benzylische Hydroxylierung unter Verwendung eines chiralen Iodkatalysators in doppelter Funktion als Oxidationsmittel und als chiraler Ligand eines Cu-co- katalysators.

Schließlich wurde die enantioselektive Zyclisierung von ungesättigten Amiden unter Verwendung von chiralen Aryliodiden mit der Möglichkeit zur Synthese von Oxazolinderivaten beschrieben. Die Vorzüge dieser Methode können praktisch zur Herstellung von Naturstoffen und biologisch aktiven Verbindungen genutzt werden.

1. Chapter 1: General Introduction

1.1. Hypervalent Iodine Compounds

$PhICl_2$ was the first organic hypervalent iodine reagent synthesized by the German chemist C. Willgerodt in 1886.[1] The chemistry of hypervalent iodine compounds has attracted a great deal of attention in the last two decades because the chemical properties and applications of iodanes are similar to those of often-toxic heavy transition metals. Hypervalent iodine reagents have been extensively used in organic synthesis and have the advantages of being diverse, readily available, mild, and environmentally friendly.[2–6] The most widely applied reagents are, depending on the oxidation state of the central hypervalent iodine atom, aryl-λ^5- and aryl-λ^3-iodanes. Aryl-λ^5-iodanes, with the Dess–Martin periodinane as the most prominent example, are usually applied in "dehydrogenative" oxidations such as the mild conversion of alcohols into ketones or aldehydes.[7–10] At the same time, aryl-λ^3-iodanes are well known as efficient mediators in oxidative coupling reactions and as electrophilic group transfer reagents.[11–14] Prominent examples of common hypervalent iodine reagents are shown in Figure 1.

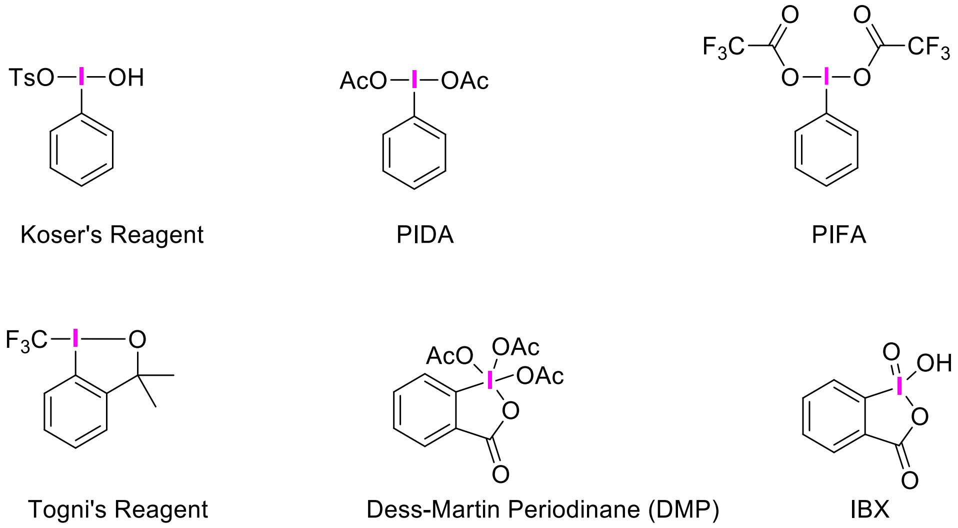


Figure 1. Commonly used hypervalent iodine reagents.

1.1.1. General Reactivity Principles

Hypervalent iodine reagents are widely used in organic synthesis not only because they are environmentally friendly but also due to their straightforward availability. Furthermore, the electrophilic nature of these reagents, together with their strong leaving-group ability (10^6 times that of a triflate) when bound to sp^3-carbons, are the reasons behind their selectivity and reactivity.[3]

The aryl-λ^3-iodanes $ArIL_2$ (L: heteroatom ligands) have a pseudotrigonal bipyramidal geometry. In this structure, the most electronegative groups (heteroatom ligands) are in the apical position. The aryl group (less electronegative) is bonded to the iodine center by a covalent bond and lies in the equatorial position. The molecular orbital (MO) is characterized by a hypervalent, three-center, four-electron bond (3c-4e) with one electron from one each ligand (L) and two electrons from the doubly occupied 5p orbital on the central iodine atom (Figure 2). In this model, three molecular orbitals can be formed: bonding, non-bonding, and anti-bonding. The non-bonding orbital has a node on the central iodine that makes the hypervalent bond highly polarized; hence, the electrophilic nature at the center of the iodine atom with a partial negative charge on the ligands. Thus, the $ArIL_2$ is best stabilized when there are more electronegative atoms in the apical position.

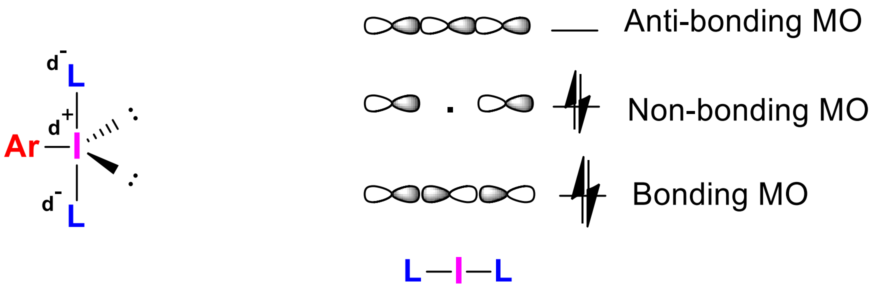
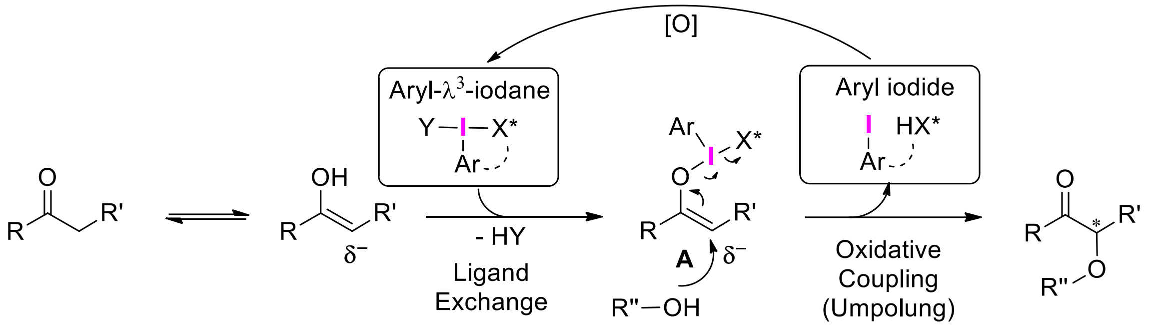


Figure 2. Pseudotrigonal bipyramidal structure and molecular orbital of the 3c-4e-bond in aryl-λ^3-iodanes.

The reaction mechanisms of reactions involving λ^3-iodanes of type $ArIL_2$, α-oxygenations of enolic carbons, are based on an initial ligand exchange at the hypervalent iodine center with the enolic oxygen to give central intermediate **A**, followed by an S_N2'-nucleophilic substation with the oxygen nucleophile at the enolic carbon. During this key step, the hypervalent iodine center is reduced in a 2-electron reduction to give a standard valence aryl iodide. The conversion of the hypervalent iodine atom into its normal valence state is the driving force in these important oxidative couplings. When a chiral hypervalent iodine compound is utilized, a chiral intermediate **A** will be formed that leads to enantioenriched α-oxygenated carbonyl derivatives via diastereotopic transition states (Scheme 2).

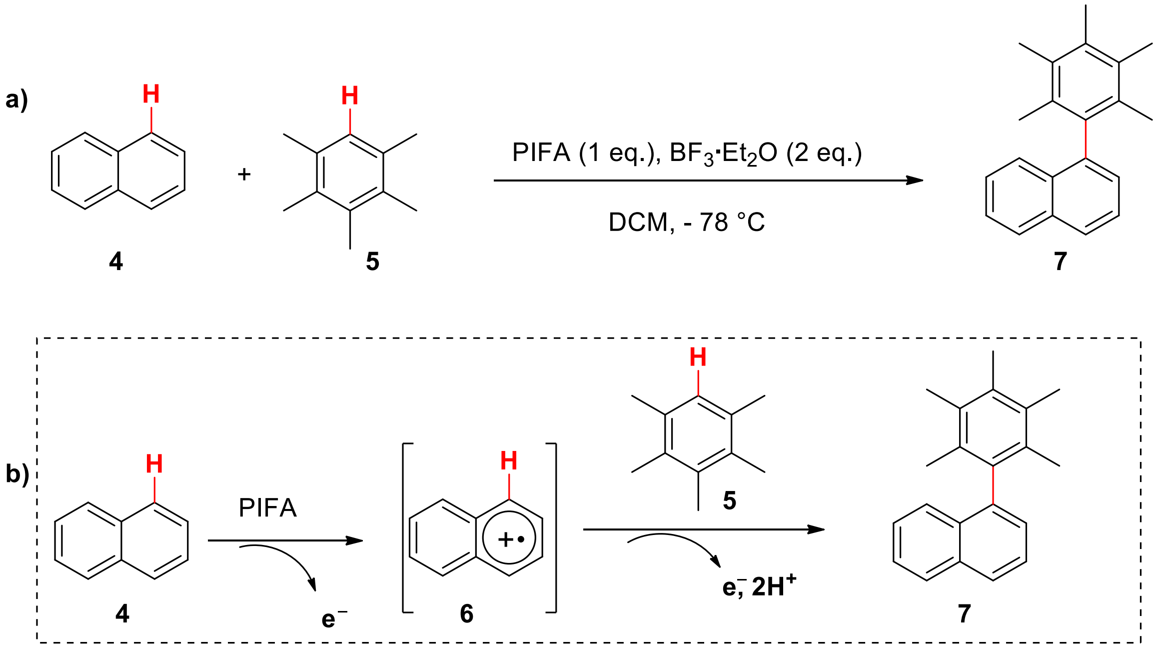


Scheme 2. The principal mechanism of the aryl-λ^3-iodane–mediated α-oxygenation of enolic carbons.

1.1.2. Synthetic Applications

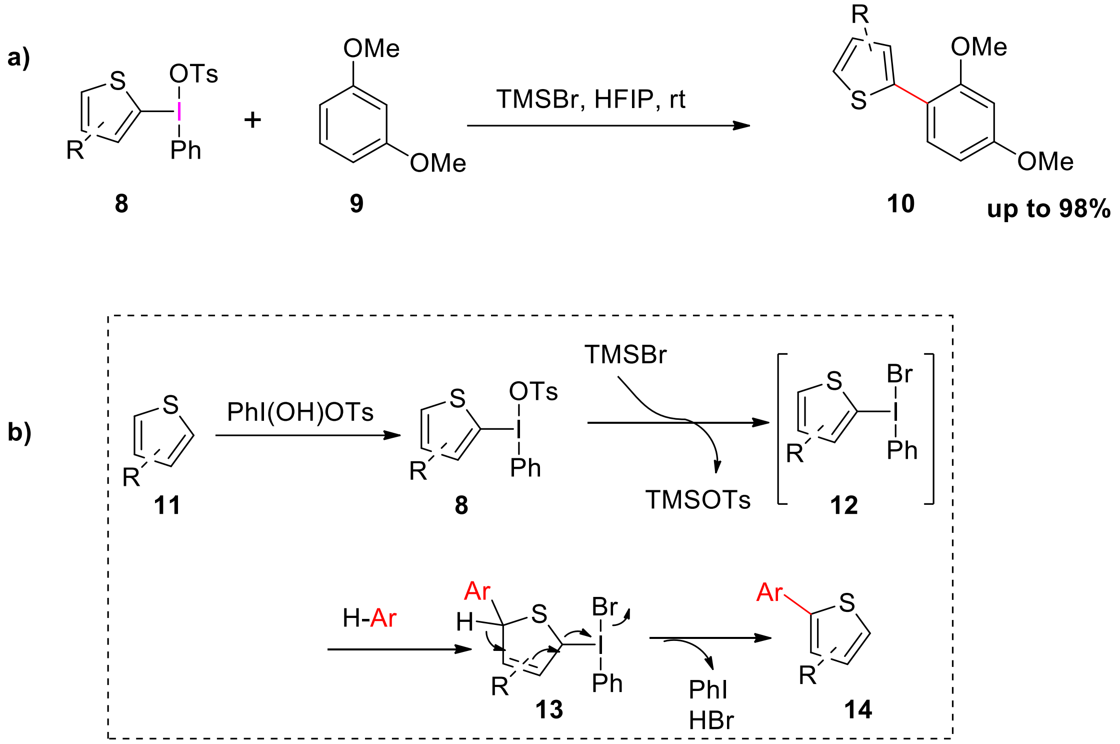
1.1.2.1. Oxidative Formation of Carbon–Carbon Bonds

C–C bond formation is an important practical application in hypervalent iodine chemistry. The first metal-free C–C bond formation was reported by Dohi *et al.* for cross-coupling of naphthalene and pentamethyl benzene mediated by PIFA and BF$_3$·Et$_2$O reagents (Scheme 3-a).[15] The mechanism of this reaction involves the single-electron-transfer oxidation of electron-rich aryl, which would lead to generating aryl cation radical **6** by treating compound **4** with a suitable oxidant. Following this, an existing aromatic molecule **5** could perform *in-situ* trapping of the intermediate **6**, resulting in another electron oxidation and deprotonation, which would lead to C–C bond formation to produce compound **7** (Scheme 3-b).



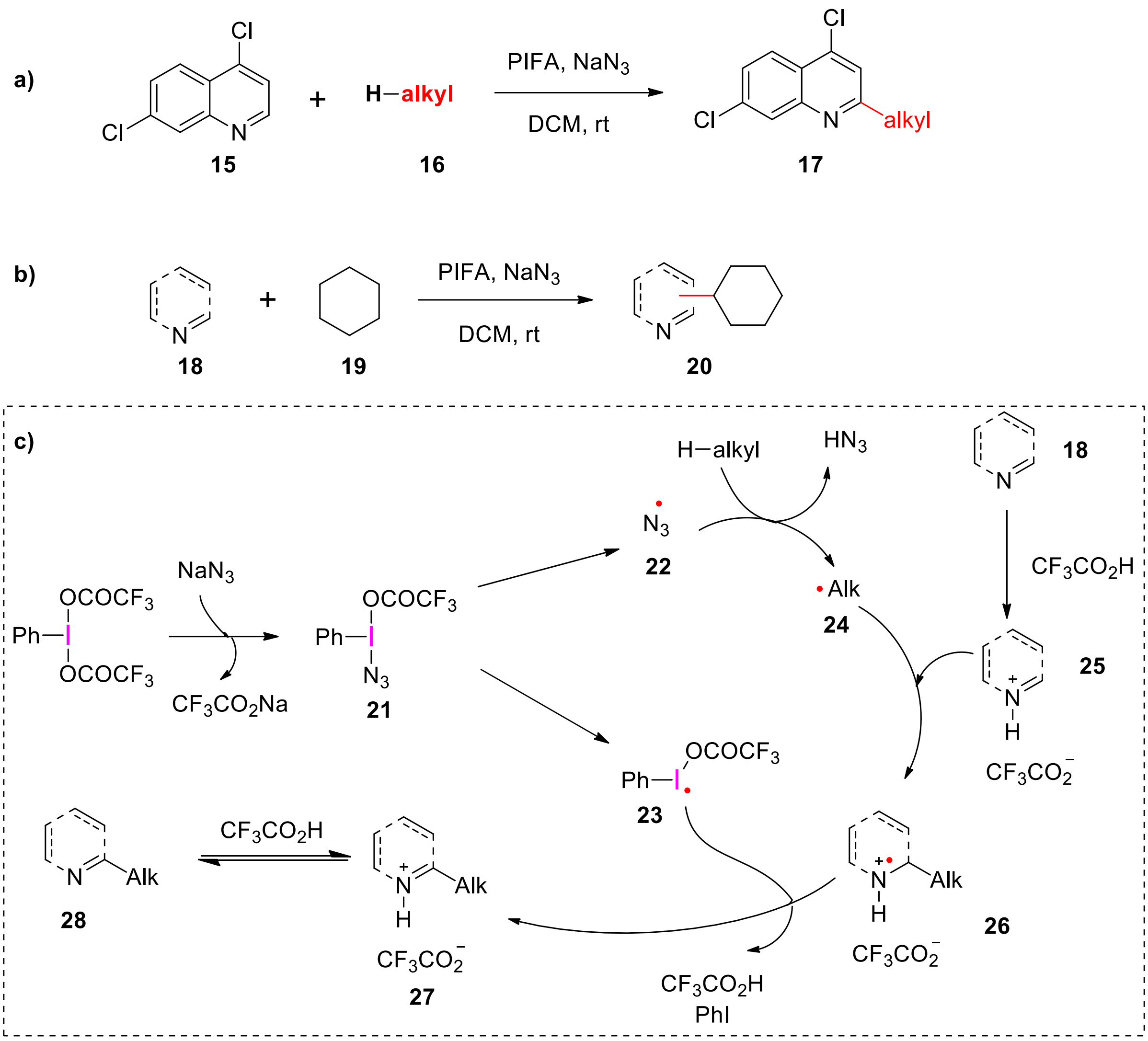
Scheme 3. Aryl cross-coupling mediated by PIFA.

One year later, Kita *et al*. reported a novel metal-free selective C–C coupling for the thiophenes via sequential addition of TMSBr and an arene to an α-thienyliodonium tosylate **8**. The reaction was performed under mild conditions, giving a high yield and high regioselectivity of the biaryl products **10** (Scheme 4-a).[16] The mechanism contains two sequential steps. First, the Koser's reagent reacts selectively with the electron-rich heteroaromatic compounds **11** at the 2-position to form a stable iodonium salt **8,** which will be activated by TMSBr in HFIP to form the intermediate **12**. Second, the elimination of iodobenzene and formal hydroarylation with nucleophiles will give biaryl products (Scheme 4-b). This reaction did not occur in the absence of TMSBr, so Koser's reagent was not enough to perform this reaction.



Scheme 4. Cross-coupling reaction of thiophene with 1,3-dimethoxybenzene.

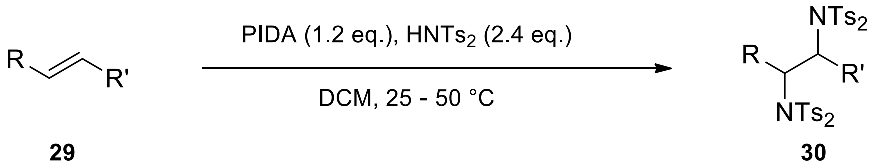
Antonchick *et al*. developed an efficient method for the oxidative cross-coupling of heteroarenes **15** with functionalized alkanes **16** using a mixture of PIFA and NaN_3. Various substrates of desired products were formed under mild conditions, with short reaction times at ambient temperature (Scheme 5-a,b).[17] The mechanism of this reaction is presented in (Scheme 5-c). Initially, the intermediate **21,** which is formed by reacting PIFA with NaN_3, undergoes thermolysis to give an azide radical **22** and an iodine radical **23**. Then, the azide radical **22** reacts with the alkane **16** to give the alkyl radical **24,** which has a nucleophilic character. Trifluoroacetic acid will protonate the heteroaromatic ring to form the corresponding salt **25**. After that, the alkyl radical **24** will attack the salt at the poorest electron position to form radical cation **26**, which will be oxidized by the iodine radical to make the cross-coupling product **28** after deprotonation.



Scheme 5. Oxidative cross-coupling of alkanes with heteroarenes.

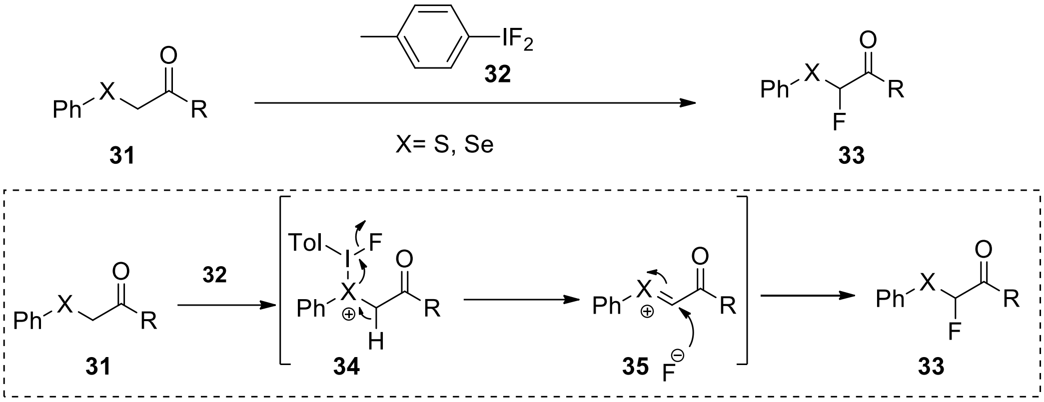
1.1.2.2. Formation of Carbon–Heteroatom Bonds

Hypervalent iodine reagents have been used in diverse reactions to lead to carbon–heteroatom bond formation for a wide range of substrates. One of the most common examples is the vicinal diamination of alkenes **29,** employing PIDA and $HNTs_2$.[18] This example allows for a diverse scope of substrates, including terminal and internal alkenes, styrenes, and cyclic alkenes (Scheme 6).



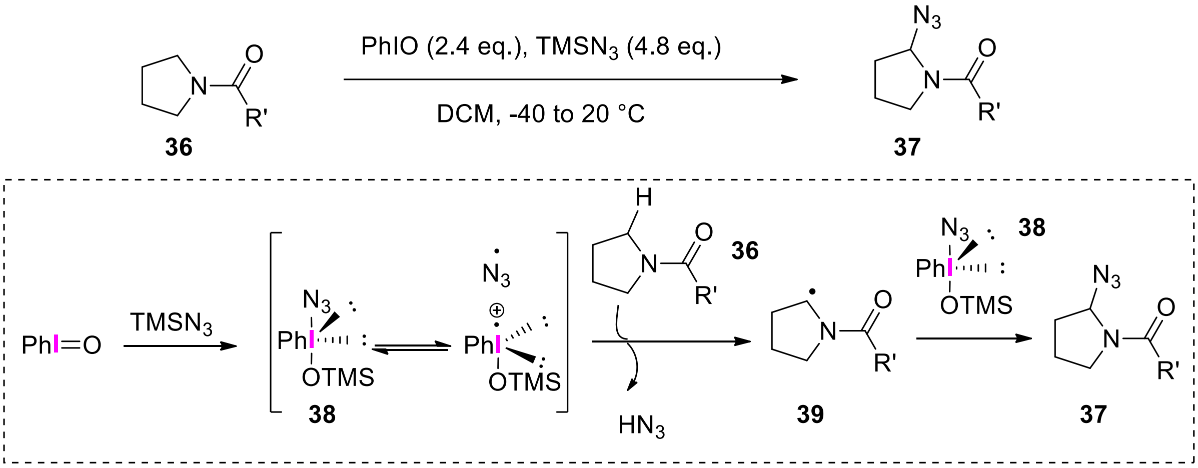
Scheme 6. Vicinal deamination of alkenes mediated by PIDA.

α-Fluorination of selenides or sulfides compounds **31** has been reported by utilizing (difluoroiodo)toluene **32** through a fluoro-Pummerer reaction to produce displacement of the sulfur or selenyl groups by a nucleophile via activation by hypervalent iodine **32**. The PhX-ITol(F)$^+$ group has hypernucleofugicity, which leads to the substitution of the phenyl-X group by a fluoride. (Scheme 7).[19,20]



Scheme 7. Carbon–heteroatom bond-forming reactions mediated by hypervalent iodine reagents.

Another example of carbon–heteroatom bond formation is the functionalization of carbonyl compounds, such as the C(sp^3)–H azidation of *N*-carbonyl pyrrolidine derivatives **36,** by using iodosobenzene PhIO in the presence of trimethylsilyl azide to form hypervalent iodine **38,** which has an azide radical and an iodine-centered radical due to homolysis of the weak I–N bond. Then, the azide radical can abstract a hydrogen atom from compound **36** to form **39**, which will react with the hypervalent iodine **38** to form compound **37** with high yields of up to 82% (Scheme 8).[21]

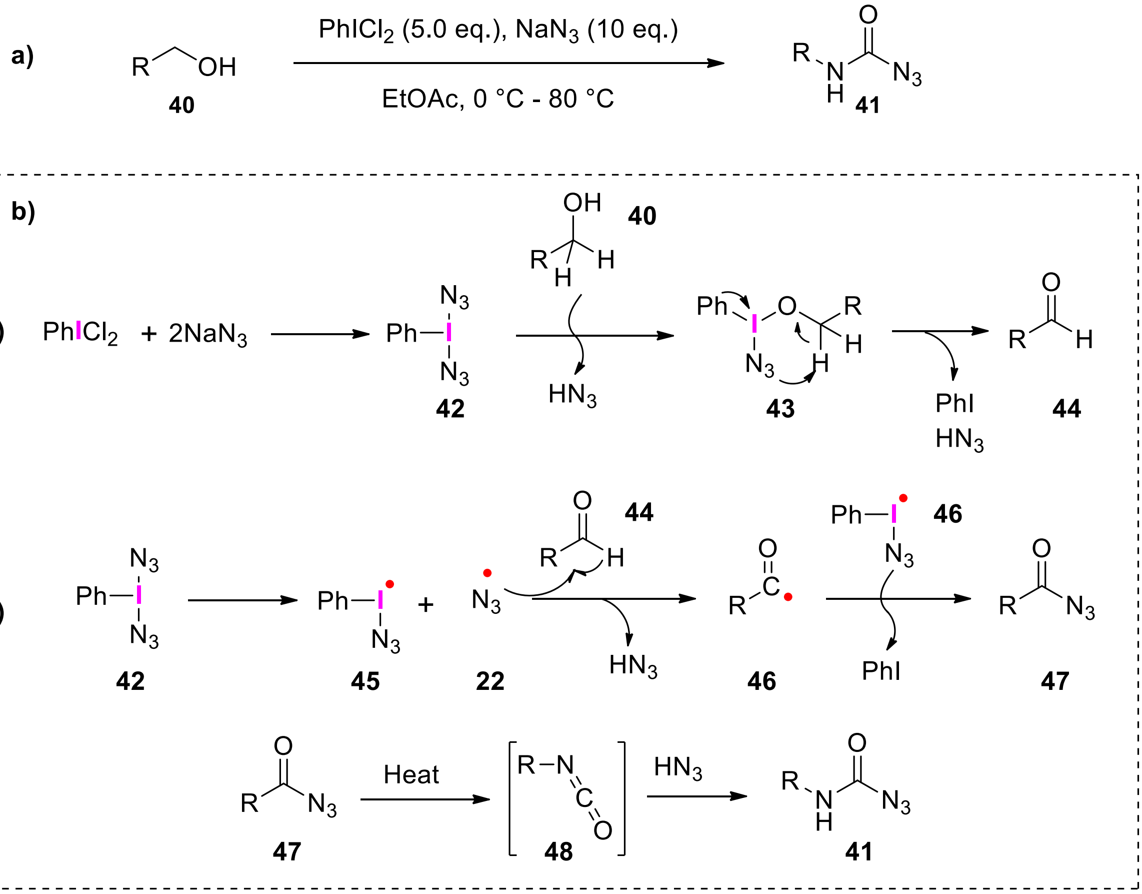


Scheme 8. C(sp^3)–H azidation of *N*-carbonyl pyrrolidine mediated by hypervalent iodine.

