ERASMUS MUNDUS JOINT MASTER DEGREE IN SUSTAINABLE CATALYSIS

ENANTIOSELECTIVE AZIRIDINATION OF DIENYL CARBAMATES EN ROUTE TO SPHINGOLIPID MIMICS

MASTHER THESIS

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ABSTRACT

The enantioselective aziridination of dienyl carbamates is a pivotal step in the synthesis of sphingolipid mimics. In our prior research, we developed a sequential oxyamination protocol for dienyl carbamates, yielding racemic oxazolidinones that were subsequently converted into enantioenriched sphingosine analogues.

Then, our efforts focused on the metal-free intramolecular asymmetric oxyamination of alkenes via aziridination, addressing the scarcity of efficient enantioselective methods for aziridine synthesis. Traditionally, hypervalent iodine reagents have been used as oxidants for preparing iminoiodanes or generating metallonitrenes in situ, providing eco-friendly alternatives to transition metal complexes.

Building on this foundation, our current study investigates lactate-based (diacetoxyiodo)arenes as chiral reagents for the asymmetric oxyamination of dienyl carbamates. In this sense, the objective of this research is to develop innovative processes for the asymmetric synthesis of key anti-2-amino-3-hydroxy intermediates en route to sphingolipid mimics. Also, we aim to enhance the enantioselective synthesis of aziridines using I(III) reagents and to develop novel procedures for intramolecular aziridination, leveraging the intermediacy of aminoiodanes.

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ABBREVIATIONS AND ACRONYMS

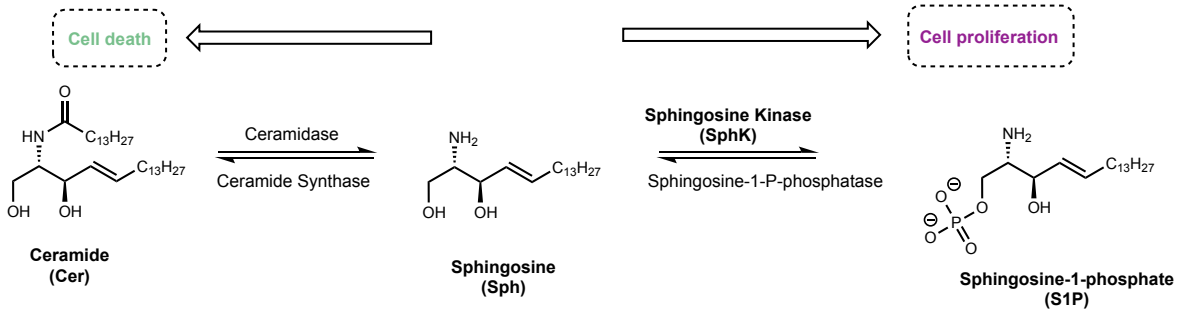
A	ACN	Acetonitrile
	AcOH	Acetic acid
D	DCM	Dichloromethane
	DIAD	Diisopropyl azodicarboxylate
E	Et_2O	Diethyl ether
	EtOAc	Ethyl acetate
	HPLC	High Performance Liquid Chromatography
	Hx	Hexane
	m-CPBA	*meta*-Chloroperbenzoic Acid
M	m	Multiplet
	Me	Methyl
	MeOH	Methanol
	MS	Molecular sieves
P	Ph	Phenyl
	PhIO	Iodosylbenzene
	PIDA	(Diacetoxyiodo)benzene
	PPh3	Triphenylphosphine
Q	q	Quadruplet
S	s	Singlet
	Sph	Sphingosine
	SphK	Sphingosine Kinase 1
	SphK2	Sphingosine Kinase 2
T	t	Triplet
	TAI	Trichloroacetyl isocyanate

	THF	Tetrahydrofuran
	TLC	Thin layer chromatography
	Ts	Tosyl
U	UV/Vis	Ultraviolet/Visible

1. INTRODUCTION

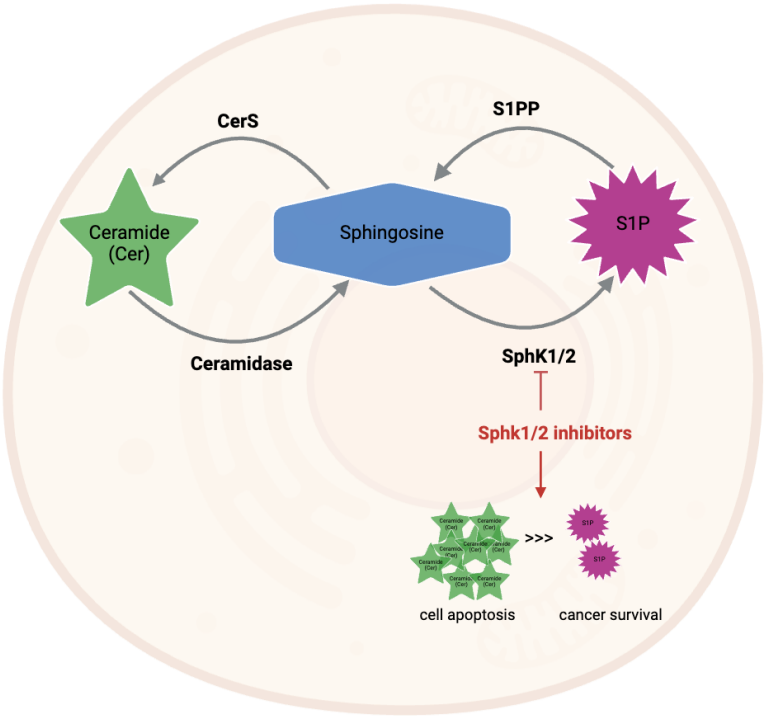
1.1. Sphingosine kinase as a new target for cancer treatment

Over the past three decades, certain sphingolipids, termed bioactive sphingolipids have been found to play crucial roles in both normal and disease-related cellular functions, such as controlling cell growth, differentiation, survival, movement, and death.[1,2] There are three well-studied bioactive sphingolipids: ceramide (Cer), sphingosine (Sph) and sphingosine-1-phosphate (S1P), which are interconvertible in a complex biosynthetic pathway regulated by specific enzymes (**Scheme 1**).



Scheme 1. Sphingolipid rheostat.

Generally, high levels of Cer promote cellular effects like apoptosis (programmed cell death). In contrast, overproduction of S1P is linked to cell proliferation, migration, inflammation, differentiation, and survival, collectively resulting in anti-apoptotic effects.[3,4] S1P is generated thorugh the phosphorylation of Sphingosine by action of an enzyme, Sphingosine Kinase (SphK).There are two isoforms of SphK, namely SphK1 and SphK2, which are associated with pathways that influence cancer cell growth, survival, metastasis, and resistance to multiple drugs.[5,6] Consequently, shifting the balance toward increased ceramide production, for instance, by inhibiting sphingosine kinase activities, can enhance its pro-apoptotic effects. This approach is considered a promising strategy for effective cancer therapy (**Scheme 2**).



Scheme 2. Sphingolipid metabolic pathway.

During the past decade, there has been growing interest in developing novel inhibitors of the SphK/S1P pathway. To enhance the efficiency of known sphingosine kinase inhibitors (SKIs), various structural modifications have been performed, based on different structural classes. In this regard, the sphingosine molecule consists of three distinct chemical regions: (1) a polar head consisting of a terminal hydroxyl group, followed by two contiguous stereocentres bearing a primary amine group and a secondary alcohol; (2) a linker olefin that separates the polar head from (3) the lipophilic tail, made up of a long hydrocarbon chain (**Figure 1**). The structural modifications of sphingosine documented in the literature can be categorized into two groups: (1) modifications that preserve the polar headgroup, and (2) modifications that alter the polar head.[7] Currently, structural alterations in each region have resulted in the development of new families of sphingosine analogs, which could potentially function as inhibitors of SphK1/K2 for cancer treatment purposes.[8,9,10]

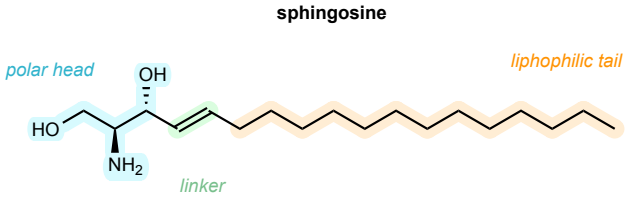
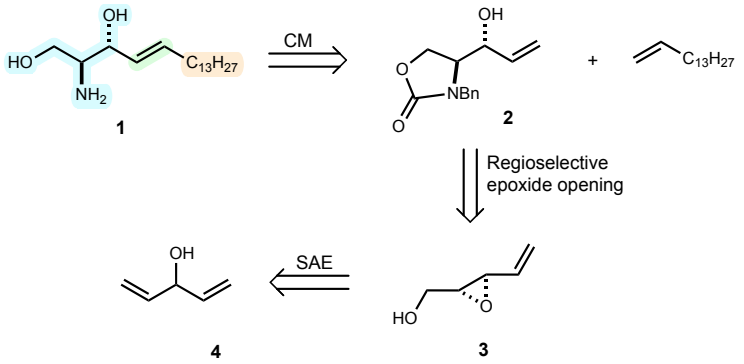


Figure 1. Sphingosine and its key structural features.