1.1.2.3. Oxidative Rearrangements

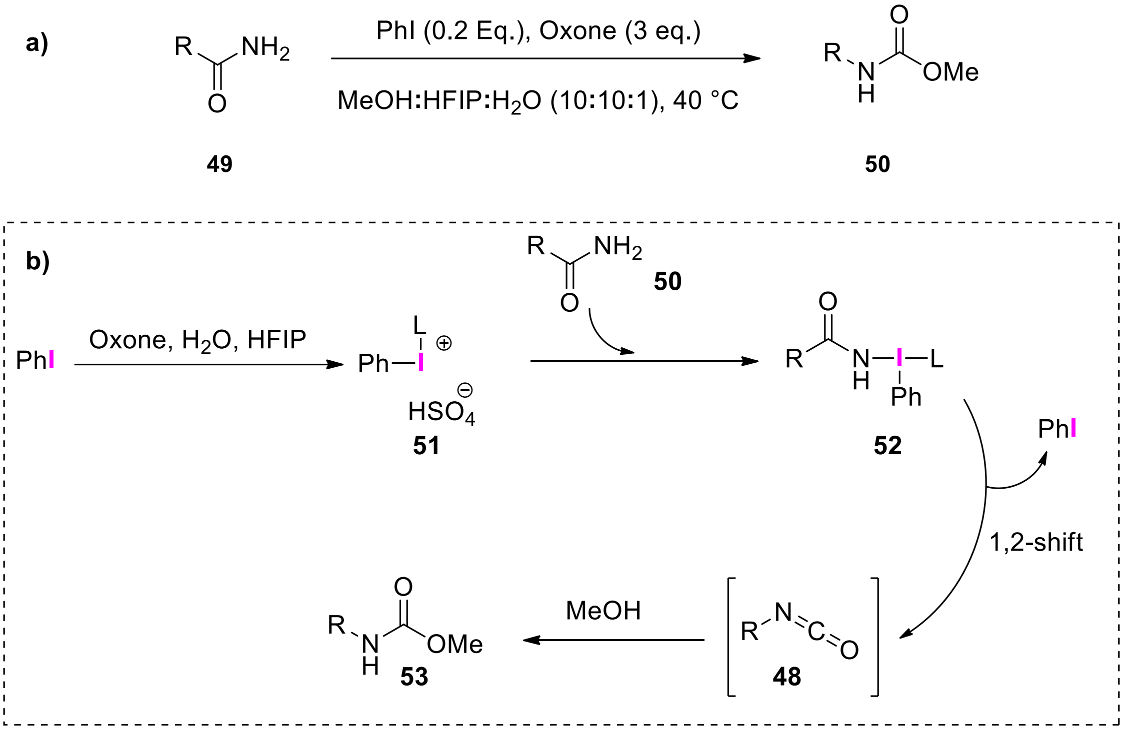
The electrophilic nature of hypervalent reagents at the iodine atom and their properties as excellent leaving groups make these reagents useful intermediates for a wide range of synthetic rearrangement reactions.

One prominent example is the one-pot conversion of primary alcohols **40** into the corresponding carbamoyl azides **41** via a Curtius rearrangement using $PhICl_2$ in the presence of sodium azide (Scheme 9-a).[22] The mechanism of this reaction involves two stages. The first stage is a ligand exchange reaction between $PhICl_2$ and NaN_3 to form bis(azido)iodobenzene **42**, which will oxidize the primary alcohol to the corresponding aldehyde **44** through the intermediate **43**. In the second stage, decomposition of **42** will result in the formation of the azidyl radical **22**, followed by two steps to produce the acyl azide **47**, then by heating at 80 °C and treating the isocyano group **48** with hydrazoic acid to give the corresponding carbamoyl azide **41** (Scheme 9-b).



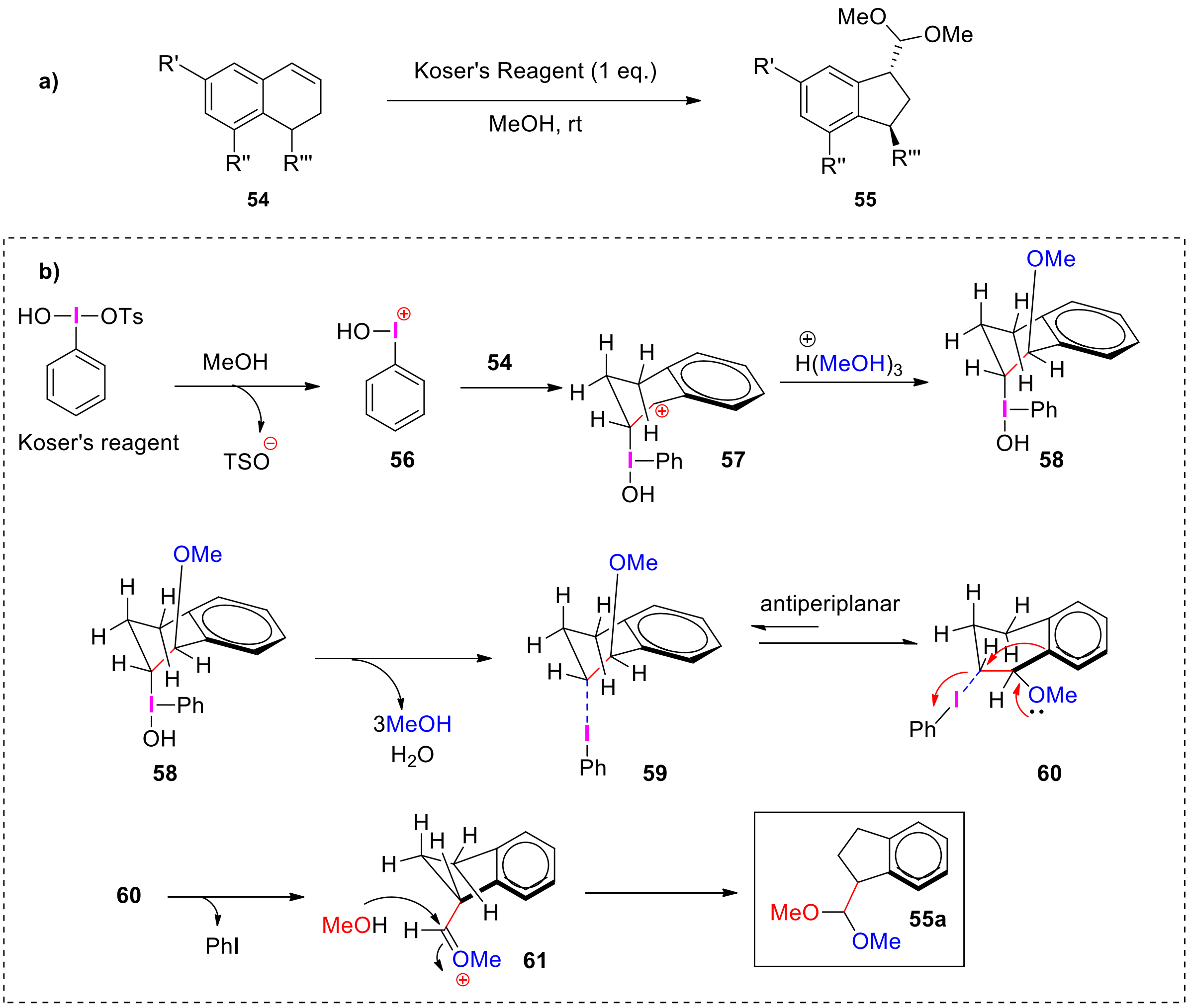
Scheme 9. Synthesis of carbamoyl azides from primary alcohols via aryl iodanes.

The Hofmann rearrangement is an earlier example that shows the ability of the hypervalent iodine to take part in rearrangement reactions by converting the carboxamides **49** to carbamates **50**. This reaction involves hypervalent iodine generated *in-situ* from PhI and Oxone as an oxidant in the presence of HFIP (Scheme 10-a).[23] The mechanism of this reaction starts via a ligand exchange reaction of **51** to give the hypervalent amidoiodane **52**, which undergoes the reductive elimination of PhI and the 1,2-shift at the electron-poor nitrenium nitrogen atom to form isocyanate **48**. The addition of methanol then generates the carbamate **53** (Scheme 10-b).



Scheme 10. Hofmann rearrangement of carboxamides to carbamates mediated by hypervalent iodine.

Silva *et al.* reported an efficient example, the ring contraction of 1,2-dihydronaphthalene derivatives **54** promoted via Koser's reagent to form acetal **55**.[24] This work also presented a new approach for the synthesis of (±)-indatraline in 9 steps involving two diastereoselective rearrangements mediated by iodine(III) with an overall yield of 29% (Scheme 11-a). The mechanism starts with the ionization of Koser's reagent to form $PhIOH^+$ **56**. Then, a benzylic carbocation **57** is formed by electrophilic addition to the double bond of alkene **54**; the *trans*-addition of MeOH cluster to carbocation will occur over the *cis*-addition due to the lower free energy and lower potential energy it possesses.[25] The next step involves migration of the aryl group to displace PhI, followed by H_2O elimination and the required antiperiplanar for the arrangement. Then, the ring contraction leads the five-member ring to form compound **55a** (Scheme 11-b).



Scheme 11. Ring contraction reactions mediated by iodine (III).

2. Chapter 2: Chiral Hypervalent Iodine Catalysts

2.1. Introduction to Chiral Hypervalent Iodine Catalysts

The ongoing demand to prepare enantiopure compounds has driven the development of numerous chiral hypervalent iodine compounds to be use in enantioselective reactions. The two most common strategies to achieve chiral hypervalent iodine (III) reagents are: (i) chiral ligand **L*** attachment to the hypervalent iodine centers via ligand exchange; these ligands are usually chiral acids or alcohols **62**; and (ii) hypervalent iodine reagents with chiral substituents at the aromatic ring **63**. In addition, hypervalent iodate anions can be coordinated by their reactive ion-pairs with chiral cations in a lesser-known reagent class **64**.[2,26,27] Similar strategies should be possible for the chiral iodine (V). One method to prepare planar chiral hypervalent iodine (V) reagents with crown ether backbones has been recently published[28] (Figure 3).

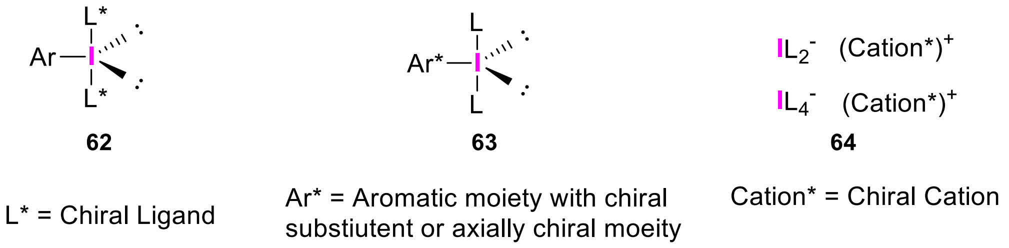
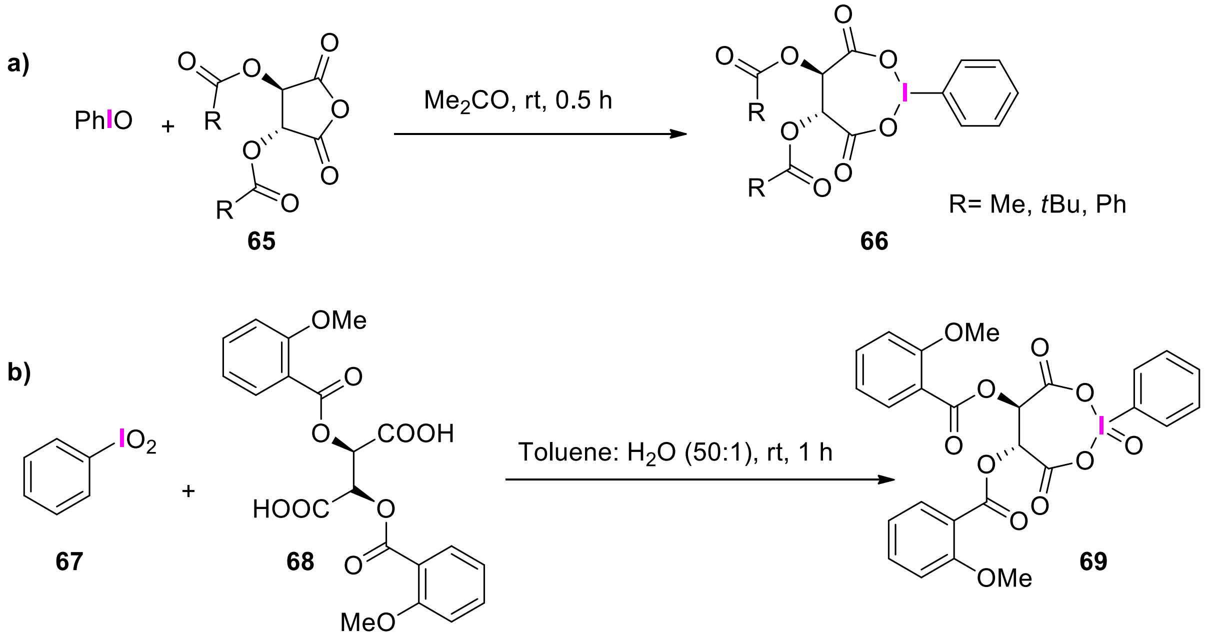


Figure 3. Chiral hypervalent iodine types.

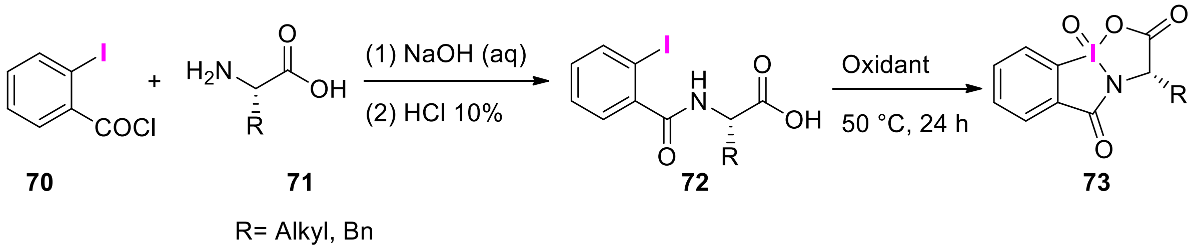
2.1.1. Hypervalent Iodine Reagents with Chiral Ligands

In 1907, Pribam reported the first chiral iodine reagent obtained from a mix of iodosobenzene and L-tartaric acid.[29] After eight decades, Imamoto *et al.* introduced a new class of chiral aryl hypervalent iodine reagents **66** that is prepared by treating PhIO with different L-tartaric acid anhydride derivatives **65**.[30] Promising initial results were achieved by using these reagents on asymmetric oxidations of sulfides to sulfoxides (Scheme 12-a). Later, Kita *et al.* synthesized the chiral iodine (V) reagent **69** starting from $PhIO_2$ **67** using chiral tartaric acid derivatives **68**. This reaction was the first example of the catalytic use of chiral hypervalent iodine for the oxidation of sulfides to sulfoxides (Scheme 12-b).[31]



Scheme 12. Synthesis of chiral I(III) and I(V) derivatives.

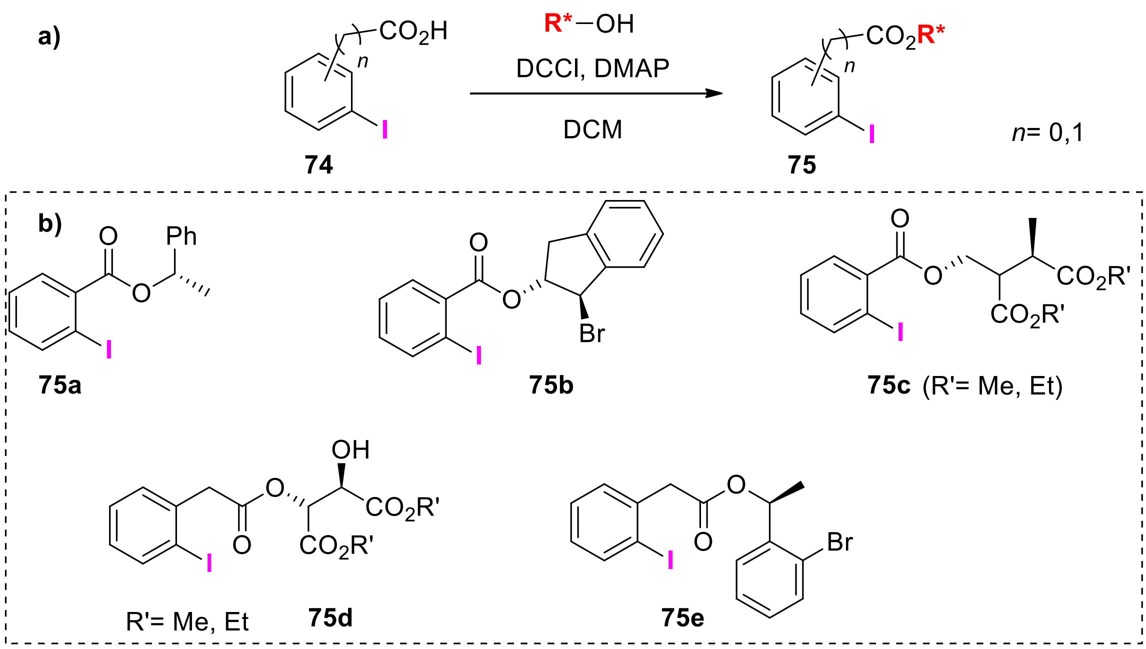
Zhdankin *et al.* synthesized various classes of chiral iodine (V) reagents using different amino acids **71** as chiral species.[32] The synthetic procedure started by reacting 2-iodobenzoyl chloride **70** with chiral alkyl or aromatic amino acids to prepare 2-iodobenzamides **72,** which were oxidized readily by potassium bromate ($KBrO_3$) or Oxone® ($2KHSO_5/KHSO_4/K_2SO_4$) to form chiral I(V) reagents **73**. These reagents give good yields for sulfide oxidations, but the enantiomeric excesses were very low, with 16% *ee* (Scheme 13).



Scheme 13. Synthesis of I(V)-reagents using amino acids as chiral ligands.

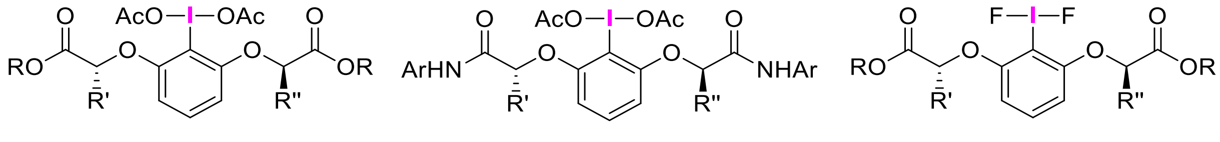
2.1.2. Chiral Substituents on the Iodoarene Backbone

The chirality of the most common aryl iodine reagents comes from one or more chiral substituents on the iodoarene backbones, so various methods to prepare these compounds have been developed. Wirth *et al*. synthesized C1-symmetric chiral iodoarene reagents through the esterification of **74** with chiral alcohols[33] and then oxidation of the esters to form the corresponding I(V) reagents **75**. The synthesis of these chiral iodoarenes is shown in Scheme 14-a, and some examples are shown in Scheme 14-b.



Scheme 14. Synthesis of I(V)-reagents using amino acids as chiral ligands.

C2-symmetric chiral hypervalent iodine reagents containing lactic acid derivatives showed adequate reactivity and selectivity in comparison with C1-symmetric chiral hypervalent iodine reagents (Figure 4).[34–37] These are considered the most successful chiral aryl λ^3-iodanes with several applications. For example, catalyst **76** showed good reactivity and selectivity in oxidative rearrangement of olefins with up to 91% *ee,* and α-oxytosylation of propiophenone enol acetate with up to 67% *ee,* while catalyst **77** gave higher selectivity in the α-oxytosylation reaction with up to 79% *ee,* and up to 92% *ee* in oxidative spirolactonization.[38–40] Catalyst **78** is widely used in different fluorination reactions, such as intramolecular metal-free aminofluorination of hexenamines, and provides the desired products in high stereoselectivity with up to 99% *ee* after crystallization.[36] It is also used in asymmetric difluorination of β-monosubstituted styrenes and trisubstituted cinnamate ester derivatives to yield the desired products with good yields and high enantioselectivities of 67% and 92% *ee*, and 74% and 94% *ee*, respectively.[41]

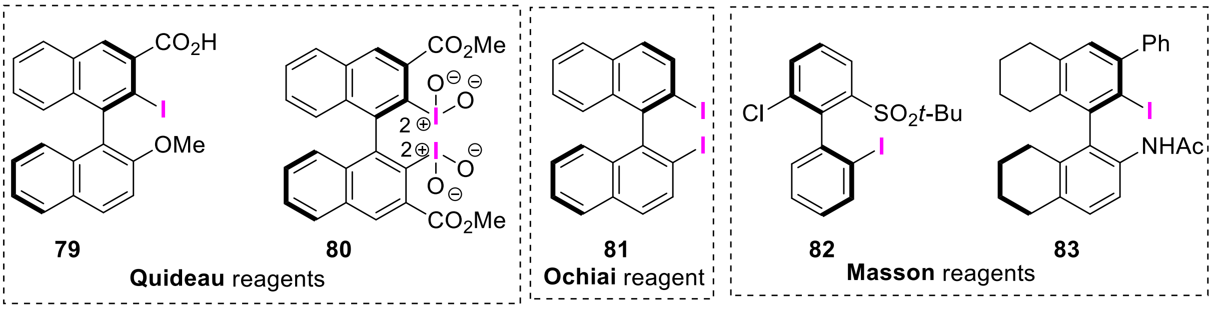


76 **77** **78**

Figure 4. Lactate-based C2-symmetric chiral hypervalent iodine reagents.

2.1.3. Chiral Iodoarenes with Axial Chirality

Various chiral aryl iodine reagents possessing axial chirality have been reported.[42–48] Quideau *et al*. reported the first example of chiral biarylic iodines; their objective was to prepare IBX analogues with an axis of chirality close to the iodine center **79**. This scaffold showed promising results in asymmetric hydroxylative phenol dearomatization of up to 50% *ee* through the *in-situ* generation of chiral hypervalent iodine. Later, the same group was able to cleanly oxidize **79** *ex-situ* to generate several chiral hypervalent iodanes and evaluate their performance in asymmetric hydroxylative phenol dearomatization. They found that the catalyst **80** gave the best results of up to 73% *ee*, due to the I(V)-type geometry (and reactivity) of the hypervalent iodine center **80**, as well as the modulation of the dihedral angle around the chiral biaryl axis, which are possible key factors in its improved ability to induce asymmetry.[44,48] Ochiai *et al.* generated axial chirality by synthesizing a binaphthyl-based chiral aryl iodide **81**.[42] This catalyst, used in the α-tosylation of propiophenone, gave poor enantioselectivities and moderate yields. Masson *et al.* recently reported a unique axial chiral, non-C2-symmetric iodoarene **82** and used it in direct α-oxysulfonylation of ketones with good yields and respectable *ee*.[45] Later, the same researcher also reported a non-C2-symmetric iodoarene precatalyst **83** having an amide group on the 2′-position. Tests of this catalyst in spirolactonizations gave only poor *ee*s (Figure 5).[49]



79 **80**
Quideau reagents

81
Ochiai reagent

82 **83**
Masson reagents

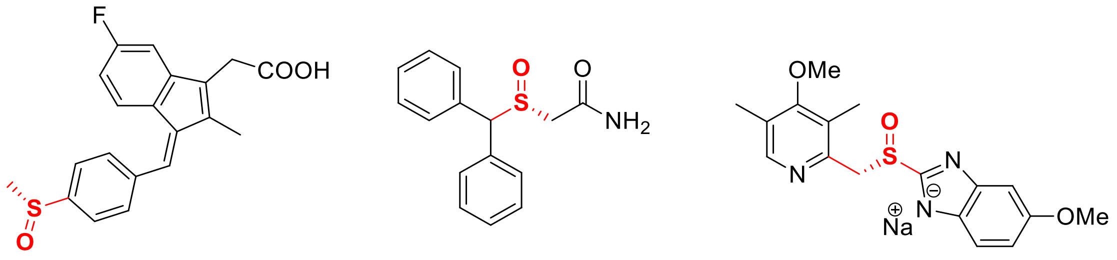
Figure 5. Axially chiral iodoarene reagents.