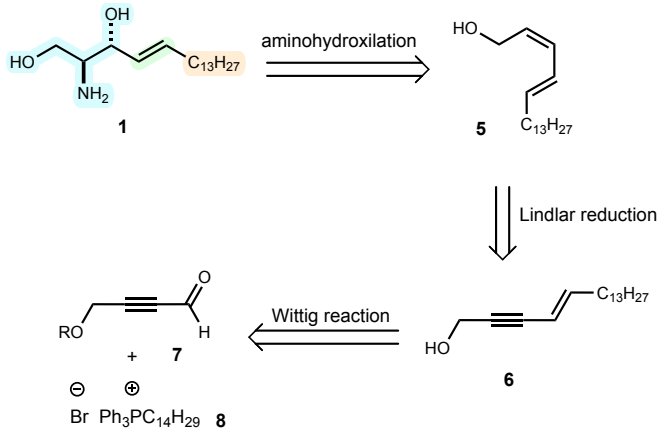
1.2. General approaches for the synthesis of sphingosine

Over the years, different research groups have dedicated significant effort to synthesizing sphingosine analogs using different approaches. In 2004, Peter Somfai reported the synthesis of D-erythro-sphingosine using a cross-metathesis approach.[11] In this method, Compound **1** was assembled via a cross-metathesis reaction with Grubbs' phosphine-free catalyst to introduce the required *E*-olefin moiety, as illustrated in the **Squeme 3**. Subsequently, polar head group **2** was derived from epoxide **3**, which is prepared from divinylcarbinol **4** by a Shapless asymmetric epoxidation (SAE). This strategy facilitated the practical synthesis of compound **1**, achieving a 51% yield over five steps. Moreover, this flexible approach enables the synthesis of sphingolipids with different aliphatic chains by employing various olefins in the cross-metathesis reaction.



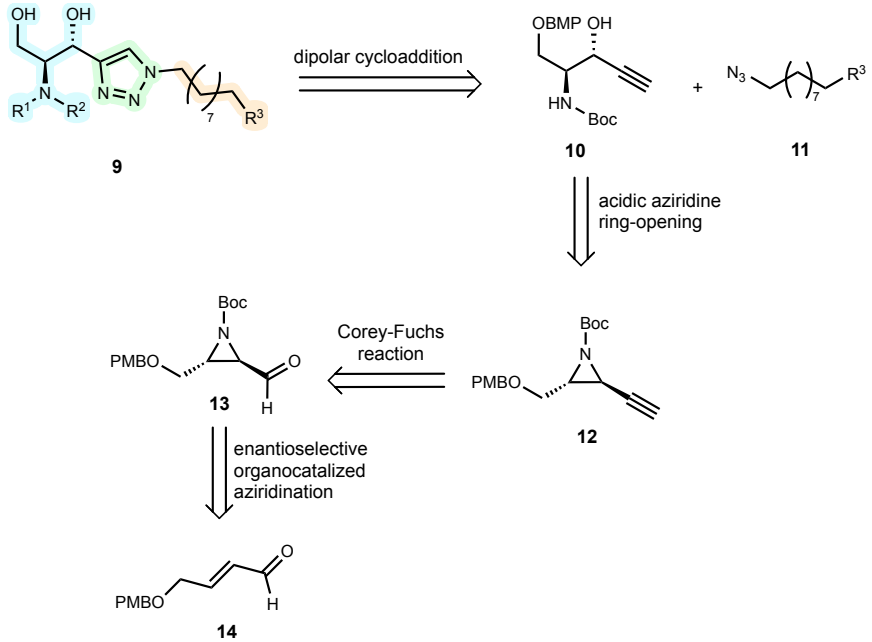
Scheme 3. Retrosynthetic analysis of D-erythro-sphingosine using a cross-metathesis approach.

Later, in 2008, our group developed an effective method for synthesizing racemic D/L-erythro-sphingosine.[12] This approach centered around a critical aminohydroxylation reaction, which introduced chiral aminohydroxylic groups in the final step using diene **5**. Moreover, diene **5**, crucial for its specific *E*,*Z*-configuration, was synthesized by reducing compound **6**. Initially, compound **6** was derived from aldehyde **7** through a Wittig reaction (**Scheme 4**). Finally, D/L-erythro-sphingosine **1** was successfully synthesized in eight steps, demonstrating complete control over regio- and stereoselectivity, and achieving an overall yield of 33%.



Scheme 4. Retrosynthetic analysis of D-erythro-sphingosine using an aminohydroxylation reaction as the key step.

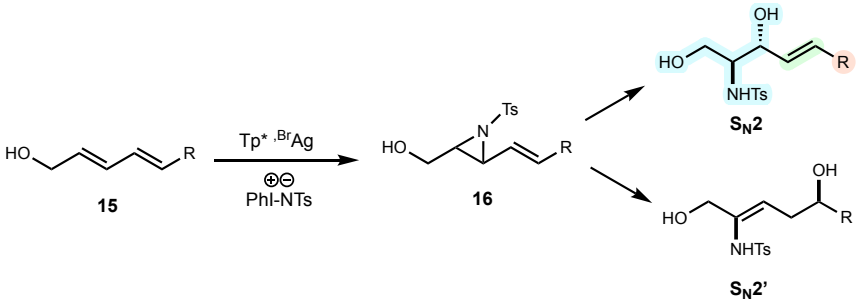
In 2018, our group advanced by reporting the synthesis and *in-vitro* evaluation of fluorinated triazole-containing sphingosine analogs.[13] This was achieved by first accessing enantioenriched alkynylaziridines **13** through a proline-organocatalyzed aziridination reaction of α,β-unsaturated aldehydes **14**, followed by a homologation reaction (**Scheme 5**). Afterward, selectively opening the ring in intermediate **12** and combining it with triazole click chemistry using fatty alkyl azides resulted in the synthesis of a varied collection of 16 sphingosine analogs featuring a shared triazole structure.



Scheme 5. Retrosynthetic analysis using organocatalyzed aziridination and the Corey–Fuchs reaction as the key steps.

An alternative strategy for synthesizing compounds with vicinal amino alcohols involves the oxyamination of dienols to produce vinylaminodiols, using aziridines as key intermediates. In this context, our group introduced in 2014 a chemo-, regio-, and stereoselective method for the silver-catalyzed aziridination of dienes.[14] As it is illustrated in **Scheme 6**, this reaction employs silver complexes with

trispyrazolylborate ligands (Tpx) to catalyze the aziridination of 2,4-diene-1-ols **15**, yielding vinylaziridines **16** in high yields. The process involves the metal-mediated transfer of NTs (Ts = *p*-toluenesulfonyl) units from *N*-tosyliminobenzyliodinane (PhI=NTs). The reaction shows a strong preference for aziridination at the double bond adjacent to the hydroxyl group, achieving a regioselectivity ratio of approximately 9:1. Additionally, this process is stereospecific, maintaining the initial geometry of the double bond in the aziridine product (*Z* or *E* olefins yield *cis* or *trans* aziridines, respectively). The synthesized vinylaziridines can then be selectively opened with oxygen, nitrogen, or sulfur nucleophiles through selective **S_N2** or **S_N2'** processes, resulting in a variety of unsaturated amino alcohols.

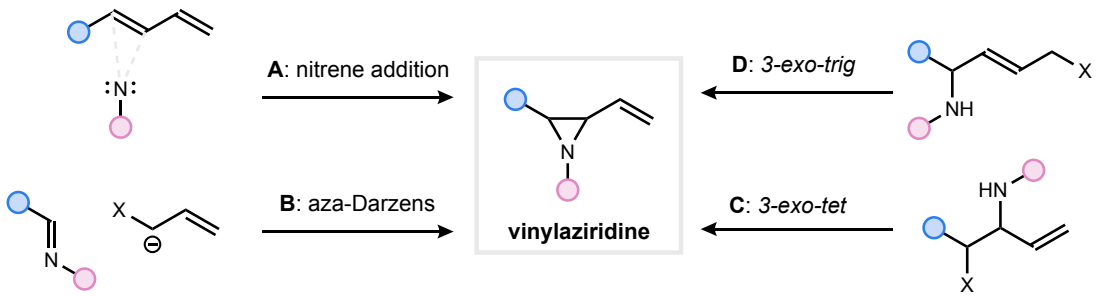


Scheme 6. Silver-catalyzed aziridination of dienols.

As previously described, over time various approaches for synthesizing sphingosine have been developed. Most of these methods achieve good conversion, regio- and stereoselectivity, and moderate to good yields. However, they often involve multiple reaction steps. In this context, the synthesis of unsaturated amino alcohols via the formation of vinyl aziridine as a key intermediate has gained our attention.