2.2. Chiral Iodoarenes for Enantioselective Oxidative Reactions

In recent years, many chiral hypervalent iodine compounds have been developed and utilized in enantioselective oxidative coupling transformations. Due to their relevance in this thesis, α-oxygenations, sulfoxylations such as intra- and intermolecular dearomative oxygenations of naphthols and phenols, α-oxysulfonations, and (spiro)lactonizations will be discussed in detail.

2.2.1. Asymmetric Oxidation of Sulfides to Sulfoxides

Synthesis of optically active chiral sulfoxide compounds is a challenge in organic chemistry.[50–52] These compounds have been used in two important areas: as chiral ligands and chiral auxiliaries in asymmetric synthesis[50,53] and as pharmaceutical compounds[54] such as Clinoril®, Nuvigil®, and Nexium® (Figure 6).



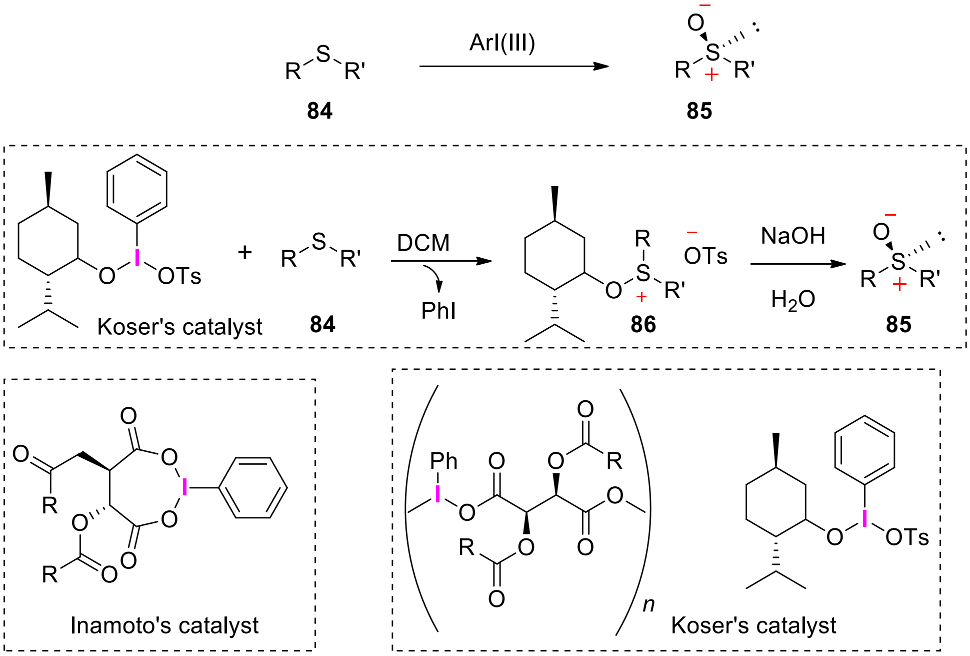
Clinoril® (Sulindac)
Antiarthritic

Nuvigil® (Armodafinil)
Wakefulness stimulant

Nexium® (Esomeprazole sodium)
Proton pump inhibitor

Figure 6. Chiral optically active sulfoxide in drugs.

Koser reported new chiral hypervalent iodine reagents used in asymmetric oxidation prochiral sulfides **84** to prepare chiral optically active sulfoxides **85** (Scheme 15) with a good yield and of up to 53% *ee*.[55] Six years later, Koser designed another chiral iodoarene reagent by attaching a menthol ligand to an iodine (III) moiety. This reagent gave moderate diastereoselectivity of chiral sulfoxides. However, following recrystallization and base-mediated hydrolysis, the *ee* increased to 99%.[56] Kita *et al.*[31] performed the oxidation of sulfides to sulfoxides using a combination of $PhIO_2$ with a chiral tartaric acid derivative and a catalytic amount of CTAB to achieve the activation and solubilization of $PhIO_2$.

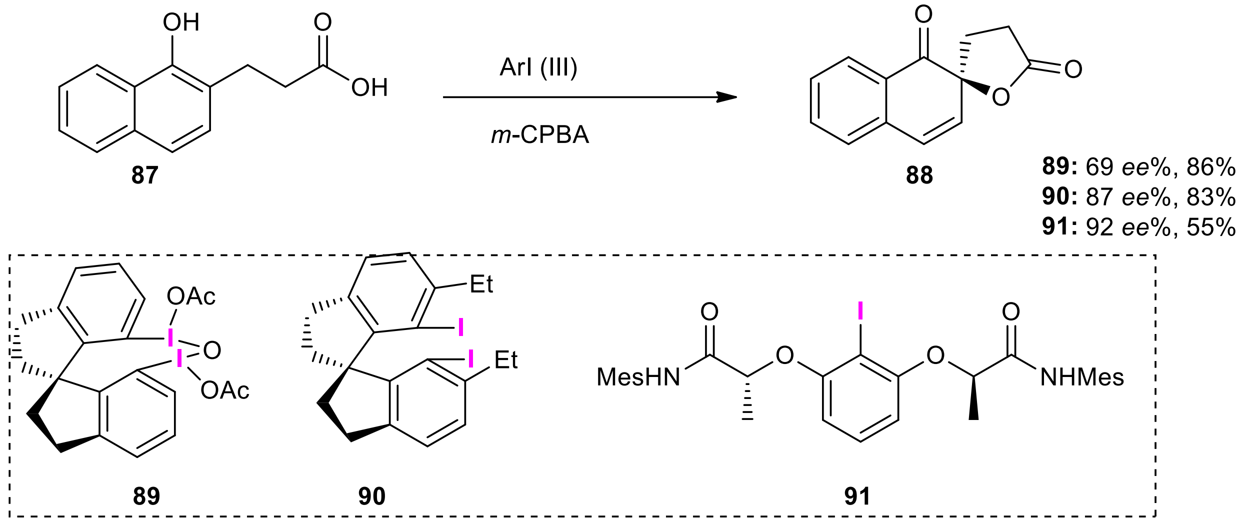


Scheme 15. Asymmetric oxidation of sulfides to sulfoxides.

The chiral sulfoxide compounds were obtained with good yields and of up to 72% *ee*. Since then, various chiral hypervalent iodine reagents have been synthesized and tested in the oxidation of sulfides to sulfoxides without improving the enantioselectivities.[33,57]

2.2.2. Oxidative Dearomatization of Phenols

Using chiral hypervalent iodine reagents to synthesize a chiral molecular scaffold from dearomatized compounds is a very successful and efficient method, especially with the milder conditions required compared with other oxidants. Various phenols were tested in the first attempt to perform an enantioselective phenols dearomatization reaction reported by Pelter *et al.*[58] using the chiral iodoarene reagent **66**. Unfortunately, all cases provided racemic products. Kita *et al.* reported the first example of asymmetric dearomatization of naphthols **87** using a chiral hypervalent iodine reagent **89** in a stoichiometric amount to obtain spirolactone **88** with good yields of up to 86% and moderate *ee* of up to 69%.[15] They were able to improve the stereoselectivity of the spirocyclic compounds to 87% *ee* through the steric effects that come from the ethyl group at the ortho position of the aryl **90**.[59] Later, Ishihara *et al.* developed a new class of C2-symmetric chiral iodoarenes **91** in which the n–σ* interactions between the electron-deficient iodine (III) center and carbonyl groups or intramolecular H-bonding between the ligands and the acidic hydrogen helped provide excellent enantioselectivity with up to 92% *ee* (Scheme 16).[35]



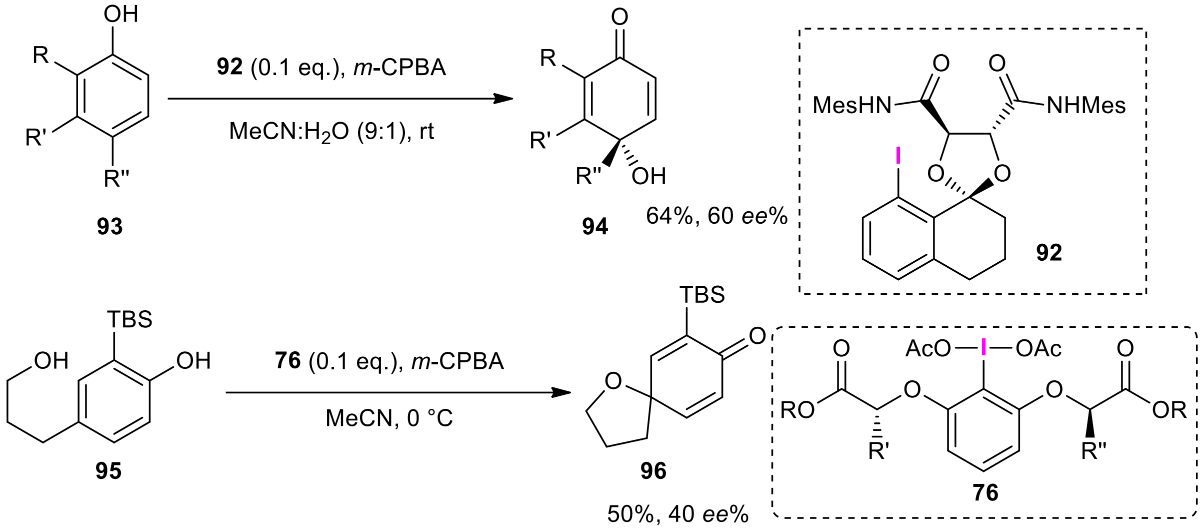
87 **88** **89** **90** **91**

89: 69 *ee*%, 86%
90: 87 *ee*%, 83%
91: 92 *ee*%, 55%

Scheme 16. Asymmetric oxidation of sulfides to sulfoxides.

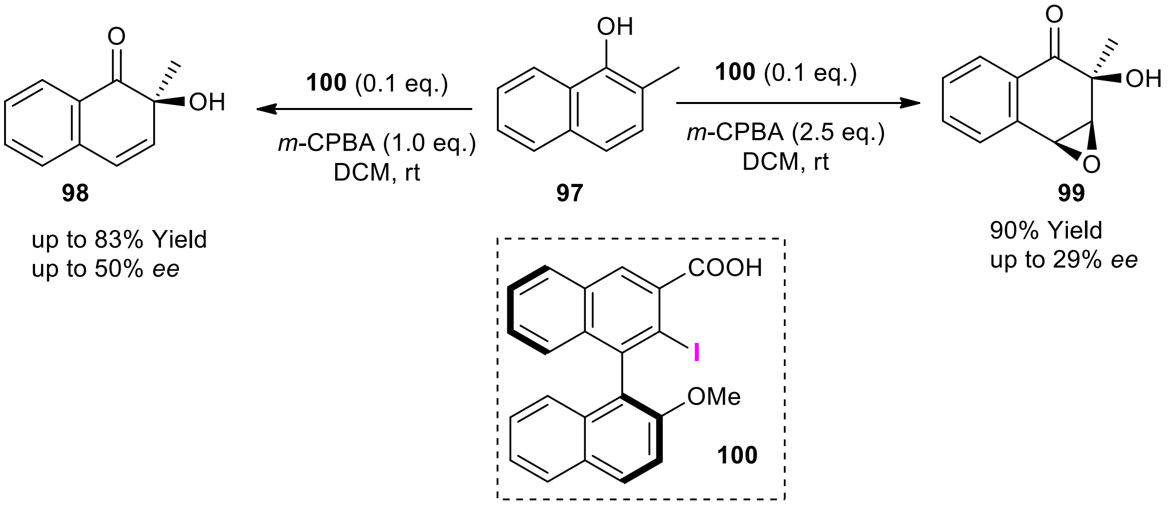
In 2013, Harned *et al.* prepared the tricyclic chiral iodines **92** and used them in the oxidative dearomatization of phenols **93** to generate *p*-quinols **94** in good yield with

60% *ee*.[60] The same catalyst was used by Quideau to prepare the 2,5-cyclohexadienone derivative **96** with 40% *ee* (Scheme 17).[61]



Scheme 17. Enantioselective dearomatization of phenols mediated by chiral hypervalent iodine (III) reagents.

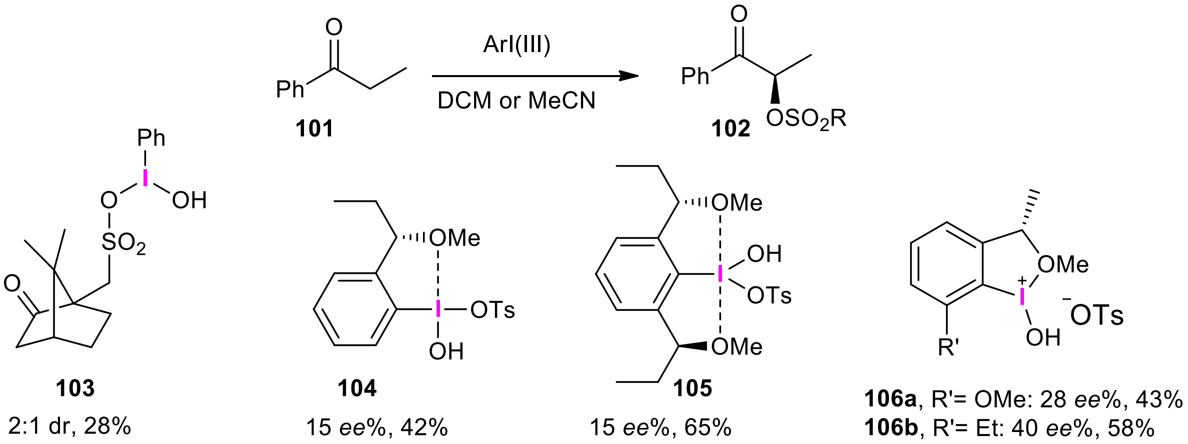
Quideau reported the axial chiral aryl iodides based on a binaphthyl system **100** and used them in hydroxylation dearomatization of phenols **97** to obtain a hydroxylated compound **98** with a good yield and 50% *ee*.[44] Using an excess of *m*-CPBA led to production of the corresponding epoxide **99** with a high yield and up to 29% *ee* (Scheme 18).



Scheme 18. Chiral binaphthyl iodoarenes in a dearomatization reaction.

2.2.3. α-Functionalization of Carbonyl Compounds

Various strategies to attach groups such as phosphoryloxy-, acetoxy-, and alkoxy-groups at the α position of carbonyl compounds have been applied. Transition metals have been used to accomplish this asymmetric transformation.[62–65] The α-functionalization of carbonyl compounds can be achieved by chiral hypervalent iodine reagents. Varvoglis *et al.* reported the first example of asymmetric α-sulfonyloxylation of non-symmetrical ketones **101** using a chiral hypervalent iodine reagent **103**.[57] The reaction gave good regioselectivity, but all cases investigated showed poor diastereoselectivities (Scheme 19). An asymmetric α-oxytosylation of propiophenone was reported by Wirth *et al.* using chiral iodoarenes **104** and **105,** but the products were obtained with low *ee* of up to 15%.[66]



Scheme 19. Asymmetric α-oxytosylation of propiophenone with various iodanes.

Later, they modified the structure by increasing the distance of the (tosylate)–oxygen iodine to give the reagent **106,** and the desired product was obtained with *ee* of up to 28% (Scheme 16).[67] Some years later, the same group modified the structure of **106a** by exchanging the OMe group with ethyl **106b** and improved the *ee* of product **102** to 40%.[68] Very recently, Wirth *et al.* synthesized a new class of C–N axial chiral hypervalent iodine reagents **107a-c** from aniline derivatives. They also studied the X-ray structures of these reagents. They concluded that the stereoselectivity of product **102** is controlled by the C–N chiral axis, not by the chiral lactate moiety (Figure 7). These reagents were utilized in the α-oxytosylation of ketones to obtain **102** in high yields of up to 96% with a good *ee* of up to 80%.[69]

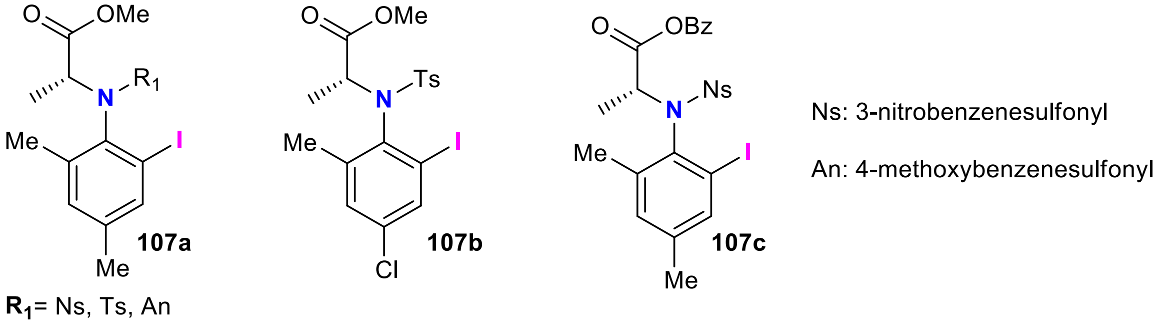
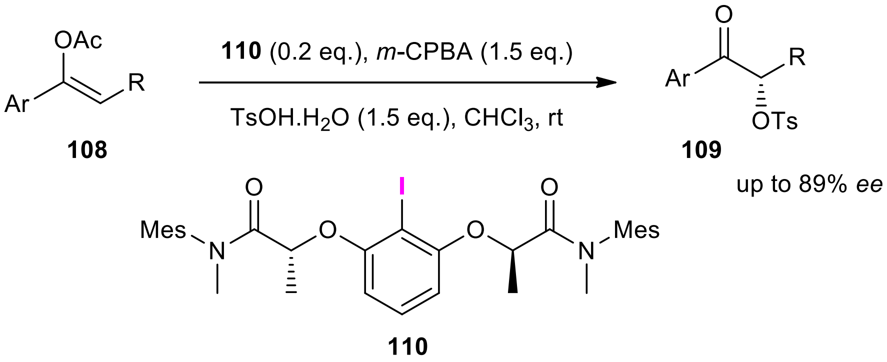


Figure 7. C–N axially chiral iodoarenes.

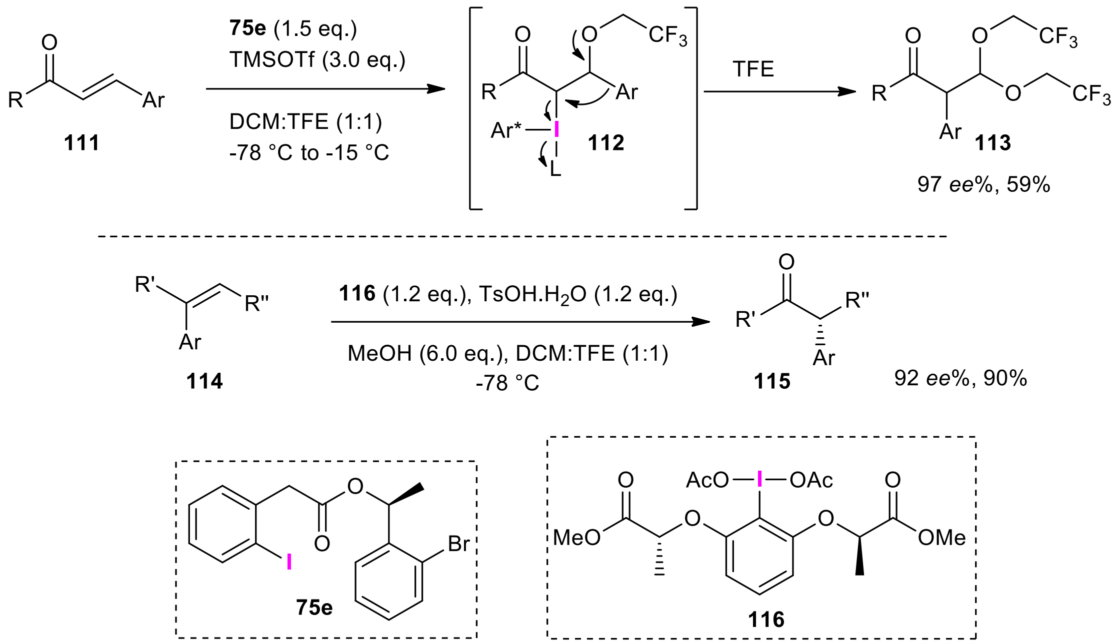
Legault *et al.* studied the mechanism of the α-oxytosylation of ketones[70] in depth and applied this method on enol esters **108** using catalytic amounts of C2-symmetric chiral iodoarene **110** in the presence of *m*-CPBA to form the desired products **109** with high yields and up to 89% *ee* (Scheme 20).[39] The mechanism of this reaction was already discussed and shown in Scheme 2.



Scheme 20. Asymmetric α-sulfonyloxylation of vinyl acetates.

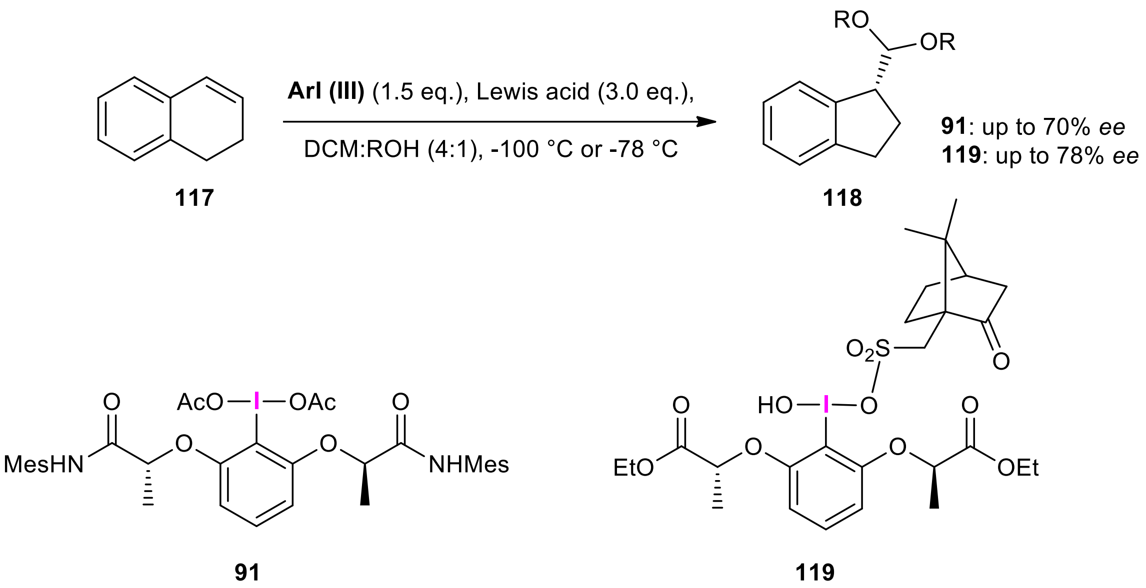
2.2.4. Rearrangement Reactions

The properties of hypervalent iodine reagents allow them to act as excellent leaving groups, and their electrophilic nature makes them suitable reagents for various rearrangement reactions. Wirth *et al.* reported the first example of a stereoselective oxidative rearrangement reaction mediated by chiral hypervalent iodine to activate aryl-substituted alkenes **111** to form stabilized phenyliodinated intermediates **112**, followed by a stereoselective 1,2-aryl migration to synthesize α-arylated products **113** in moderate yields and with up to 97% *ee*.[71] In 2016, the same group developed a new chiral hypervalent iodine reagent **116** that reacted with diarylalkene derivatives **114** to generate α-arylated ketones **115** in yields of up to 90% and with up to 92% *ee* (Scheme 21).[38]



Scheme 21. Rearrangement via aryl-migrations mediated by Ar*IL$_2$ reagents.

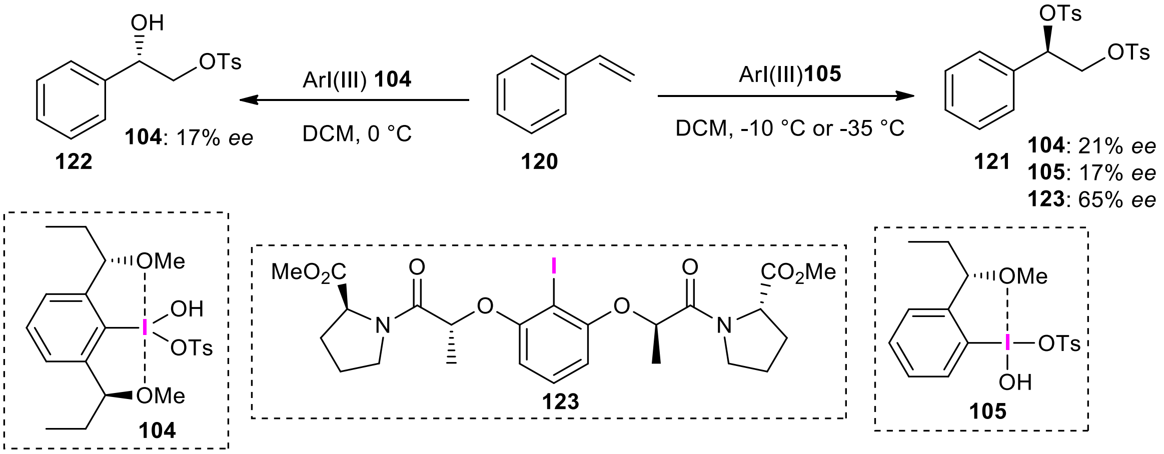
Wirth *et al.* developed an enantioselective ring contraction of tetralone using chiral hypervalent iodine **91**, which was achieved with triflic acid to obtain the desired indanes **118** of 59% *ee* at −78 °C using TfOH. The enantioselectivity was improved to 70% *ee* at a lower temperature (−100 °C) with TMSOTf as the Lewis acid (Scheme 22).[71] In 2016, Silva *et al.* performed this reaction employing another chiral hypervalent iodine **119** used *in-situ* from the corresponding iodoarene and *m*-CPBA to generate the indanes from 1,2-dihydronaphthalenes **117.** They also used an extra chiral ligand (+)−CSA- to control the stereoselectivity of products **118** with up to 78% *ee*.[72] Many researchers have used achiral iodoarenes and applied this reaction to various cycloalkanones and cycloalkenes.[73–78] Iodoarene reagents have also been used in ring expansion reactions by Koser[79], Hara[80], and Silva[81], but none of these examples are enantioselective.



Scheme 22. Ring contraction reaction mediated by Ar*IL$_2$ reagents.

2.2.5. Alkene Functionalizations

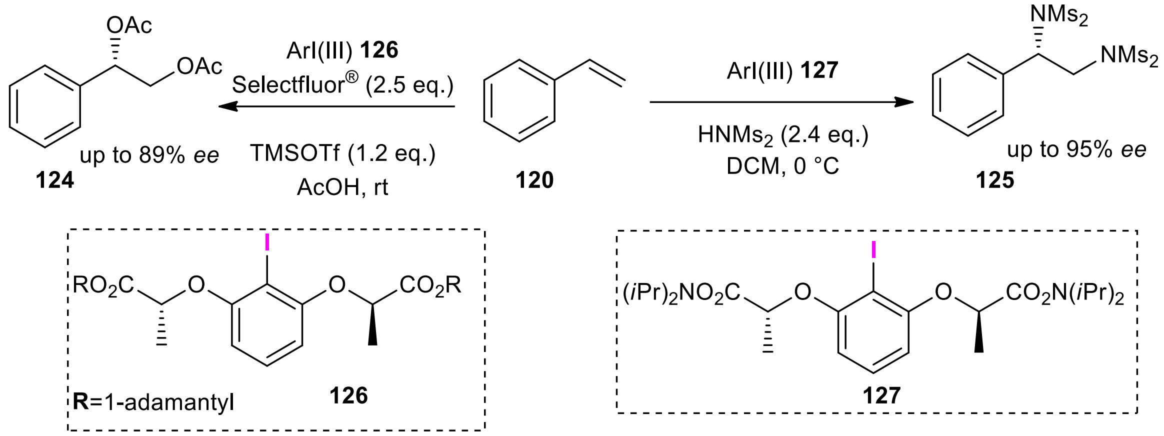
Alkenes are important functional groups in organic synthesis and are considered key intermediates for other fundamental functional groups to prepare chiral compounds. Wirth *et al.* reported the first attempt to carry out the enantioselective difunctionalization of alkenes using chiral hypervalent iodine reagents **104** or **105** to transform styrene **120** into the ditosylated compound **121** or the monotosylated compound **122** with up to 21% *ee* and 17% *ee*, respectively.[66] The same group was able to improve the stereoselectivity of the ditosylation to 65% *ee* by using a catalytic amount of chiral hypervalent iodine **123** in the presence of TFA to activate the alkenes (Scheme 23).[67,82]



Scheme 23. Enantioselective ditosylation of styrene by Wirth *et al*.

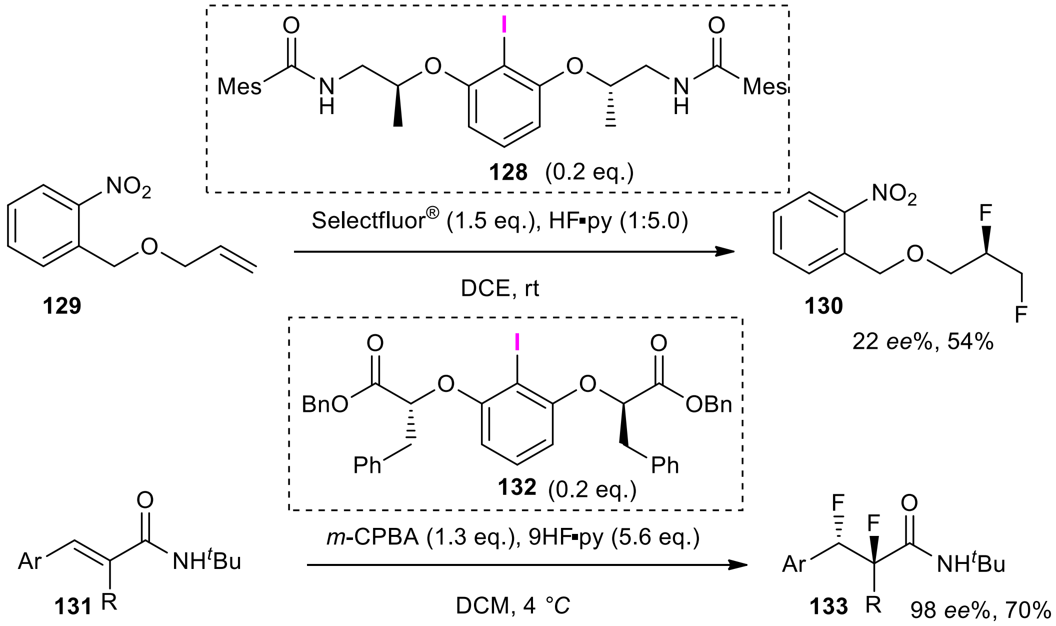
Further difunctionalizations of alkenes have been reported. Fujita *et al.* presented the first attempt for an asymmetric diacetoxylation of alkenes following the Prévost and

Woodward reaction using chiral hypervalent iodine **126** to generate product **124** with up to 89% *ee*.[83] Muñiz *et al.* demonstrated the asymmetric diamination of styrene promoted by chiral hypervalent iodine **127** to obtain product **125** in moderate yields with up to 95% *ee* (Scheme 24).[84]



Scheme 24. Enantioselective difunctionalization of styrene mediated by Ar*IL$_2$ reagents.

Catalytic difluorination of alkenes was presented by Gilmour *et al.* in 2016, using a combination of a precatalyst **128** with Selectfluor as an oxidant, while HF·py was used as the fluoride source.[85] Although they generated product **130** with only 22% *ee*, this attempt paved the way for other research groups to perform asymmetric fluorination of alkenes. In the same year, Jacobsen *et al.* reported the 1,2-difluorination of cinnamides **131** mediated by a hypervalent iodine reagent, which was generated *in-situ* from precatalyst **132** and *m*-CPBA. They used 9HF·py as a fluoride source to obtain products **133** with high enantioselectivity and up to 98% *ee* (Scheme 25).[86]



Scheme 25. Enantioselective difluorination of alkenes mediated by Ar*IL$_2$ reagents.

2.2.6. Synthesis of Chiral (Spiro)oxazolines

Oxazoline units constitute the core moiety of marine and terrestrial biologically active natural products and bioactive molecules (Figure 8).[87–90] Moreover, oxazolines have been used in organic syntheses of molecules such as chiral ligands, protective groups, and chiral auxiliaries.[91–94] Oxazine, thiazolines, and imidazolines are also useful compounds in organic synthesis and biologically active compounds.[95,96]

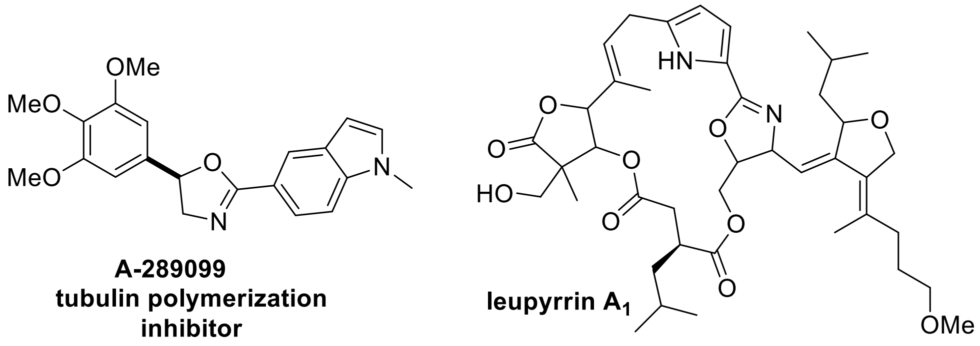
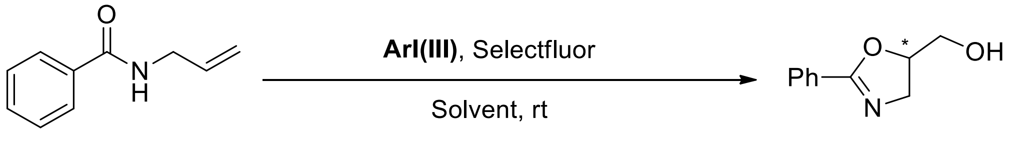


Figure 8. Examples of natural products containing an oxazoline unit.

Numerous synthetic methods to prepare 2-oxazoline structures have been reported starting from aldehydes, nitriles, carboxylic acid, carboxylic ester, β-hydroxyamides, and others.[97–103] Among these strategies, the cyclization of unsaturated amides is still considered as an efficient and direct method to construct 2-oxazolines.[101,104–106] The limitations on these methods, such as extreme conditions, use of transition metals, lack of diversity of the scope substrates, and low yields with moderate enantioselective results,[103,107,108] encouraged us to develop a new mild catalytic method to prepare 2-oxazoline compounds **135** in high yields and with excellent enantioselectivities by utilizing our new chiral aryl iodide catalysts (Scheme 26).



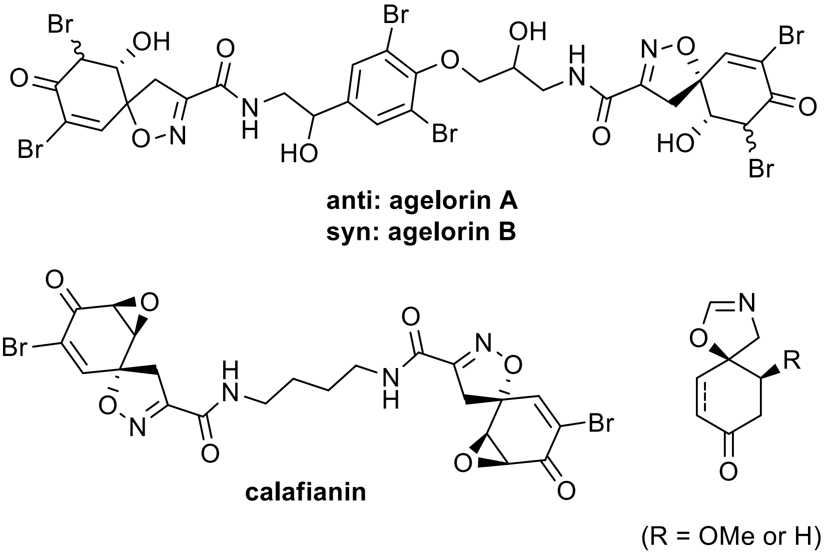
134

135

11%, 69% *ee*

Scheme 26. Cyclizations of unsaturated amides mediated by Ar^*IL_2 reagents.

On the other hand, Spirocyclic compounds are well represented in many natural products and commercial drugs.[109–114] These scaffolds have the main advantage of providing 3D spatial arrangements due to the tetrahedral nature of the spirocarbon atom. Hence, this allows these compounds to bind to enzymes and other biological receptors more easily than to largely planar (hetero)aromatic systems, providing the capability to simultaneously project features in all three dimensions.[115] Furthermore, these compounds may be used to improve the efficiency of the 3D orientation of the pharmacophore in order to optimize H-bonding, hydrophobic, and π-stacking interactions.[116,117] In general, most of the spiro compounds can be found in abundance in nature. In contrast, spirooxazolines are found in only a few natural compounds, such as agelorin A and B from marine sponges of the genus *Agelas*,[118] calafianin from the sponge *Aplysina gerardogreeni*,[119] and the three oxazoline derivatives extracted from the plant *Gemmingia chinensis* (Figure 9).[120] The benefits of the spirocyclic compounds and their utility in medicinal chemistry and materials science are encouraging chemists to develop new strategies to synthesis these compounds. Several methodologies for the synthesis of spirocyclic compounds have been reported, based on radical cyclization strategies, rearrangement alkylation, oxidative or reductive coupling reactions and cycloadditions.[121–124] Although spirooxazoline compounds have many merits, there are just three studies that have published construction methods for them. Li *et al.* reported a synthesis route to convert ketones into spirooxazoline**,** which has anxiolytic activity.[125] Zhu *et al.* synthesized spirocyclic difluorinated oxazoline compounds using a photochemical cycloaddition reaction.[126] Recently, Moran *et al.* determined a new method for synthesizing spirooxazoline through the oxidative cyclization of phenols containing pendent amides mediated by iodine(III). They also applied this reaction to naphthol using chiral iodoarenes, but this precatalyst showed poor reactivity and selectivity, with 36% yield and 14% *ee.*[127]

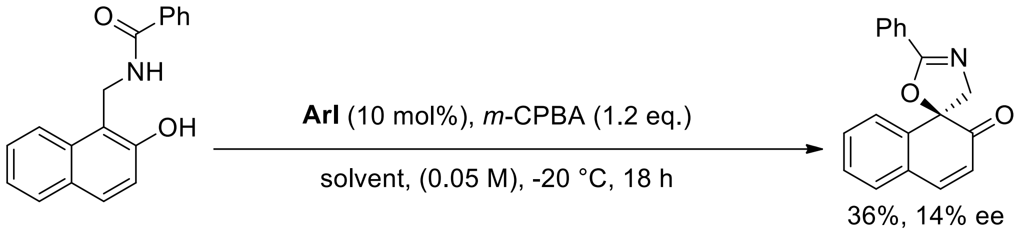

anti: agelorin A
syn: agelorin B

calafianin

(R = OMe or H)

Figure 9. Examples of natural products containing spirooxazoline.

Due to the limited literature reports describing the synthesis of these compounds and the poor results in both yield and enantioselectivity, we decided to use chiral hypervalent iodine catalysts to synthesis of chiral spirooxazoline compounds **137** through the asymmetric oxidative dearomtization of naphthols **136** (Scheme 27).



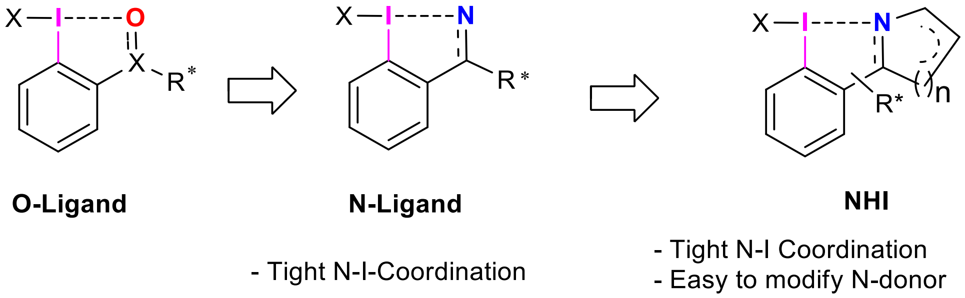
136 **137**

Scheme 27. Asymmetric oxidative cyclization of naphthols via HVI.

3. Chapter 3. Design and Synthesis of Novel Chiral *N*-Heterocyclic Iodanes

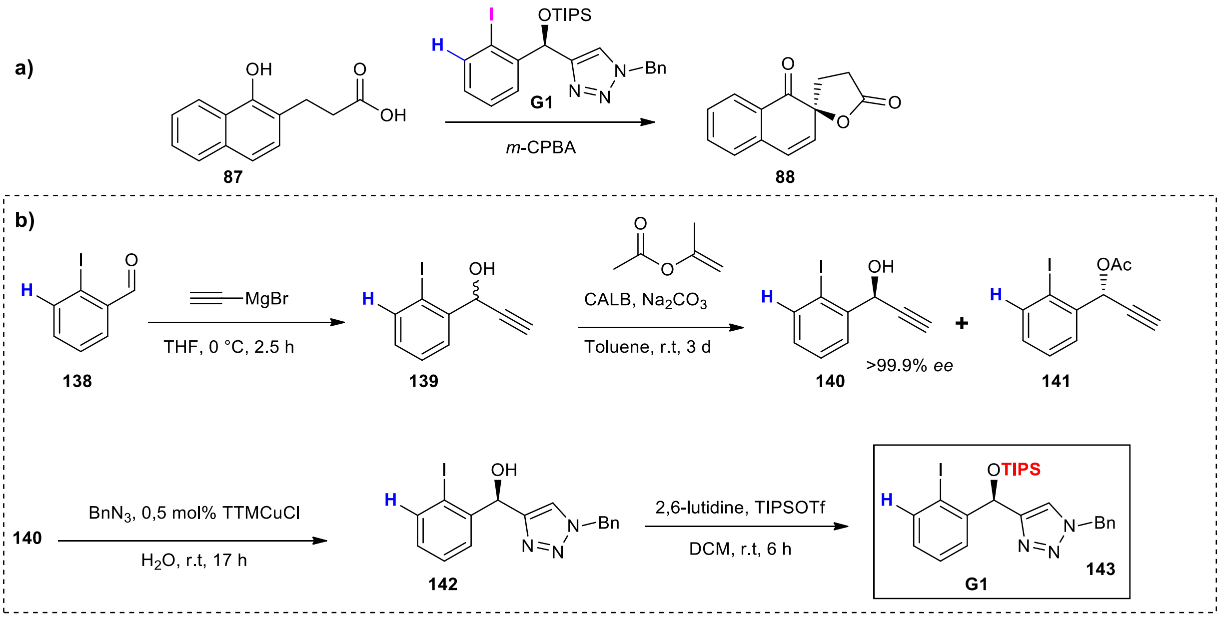
3.1. Structure of *N*-Heterocyclic Iodanes

Even though the structural variety of the investigated chiral aryl iodides appears to be high, the coordination of the central iodine atom is usually achieved through oxygen-based Lewis bases such as ethers, sulfonates, or amides. These functional groups stabilize the hypervalent iodine atom either by direct I–O coordination or by forming a hydrogen bond to another oxygen-based ligand. Given the great success of nitrogen-based Lewis bases, in particular *N*-heterocycles, as ligands in transition metal chemistry, it is surprising that the development of chiral hypervalent iodine compounds based on *N*-heterocycles as easy-to-modify stabilizing functional groups has received so little attention (Scheme 28).[39,71]



Scheme 28. Evolution of chiral hypervalent iodine compounds from **O**- to ***N***-ligands. NHI: *N*-heterocycle–stabilized iodane.

Our group recently investigated the effect of achiral *N*-heterocycle–stabilized iodanes (NHIs) and found that the *N*-heterocycle has a previously unobserved influence on the reactivity of the iodane in sulfide oxidations.[14,128] We also introduced novel triazole-based chiral hypervalent iodine catalysts of type **1** (Scheme 29-a). The synthesis of this “first-generation” catalyst **G1** is highly robust. In particular, the introduction of the chiral benzyl alcohol is straightforward and based on a highly efficient kinetic resolution (Scheme 29-b).[129] Because this process is not based on a chiral precursor, as are many other hypervalent iodine compounds, these chiral triazoles are easily accessible in both enantiomeric forms. Initial investigations revealed a good performance of this catalyst in the Kita-spirocyclization of 1-naphthols. So far, this is the best C1-symmetric chiral catalyst for this reaction, although reactivity is still low. In particular, C2-symmetric catalysts give higher selectivities.



Scheme 29. Evolution of chiral NHIs.

However, the highly modular and robust synthesis of these novel catalysts allows fast synthetic modifications and hence a rational understanding of their structure/reactivity relationship. In 2015, Legault found that introducing steric *ortho*-substituents such as amides **144**,**145** to the iodine center increased the reactivity of this catalyst in α-tosyloxylation of carbonyl compounds.[39] In the oxidized state, an out-of-plane distortion of both the amide unit and the I–OH bond caused by the methyl group lowers the overall stability of the iodine(III) intermediate (Figure 10). This significantly improves reactivity by speeding up further ligand exchange processes and preferring the final reductive collapse of iodine(III) into its monovalent iodine(I) state in the oxidizing coupling step. This phenomenon is called "hypervalent twist" and was also observed in compounds **146** and **147** [130–132]

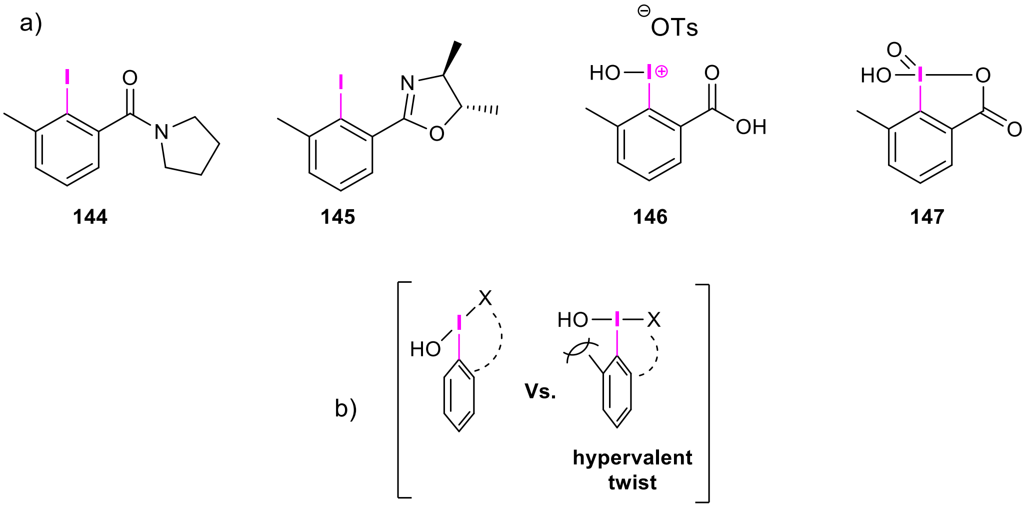
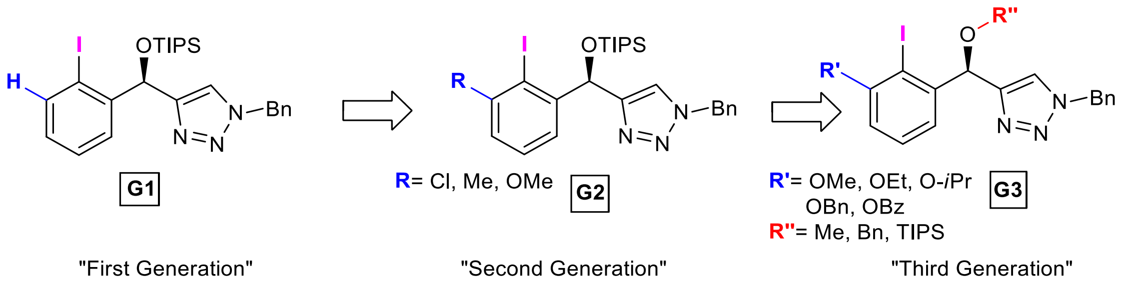


Figure 10. *o*-Methyl substituted iodoarenes and hypervalent twist.

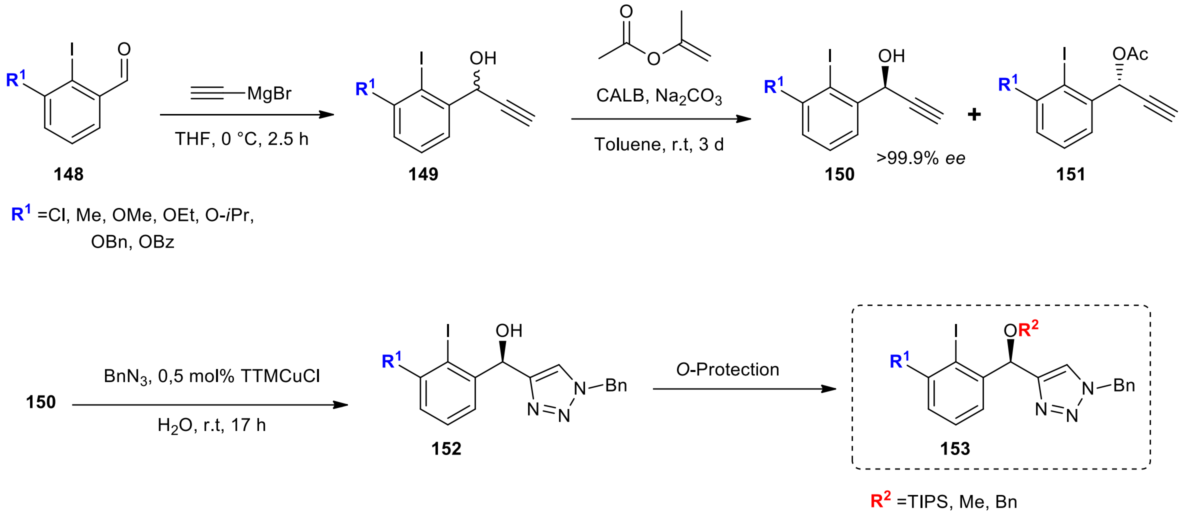
Based on this theory, the main goal of this thesis was to modify the *ortho* position to the hypervalent iodine center of the original catalyst **G1**, since substitutions at this position as in **G2** have been recently described as having a significant impact on the selectivity and reactivity of chiral hypervalent iodine-based catalysts. We found that introducing a donating group in the *ortho* position increased the reactivity and selectivity of the iodoarenes in different oxidative reactions. Further structural modifications were made to this design by using a slightly stronger aliphatic donating group in the *ortho* position or using an aromatic group. Again, the catalyst performance improved in the presence of the strongest donating group in the *ortho* position. We also used different protection groups to screen their effect on the reactivity and selectivity of these catalysts **G3**. Among the alky-, benzyl-, and triisopropyl silane (TIPS) groups, the best performance of these catalysts was achieved when the TIPS group was utilized as a protection group (Scheme 30).



Scheme 30*.* Evolution of chiral NHIs.

3.2. Synthesis of *N*-Heterocyclic Iodane Catalysts

The synthetic procedure for *ortho*-modified catalysts **143** is shown in Scheme 29. Aldehydes **148** undergoing 1,2-addition with ethinyl magnesium bromide should yield racemic propargyl alcohols **149**.[133] At this point, an enzymatic kinetic resolution with Candida antarctica Lipase B (CALB) will give enantiopure propargyl alcohols **150** and the corresponding acetates **151**. Final [3+2]-cycloaddition with benzyl azide to **152** followed by O-protection gives the triazoles **153** (Scheme 31).