1.3. Synthetic approaches to vinylaziridines

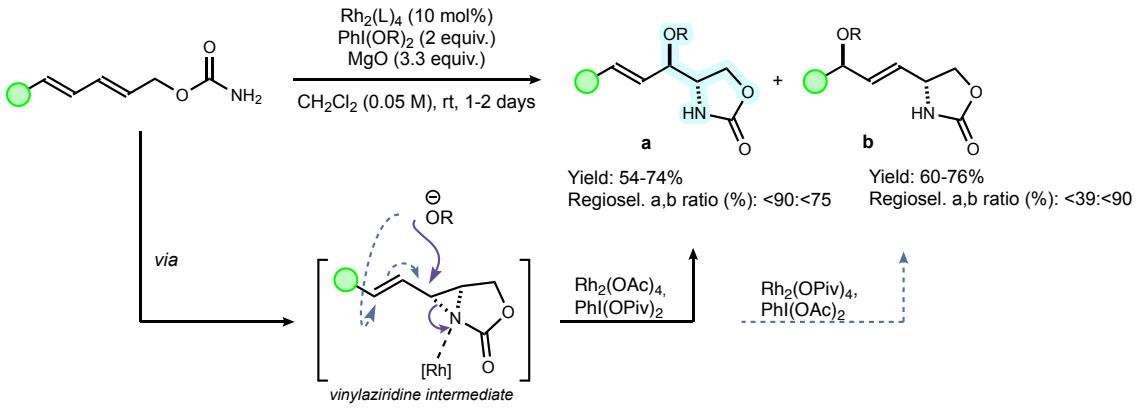
Vinylaziridines are synthetically useful intermediates that can undergo a wide variety of transformations. Their reactivity has been studied extensively,[15] which is largely governed by the strained three-membererd aziridine ring, coupled with the potential for subsequent double bond functionalization, renders them versatile components in organic synthesis.[15] Vinylaziridines can be synthesized in a number of different ways, including: reaction of a nitrene equivalent with a conjugated diene[16](**A**), reaction of an allylic carbene equivalent (aza-Darzens-type) (**B**),[17] and cyclisation amino alcohol derivatives bearing a suitable leaving group (**C, D**) (**Scheme 7**).[18]



Scheme 7. General synthetic routes to viniylaziridines

As versatile building blocks in organic synthesis, vinylaziridines serve as important precursors for vicinal amines, amino alcohols, amino acids, amino sugars, and azaheterocycles.[19] These compounds are crucial intermediates in the synthesis of more complex molecules.[19]

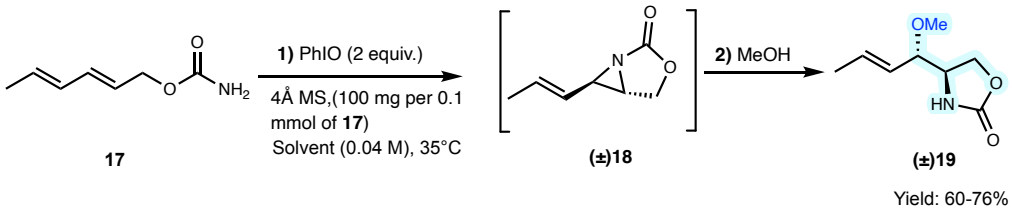
This research group previously described that the reaction of dienyl carbamates with $PhI(OR)_2$ in the presence of rhodium catalysts produces vinyl aziridines, which are then regio- and stereoselectively opened *in situ* to yield oxyamination products. This process occurs via intramolecular alkene aziridination through the formation of a rhodium nitrene species and subsequent S_N2 opening with $Rh_2(OAc)_4/PhI(OPiv)_2$ or an S_N2' opening with $Rh_2(OPiv)_4/PhI(OAc)_2$.[9] (**Scheme 8**). However, this protocol has some limitations, one being that the *in-situ* ring opening of the aziridine intermediate prevents the discretionary use of an external nucleophile.



Scheme 8. Tandem transition metal-catalyzed intramolecular aziridination of dienes followed by a regiocontrolled ring-opening with oxygen nucleophiles.

Furthermore, as part of our group's continuous efforts to develop protocols for the synthesis of sphingosine-like 3-heteroatom-substituted-2-amino-1-ol derivatives, a metal-free diene aziridination-ring opening strategy using hypervalent iodine reagents was disclosed.[10] In this protocol, PhIO is used to mediate intramolecular aziridination of a double bond with a tethered carbamate, followed by sequential

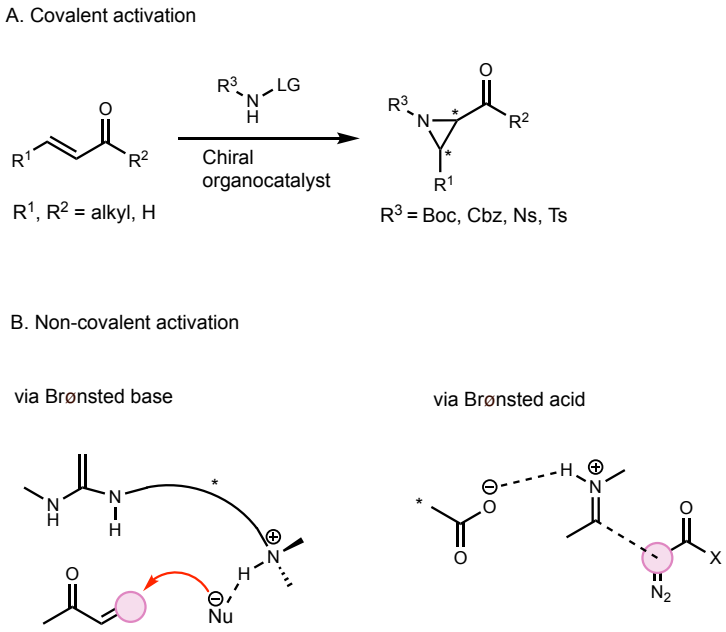
ring-Opening of the stable aziridine intermediate with different external nucleophiles (O-, N-, and S-based nucleophiles), resulting in various racemic oxazolidinones (**Figure 9**). Nevertheless, this method is limited to the synthesis of racemic oxazolidinones, which nonetheless can be separated via a organocatalytic kinetic resolution.[20]



Scheme 9. Synthesis of vinylaziridines by metal-free intramolecular diene aziridination and in situ ring-opening

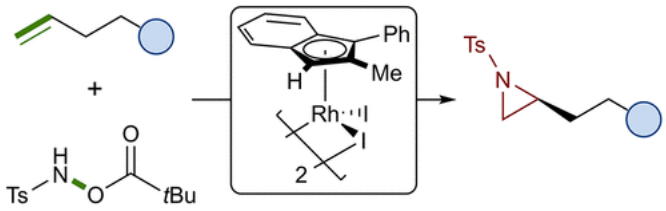
1.4. Chiral Hypervalent Iodine Reagents for Asymmetric Synthesis

Asymmetric alkene aziridination can be achieved through various methods. One approach is the organocatalyzed aziridination of electron-deficient olefins, which can be accomplished via two different activation modes. The first mode, covalent activation, involves the use of chiral amine catalysts with *a,β*-unsaturated ketones and aldehydes. This enables the reversible formation of chiral iminium ions or enamines, which then undergo stereoselective aziridination (**Scheme 10, A**).The second mode, non-covalent activation, employs chiral H-bond donor (or acceptor) catalysts to facilitate stereocontrolled aziridination through non-covalent interactions (**Scheme 10, B**).[21,22]



Scheme 10. A. General asymmetric aziridination of α,β-unsaturated carbonyl compound via covalent catalysis (Boc: tert-butoxycarbonyl; Cbz: benzyloxycarbonyl; Ns: p-Nitrophenylsulphonyl; Ts: p-Toluenesulphonyl; LG: leaving group). **B.** Example of non-covalent interaction implicated in aziridination process.

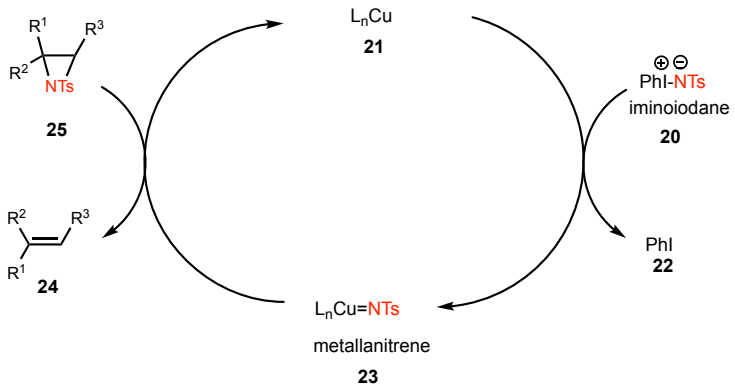
Furthermore, recent advancements include the aziridination of inactivated terminal alkenes using a planar chiral Rh(III) Indenyl Catalyst.[23] This approach achieves alkene aziridination by introducing metal-nitrenes to alkenes in the presence of chiral ligands (**Scheme 11**).



Scheme 11. Enantioselective aziridination of unactivated terminal alkenes using a planar chiral Rh(III) indenyl catalyst.[23]

Similarly, hypervalent iodine reagents have traditionally been used for the aziridination of olefins through the metal-catalyzed generation of nitrenes from iminoiodanes.[24] Building on the foundational work of Evans[25] and Jacobsen,[26] significant progress has been made in developing Cu(II)-catalyzed methods that utilize either discrete or in situ-generated hypervalent iminoiodinane nitrene sources. These advancements also resulted in the creation of the first widely accepted schematic catalytic cycle for the aziridination reaction (**Scheme 12**). The catalytic cycle begins with the interaction between the metal catalyst **21** and the iminoiodane **20**. The iminoiodane transfers the NTs moiety to the metal, producing a

metallanitrene **23** and PhI **21**. The metallanitrene then behaves like a nitrene, reacting with an olefin and releasing aziridine **25**.



Scheme 12. General view of the copper-catalyzed aziridination using PhINTs.

Despite the methods reported for asymmetric alkene aziridination, which also involve the use of hypervalent iodine reagents as oxidants to prepare iminoiodane reagents similar to PhI=NTs or to generate metallonitrenes *in situ* from nitrogenated derivatives and a metal catalyst, more recently, chiral hypervalent iodine (III) compounds have emerged as eco-friendly alternatives to transition metal complexes for asymmetric oxidation. This is owing to their highly electrophilic nature and remarkable leaving group ability.

Before delving into chiral hypervalent iodides, it is essential to understand some general properties of hypervalent iodine compounds. In this sense, hypervalent iodine reagents offer unique and advantageous characteristics, providing an effective alternative to transition metal complexes for the synthesis of various biologically active structures.[27] Although their structure and reactivity are generally similar to those of transition metal derivatives, and their reactions are typically described using familiar terms like ligand exchange, oxidative addition, reductive elimination, and ligand coupling, hypervalent iodine stands out due to its environmentally benign nature and relative affordability compared to heavy metals.

Hypervalent iodine complexes exhibits unique bonding characteristics; due to its large atomic size iodine does not typically form π-bonds between atoms. Instead, typically adopting a T-shaped geometry, these complexes feature two electronegative ligands occupying the axial positions. This arrangement facilitates the formation of a linear three-center four-electron (3c-4e) bond, known as a *hypervalent bond*, through interaction between the filled 5p orbital of the central iodine atom and the half-filled orbitals of the trans ligands (L1 and L2). This interaction results in the formation of three molecular orbitals: bonding, nonbonding, and antibonding.[28]

Due to the node in the highest occupied molecular orbital (HOMO) at the central iodine, hypervalent bonds exhibit a highly polarized nature, making the axial positions preferential for more electronegative ligands. Conversely, an electropositive ligand situated in the equatorial position forms a conventional covalent bond with the central iodine atom.[29] This distinctive bonding explains the special structural properties and reactivity patterns observed in hypervalent iodine compounds.

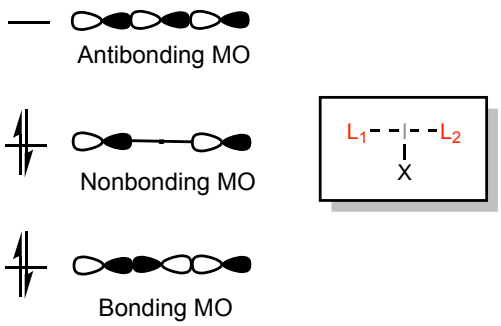


Figure 2. Molecular orbitals of the 3c-4e bond formed in the hypervalent iodine (III) complexes.

Furthermore, these reagents are widely used in organic synthesis as selective oxidants and environmentally friendly reagents. Synthetic uses of hypervalent iodine reagents in halogenation reactions, various oxidations, rearrangements, aminations, C−C bond-forming reactions, and transition metal-catalyzed tranformatiuons.[27,30]

Now, turning our attention back to chiral hypervalent iodines, various classes of chiral hypervalent iodine reagents have been reported in the literature. To understand the design and development of catalyst families for enantioselective reactions using iodine (III/V), it is crucial to recognize the different types of chirality incorporated into their structures. These strategies can be classified into four categories based on the type of chirality (**Figure 3**).

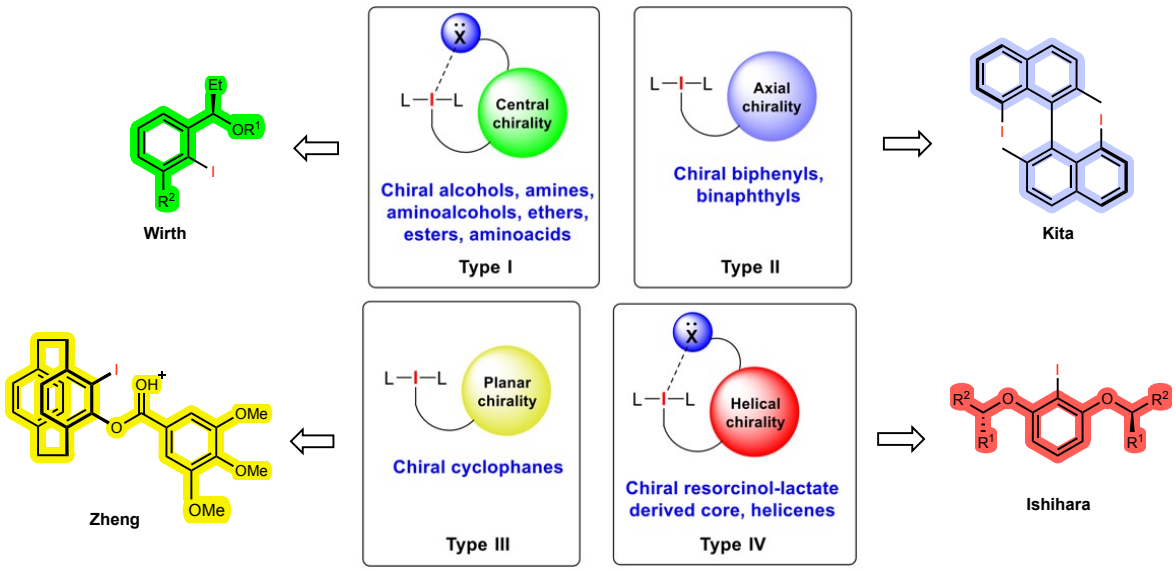


Figure 3. Strategies to control stereoselectivity.[30]

Type I hypervalent iodine reagents or catalysts are created *in situ* by oxidizing chiral iodoarenes. These reagents use central chirality from one or more stereogenic centers within the carbon structure to control the stereochemistry in asymmetric reactions. Various chiral groups, such as chiral alcohols, amines, amino alcohols, and amino acids, can be incorporated into these reagents. These groups not only help control the stereochemistry but also stabilize the hypervalent iodine intermediate through intramolecular coordination. For example, Wirth and colleagues developed a iodoarene with a chiral stereocenter *ortho* to the iodine atom on the aromatic ring. Additionally, a variety of iodobenzenes with chiral stereocenters on the side chain have been synthesized and used in enantioselective oxidative reactions.[31]

Other important structural types involve incorporating axial and planar chiralities, known as **Type II** and **Type III**. These types use chiral biphenyls, binaphthyls, or chiral cyclophanes as chiral inductors to achieve high stereoselectivity. For instance, Kita and coworkers reported using a chiral atropisomeric 8,8'-diiodobinaphthalene for asymmetric dearomatizing spirolactonizations in hypervalent iodine oxidations.[32] On the other hand, Zheng and colleagues developed planar chiral iodoarenes and applied them in the catalytic enantioselective fluorination of β-ketoesters.[33]

Despite the preparation of many chiral reagents using approaches of type I, II and III, the induction achieved has generally been limited, with only a few transformations producing high enantiomeric excesses. While there has been reasonable success in terms of enantiocontrol, there is still significant room for improvement. However, the incorporation of helical chirality (**Type IV**) around hypervalent iodine atoms has proven to be the most successful strategy, showing the most promise for future

asymmetric hypervalent iodine-promoted oxidations. This success is also attributed to their versatile nature and the straightforward introduction of chemical modifications (R1, R2, R3). This innovative approach was initially introduced by Fujita[34] in 2010 and further developed by Ishihara[35]. The C_2 symmetric structures, which exhibit intriguing chiral features, are derived from a resorcinol core with conformationally flexible chiral lactate (**A**) or lactamide (**B**) arms.

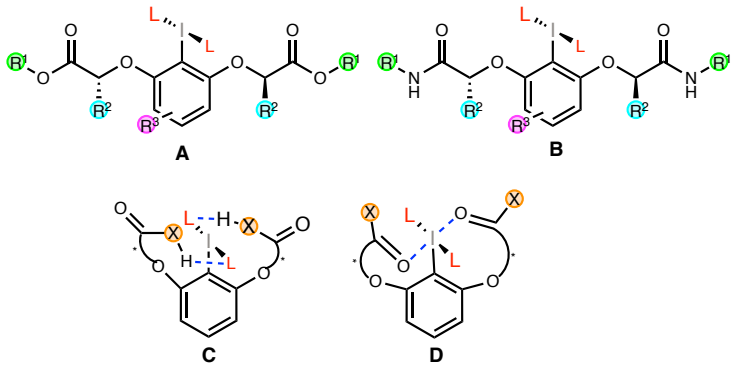
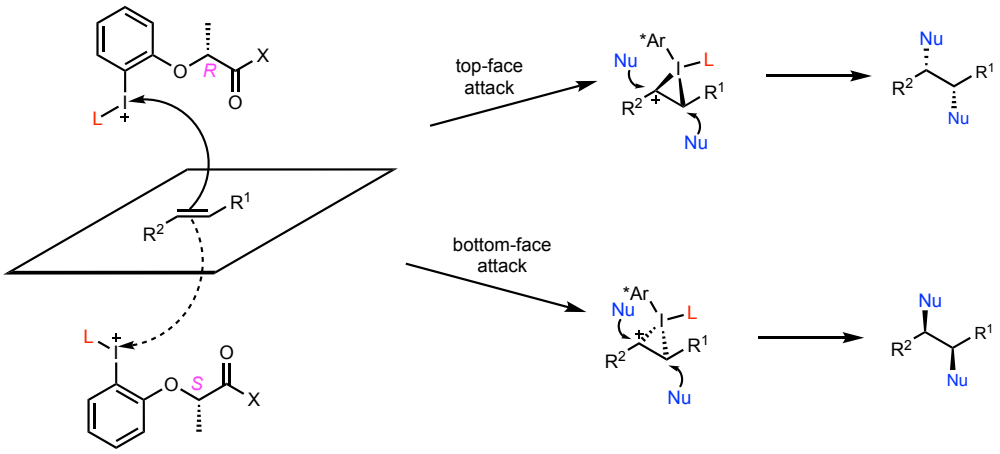


Figure 4. Chiral resorcinol-lactate derivatives presenting helical chirality.