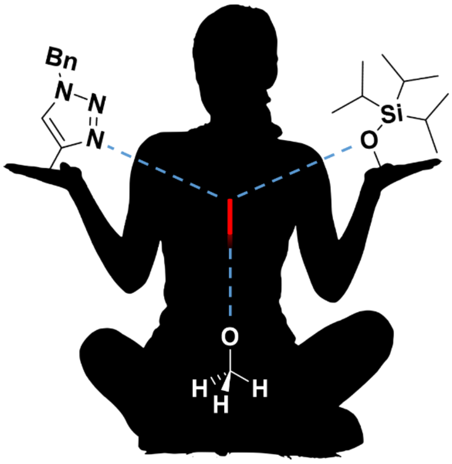
Scheme 31. Synthetic procedure of triazoles.

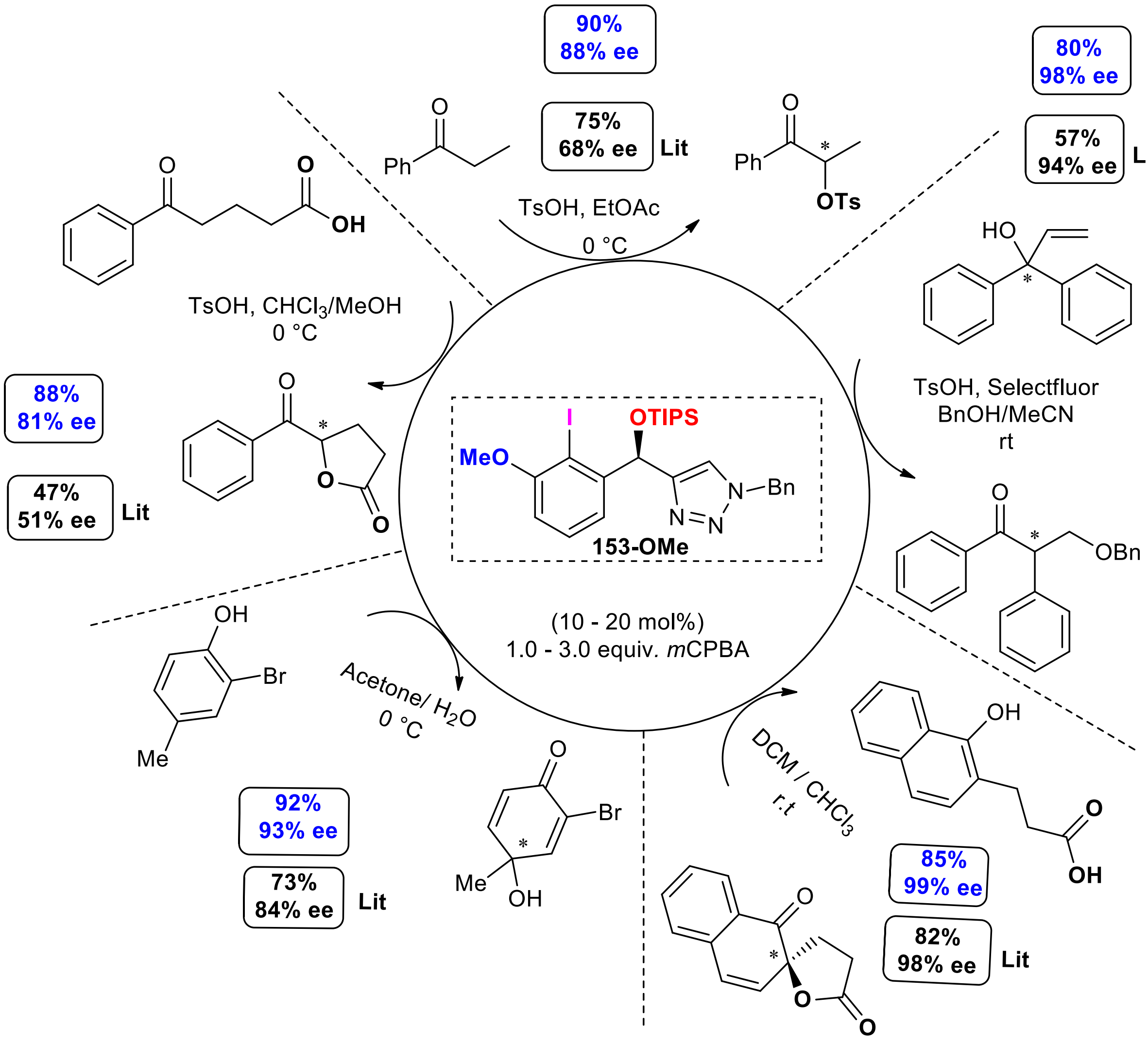
Following this synthesis, a variety of new chiral iodoarenes have been synthesized and applied to several enantioselective oxidative transformation reactions.

4. Summary of the Publications

4.1. First Publication: A Triazole-Substituted Aryl Iodide with Omnipotent Reactivity in Enantioselective Oxidations

Chiral hypervalent iodine catalysts (III) are commonly used in organic synthesis. Despite serious effort and an unseen variation of chiral C1- and C2-symmetric aryl iodides as catalysts, only moderate enantioselectivities and high catalyst loadings are observed, which is a major drawback in comparison to efficient metal-catalyzed transformations, such as hydrogenations. While phenolic dearomatizations, such as the Kita-spirolactonization or phenol dearomatizations, work reasonably well with selectivities of up to 92% *ee*,[40] enantioselective α-oxygenations of ketones are still not synthetically useful with maximum enantioselectivities of 68% *ee* for direct oxysulfonations and only 51% *ee* for lactonizations.[45] Each reaction can be performed with only one specific chiral iodoarenes, but so far, there is no chiral aryl iodoarene that can be used in different important transformations and provide remarkable results. In this article, three different second-generation catalysts bearing a chlorine, methyl or methoxy-substituent have been successfully synthesized and tested in model reactions. In particular, the *ortho*-OMe-substituted derivative outperformed the unsubstituted first-generation catalyst in terms of reactivity and selectivity. This catalyst is not only better than the first-generation, triazole-based catalyst, but it also gave the best results so far amongst the chiral hypervalent iodine compounds in five different enantioselective oxidative transformations, such as α-oxygenations of ketones, phenol dearomatizations, Kita-spirolactonization, lactonizations, and hydroxylation. Dearomatization of phenols and oxidative rearrangement of allylic alcohols are described in the literature. The summarized results are shown in Scheme 32.[134]





Scheme 32. Enantioselective reactions mediated by catalyst **153-OMe**.

Title of the Publication: “A Triazole-Substituted Aryl Iodide with Omnipotent Reactivity in Enantioselective Oxidations”

Ayham. H. Abazid, B. J. Nachtsheim, *Angew. Chem. Int. Ed.* **2020**, *59* (4), 1479–1484.

The supporting information, including a complete optimization table, detailed experimental procedures, characterization data, and copies of NMR spectra, is available free of charge on the journal′s website.

Abstract: A widely applicable triazole-substituted chiral aryl iodide is described as a catalyst for enantioselective oxidation reactions. The introduction of a substituent in the ortho position to the iodide is key for its high reactivity and selectivity. Besides a robust and modular synthesis, the main advantage of this catalyst is the excellent performance in a plethora of mechanistically diverse enantioselective transformations,

such as spirocyclizations, phenol dearomatizations, α-oxygenations, and oxidative rearrangements. DFT-calculations of *in-situ* generated [hydroxy(tosyloxy)iodo]arene isomers give an initial rationale for the observed reactivity.

Author Contribution to this Publication: The synthesis of chiral hypervalent iodine catalysts and screening of the reactivity of these compounds in five different enantioselective reactions was performed and developed by me. In this project, I wrote the supporting information. The manuscript was written by me and B. J. Nachtsheim. B. J. Nachtsheim was the principal investigator and edited the article.

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A Triazole-Substituted Aryl Iodide with Omnipotent Reactivity in Enantioselective Oxidations**

*Ayham H. Abazid and Boris J. Nachtsheim**

Abstract: *A widely applicable triazole-substituted chiral aryl iodide is described as catalyst for enantioselective oxidation reactions. The introduction of a substituent in ortho-position to the iodide is key for its high reactivity and selectivity. Besides a robust and modular synthesis, the main advantage of this catalyst is the excellent performance in a plethora of mechanistically diverse enantioselective transformations, such as spirocyclizations, phenol dearomatizations, α-oxygenations, and oxidative rearrangements. DFT-calculations of in situ generated [hydroxy(tosyloxy)iodo]arene isomers give an initial rational for the observed reactivity.*

Hypervalent iodine compounds are versatile oxidants which have been utilized with great success in a plethora of oxidative coupling reactions[1] and in natural product synthesis.[2] In related enantioselective processes, a chiral aryl iodide precursor can be used in catalytic amounts in combination with a terminal co-oxidant to generate a chiral hypervalent iodine compound in situ. This chiral oxidant is subsequently capable of transferring its chirality onto the desired coupling products through diastereotopic transition states in the key oxidative C–X bond forming step.[3]

Since the discovery of the first enantioselective transformation catalyzed by a chiral aryl iodide in 2007 by Wirth and co-workers,[4] more than a dozen highly diverse C1- and C2-symmetric chiral aryl iodides have been developed.[5] Successful catalysts, such as **1**–**4** (Figure 1), usually show a good reactivity and selectivity in only one distinct class of oxidative transformation. So far there is no omnipotent chiral aryl iodide available that performs well throughout the most important oxidative transformations and hence can be seen as broadly applicable catalyst for iodane-based enantioselective couplings. Our group is heavily interested in the development of *N*-heterocycle-stabilized iodanes (NHIs) as a new class of stable and at the same time highly reactive hypervalent iodine compounds.[6,7] With the aim to design novel chiral aryl iodides which are robust to synthesize in a modular sequence and show a good performance throughout a diverse range of enantioselective oxidations, we recently developed the novel triazole-substituted aryl iodide **5** (Figure 2) and evaluated its reactivity in the Kita-spirocyclization of 1-naphthols.[8]

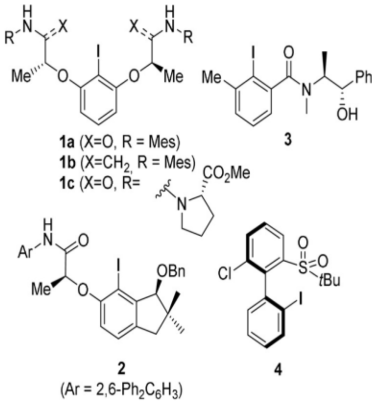

Figure 1. Best-performing chiral aryl iodide catalysts for enantioselective oxygenations.

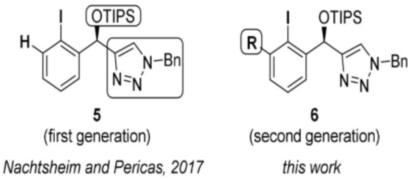

Figure 2. Structure of first- and second-generation triazole catalysts.

Even though this "first-generation" catalyst gave the so far highest enantioselectivities in direct comparison to other C1-symmetric aryl iodides for this reaction, reactivities were low. Well-established C2-symmetric aryl iodides, such as spirobiindanes developed by Kita or resorcinol ethers **1** developed by Uyanik and Ishihara, showed significantly higher stereoinduction and yielded the desired chiral lactones in better yields.[9] Due to the promising initial results with catalyst **5** and its highly modular and robust synthesis, we further developed "second-generation" triazole catalysts **6** (Figure 2) bearing a simple *ortho*-modification at the aryl iodide. We therefore synthesized *ortho*-Cl, -Me, and -OMe-substituted derivatives **6a**–**c** (Scheme 1). Their synthesis is

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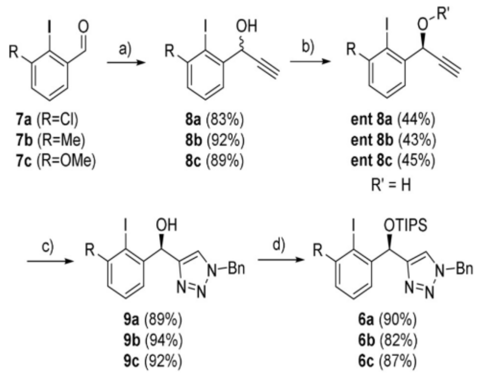
[**] A previous version of this manuscript has been deposited on a preprint server (https://doi.org/10.26434/chemrxiv.9747674.v1).

Supporting information, including detailed optimization studies, experimental procedures, analytical data (^{1}H, ^{13}C, and chiral HPLC analysis), and the corresponding spectra, and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/anie.201912023.

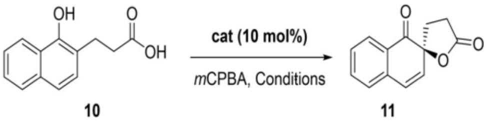


Scheme 1. Catalyst synthesis. Reaction conditions: a) **7** (1 equiv), ethynylmagnesium bromide (1.25 equiv) at 0 °C for 2.5 h. b) **8** (1 equiv), CALB (6 mg/mmol of **8**), isopropenyl acetate (1.5 equiv) in toluene at room temperature for 3 days c) **ent 8** (1 equiv), benzyl azide (1.3 equiv), TTMCuCl (0.005 equiv) in water at room temperature for 17 h. d) **9** (1 equiv), 2,6-lutidine (2 equiv), trialkylsilyl trifluoromethanesulfonate (1.2 equiv), in DCM at 0 °C for 6 h. The starting aldehydes are known in the literature and commercially available. For detailed synthetic procedures, see the Supporting Information.

straightforward and was completed on a gram scale for each chiral triazole starting from the iodinated carbaldehydes **7a–c**. Addition of ethynylmagnesium bromide gave the racemic propargylic alcohols **8a–c**, which were treated with the esterase CALB and isopropenyl acetate to give the enantiopure alcohols **ent 8a–c** in excellent selectivity. Since both products of the kinetic resolution, the free alcohol and the enantiomeric acetate, can be separated effortlessly, this route gives an efficient access to both enantiomers of the final catalysts. Copper-mediated Huisgen 1,3-dipolar cycloaddition of the free alcohols with benzyl azide gives triazoles **9a–c**. The final catalysts **6a–c** were observed through final TIPS-protection.

Having these second-generation catalysts in hand, we investigated their performance in the Kita-spirocyclization of 1-naphthol carboxylic acid **10** (Table 1). In comparison to **5**, the *ortho*-Cl-substituted catalyst **6a** had a higher reactivity yielding the spirolactone (*R*)-**11** with improved yields after shorter reaction times but with a slightly lower enantioselectivity. Ortho-Me-substituted catalyst **6b** was more reactive than **5** and **6a**, which correlated with an increased enantioselectivity of 78 % *ee*. The highest reactivity and enantioselectivity was observed with OMe-substituted catalyst **6c** giving **11** in 81 % yield and 82 % *ee*. We further optimized the reaction conditions and found that a 1:1 mixture of DCM/$CHCl_3$ and addition of ethanol increased the enantioselectivity of **11** to 99 % *ee* (Table 1, entry 6). These are the highest enantioselectivities ever observed in this representative model reaction. **6c** even outperforms all of the well-established C2-symmetric chiral aryl iodides, such as the C2-symmetric resorcinols **1a** and **1b**.[10] Surprised by the significantly increased reactivity based on this simple synthetic modification we wanted to evaluate the general applicability of **6c** in other, more challenging, oxidative C–O bond forming reactions (Scheme 2). First, we investigated the oxidative dearomatization of 4-substituted phenols to *para*-quinols. Even with sterically highly demanding aryl iodide catalysts, this reaction gives low enantioselectivities due to the high distance between the phenolate, which is bound to the hypervalent iodine center, and the hydroxylated C4. Even the successful resorcinol-derived aryl iodides **1** give only moderate selectivity of up to 50 %. In 2018, Maruoka and coworkers introduced a specially designed C1-symmetric indanol-based aryl iodide **2**, which was so far the best performing catalyst for this reaction.[11] We were pleased to find that with 10 mol % **6c**, 2-bromo-4-methylphenol **12** could be efficiently dearomatized into the 2-bromo *para*-quinol **13** in 92 % yield and 93 % *ee*, again a novel best mark for this transformation (Scheme 2a).

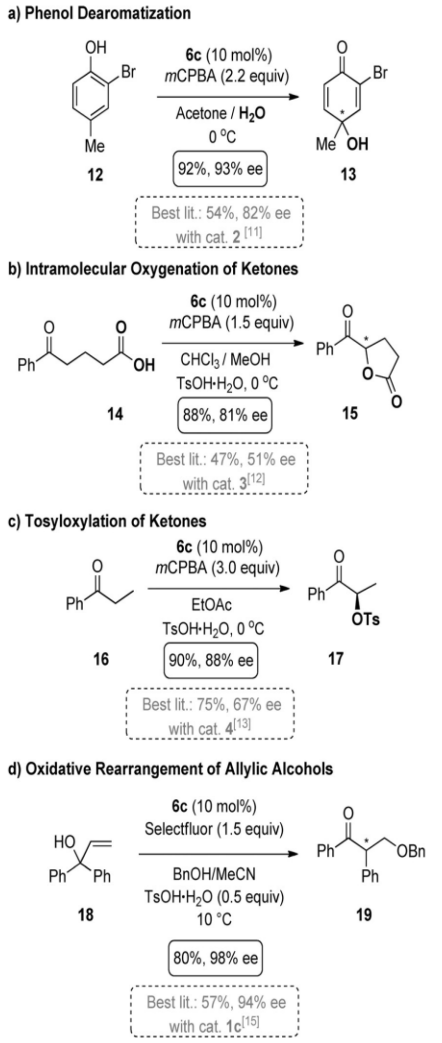
Table 1: Optimization of the Kita-spirolactonization.



Entry[a]	Triazole	Solvent	T [°C]	t [h]	Yield[b] [%]	ee[c] [%]
1	**5**	DCM	0	36	36	64
2	**6a**	DCM	0	32	54	60
3	**6b**	DCM	0	24	62	78
4	**6c**	DCM	0	22	81	82
5	**6c**	DCM/$CHCl_3$	0	24	85	97
6	**6c**	**DCM/$CHCl_3$ + 6 equiv EtOH**	**−10**	**32**	**85**	**99**

[a] Reaction conditions: **10** (0.09 mmol), cat (0.009 mmol, 10 mol %), *m*CPBA (0.12 mmol, 1.3 equiv), solvent (0.02 M). [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC.

We then investigated the intramolecular α-oxygenation of 5-oxo-5-phenylpentanoic acid **14** to 5-benzoyldihydrofuran-2(3*H*)one **15**. Here, the C1-symmetric pseudoephedrine-substituted aryl iodide **3**, as developed by Moran, gave the best results so far (47 % yield and 51 % *ee*).[12] Again, **6c** is a superior catalyst for this transformation and yielded the desired lactone **15** in 88 % yield and 81 % *ee* (Scheme 2b). We then tested the performance of **6c** in the α-tosyloxylation of propiophenone. This was the first oxygenation to be catalysed by a chiral aryl iodide catalyst as developed by Wirth and coworkers in 2007.[4] However, even after more than a decade of this first enantioselective report, numerous efforts to design efficient chiral aryl iodide catalysts did not result in synthetically adequate enantioselectivities due to hard to control concurring S_N2-and S_N2'-based reaction pathways. In 2017, Masson and co-workers developed the sulfone-containing aryl iodide **4** as the best performing catalyst for this reaction giving **17** in 67 % *ee*.[13] Again, **6c** showed superior results in this transformation. A combination of 10 mol % **6c** and *m*CPBA as co-oxidant resulted in an efficient conversion of propiophenone **16** to **17** in 90 % yield and 88 % *ee* (Scheme 2c). Apart from oxygenations, hypervalent iodine compounds can be applied efficiently in enantioselective rearrangements.[14] Very recently, Gong and co-workers developed the oxidative rearrangement of allylic alcohols to β-oxygenated ketones with the lactic-acid-derived catalyst **1c**.[15] We utilized this useful reaction as another benchmark for **6c** (Scheme 2d). Treatment of the tertiary allyl

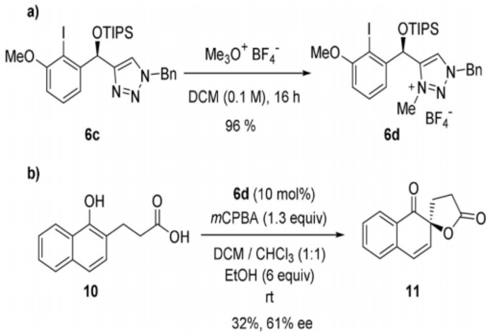


Scheme 2. Enantioselective oxygenations and rearrangements catalyzed by **6c** in comparison with the best literature values. Detailed optimizations for each reaction are discussed in the Supporting Information. Due to missing comparable literature samples, the absolute configuration of the major isomers for **13**, **15**, and **19** has not been finally determined.

alcohol **18** with 10 mol% **6c**, Selectfluor as co-oxidant, and benzyl alcohol, resulted in the formation of the rearranged β-oxygenated ketone **19** in 80% yield and 98% *ee*.

After catalyst **6c** showed this superior performance among a variety of mechanistically diverse transformations, we decided to gain a better rational about the underlying structural aspects that cause the high reactivity of **6c**, in particular in direct comparison to the first-generation catalyst **5**.

It was of particular interest, which secondary bonding interactions stabilize the oxidized hydroxy iodobenzene. After initial oxidation, the iodane can be further stabilized either by an oxygen lone pair of the TIPS-protected benzyl alcohol or by N3 of the triazole giving two potential isomers. Both isomers could further react in distinct ligand exchange and oxidation pathways and this competition should result in diminished yields and enantioselectivities. To confirm this finding for **6c** and to verify the importance of an N–I interaction for the performance of this catalyst we synthesized the *N*-methyl triazolium tetrafluoroborate **6d** by treatment of **6c** with Meerwein salt (Scheme 3a). This catalyst was then used in the Kita-spirolactonization. Here we found that **6d** has a diminished reactivity compared to **6c** giving the spirolactone in only 32% yield and 61% *ee* (Scheme 3b). This poor reactivity is comparable to the reactivity of the first-generation catalyst **5**. Legault and co-workers and our group recently demonstrated that a stabilization of cationic iodane species by covalently attached *N*,*O*-heterocycles, such as oxazoles and oxazolines, is favored through dative N–I bonding interactions as indicated by N–I distances being significantly shorter than O–I distances in calculated structures.[16] In solid-state structures only the N-bound intermediates were observed.[6]



Scheme 3. a) Synthesis of *N*-methyl triazole **6d**. b) Evaluation of the performance of **6d** in the Kita-spirolactonization.

Even though the N-methylation experiment is a first hint for an intramolecular N–I interaction in the active species of **6c**, it does not explain the observed effect of the *ortho*-substituent. Besides the donor ligand, the angle between the plane of the iodoarene and the I–OH bond is an important structural feature which is heavily influenced by *ortho*-substituents, as described by Legault and co-workers.[17] Since all attempts to produce suitable crystals for X-ray analysis were not successful, DFT calculations were performed for a deeper structural understanding of the catalyst structure and its reactivity.[18] Energy minima of oxidized [hydroxy(tosyloxy)iodo]arenes **5-OH** and **6c-OH** were searched by preoptimization with Grimme's tight-binding method GFN2-xTB[19] and further fine optimized on a PBEh-3c/ma-def2-SVP(O,N)/def2-TZVP(I) level of theory.[20] Single point energies were calculated with the double hybrid PWPB95-D3 functional together with ma-def2-TZVP-(O,N)/def2-TZVPP(I) basis sets.[21] Preoptimization with GFN2-xTB resulted in four distinct energy minima for each catalyst (Figure 3). In good agreement with theoretical investigations by Legault et al., initial calculations based on dissociated species with a separated tosylate anion and an

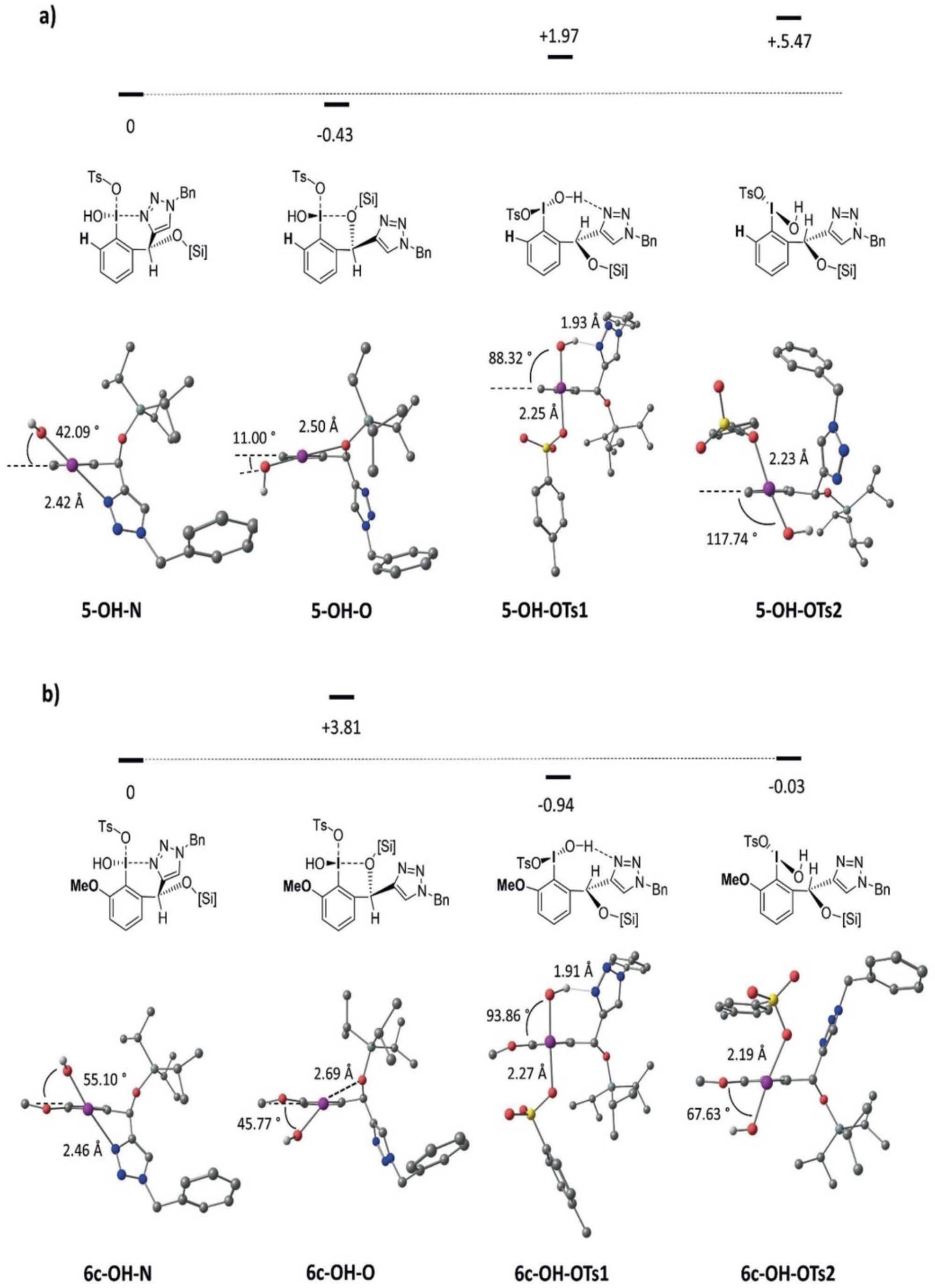


Figure 3. Calculated structures and relative free energies (G in kcal mol^{-1}) of hydroxy(tosyloxy) iodobenzene isomers of **5-OH** (a) and **6c-OH** (b). For isomers **5/6c-OH-N** and **5/6c-OH-O** the tosylate counterion has been omitted in the illustration. All non-heteroatom-bound hydrogens have been omitted as well. Structure optimization and frequency analysis was performed on the PBEh-3c/ma-def2-SVP(O,N)/def2-TZVP(I) level of theory. Final single-point energies were calculated on a PWPB95/ma-def2-TZVP(O,N)/def2-TZVPP(I) level of theory using a continuum solvation model (CPCM) in $CHCl_3$.

iodonium cation revealed that the dissociation process is highly endergonic. (Supporting Information, Scheme S1).[22] Therefore, dissociated iodonium complexes were not further considered. Minimized structures of **5-OH** are summarized in Figure 3 a, minimized structures of **6c-OH** are summarized in Figure 3 b. For both catalysts two isomers (**5/6c-OH-N** and **5/6c-OH-O**) show a direct stabilization of the hypervalent iodine atom through dative N–I or O–I interactions.