In this context, intramolecular n−σ* interactions occur between the electron-deficient hypervalent iodine and the lone pair of electrons on the carbonyl group in esters and amides (**D**, Figure **4**). Additionally, potential hydrogen bonds between N−H groups and basic atoms in ligands (**C**, Figure **4**), as well as other noncovalent interactions like π-π stacking, contribute to forming a three-dimensional structure that generates a unique helical fold.[36] Thus, these helical fold chiral arms form a distinctive structure that plays a crucial role in determining the stereochemistry of several asymmetric transformations.

Thus, facial differentiation induced by lactate stereogenic centers is a common phenomenon observed in esters, secondary amides, and tertiary amides. The chiral helicity created by these centers provides an ideal environment for achieving enantioselective oxidations. The terminal functional group on the ester or amide sidechain can influence this chiral environment through its steric bulkiness and electronic interactions. Thus, modifying these terminal functional groups effectively tunes the stereoselectivity in oxidative transformations.

In the context of alkene oxidations, the chiral environment around the iodine center plays a crucial role in efficiently distinguishing between alkene stereofaces. The stereochemical outcomes of oxidative difunctionalizations illustrate that lactate-based reagents exhibit a predictable facial selectivity pattern. Specifically, electrophilic attacks by (*R*)-reagents predominantly occur on the top-face of the alkene, while attacks by the antipodal (*S*)-reagents preferentially target the bottom-face (**Scheme 13**).[37]



Scheme 13. Facial selectivity of lactate-based hypervalent iodines.

1.5. Enantioselective aziridination of olefins mediated by hypervalent Iodine (III)

As previously mentioned, asymmetric alkene aziridination can be achieved through various methods, the most popular ones include the organocatalyzed aziridination of electron-deficient olefins[22] and alkene aziridination by introducing metal-nitrenes to alkenes in the presence of chiral ligands.[23] However, despite significant advancements in chiral hypervalent iodine chemistry over the past twenty years, there are still few publications on metal-free asymmetric aziridination of olefinic substrates using iminoiodane formation.

One notable example is *N*-tosyliminophenyliodane (PhINTs), the most important iminoiodane, commonly used as a nitrene precursor for aziridination of alkenes and amidation reactions of various organic substrates. According to the N-X-L designation (N: number of valence electrons of the central atom, X: central atom, L: number of ligands), iodonium imides are classified as 10-I-2 species. In these compounds, iodine forms a normal sigma bond with a benzene ring and a formal double bond with the NSO_2R ligand, which is considered a two-center-four-electron bond (**Figure 5, A**).[38]

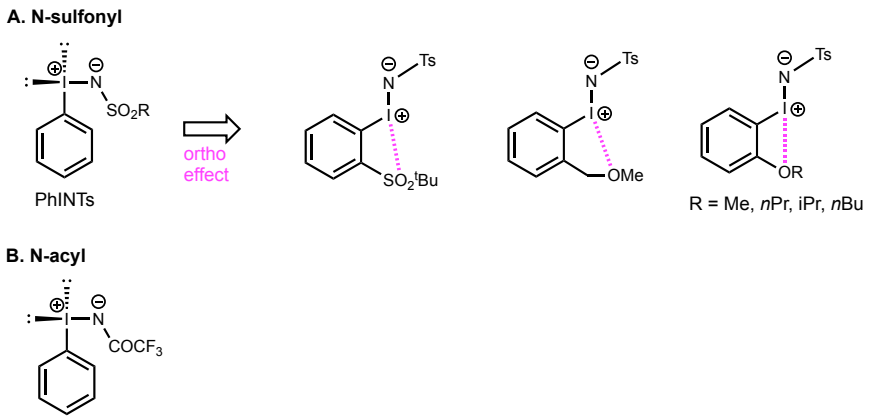
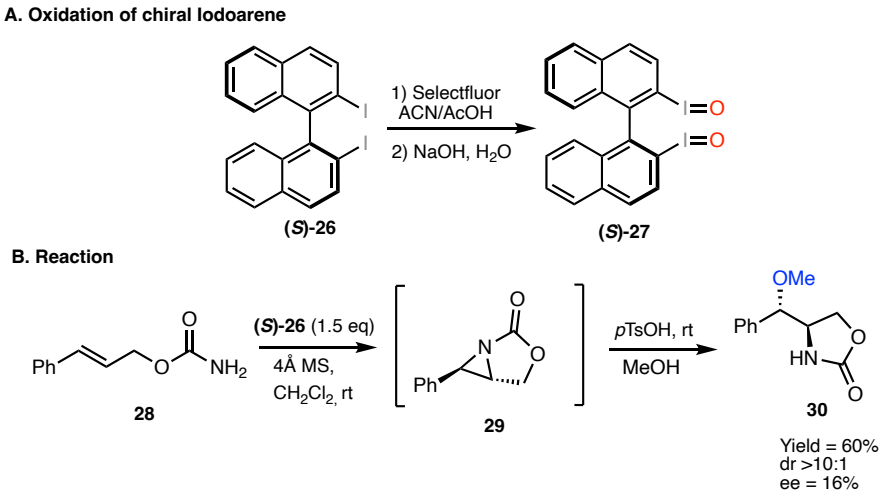


Figure 5. Representative iminoiodanes and the ortho effect.

One reason for the lack of publications on metal-free asymmetric aziridination of olefinic substrates using iminoiodane formation is the limited solubility of iminoiodanes in most organic solvents. Additionally, while most iminoiodanes are stable at room temperature, they need to be stored under an inert atmosphere at low temperatures due to their thermal sensitivity. Some of these compounds can be explosive, and violent decomposition can occur if they are melted. This sensitivity and potential hazard make them challenging to handle and work with in a laboratory setting.[38]

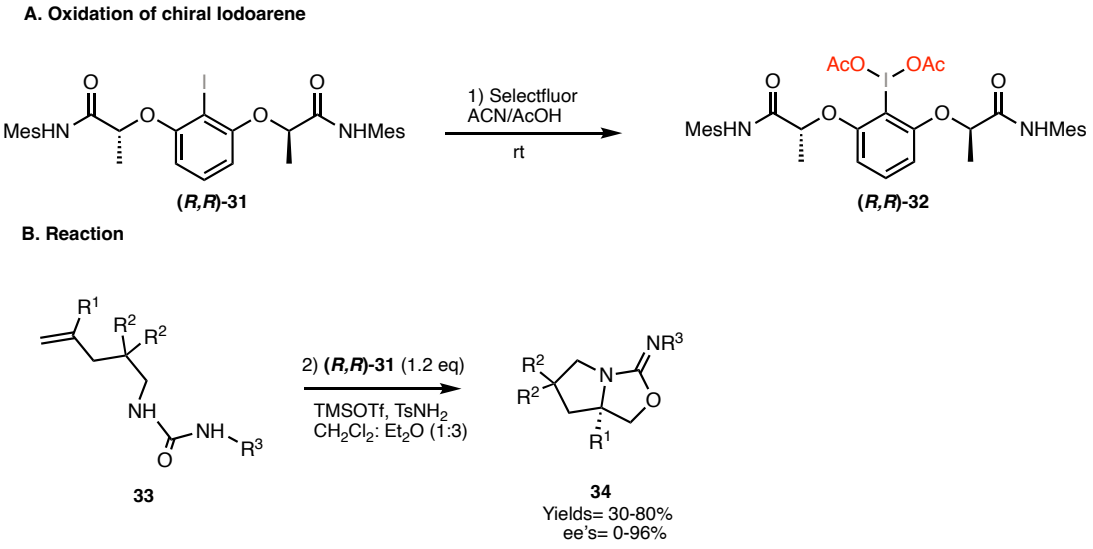
The limitations concerning their low solubility in organic sovents have been addressed by introducing an ortho-coordinating substituent.[39] Iminoiodinanes with ortho-sulfonyl groups,[40] alkoxy groups,[41] and methoxymethyl groups[42]have been developed as notable examples (**Figure 5, A**). Furthermore, most the reported *N*-protecting groups are limited to *N*-sulfonyl groups, and only one report has been made on the synthesis and reactivity of an *N*-acyliminoiodane presumably because of their lability toward Hofmann rearrangement and/or hydrolysis (**Figure 5, B**).[43]

Despite this, Xu, Che, and their team[44] reported the aziridination of allylic carbamates using the hypervalent diiodine(III) **(*S*)-27**, which they prepared by a straightforward modification of Kita's method,[45] using Selectfluor oxidation of (***S*)-26** (**Scheme 14**). The resulting aziridine **29** was subsequently opened with methanol in an acidic medium to produce product **30**, which had a satisfactory yield of 60% and high diastereoselectivity, but only 16% enantiomeric excess.



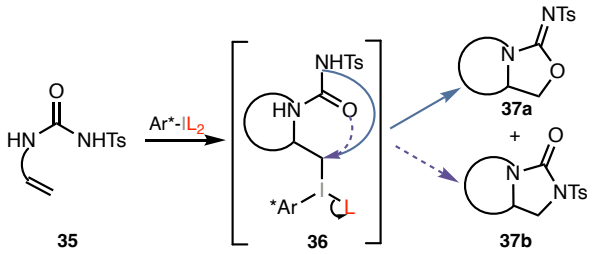
Scheme 14. Asymmetric aziridination by Xu, Che, and co-workers.

Later on, Wirth and colleagues[46] investigated the asymmetric intramolecular oxyamination of various *N*-substituted ureas with alkenes using chiral hypervalent iodine reagent chemistry (**Scheme 15**). For this purpose, they utilized the chiral λ^3-iodane (***R,R*)-32,** derived from the first-generation precatalyst (***R,R*)-31** reported by Ishihara and his team.[35] This reagent proved to be the most efficient catalyst for the reaction. The method produced bicyclic compounds **34** with good, isolated yields and moderate to good enantiomeric excesses. In these transformations, the addition of TMSOTf and $TsNH_2$ was crucial for achieving the desired results and selectivity. Specifically, adding *tert*-butyldimethylsilyl triflate (TBDMSOTf) or trimethylsilyl triflate (TMSOTf) to (diacetoxyiodo)benzene in situ were described to generate the more reactive $PhI(OTf)_2$, resulting in a significantly faster reaction with improved combined yields of up to 96%.



Scheme 15. Asymmetric Oxyamination by Wirth and Co-workers.

In this context, the general mechanism suggests that once the double bond is activated by the hypervalent iodine reagent, the first nucleophile reacts to form intermediate **35**. The hypervalent iodine group, now bonded to an sp^3-hybridized carbon atom, serves as an excellent leaving group, much more reactive than triflates or tosylates.[47] This subsequent substitution reaction directly leads to the formation of bicyclic compounds **36**. Depending on the reaction conditions, these cyclizations can produce either isoureas **37a** or diamination products **37b** (**Scheme 16**).[48]



Scheme 16. Cyclization of urea bisnucleophiles with alkenes using hypervalent iodine reagents (Ar-IL2) for the synthesis of isoureas **37a** or of cyclic ureas **37b**.

Subsequent nitrogen deprotection and basic cleavage of the isourea heterocycle intermediate ultimately provided access to enantioenriched vicinal amino alcohols. This protocol allowed for various backbone substitutions, though different nitrogen substituents yielded varying results.

In this regard, as part of the group's effort to develop new synthetic strategies for preparing unsaturated vicinal hetero-amino alcohols, which can be used as building blocks for synthesizing sphingosine analogues, we can employ these strategies for enantioselective aziridination and ring opening of dienyl carbamates using chiral hypervalent iodine reagents.

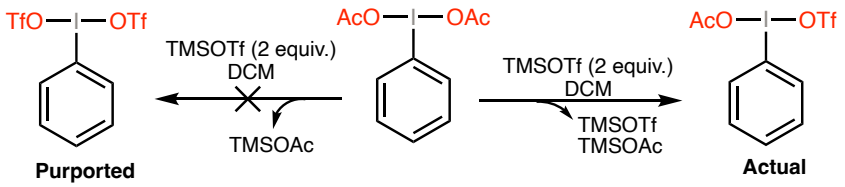
1.6. Enhancing the reactivity of chiral hypervalent iodine complexes

As previously mentioned, hypervalent iodine (III) reagents are extensively utilized as oxidizing agents in different chemical transformations. The oxidative capacity of $ArIL_2$ compounds can be enhanced by altering either the ligand (L) or the substituents on the aryl (Ar) group. Radzhabov and colleagues quantified this in a theoretical study that examined the effects of triflate and various acetoxy ligands.[49]

In this sense, commercially available $ArI(OAc)_2$ (+0.91 V) was found to be the least oxidizing among the derivatives studied, while $ArI(OTf)_2$ was the most oxidizing at +2.24 V. $ArI(OTFA)_2$ fell in between, with an oxidative capacity of +1.49 V. Generally, less nucleophilic ligands result in a greater oxidative capacity due to the more electron-poor iodine center. Modifying the aryl group by adding electron-withdrawing or electron-donating substituents also affects the oxidative capacity through electronic modulation. However, this effect is less pronounced than changing the ligand itself. For instance, with $ArI(OAc)_2$, a *para*-NO_2 substituent increases the oxidative potential to +0.97 V, while a *para*-methoxy

substituent decreases it to 0.88 V. Additionally, substituents on the ligand can significantly suppress decomposition processes, enhancing the stability of the complex.

Nevertheless, the true nature of the purported $PhI(OTf)_2$ is still debated, with some reports claiming the likely species is in fact PhI(OAc)(OTf) (**Scheme 17**).[50]



Scheme 17. Reaction of $ArI(OAc)_2$ with two equivalents of TMSOTf showing the formation of ArI(OAc)(OTf) instead of $ArI(OTf)_2$.

As previously discussed, chiral hypervalent iodine complexes exhibit the *trans* influence, which highlights their structural and electronic attributes. These complexes typically adopt a T-shaped geometry with two electronegative ligands positioned axially. This *trans* influence quantifies how a ligand weakens the bond opposite to itself in the complex's equilibrium state.[51]

In this regards, the stability of hypervalent iodine complexes $ArI(L_1,L_2)$ is closely linked to the mutual *trans* influence of the ligands L_1 and L_2 positioned axially (**Figure 6**). According to Ochiai et al.,[52] a *trans* configuration of L_1 and L_2 is more stable when both ligands exert moderate trans influence, or when one ligand has strong *trans* influence and the other weak. This principle helps explain the stability of complexes like $Ar[I(OAc)_2]$, where OAc represents a ligand with moderate *trans* influence. Conversely, it clarifies why complexes such as Ar[I(OAc)(OTf)], with a combination of moderate (OAc) and weak (OTf) *trans* influences, are more stable compared to $ArI(OTf)_2$, which exhibits lower stability due to its minimal *trans* influence. Futhermore, *trans* influences also seem to explain why iodosylbenzene, $(PhIO)_n$, adopts an oxo-bridged zigzag polymer structure in contrast to $PhI(OH)_2$, which is monomeric.[52]

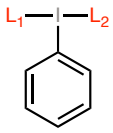


Figure 6. Acyclic hypervalent iodine with L_1 and L_2 in axial position.

In this regard, as part of the group's effort to develop new synthetic strategies for preparing unsaturated vicinal hetero-amino alcohols, which can be used as building blocks for synthesizing sphingosine analogues, we can employ these reported strategies for the enantioselective aziridination mediated by hypervalent iodine (III) reagents and ring opening of dienyl carbamates using chiral hypervalent iodine reagents.

2. AIMS AND OBJECTIVES

As part of our research group's efforts to develop new methods for the preparation of unsaturated vicinal hetero-amino moieties towards sphingolipid mimics, we aimed to investigate the application of lactate-based λ^3-iodanes **39** in the enantioselective aziridination of model dienyl carbamate **17**. According to literature, these lactate-based λ^3-iodanes have proven to be highly successful and efficient due to their ability to incorporate helical chirality around hypervalent iodine atoms. This property allows them to exert asymmetric control over the formation of the key vinylaziridine intermediate **18.**[35, 46] Consequently, our study proposes investigating several iodine(I) precursors with different substituted lactate units to facilitate the aziridination of diene **17**. Furthermore, we aim to compare various protocols for oxidizing these iodine(I) compounds to iodine(III), which can function as oxidants for conducting asymmetric aziridinations.