These oxidized isomers are nearly equal in energy for **5-OH**, whereas for **6c-OH** the N-bound isomer is favored by 3.81 kcal mol^{-1}. In these isomers the tosylate counterion (not shown) is usually bound in an apical position with typical TsO–I bond length of more than 2.6 Å. In the other observed isomers (**5/6c-OH-OTs1** and **5/6c-OH-OTs2**) the tosylate acts as the key ligand building the linear hypervalent bond in the oxidized state together with the OH group (TsO–I bond length of 2.19–2.25 Å). In **5/6c-OH-OTs1** the hydroxy group is located *cis* to the triazole ring and is engaged in hydrogen bonding with the *N*-heterocycle. For **6d** this hydrogen bond is not operational and therefore this isomer would be destabilized. Furthermore, the oxidation with *m*CPBA should be favored through an initial hydrogen bonding between the triazole and the transferred terminal hydroxy group of the peracid.

However, for isomer **5/6c-OH-OTs2**, the hydroxy ligand is located *trans* to the triazole ring and hence no further intramolecular secondary interactions can be observed. For **5-OH** the TsO-bound isomers are significantly higher in energy (+1.97 and +5.47 kcal mol^{-1}) compared to the triazole-bound isomer **5-OH-N**. In contrast, the TsO-stabilized isomers of **6c** are equal or slightly lower in energy compared to **6C-OH-N**. In particular, the relatively high stability of **6c-OH-OTs1** is remarkable due to the high dihedral angle of 93.86 between C(1)/C(6) of the arene ring and the I–O bond. Usually, linear arrangements are preferred in which the arene is in plane with the hypervalent bond. This can be nearly found in **5-OH-O**. This isomer has the smallest dihedral angle of 11.00°. A high dihedral angle between the arene ring and the hypervalent bond, defined by Legault and co-workers as "hypervalent twist",[16] together with the good leaving-group ability of the tosylate ligand as found in **6c-OH-OTs1** are crucial for further ligand exchange reactions with phenolic or enolic oxygens to initiate the discussed enantioselective coupling reactions. We are therefore confident that these calculations give a good initial rational for the high reactivity of catalyst **6c** and are an ideal starting point for further catalyst improvements and theoretical investigations concerning the underlying mechanisms of each investigated enantioselective transformation.

In summary, the triazole-substituted aryl iodide **6c** is the most versatile chiral aryl iodide catalyst that has been developed so far for enantioselective reactions based on in situ generated hypervalent iodine compounds. This single catalyst shows a remarkable reactivity in the Kita-spirocyclizaton, the α-tosyloxylation of propiophenone, oxidative lactonizations, and in the oxidative rearrangement of allyl alcohols. To our knowledge the observed enantioselectivity for every investigated reaction is the highest ever reported and hence this catalyst can be defined as omnipotent. The initial DFT calculations indicate a significant role of the triazole as a stabilizing donor both in a potential N-bound state or as a hydrogen-bond acceptor in a [hydroxy(tosyloxy)iodo]arene derivative. This forces the geometry of the hypervalent iodine centre into a reactive bent state with an unusual vertical alignment between the hypervalent bond and the arene. In-depth theoretical investigations are now necessary for every investigated reaction to fully explain the observed omnipotence. With this information rational fine tuning of this highly modular catalyst for further enantioselective oxidations will be possible.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric oxidation · chiral hypervalent iodine compounds · organocatalysis · oxidation · stereoselective synthesis

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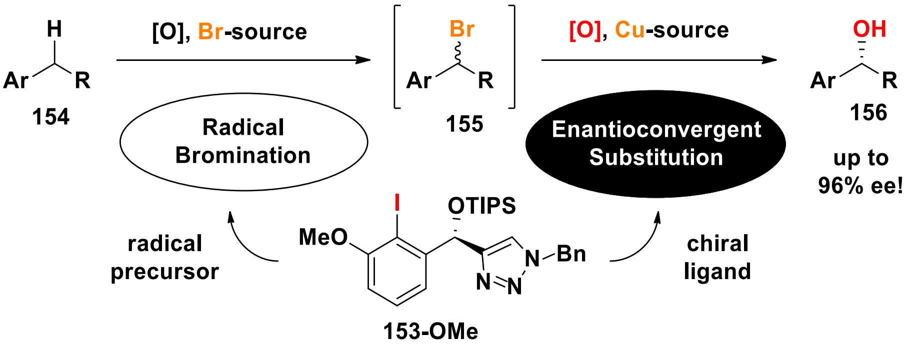
4.2. Second Publication: An Enantioconvergent Benzylic Hydroxylation Using a Chiral Aryl Iodide in a Dual Activation Mode

Synthesis of chiral molecules is an eminent goal in organic chemistry, and the direct functionalization of C-H bonds is among the most robust tools for this duty. Oxidation is the most efficient method to convert C-H bonds into several functional groups. For instance, oxidation of the secondary benzylic (sp3) C-H bond to produce benzylic alcohols has received much attention in the past decades due to the wide applications of those compounds such as the synthesis of biologically active, important intermediates and several medical applications. Several strategies for reaching this goal are described in the literature, including transition metals, chemical oxidations, and electrochemical oxidations.[135–138] Most of these strategies have a lack of results in terms of yield or enantioselectivity. Herein, we present the first unique example for the enantioselective hydroxylation of a secondary benzylic C-H bond employing catalytic amounts of chiral hypervalent iodine catalyst **153-OMe** and copper bromine in the presence of *m*-CPBA as an oxidant to afford chiral benzyl alcohol derivatives in yields of up to 95% with up to 96% *ee* (Scheme 33). Various aryl or heteroaryl substrates were examined, providing the corresponding chiral secondary alcohols.[139]



Scheme 33. Enantioselective hydroxylation C-H benzylic bond mediated by catalyst **153-OMe**

Furthermore, the regioselectivity hydroxylation of a benzylic C-H bond in the presence of a tertiary C-H bond was studied in this reaction. We performed comprehensive mechanistic studies to explain the mechanism of this reaction. We isolated and a brominated intermediate that proved the necessity of the chiral iodoarene to transfer the bromine radical into the benzylic position in the first step and later to act as a chiral ligand in the second step with copper salt to form the copper complex that controls the stereoselectivity of the reaction.

Title of the Publication: “An Enantioconvergent Benzylic Hydroxylation Using a Chiral Aryl Iodide in a Dual Activation Mode”

Ayham. H. Abazid, N. Clamor, B. J. Nachtsheim, *ACS. Catal.* **2020**, *10* (15), 8042–8048.

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The supporting information, including a complete optimization table, detailed experimental procedures, characterization data, and copies of NMR spectra, is available free of charge on the journal's website.

Abstract: The application of a triazole-substituted chiral iodoarene in a direct enantioselective hydroxylation of alkyl arenes is reported. This method allows the rapid synthesis of chiral benzyl alcohols in high yields with stereocontrol, despite its nontemplated nature. In a cascade activation consisting of an initial irradiation-induced radical C–H-bromination and a consecutive enantioconvergent hydroxylation, the iodoarene catalyst has a dual role. It initiates the radical bromination in its oxidized state through a bromoiodane formed *in-situ*, and in the second, Cu-catalyzed step, it acts as a chiral ligand. This work demonstrates the ability of a chiral aryl iodide catalyst to act both as an oxidant and as a chiral ligand in a highly enantioselective C–H-activating transformation. Furthermore, this concept presents an enantioconvergent hydroxylation with high selectivity using a synthetic catalyst.

Author Contribution to this Publication: The benzylic C-H hydroxylation was discovered and developed by me (Ayham H. Abazid). In this project, I carried out all optimization reactions and synthesized and characterized 23 compounds. N. Clamor synthesized and characterized three compounds.

The manuscript was written by me and B. J. Nachtsheim, the supporting information was written by me. B. J. Nachtsheim was the principal investigator and edited the article.

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An Enantioconvergent Benzylic Hydroxylation Using a Chiral Aryl Iodide in a Dual Activation Mode

Ayham H. Abazid, Nils Clamor, and Boris J. Nachtsheim*

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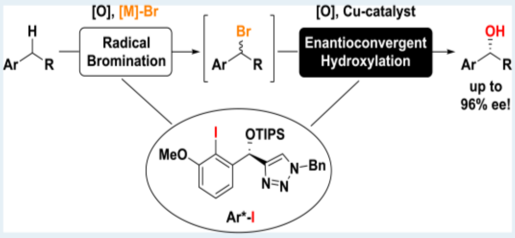

ABSTRACT: The application of a triazole-substituted chiral iodoarene in a direct enantioselective hydroxylation of alkyl arenes is reported. This method allows the rapid synthesis of chiral benzyl alcohols in high yields and stereocontrol, despite its nontemplated nature. In a cascade activation consisting of an initial irradiation-induced radical C−H-bromination and a consecutive enantioconvergent hydroxylation, the iodoarene catalyst has a dual role. It initiates the radical bromination in its oxidized state through an in-situ-formed bromoiodane and in the second, Cu-catalyzed step, it acts as a chiral ligand. This work demonstrates the ability of a chiral aryl iodide catalyst acting both as an oxidant and as a chiral ligand in a highly enantioselective C−H-activating transformation. Furthermore, this concept presents an enantioconvergent hydroxylation with high selectivity using a synthetic catalyst.

KEYWORDS: *chiral alcohols, enantioselective oxidation, enantioconvergent catalysis, hypervalent iodine, photochemistry*

INTRODUCTION

The direct hydroxylation of C(sp^3)−H bonds is one of the most efficient reactions to introduce molecular complexity into unfunctionalized bulk chemicals.[1,2] Once introduced, the resulting alcohols are either a fundamental part of the desired target molecule or they can be readily transformed to other useful functionalities. Hydroxylations of benzylic C(sp^3)−H bonds are of particular interest, because of the intrinsic reactivity of the benzylic C−H bond allowing a highly regioselective C−H activation in the presence of other aliphatic C−H bonds.[3,4] Based on cytochrome P-450 oxygenases as a natural blueprint,[5] a variety of chiral metal-porphyrine complexes were developed for enantioselective hydroxylations.[6] In a first report in 1989 by Groves and co-workers, chiral iron porphyrins could be applied in combination with iodosobenzene as an oxygen donor to hydroxylate ethylbenzene in 40% yield and 41% enantiomeric excess (ee).[7] Template-directed procedures give excellent selectivities, although only well-selected substrates that can noncovalently interact with the chiral catalyst through hydrogen-bonding patterns can be addressed efficiently.[8,9] It is surprising that even more than three decades after the initial finding of Groves, simple alkyl benzenes are still difficult to hydroxylate in good yields and enantioselectivities through purely synthetic catalysts.[10,11] Hypervalent iodine reagents are commonly used oxidants for oxidative couplings and in group and oxygen transfer reactions.[12−14] They can be also applied in benzylic hydroxylations, as demonstrated by Groves in his early report, as well as in high-valency transition-metal chemistry[15] and in photoredox catalysis.[16] The use of chiral iodanes or their aryl iodide precursors in catalytic enantioselective benzylic hydroxylations is so far unknown.[17] During our systematic studies of *N*-heterocycle-stabilized iodanes (NHIs),[18] we recently introduced triazole-substituted aryl iodides **1** (Figure 1) as chiral iodane precursors and successfully verified their excellent performance in a plethora of enantioselective oxidative transformations.[19] In a new approach we herein demonstrate their unique ability to act in a dual way, initially as a iodane-based halogen donor for a nonstereoselective radical-mediated halogenation and as a chiral ligand in a so-far-undescribed enantioconvergent hydroxylation.[20,21]

Combining **1** with a co-oxidant and a halogen anion should initially form a stabilized halogen(aryl)-λ^3-iodane, to initiate the C−H activation and then ligate a transition metal during the second, enantioconvergent, reaction step. The combination of bromide sources and aryl-λ^3-iodanes is known to activate benzylic C−H-bonds through the in situ formation of bromoiodanes, followed by a light-induced homolytic cleavage of the labile I−Br bond.[22]

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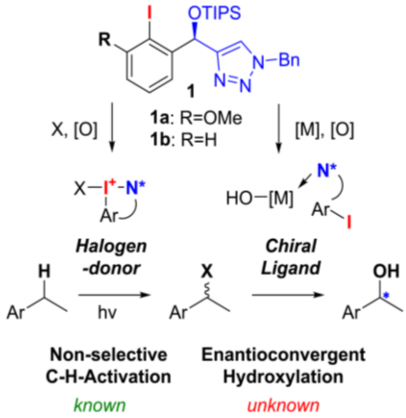


Figure 1. Working model for the dual activation of alkyl arenes using catalysts of type **1**.

RESULTS AND DISCUSSION

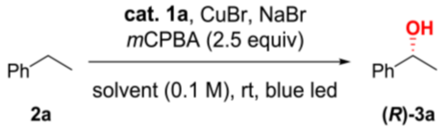
Based on the fact that many radical-mediated enantioconvergent substitutions, in particular alkylations of secondary alkyl halides, can be catalyzed by Cu(I) salts,[23,24] CuBr was initially used as an additive, acting as the bromide donor and the transition-metal catalyst. To test our hypothesis, the direct hydroxylation of ethylbenzene **2a** was investigated (Table 1). As expected, under heating in dichloromethane (DCM), no reaction was observed (Table 1, entry 1). To our delight, irradiation with a blue LED (465 nm) gave the desired product (***R***)-**3a** in 68% yield and 71% ee, using 150 mol % CuBr (Table 1, entry 2). While aromatic solvents such as toluene give a diminished yield and selectivity (Table 1, entry 3) using acetonitrile gave (***R***)-**3a** in 75% yield and 90% ee (Table 1, entry 4). Since the Cu(I)-additive should initially only act as an activator for I−Br bond activation, it should be sufficient to add catalytic amounts of CuBr and another, less-expensive, bromide source in stoichiometric quantities. Indeed, if only 20 mol % of CuBr, in combination with 1.5 equiv of NaBr as an additive, was used, the reaction still proceeds with almost the same outcome (Table 1, entry 5). Under these conditions, catalyst loading of **1a** could be decreased to 15 mol % without affecting yield and selectivity (Table 1, entry 6). Under strictly dry reaction conditions (Table 1, entry 7), no product formation was observed, which implies water as the hydroxy source in this process. In agreement with our recent findings, catalyst **1b**, without the important *ortho*-substituent at the aryl iodide, performs worse (Table 1, entry 8).

Under these optimized conditions, the applicable substrate scope was examined (Scheme 1). Initially, simple electron-rich ethyl arenes were investigated. 4-Methyl- and 4-methoxy-substituted derivatives reacted superior, giving the desired benzyl alcohols **3b** and **3c** in high yields with 96% and 95% ee. Free hydroxy groups are tolerated as well, giving **3d**−**3f** in still good yields and 72%−87% ee.

The effect of electron-withdrawing groups at the arene was then investigated. All possible bromo-substituted isomers reacted well, giving **3g**−**3i** in overall good yields of 76%−79%, with the best enantioselectivity being observed for the 3-Br derivative (95%). Ethyl-substituted nitro arenes gave compounds **3j** and **3k** in even better yields (90 and 89%) and excellent 93% and 95% ee. Synthetically versatile nitriles and free carboxylic acids are also well-tolerated, yielding benzyl alcohols **3l** and **3m** in good yields and 83% and 95% ee. Indane and tetrahydronaphthalene give **3n** and **3o** in yields of 79% and 77%, respectively, with 85% and 95% ee, respectively. For these substrates, small amounts of dihydroxylation products (<10%) were observed. Next, the aliphatic side chain of the ethyl benzene was varied. *n*-Propyl- and *n*-butyl benzene gave **3p** and **3q** in yields and selectivities comparable to the model substrate. The same was observed for 1,2-diphenylethane, giving **3r** in 79% and 93% ee. 2-Phenyl acetic acid yielded (*R*)-mandelic acid **3s** in 64% and 88% ee. Next, multiple bond substitution in the benzylic side chain was examined. Once again, the method showed a high robustness among those substrates.

Allyl benzene was directly hydroxylated to yield the allyl alcohol **3t** in 83% ee. Propargyl alcohol **3u** was isolated with even higher selectivities of 90% ee, although the yield was lower (61%), probably because of a slight decomposition of the delicate propargylic alcohol. Finally, a variety of ethyl-substituted heterocycles as substrates were investigated. 2-Ethyl furane did not result in product formation, because of decomposition of the starting material. The corresponding thiophene gave **3v** in 89% ee and 54% yield. Even ethyl pyridines were tolerated under the applied oxidative conditions, despite potential oxygenations of the ring nitrogen

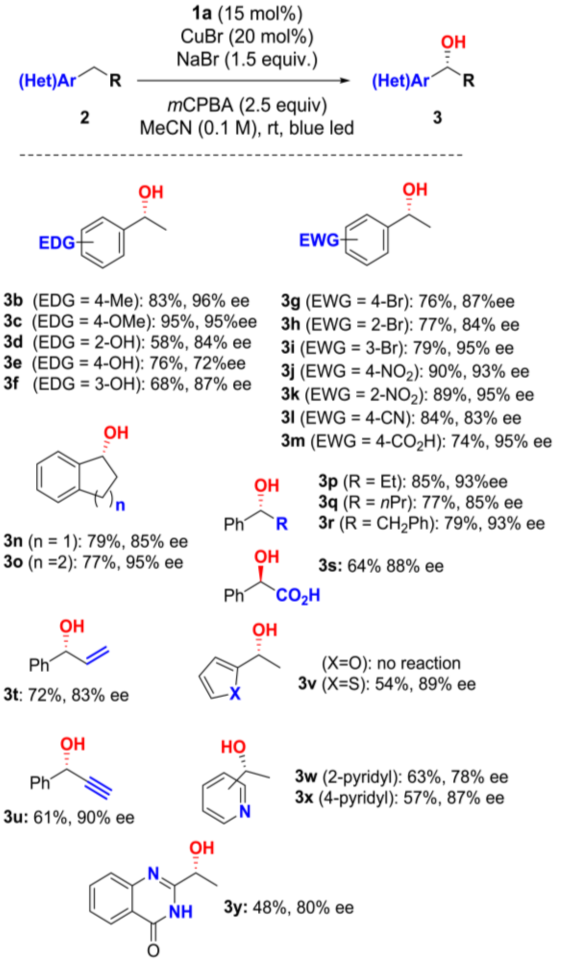
Table 1. Optimization of the Reaction Conditions



entry	1a [mol %]	CuBr [mol %]	NaBr [mol %]	solvent	time, *T* [h]	yield [%]	enantiomeric excess, [%]
1[a]	20	150	0	DCM	12	0	–
2	20	150	0	DCM	20	68	71
3	20	150	0	PhMe	30	25	40
4	20	150	0	CH_3CN	14	75	90
5	20	20	150	CH_3CN	14	74	90
6[b]	**15**	**20**	**150**	**CH_3CN**	**14**	**74**	**90**
7[c]	**15**	**20**	**150**	**CH_3CN**	**14**	**0**	**0**
8[d]	**15**	**20**	**150**	**CH_3CN**	**8**	**48**	**63**

[a] The reaction was performed at 60 °C for 12 h without light. [b] These conditions will be further referred as "optimized conditions". [c] Dry acetonitrile and water-free *m*CPBA were used in the reaction. [d] Catalyst **1b** was used instead of **1a**.

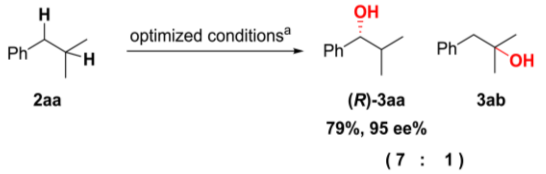
Scheme 1. Substrate Scope



giving 2- and 4-pyridyl-substituted alcohols **3w** and **3x** in moderate yields and 78% and 87% ee. Even 4-ethyl quinazolinone could be directly hydroxylated to **3y** with 80% ee.

It was also of interest whether the applied reaction conditions allow the regioselective C−H-activation of the benzyl C−H-bond in the presence of tertiary C−H bonds: also potential hot spots for the initial radical-mediated halogenation. Therefore, substrate **2aa** was subjected to our optimized reaction conditions and indeed a mixture of the isomers **3aa** and **3ab** in a ratio of 7:1 and 95% ee for *(R)*-**3aa** was observed (Scheme 2). Thus, activation of the benzylic C−H is strongly favored.

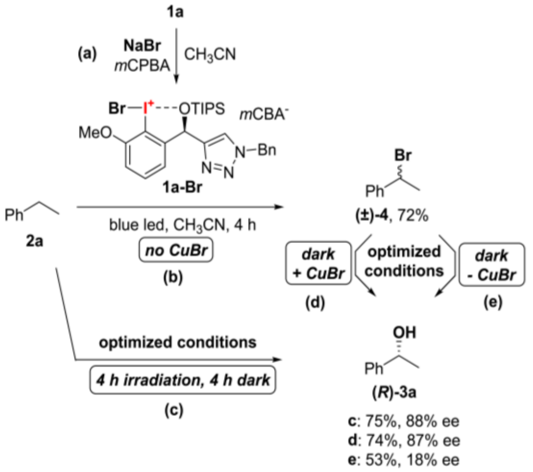
Scheme 2. Investigating the Regioselectivity



[a] Slight deviation: reaction temperature was decreased to 0 °C after 4 h.

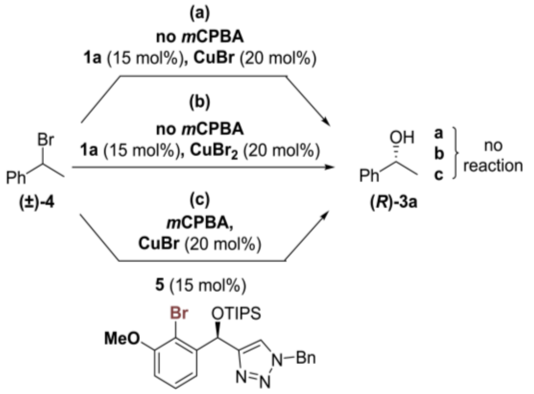
After this comprehensive elaboration of the substrate scope, we intended to get a deeper understanding of the underlying reaction mechanism and, in particular, prove the initially proposed dual role of the catalyst in this process and the unique enantioconvergent hydroxylation. For the first step, the radical-mediated halogenation, a brominated catalyst must be formed with a labile I−Br bond that breaks homolytic to induce the radical-mediated benzyl C−H-abstraction. Treatment of **1a** with NaBr and *m*CPBA allowed us to isolate a white solid, which was identified via nuclear magnetic resonance (NMR) and mass spectroscopy (MS) as being the brominated derivative **1a-Br** (Scheme 3a). Treatment of **2a** with this compound without a copper source under light irradiation yielded the benzyl bromide **4** in a very clean reaction and 72% yield as a racemate (Scheme 3b). Even if benzyl bromide would be formed enantio-enriched, its known tendency to racemize in polar solvents would yield the racemate under the given reaction conditions.[25] This experiment implies that, once the benzyl bromide is formed, the second step of the transformation must be an enantioconvergent reaction in which irradiation should not be essential anymore. To verify this hypothesis, **2a** was reacted again using the optimized conditions, but with only 4 h of light irradiation, followed by further stirring for 4 h in darkness (Scheme 3c). Under these conditions, the desired benzyl alcohol was observed in almost the same yield and enantioselectivity as under full-time irradiation.