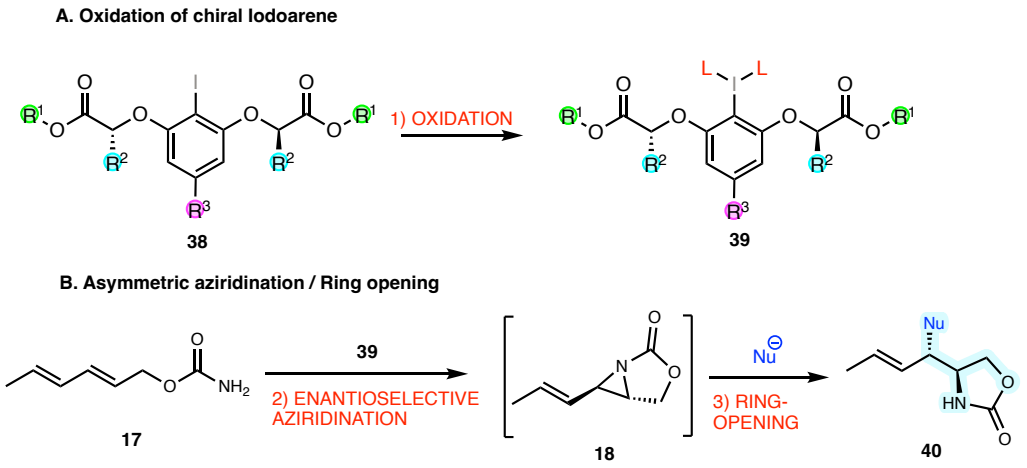
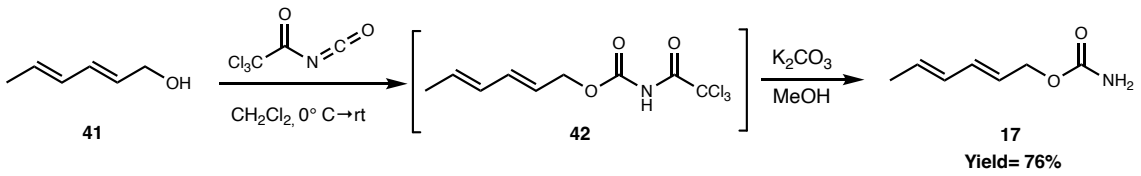


Figure 7. Proposed lactate-based λ^3-iodane reagents, followed by the asymmetric intramolecular aziridination of model dienyl carbamate **17**.

3. RESULTS AND DISCUSION

3.1. Synthesis of model dienyl carbamate

Model carbamate **17** can be synthesized by reacting commercially available (2*E*,4*E*)-hexa-2,4-dien-1-ol **41** with trichloroacetyl isocyanate (TAI) to form the corresponding trichloroacetyl carbamate **42** *in situ*, followed by methanolysis in the presence of K_2CO_3 (**Scheme 18**).[53]



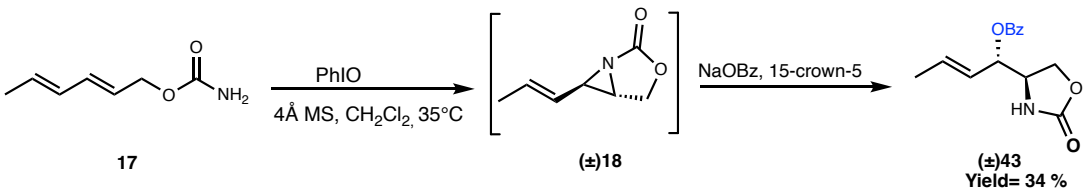
Scheme 18. Carbamoylation and methanolysis of dienyl allylic alcohols 41 to dienyl carbamates 17.

In this process, the final carbamate is purified using column chromatography and recrystallized by slowly diffusing pentane into a saturated THF solution, yielding a white solid in 76% yield. At first sight, the carbamate appears to be pure based on ^{1}H and ^{13}C-NMR after column chromatography. Despite that, a crystallization step is needed, as preliminary tests conducted by our group involving PhIO-mediated aziridination showed that using non-recrystallized substrates resulted in inconsistent outcomes, often producing significant amounts of a chlorinated byproduct. This byproduct likely originated from a chlorine-containing impurity undetectable by NMR.

3.2. PhIO mediated intramolecular diene aziridination of model dienyl carbamate /ring opening: HPLC optimization.

Based on previous research conducted by Dr. Irene Giménez[10], model carbamate **17** underwent an intramolecular aziridination in DCM using PhIO and 4Å molecular sieves. The vinylaziridine intermediate **(±)-18**, although stable under reaction conditions, was not isolated but was directly subjected to nucleophilic treatment to obtain the ring-opening product. After confirming the complete consumption of the starting carbamate through TLC monitoring, the aziridine ring-opening step was carried out. Sodium benzoate and 15-crown-5 were then added to the reaction mixture, resulting in the

formation of the substituted racemic mixture of benzoylated oxazolidinone **(±)-43**, which was obtained in a 34% yield (**Scheme 19**).



Scheme 19. One-pot intramolecular aziridination/ring-opening of model carbamate 16, following Gimenez-Nueno´s optimized conditions.[10]

Building on this research, the first strategy of our project involved optimizing chiral HPLC conditions to separate the racemic mixture of enantiomers obtained from the Gimenez-Nueno´s reported PhIO-mediated intramolecular diene aziridination of model dienyl carbamate and subsequent ring opening. Sodium benzoate was chosen as the external nucleophile for the ring-opening step due to its UV visibility, allowing for detection using the available HPLC-UV equipment.

To optimize the separation, we tested different chiral columns (see Suporting Information). The best conditions were achieved using a Chiralpak IC column with an 80:20 hexanes: ethanol mixture as the mobile phase at a flow rate of 1.0 mL/min and detection at 220 nm. Under these conditions, the enantiomers had a retention time (tr) of 15.1 and 16.8 minutes respectively. These results are in agreement with those previously reported by Gimenez-Nueno in her thesis.[54]

Based on previous results from the group's study on (*R*)-BTM-catalyzed kinetic resolution of oxazolidinones, we successfully identified the enantiomers in the racemic mixture. The oxazolidinones (***R,S*)-43** and (***S,R*)-43** were distinguished by their respective retention times (**Figure 8**).

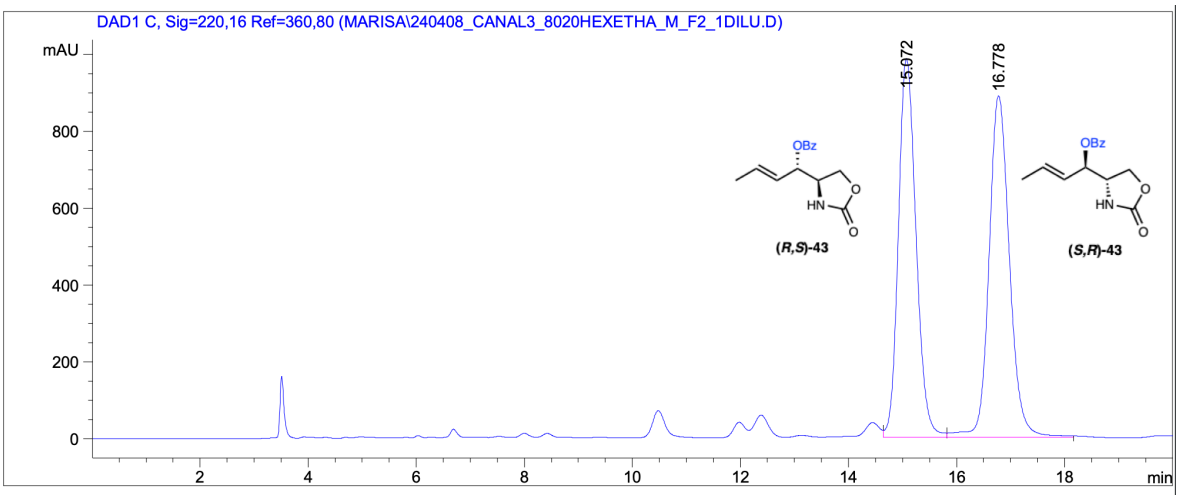


Figure 8. HPLC-UV chromatogram with separated racemic oxazolidinones **(*R*,*S*)-43** and **(*S*,*R*)-43**.

Then, in order to confirm the presence of our compound, a mass spectrometry experiment was conducted using electrospray ionization and an orbitrap detector. We were able to identify the protonated molecular ion $[M+H]^+$, the sodium adduct ion $[M+Na]^+$, and the protonated dimer ion $[2M+H]^+$ (**Figure 9**).

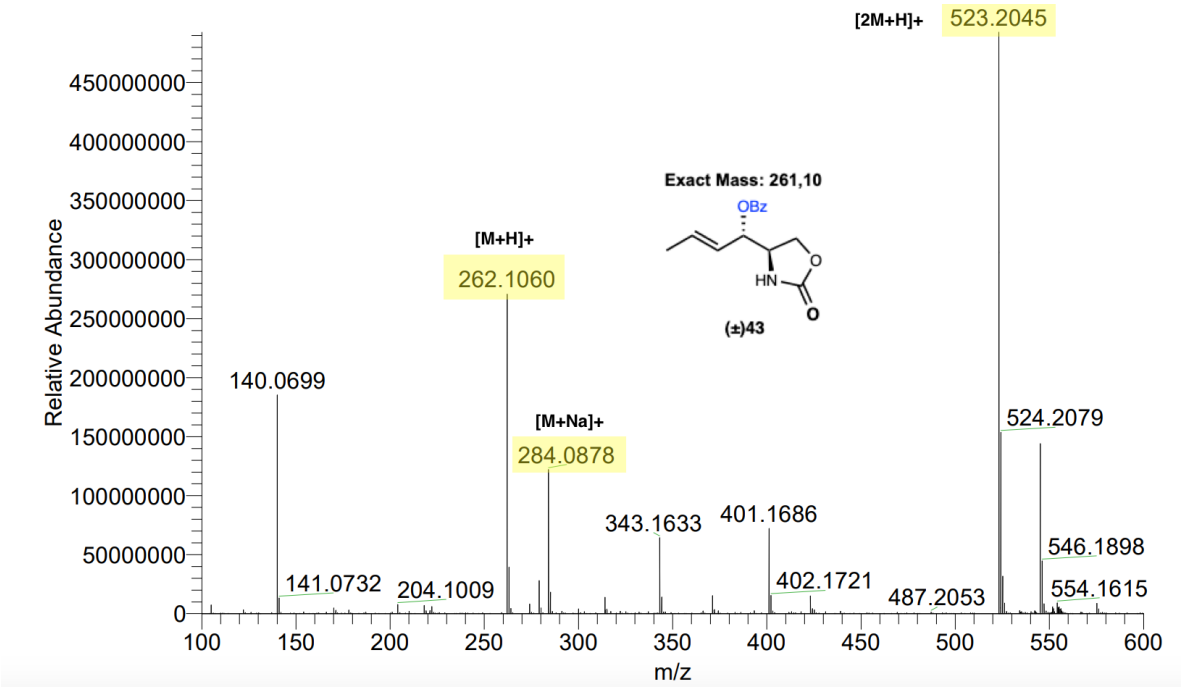


Figure 9. Mass Spectrum of oxazolidinone **(±)-43.**

After having studied the experimental procedure and gained experience with these reactions, as well as successfully optimizing conditions for the separation of the enantiomers, the initial studies on the asymmetric aziridination of model dienyl carbamate using chiral iodine-(III) reagents were initiated.