Scheme 3. Bromination with Isolated Catalyst 1a-Br To Prove the First Step of the Dual Activation Mechanism



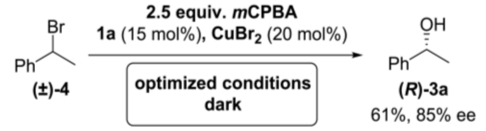
Next, **4** was treated under the optimized conditions, without irradiation (Scheme 3d). Here, **3a** was isolated in almost the same quantities and ee values as in the previous experiments. The necessity of CuBr as an additive which was intended to catalyze exclusively the second step, was questioned as well. When the reaction was repeated, without adding CuBr (Scheme 3e), **3a** could still be isolated in 53% yield, but almost entirely as a racemate (18% ee). From these experiments, it was concluded that Cu is not necessary for the initial C−H activation but plays a fundamental role in the enantioconvergent hydroxylation. Here, **1a** must act as a *N*-ligand coordinating through its triazole functionality, and therefore no oxidative conditions should be necessary. Further control experiments were performed starting from racemic **4** under our optimized conditions, without the addition of *m*CPBA, but adding either CuBr or $CuBr_2$ (see Schemes 4a and 4b). In both experiments, no conversion to **3a** was observed. Thus, even in the second step, the oxidant is necessary, but not just to oxidize the Cu(I) species. Obviously, a hypervalent iodine compound must also be important in the enantioconvergent step.

Scheme 4. Control Experiments To Elucidate the Stereoconvergent Hydroxylation



As a further support, the chiral bromobenzene **5** was prepared. Aryl bromides cannot be oxidized with *m*CPBA into a hypervalent state and therefore, as observed, no reaction should occur (Scheme 4c). For gaining more insights about the potential active oxidation state of the involved Cu-species, this experiment was repeated starting from benzyl bromide under oxidative conditions but now adding $CuBr_2$ instead of CuBr (Scheme 5). Under these conditions **3a** was isolated in slightly lower yields (61%) but similar enantioselectivity (85% ee). When $CuBr_2$ was used in stoichiometric amounts without *m*CPBA, no reaction was observed. Thus, the co-oxidant is either involved in the formation of even-higher oxidized Cu(III)-hydroxy-complexes and/or a second iodane formation.

Scheme 5. Enantioconvergent Hydroxylation with $CuBr_2$.[a]



[a] Reaction conditions: (±)-**4** (0.11 mmol), CH_3CN (0.1 M).

A hydroxylated catalyst **1a-OH** could not be isolated as a pure substrate for further control experiment, because of its high reactivity based on the *ortho*-effect of the methoxy group and the induced hypervalent twist.[26] However, NMR experiments strongly support a hydroxylation under reductive collapse of the iodane, as exemplified by ^{13}C chemical shifts of the characteristic iodine-bound aryl signal (Figure 2). This ipso-carbon in **1a** (blue) and the meta-carbon (green) have typical chemical shifts of ∼90 and 110 ppm (Figure 2a). Upon addition of *m*CPBA to yield **1a-OH** as a mixture of different isomers, both signals clearly disappear and shift downfield to >115 ppm (Figure 2b). The addition of CuBr regenerates **1a**, demonstrated by the reappearance of both signals (Figure 2c). A significant line broadening of the signals in the corresponding proton NMR implies the existence of paramagnetic Cu(II) in the reaction mixture (see the Supporting Information). The transient formation of Cu(III) species, for example, as a Cu(III)-hydroxy, should also be considered. Unfortunately, Cu-triazole complexes could not be isolated; therefore, in-depth understanding of the enantioconvergent step remains elusive.

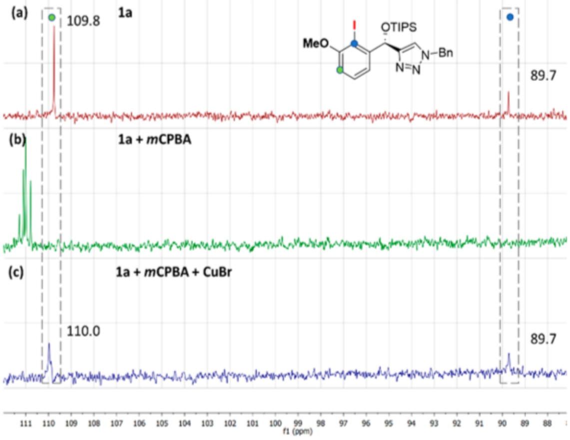


Figure 2. ^{13}C NMR shifts for in situ oxidation of **1a** between 85 ppm and 112 ppm: (a) **1a** alone, (b) **1a** + *m*CPBA, and (c) **1a** + *m*CPBA + CuBr.

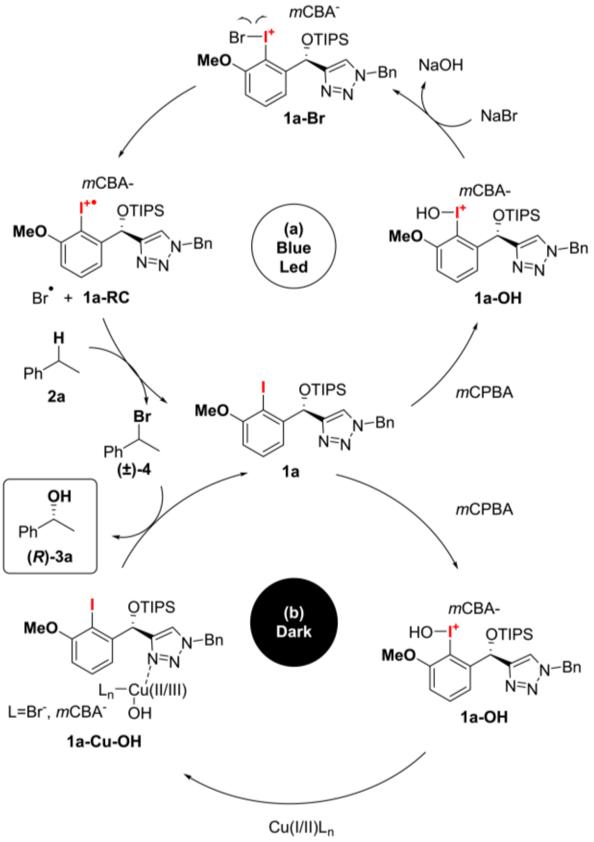
However, based on the initial control experiments, the catalytic cycle as shown in Scheme 6 is proposed. In the initial irradiation-mediated cycle (Scheme 6a), **1a** is oxidized into the hydroxyiodobenzene **1a-OH**. Ligand exchange with NaBr gives the bromoiodobenzene **1a-Br**, which underlies rapid I−Br bond cleavage under irradiation yielding a bromine radical and the radical cation **1a-RC**. Radical benzylic bromination initiated by either species converts the alkyl benzene into the benzyl bromide as a racemate. In the second cycle (Scheme 6b), **1a** is oxidized again in the initial step to **1a-OH**. The iodane then hydroxylates the Cu salt, either yielding a chiral Cu(II) or a Cu(III)-hydroxy complex **1a-Cu-OH**.

Depending on the oxidation state of the active Cu-complex, either a radical or a S_N-type enantioconvergent hydroxylation with the emerging benzyl bromide from cycle (a) yields (***R***)-**3a**. In a potential radical pathway, a benzylic radical could be trapped by the chiral Cu(II)-complex to form a chiral Cu(III)-complex, which collapses in a final reductive elimination to give the chiral benzyl alcohol. Although deep mechanistic details of the second step remain elusive, it can be concluded that, because of the high racemization tendency of **4**, this overall reaction is a stereomutative enantioconvergent reaction.

■ CONCLUSIONS

In conclusion, this work demonstrates the ability of chiral aryl iodides substituted with *N*-heterocycles to be used in enantioselective benzylic hydroxylations through a double role, acting as oxidant and as a chiral ligand in a consecutive reaction sequence consisting of a benzyl bromination and a Cu-mediated substitution. The verification of (±)-benzyl bromide as a reaction intermediate verifies that the second, Cu-mediated reaction, is an enantioconvergent hydroxylation. The reaction tolerates a wide variety of substrates, including electron-rich and electron-poor alkyl benzenes and exocyclic π-bonds, as well as alkyl-substituted *N*-heterocycles. Further-

Scheme 6. Mechanistic Proposal



more, a high regioselectivity for the benzylic C–H-bond in the presence tertiary C–H-bonds was observed. This reaction cascade offers great potential for other enantioselective oxidative benzylic C–H-activations, although the mechanism of the enantioconvergent step still needs to be further elaborated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c02321.

Experimental procedures and characterization data (PDF)

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Author Contributions

The manuscript was written by B.J.N. Experimental work was performed by A.H.A. and N.C. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

*m*CPBA, *meta*-chloroperbenzoic acid; *m*CBA, *meta*-chlorobenzoic acid; DCM, dichloromethane

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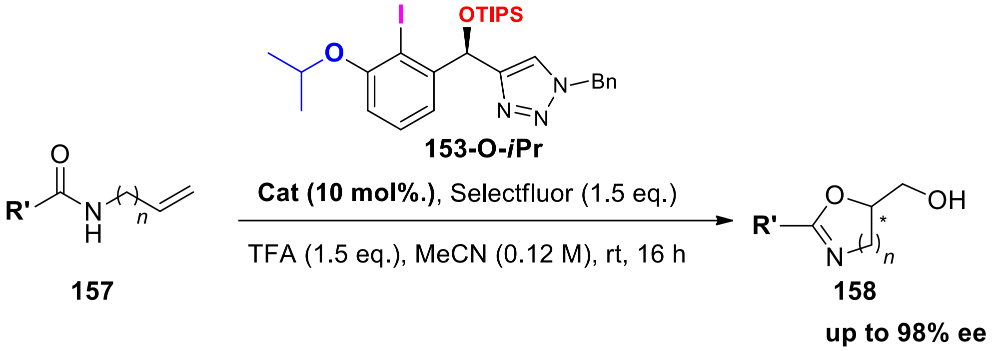
4.3. Third Publication: Stereoselective Oxidative Cyclization of *N*-Allyl Benzamides to Oxaz(ol)ines

Herein, we initially optimized the second-generation catalysts by modifying the *ortho*-position of the iodoarene with aliphatic and aromatic alkoxy groups. Then we modified the protection group by using methyl or benzyl groups instead of the TIPS group. Ten chiral aryl iodides of a third generation have been synthesized and used in the catalytic enantioselective cyclization of *N*-allylcarboxamides to obtain oxazolines and oxazine compounds with yields of up to 94% and enantioselectivities of up to 95%. The ortho-O*i*Pr-substituted **153-O-*i*Pr** provides the best results compared with the other third- and second-generation catalysts (Scheme 34). Thiazolines, imidazolines and aliphatic oxazolines were also synthesized from suitable starting materials in good yields and enantioselectivities. Oxazolines with a quaternary carbon could be synthesized readily by this method with high yield and excellent enantioselectivities. In addition, different derivatives of compound **158** were synthesized by functionalizing the hydroxyl group into various groups such as iodine, azide, triflate, acetate, amine, and aldehyde.



Scheme 34. Enantioselective cyclization of *N*-allylcarboxamides mediated by catalyst **153-O-*i*Pr.**

Title of the Publication: “Stereoselective Oxidative Cyclization of *N*-Allyl Benzamides to Oxaz(ol)ines”

Ayham H. Abazid, Tom Hollwedel and Boris J. Nachtsheim, *Chem Rxiv*. **2021.** https://doi.org/10.26434/chemrxiv.14501556.v1

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The supporting information, including a complete optimization table, detailed experimental procedures, characterization data, and copies of NMR spectra, is available free of charge on the journal′s website.

Abstract: This study presents an enantioselective oxidative cyclization of *N*-allyl carboxamides via a chiral triazole-substituted iodoarene catalyst. The method allows the synthesis of highly enantioenriched oxazolines and oxazines, with yields of up to 94% and enantioselectivities of up to 98% ee. Quaternary stereo centers can be constructed and, besides *N*-allyl amides, the corresponding thioamides and imideamides are well tolerated as substrates, giving rise to a plethora of chiral 5-membered *N*-heterocycles. By applying a multitude of further functionalizations, we finally demonstrate the high value of the observed chiral heterocycles as strategic intermediates for the synthesis of other enantioenriched target structures.

Author Contribution to this Publication: In this project, I carried out all optimization reactions and synthesized and characterized seven hypervalent iodine catalysts. I also synthesized and characterized the oxazoline and oxazines derivatives and seven compounds of the derivatization of oxazoline. Tom-Niklas Hollwedel synthesized and characterized four hypervalent iodine catalysts under my supervision.

I wrote the manuscript and the supporting information. B. J. Nachtsheim was the principal investigator and edited the article.

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Letter

Stereoselective Oxidative Cyclization of *N*-Allyl Benzamides to Oxaz(ol)ines

Ayham H. Abazid, Tom-Niklas Hollwedel, and Boris J. Nachtsheim*

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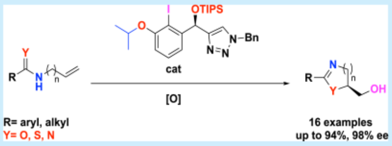
ABSTRACT: This study presents an enantioselective oxidative cyclization of *N*-allyl carboxamides via a chiral triazole-substituted iodoarene catalyst. The method allows the synthesis of highly enantioenriched oxazolines and oxazines, with yields of up to 94% and enantioselectivities of up to 98% ee. Quaternary stereocenters can be constructed and, besides *N*-allyl amides, the corresponding thioamides and imideamides are well tolerated as substrates, giving rise to a plethora of chiral 5-membered *N*-heterocycles. By applying a multitude of further functionalizations, we finally demonstrate the high value of the observed chiral heterocycles as strategic intermediates for the synthesis of other enantioenriched target structures.



Partially hydrogenated *N*-heterocycles (azolines), in particular 2-oxazolines, 2-thiazolines, and 2-imidazolines, are important synthetic targets, not only due to their abundance in biologically active compounds[1,2] but also due to their high value as useful synthetic building blocks.[3−5] Enantiopure derivatives substituted at C4, at C5, or at both saturated carbons are of particular importance due to the stereochemical requirements of the desired products or the chiral building blocks made by them. Enantiopure 4-oxazolines are also widely applied as core structural motifs, for example in chiral ligands for enantioselective transition-metal-catalyzed reactions.[6]

Enantiopure 5-oxazolines are found in biologically active compounds such as shahidine—the parent compound of the strong antioxidant aegilin,[7] nagelamide alkaloids,[8] and the tubulin-binder A289099 (Figure 1).[2] While synthetic approaches for 4- and 4,5-disubstituted chiral 2-azolines are well established,[4,5,9] the synthesis of enantiopure monosubstituted 5-azolines is underdeveloped (Scheme 1).[10,11] The latter can be synthesized by Ru-catalyzed hydrogenations of oxazoles (Scheme 1a)[12] or by Pd-catalyzed cyclizations of allene-substituted aryl amides (Scheme 1b).[13] Organocatalytic approaches have also been established whereby a hydrogen-bonding donor in the presence of a halonium source results in enantioselective halocyclizations of *N*-allyl amides (NAAs, Scheme 1c).[14]

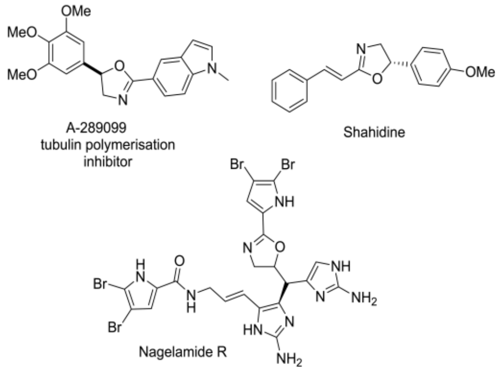
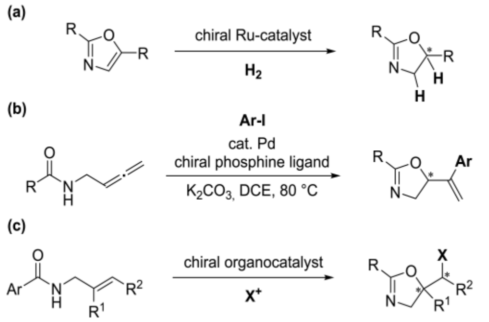


Figure 1. Examples of natural products containing a chiral C5-substituted oxazoline unit.

Scheme 1. Known Approaches for the Synthesis of 5-Oxazolines



A more general approach for the cyclization of NAAs involves their treatment with a chiral hypervalent iodine compound. This induces an oxidative cyclization via a π-complexed iodane **A**, similar to halonium sources. Iodine(III) activates π-complexed NAA to produce **B** through an intramolecular attack by the amide oxygen (Scheme 2). The

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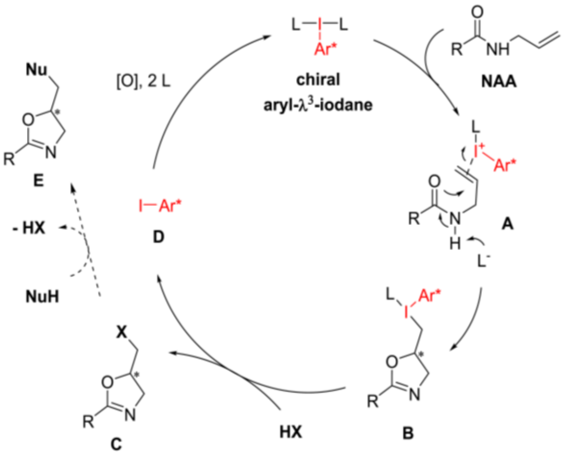
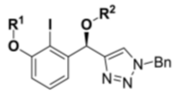
Scheme 2. General Mechanism for an Iodane-Mediated *N*-Oxidative Cyclization of NAAs



emerging alkyl-substituted iodane **B** then reacts rapidly with additives, usually added Brønsted acids HX, to form compound **C** under reduction of the iodane to the iodoarene **D**. Depending on the nature of **C**, rapid substitution often follows with external nucleophiles **NuH**, for example water or hydroxide anions, to generate the substituted oxazoline **E**. The chiral aryl iodide can then be reoxidized by an external oxidant and thus can be used in catalytic amounts.[15−17] This general method has been applied by Moran and co-workers using a well-established resorcinol-based chiral iodoarene catalyst,[18−20] but unfortunately with only moderate results, particularly regarding stereoselectivity and substrate scope, with a focus on 6-membered *N*-heterocycles.[11]

Our group recently established chiral triazole-substituted iodoarenes **1**, where the triazole has a role as a direct stabilizing donor of the hypervalent iodine center through dative N−I interaction, and applied them in a wide range of enantioselective oxidative transformations (Figure 2).[16,17,21] In this letter we report their further application to the as-yet underexplored oxidative cyclization of *N*-allyl amides.



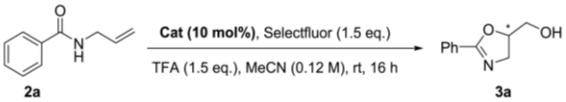
1

1a: R^1= Me, R^2= TIPS
1b: R^1= Me, R^2= Bn
1c: R^1= Me, R^2= Me
1d: R^1= Et, R^2= Me
1e: R^1= Et, R^2= Bn
1f: R^1= Et, R^2= TIPS
1g: R^1= *i*Pr, R^2= Me
1h: R^1= *i*Pr, R^2= Bn
1i: R^1= *i*Pr, R^2= TIPS
1j: R^1= Bn, R^2= TIPS
1k: R^1= Bz, R^2= TIPS

Figure 2. Structure of the chiral triazole catalysts **1**.

We started our investigations using *N*-allyl benzamide, **2a**, as the model substrate (Table 1). It was established in our early studies that an additional substituent ortho to the central iodine atom is crucial for high reactivity and stereoselectivity in reactions performed with these catalysts. Therefore, we started with the *o*-OMe-substituted iodoarene catalyst **1a**, the most successful to be used to date. During a preliminary optimization we had already established acetonitrile as the best solvent for this reaction, in combination with selectfluor as a co-oxidant and TFA as an acid additive. While using catalyst **1a**, the 5-substituted oxazoline **3a** was isolated with a 67% yield and 85% ee. Under these conditions, a fluorinated intermediate was not detected via MS. However, formation of the corresponding methyl 2,2,2-trifluoroacetate derivative of **C** (Scheme 2, X = OTFA) is likely since the reaction must be quenched with aq. NaOH, to give **3a** as the final reaction product.

Table 1. Optimization of the Reaction Conditions



entry[a]	catalyst	yield [%]	ee [%]
1	**1a**	67	85
2	**1b**	61	74
3	**1c**	62	64
4	**1d**	72	67
5	**1e**	71	74
6	**1f**	75	87
7	**1g**	83	70
8	**1h**	81	85
9	**1i**	**91**	**93**
10	**1j**	68	84
11	**1k**	80	84
12[b]	**1i**	65	93
13[c]	**1i**	48	92

[a] Reaction conditions: **2a** (0.40 mmol, 1.00 equiv), cat (0.04 mmol, 10 mol %), TFA (0.60 mmol, 1.50 equiv), selectfluor (0.40 mmol, 1.00 equiv), CH_3CN (0.12 M). [b] 5 mol % of **1i** was used. [c] The reaction was performed at 0 °C and took 36 h with 70% conversion of **2a**.

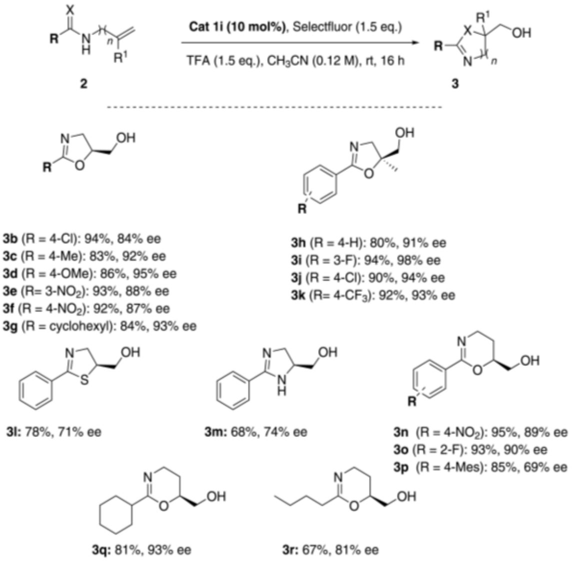
We then systematically investigated the influence of both ether substituents (R^1 and R^2) in catalysts **1** on the reaction performance. Switching the TIPS group to other alkyl groups, such as catalysts **1b**−**1e**, was found to be counterproductive and resulted in diminished enantioselectivities (see entries 2−5). We also varied the alkyl ether at R^1 and decided to introduce greater sterical bulk at this position. With R^2 being TIPS again, replacement of the methyl with an ethyl ether for R^1 (catalyst **1f**) resulted in a small but less than significant improvement of the enantioselectivity.

Introduction of an isopropyl group (catalyst **1i**) resulted in the most significant improvements, as **3a** was now isolated with a 91% yield and 93% ee. By contrast, the corresponding use of benzyl ether (**1j**) or benzoyl ester (**1k**) was less effective (see entries 10 and 11).

Decreasing the catalyst loading to 5 mol % had a negative effect on the yield. Reduction of the reaction time or performing the reaction at 0 °C did not improve the enantioselectivity but only led to lower reaction rates and incomplete conversions (see entries 12 and 13). Increasing the amount of the additive TFA had no effect on the yield of compound **3a**.

With the optimized conditions in hand, we elaborated the substrate scope of the oxidative cyclization (Scheme 3). The NAA derivatives **2b**−**f**, with additional substituents at the 2-aryl group, provided the corresponding oxazolines **3b**−**f** in yields and enantioselectivities comparable to those of the parent compound **3a** (84−95%), regardless of the electronic nature of the substituent. Comparison of the rotary power of the 4-nitro derivative **3f** with a known literature value allowed

Scheme 3. Substrate Scope



us to determine the absolute configuration of the products to be (S).[22] Cyclic aliphatic substituents (R = cyclohexyl) were tolerated as well, giving **3g** with an 84% yield and 93% ee.

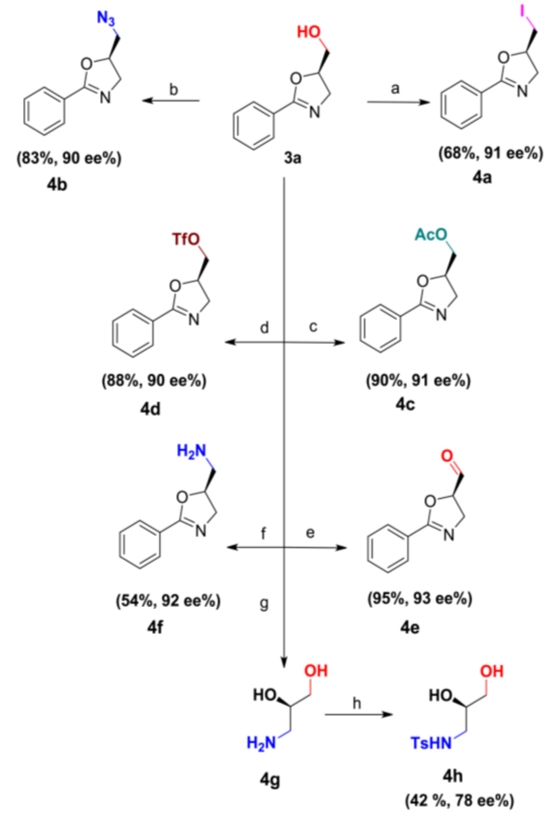
Next, we wondered whether quaternary stereocenters could be constructed.[23] We therefore decided to apply our method for the synthesis of quaternary 2-oxazolines starting from various *N*-(but-3-en-2-yl) benzamides **2h**−**2k** (R^1 = Me, R^2 = H). The desired products **3h**−**3k** could be observed in high yields of up to 94% and excellent enantioselectivities (91−98% ee). The enantioenriched thiazoline **3l** and the imidazoline **3m** were prepared for the first time by this method, although yields and enantioselectivities were significantly lower in direct comparison with their oxa derivatives (71% ee and 74% ee). It is nonetheless worth mentioning that these *N*-heterocycles are very important core structural motifs found in many biologically active compounds and this method provides a to date undescribed means of accessing them.[24]

We subsequently focused on the synthesis of 6-membered *N*-heterocycles. Application of *N*-homoallyl benzamide **2n** and **2o** (*n* = 2) provided the oxazines **3n** and **3o** in yields of 95% and 93% and enantioselectivities of 89% ee and 90% ee, respectively. The mesityl-substituted derivative gave the corresponding oxazine **3p** in comparable yields but with a diminished enantioselectivity (69% ee).

Aliphatic homoallyl amides **2q** and **2r** were subsequently investigated, giving the desired 2-cyclohexyl- and 2-*n*-butyl-substituted derivatives **3q** and **3r** in respective yields of 81% and 67% and enantioselectivities of 93% and 81% ee for each. Applications of similar compounds have been reported for the preparation of poly(2-oxazoline) gels for delayed drug delivery systems.[25] Again, our method provides unique access to these enantioenriched *N*-heterocycles.

Since 5-oxazolines are potentially useful intermediates for the synthesis of other chiral building blocks, we finally elaborated further synthetic transformations of **3a** (Scheme 4). The OH group could be replaced by iodine under Mitsunobu conditions to afford **4a** in 68% yield without a significant loss of enantiomeric excess.[26] Azidation was achieved using a method devised by Kumar and co-workers,

Scheme 4. Derivatization of Oxazoline 5a[a]



[a]Reaction conditions: (a) I_2 (1.20 equiv), PPh_3 (1.30 equiv), Pyridine (0.95 M), rt, 24 h. (b) NaN_3 (3.00 equiv), $BF_3{\cdot}Et_2O$ (1.50 equiv) Dioxane, rt, 24 h. (c) Acetic anhydride (2.00 equiv) DCM, rt, 4 h. (d) TF_2O (1.20 equiv), Pyridine (1.10 equiv), DCM, rt, 16 h. (e) MnO_2 (12.0 equiv), $CHCl_3$, 60 °C. 4 h. (f) 1-Phthalimide (1.10 equiv), PPh_3 (1.10 equiv), DIAD (1.30 equiv), THF (0.42 M), rt, 7 h, 2-Hydrazine (1.50 equiv), EtOH (5 mL), 80 °C, 0.5 h. (g) 1-$NaBH_4$ (1.20 equiv), I_2 (1.00 equiv), 2- HCl in MeOH, 24 h. (h) TsCl (1.20 equiv) MeCN, rt, 6 h.

treating **3a** with NaN_3 and $BF_3{\cdot}Et_2O$ to give **4b** in 83% yield and 90% ee.[27] Protection of the OH group to the corresponding acetates and triflates (**4c** and **4d**) was successful as well. In addition, the corresponding aldehyde could be obtained by treatment of **3a** with MnO_2, to give **4e** in 95% yield and 93% ee. Interestingly, no overoxidation of the oxazoline was observed. A Mitsunobu reaction was also utilized to prepare the primary amine **4f** in a moderate yield (54%) but sustaining the stereochemistry (92% ee).[28] Lastly, we prepared 3-aminopropane-1,2-diol by a reduction of **3a** followed by acid-mediated ring opening to give the amino diol **4g**. Since this compound could not be analyzed by HPLC, it was directly transformed into the *N*-tosylated derivative **4h**. **4h** was isolated in 42% yield but with a diminished selectivity of 78% ee. Racemization of **4h** could occur via intermediate oxirane formation by intramolecular attack of an activated form of the chiral secondary alcohol by the primary alcohol and a subsequent terminal ring opening by water.

In summary, we have established a practical method for the enantioselective oxidative cyclization of *N*-allyl amides by using an improved triazole-substituted iodoarene catalyst.[29] This method is characterized by a broad substrate scope which allows the construction of highly enantioenriched 5-oxazolines, thiazolines, and imidazolines. Quaternary stereocenters can be constructed with high efficiency as well, and the method was further extended to oxazines. Many of the constructed compounds can serve as chiral building blocks for the synthesis of interesting chiral target structures. This was demonstrated in a variety of further functionalizations, in particular of the terminal OH group.

In further investigations, we aim to apply C1-symmetric triazole-based iodoarenes in similar oxidative cyclizations to generate other useful 5- and 6-membered heterocycles. Additionally, cascade reactions in which the reactive hypervalent iodine intermediate is trapped directly by nucleophiles other than OH will also be part of future investigations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01607.

All experimental procedures and characterization data (PDF)

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Author Contributions

The manuscript was written by B.J.N. and A.H.A. A.H.A. and T.-N.H. performed the experiments.

Notes

The authors declare no competing financial interest.

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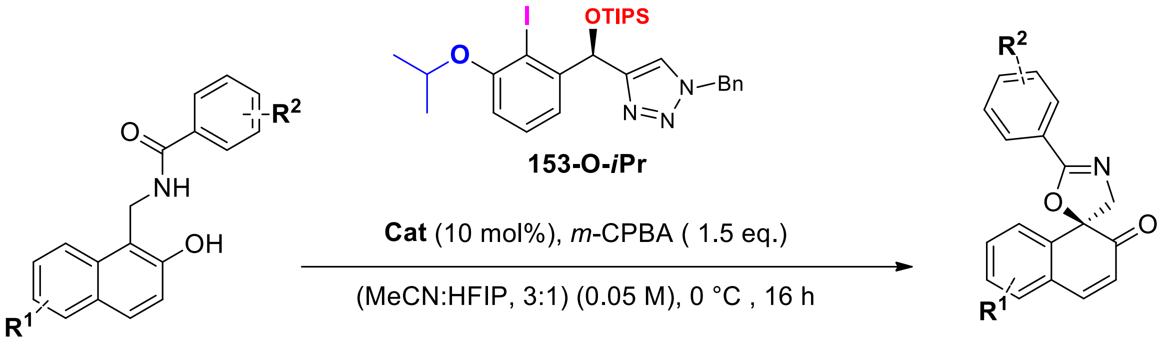
4.4. Fourth Publication: Application of Chiral Triazole-Substituted Iodoarenes in the Enantioselective Construction of Spirooxazolines

Herein, we present an enantioselective route to synthesize spirooxazoline compounds using chiral hypervalent iodine catalysts. This method provided us with the highest yields and enantioselectivities reported thus far for spirooxazolines. The reaction is compatible with a wide variety of substrates, including electron-rich and electron-poor naphthalene benzamides and *N*-heterocycles (Scheme 35). The synthetic utility of the spirooxazoline compounds is further demonstrated by simple oxidation or reduction steps. A photo-switch of the spirooxazoline molecule is shown at 350 nm for the closed form and 450 nm for the open form. This finding will be part of our future studies and might enable the use of these compounds in industrial applications.



159 **160**

Scheme 35. Synthesis of chiral spirooxazoline compounds via catalyst **153-O-*i*Pr.**

Title of the Publication: “Application of Chiral Triazole-Substituted Iodoarenes in the Enantioselective Construction of Spirooxazolines”

Ayham H. Abazid, and Boris J. Nachtsheim, *Chem Rxiv*. **2021.** https://doi.org/10.26434/chemrxiv.14648526.v1.

Chem. Comm. **2021** ,*57*, 8822-8825.

The supporting information, including a complete optimization table, detailed experimental procedures, characterization data, and copies of NMR spectra, is available free of charge on the journal′s website.

Abstract: A catalytic highly enantioselective synthesis of spirooxazolines is presented. Starting from readily available 2-naphthol-substituted benzamides and using catalytic amounts of a chiral triazole-substituted iodoarene catalyst, a variety of spi-rooxazolines can be isolated through an enantioselective oxidative dearomatization in up to 92% yield and 97% ee. The further synthetic utility of the

optically enriched spirooxazolines was examined providing a corresponding 2-naphthalenole and an oxepin.

Author Contribution to this Publication: In this project, I carried out all optimization reactions and synthesized and characterized the spirooxazoline and two compounds of the derivatization of spirooxazoline.

I wrote the manuscript and the supporting information. B. J. Nachtsheim was the principal investigator and edited the article.

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Application of chiral triazole-substituted iodoarenes in the enantioselective construction of spirooxazolines†

Ayham H. Abazid and Boris J. Nachtsheim*

A catalytic highly enantioselective synthesis of spirooxazolines is presented. Starting from readily available 2-naphthol-substituted benzamides and using catalytic amounts of a chiral triazole-substituted iodoarene catalyst, a variety of spirooxazolines can be isolated through an enantioselective oxidative dearomatization in up to 92% yield and 97% ee. The further synthetic utility of the optically enriched spirooxazolines was examined providing a corresponding 2-naphthalenole and an oxepin.

Spirocycles are well represented in many natural products and commercial drugs.[1–5] These unique molecular scaffolds have the advantage of providing stiff three-dimensional arrangements based on the tetrahedral nature of the spirocarbon. This allows enzyme pocket binding in a highly specific manner in terms of H-bonding, hydrophobic,[6] and π–stacking interactions.[7,8] While spirocycles can be found in abundance in natural products, they are only rarely found in pure synthetic pharmacophores due to their difficult enantioselective synthesis. A particular underrepresented class of synthetic spirocycles are spiro(is)oxazolines, although they can be found in a variety of natural products such as Agelorin A and B (**1a** and **1b**), isolated from marine sponges of the genus *Agelas*,[9] or Calafianin **2** from the sponge *Aplysina gerardogreeni.*[10] The oxazoline derivatives **3** were extracted from the plant *Gemmingia chinensis* (Fig. 1).[11]

The benefits of spirooxazolines as a unique class of spirocyclic compounds and their potential as highly variable scaffolds in medicinal chemistry and material science are encouraging chemists to develop new strategies for their synthesis. Synthetic strategies of spirocycles in general have been reported based on radical cyclizations,[12] rearrangements,[13] oxidative or reductive coupling reactions[14] and cycloadditions.[15]

Metal-catalyzed reactions such as the metathesis reaction, the Heck- and the Pauson–Khand reaction[16] as well as the Nazarov-cyclization[17] have been applied for the *de novo* synthesis of spirocyclic scaffolds. A variety of spirocyclic natural-products have been synthesized by metal-catalyzed approaches, such as (−)-vitrenal,[18] (+)-majusculone,[19] and α-acoradiene.[20] Another important approach for the synthesis of spirocycles is the intramolecular oxidative dearomatization of phenol and naphthol derivatives which can be efficiently accomplished through the application of hypervalent iodine reagents.[21–29] The first report for such a reaction was in 1998, when Ciufolini *et al.* reported the oxidative cyclization of tyrosine to form spirolactams, mediated by (diacetoxyiodo)benzene (DIB) in moderate yields.[30] Many variants followed.[31,32]

Enantioselective spirocyclizations, with the Kita-spirocyclization being the most prominent example, have been developed with great success as well.[33–37] In this regard, spirooxazolines have been widely neglected as target structures for oxidative cyclizations.[38,39] Recently, Moran and co-workers determined a new method for synthesizing spirooxazolines through the oxidative cyclization of phenols containing pendent amides mediated by iodine(III). In this seminal report, they also applied this reaction to 2-naphthol using chiral urea-derived iodoarenes, unfortunately with only modest results. In particular the stereoinduction was moderate with 14% ee in the best case.[40,41]

Our group recently developed chiral triazole-substituted iodoarenes and successfully applied these chiral C_1-symmetric iodoarene catalysts in a plethora of oxidative enantioselective transformations such as α-oxytosylations, (spiro)lactonizations, rearrangements and benzylic hydroxylations.[36,37,42] Intrigued by their high reactivity, we wondered whether these omnipotent catalysts can be applied in the yet underexplored generation of spirooxazolines through an oxidative spirocyclization of suitable substrates. We started our investigations using *N*-((2-hydroxynaphthalen-1-yl)methyl)benzamide **4a** as the model compound (Table 1). Oxidative spirocyclization of **4a** by a dearomatizing oxidative C–O-bond connection between the amides carbonyl oxygen and C1 of the 2-napththol unit as shown in **Int1** should give spirocyclic 2-naphthalenone **5a**.

We initially investigated four successful catalysts (**6a–6d**) from our recent work (entries 1–4).[43] It was found that catalyst

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1cc03246a

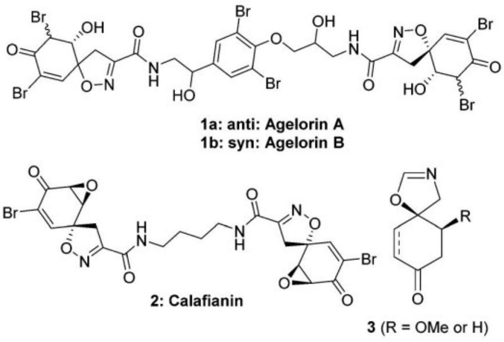
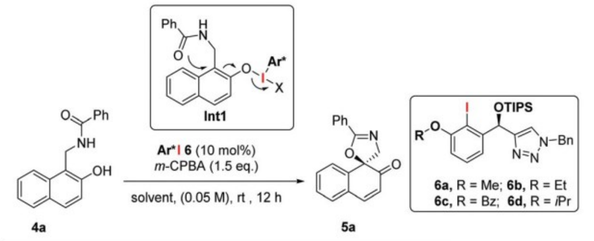


Fig. 1 Examples of natural products containing spirooxazoline.

6d showed the highest reactivity and selectivity for the desired product **5a** (entry 4). While ethyl acetate and pure hexafluoro-2-propanol (HFIP) as well as MeOH/MeCN mixtures did not improve yields and selectivities (entries 5–7), a further optimization of the reaction conditions revealed a mixture of acetonitrile and HFIP to be a highly effective solvent system (entry 8). Performing the reaction at 0 °C finally improved the stereoselectivity of product **5a** slightly to 96% ee (entry 9). The absolute configuration of **5a** was proven by comparison between a calculated CD-spectrum and the observed spectrum (see ESI,† Fig. S1).

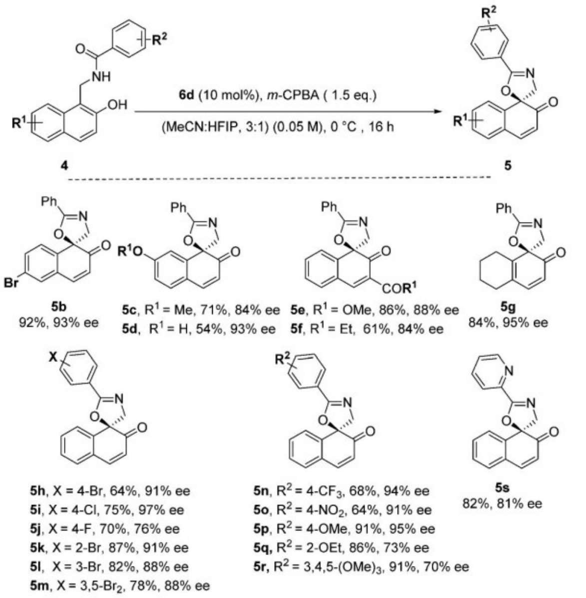
Under these optimized conditions, the applicable substrate scope was examined (Scheme 1). Initially, we introduced diverse substituents on the 2-naphthol ring. Halogen-substituents are well tolerated for example giving the 6-bromo derivative **5b** in 92% yield and 93% ee. 7-Methoxy- and hydroxyderivatives as electron rich examples can also be subjected to the spirocyclization giving **5c** and **5d** with good results. Even though the latter was isolated in high enantioselectivity (93% ee), the yield significantly dropped to 54%, possibly due to undesired oxidations of the phenol.

Table 1 Optimization of the reaction conditions



Entry[a]	Catalyst	Solvent	Yield [%]	ee [%]
1	**6a**	MeCN	60	67
2	**6b**	MeCN	68	74
3	**6c**	MeCN	63	78
4	**6d**	MeCN	76	85
5	**6d**	EtOAc	71	64
6	**6d**	HFIP	72	76
7[b]	**6d**	MeCN : MeOH	68	72
8[b]	**6d**	MeCN : HFIP	80	90
9[bc]	**6d**	MeCN : HFIP	81	96

[a] Reaction conditions: **4a** (0.15 mmol, 1.00 equiv.), cat (0.015 mmol, 10 mol%), *m*-CPBA (0.23 mmol, 1.50 equiv.), solvent (0.05 M). [b] Ratio of 3 : 1. [c] Reaction performed at 0 °C for 16 h for full conversion of **4a**.

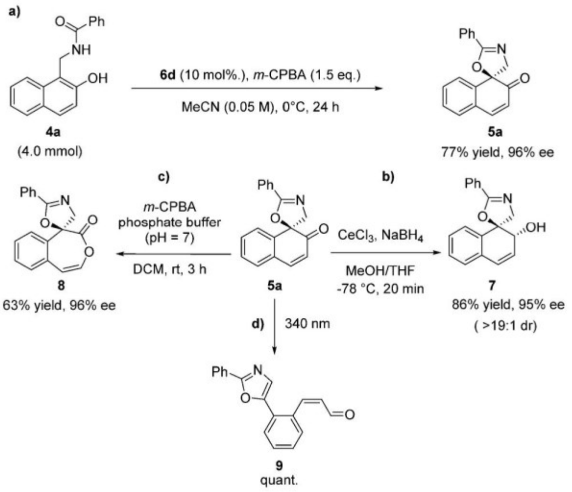


Scheme 1 Substrate scope.

3-Carboxyalkylesters and ketones gave spirooxazolines **5e** and **5f** in up to 86% yield and 88% ee. A tetrahydro 2-napthalenone can be transformed into target compound **5g** in 84% and 95% ee. Next, we varied the substitution pattern of the aryl amide. Introduction of halogen substituents yielded target compounds **5h–m** with good yields of 64–87%, and enantioselectivities of up to 97% for the 4-chloro derivative **5i**. The presence of strongly electron-withdrawing trifluoromethyl or nitro groups was tolerated as well in the cyclization, resulting in formation of **5n** and **5o** in good yields and excellent enantioselectivities of up to 94% ee. Methoxy- and ethoxy-substituted arenes **4p** and **4q** gave spirooxazolines **5p** and **5q** in high yields of 91% and 86%, respectively, with an excellent enantioselectivity for **5p** of 95% ee and a moderate enantioselectivity of 73% ee for **5q**. A highly electron rich trimethoxy-substituted derivative yielded the corresponding spirooxazoline **5r** in high yield, but with a diminished enantioselectivity of 70% ee. A 2′-pyridine-substituted amide was also tolerated in this cyclization, forming the corresponding spirooxazoline **5s** with 82% yield and 81% ee.

To prove the synthetic robustness of our method, a large-scale synthesis was performed, giving spirooxazoline **5a** in constant yield and enantioselectivity on a 4 mmol scale. (Scheme 2a).

The further synthetic utility of the optically enriched spirooxazolines was also investigated. A diastereoselective Luche reduction of **5a** yielded the C2-spirocyclic tetrahydronaphthalenole **7**, with almost the same enantiopurity (Scheme 2b).[44] The given relative configuration was determined by an NOE experiment. By addition of *m*-CPBA **5a** was oxidized through a Baeyer–Villiger oxidation to the oxepin **8**, again with excellent



Scheme 2 Synthetic applicability.

retention of the stereocenter (Scheme 2c). Interestingly, this reaction was not observed so far as a significant undesired oxidative decomposition pathway during our investigations.

Spiropyrans and spirooxazines received attention in material science due to their reversible photoresponsive properties.[45–50] Industrial applications of spirooxazines include photoresponsive sunglasses and ophthalmic lenses.[51] In this regard, the closed form **5a** could potentially undergo ring opening after photoactivation, either by heterolytic cleavage of the C(spiro)–O bond or electrocyclization, to give the open form, which absorbs at a longer wavelength due to an extended π-system.[52] We used 340 nm light for the photoisomerization reaction of spirooxazoline **5a** to construct the open form **9**, which has a yellowish color. The aldehyde **9** absorbed light at 450 nm to revert to the closed form **5a** as the racemate (Scheme 2d). This is a rare case of a switchable optical active spirooxazine and further applications in chiral optical devices are under current investigations.

In conclusion, we herein present the first highly enantioselective oxidative spirocyclization of amide-substituted 2-naphthols using chiral hypervalent iodine catalysis. This method provides a variety of enantioenriched spirooxazolines in remarkable yields and enantioselectivities.[53] The reaction is compatible with a wide variety of substrates, including electron-rich and electron-poor naphthalene benzamides as well as N-heterocycles. The further synthetic utility of these compounds allows the preparation of two interesting derivatives by a diastereoselective 1,2-reduction of the 2-naphthalenone and ring-enlargement through a Baeyer–Villiger oxidation. Finally, the principle photo-switchable properties of the so observed chiral spirooxazoline are demonstrated.

The manuscript was written by Ayham H. Abazid and Boris J. Nachtsheim. Ayham H. Abazid performed the experiments. All authors have given approval to the final version of the manuscript.

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Conflicts of interest

The authors declare no competing financial interests.

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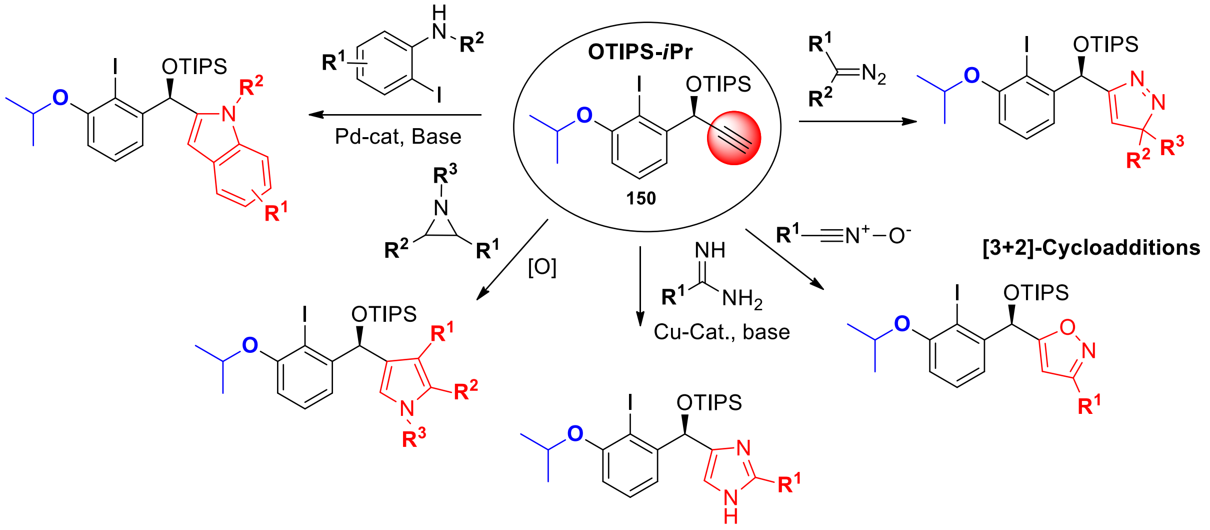
4.5. Conclusion

In this thesis, a wide library of new triazole-substituted chiral iodoarenes has been synthesized and employed in enantioselective oxidative reactions. The first publication, *A Triazole-Substituted Aryl Iodide with Omnipotent Reactivity in Enantioselective Oxidations*, reports the first omnipotent chiral aryl iodine that performs five different enantioselective reactions and provides previously unseen results. The second publication, *An Enantioconvergent Benzylic Hydroxylation Using a Chiral Aryl Iodide in a Dual Activation Mode*, reports the first application of chiral iodanes in C–H benzylic bond activation using a combination of copper and the chiral iodoarene. In this reaction, the chiral hypervalent iodine has a dual role. It acts as an oxidant in the first step and as a chiral ligand in the second step. This strategy will pave the way to explore the ability of chiral aryl iodides to insert different nucleophiles on C–H benzylic positions enantioselectively. The third publication, *Stereoselective Oxidative Cyclization of N-Allyl Benzamides to Oxaz(ol)ines*, presents the construction of chiral *N*-heterocyclics such as oxazolines, oxazines, thiazolines, imidazolines, and using chiral aryl iodides as promoters of this reaction. Compound **158** could be converted into several derivatives via conventional nucleophilic substitution methods. Our method will promote an easy way to incorporate a quaternary stereocenter selectively in many natural products and biologically active compounds. The fourth Publication, *Application of Chiral Triazole-Substituted Iodoarenes in the Enantioselective Construction of Spirooxazolines,* demonstrates an efficient method to construct spirooxazoline compounds in high yields and excellent enantioselectivities. Overall, the aim of this thesis was fully achieved. The herein developed second and third generation triazole-substituted catalysts could be synthezized in an optimized synthetic procedure in very high yields following a short and robust sequence and these chiral iodoarenes show an outstanding performance, not only in a variety of typical iodane-mediated oxidative reactions but also in so far undescribed C-H-activations in combination with transition metal.

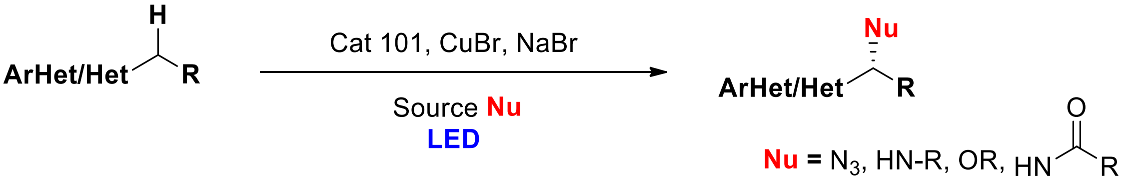
5. Outlook

In the future, fourth-generation catalysts should be created in which the *N*-heterocycle will be further modified. Based on the best performing catalyst **153-O-*i*Pr**, the influence of the *N*-heterocycle will be systematically investigated. Starting from the corresponding enantiopure O-TIPS-protected propargyl alcohol OTIPS-*i*Pr, a variety of 5-membered heterocycles should be synthezied.[140–142] Then, the model reactions discussed previously will be tested again, as will other reactions with enantioselective results (Scheme 36).



Scheme 36. Synthesis of fourth-generation catalysts.

Direct oxidation of the benzylic C–H bond of aryl/heteroaryl methane could be investigated using the same procedure described in the article 2. This concept should pave the way for benzylic substitutions such as azidations and aminations (Scheme 37).



Scheme 37. Proposed benzylic C–H substitution reactions.

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