3.3. Synthesis of chiral resorcinol-lactate derivatives

Previously described by Fujita[34] and Ishihara,[35] incorporating helical chirality via C_2 symmetric structures around hypervalent iodine atoms has proven to be the most successful strategy for asymmetric hypervalent iodine-promoted oxidations. This success is also attributed to the method's versatility and the ease of introducing chemical modifications (R1, R2, R3).

Building on this approach, chiral lactate-based precursors **(*R,R*)-46a** to **(R,*R*)-50a** were prepared through the initial Mitsunobu reaction of 2-iodo-resorcinol **44** with various lactic acid derivatives **(*S*)-45** in moderate to high yields (**Figure 10**).

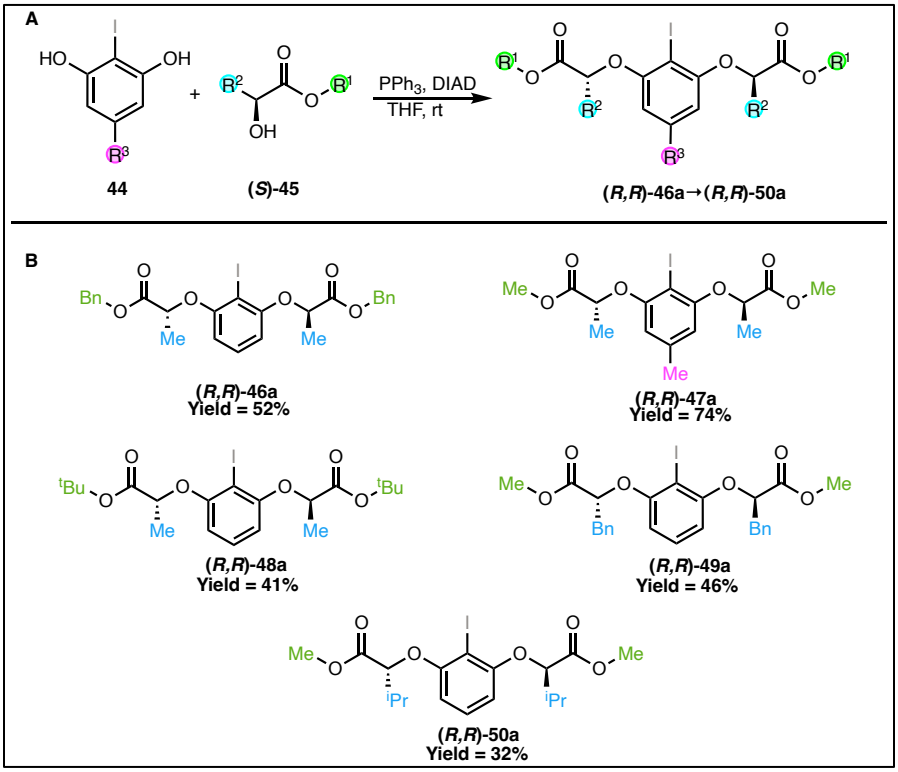
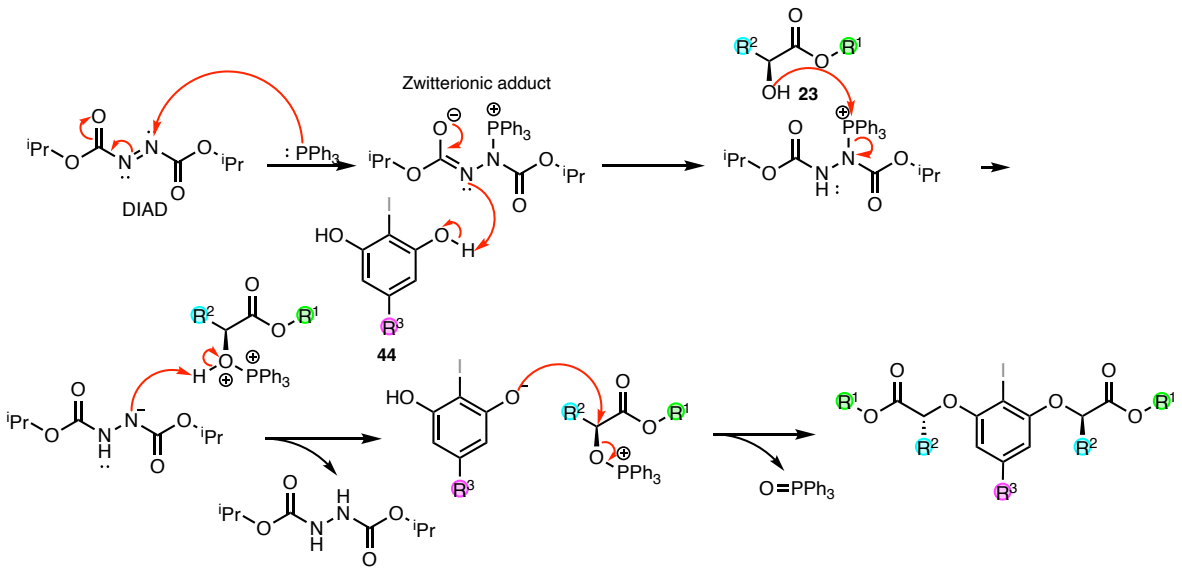


Figure 10. A. General Mitsunobu reaction for the synthesis of chiral resorcinol-lactate derivatives. B. Chiral resorcinol-lactate derivatives **(*R,R*)-46a** to **(*R,R*)-50a**.

The Mitsunobu reaction is a technique in organic chemistry used to convert primary or secondary alcohols into various compounds using diisopropyl azodicarboxylate (DIAD) or diethyl azodicarboxylate (DEAD), triphenylphosphine (PPh_3) and an acidic nucleophile, typically a carboxylic acid, phenol,

phthalimide or hydrogen azide.[55,56] In this process, triphenylphosphine initiates the reaction by attacking the azodicarboxylate, leading to the formation of a zwitterionic intermediate. This intermediate then deprotonates acidic 2-iodoresorcinol **44**. Subsequently, the less acidic secondary alcohol from (*S*)-lactic acid derivative **45** nucleophilic attacks the phosphonium ion, thus leading to an alkoxy phosphonium ion. This is an activated form of the alcohol toward nucleophilic attack, thus being ultimately attacked by the resorcinolate under S_N2 conditions. This sequence results in the desired substitution product with stereochemical inversion, yielding (*R*)-resorcinol-lactate derivatives. The reaction is driven forward by the formation of a triphenyl phosphine oxide $OPPh_3$ as a byproduct (**Scheme 20**).



Scheme 20. Mitsunobu reaction mechanism for the synthesis of chiral resorcinol-lactate derivatives.

3.4. Oxidation protocols for resorcinol-lactate based reagents.

After successfully obtaining the resorcinol-lactate based reagents **(*R,R*)-46a** to **(*R,R*)-50a**, the initial oxidation of these compounds was carefully studied to facilitate the subsequent asymmetric aziridination of the model dienyl carbamate. As described in the literature, a common method for preparing iodosylbenzene (PhIO) involves treating commercially available $PhI(OAc)_2$ with a 3N NaOH aqueous solution.[57] However, due to the chemical structure of resorcinol-lactate based reagents **(*R,R*)-46a** to **(*R,R*)-50a**, such strong basic conditions for the formation of the iodosoarene reagent must be avoided, as they can lead to racemisation of the stereogenic centres.[58] However, only a few examples have been reported, such as isolated chiral iodosylbenzene **51** and chiral iodosylbinaphthyl **52** (**Figure 28**).[46,44]

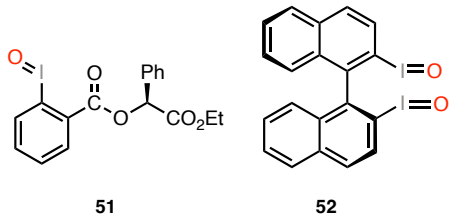


Figure 11. Chiral iodosylbenzene analogue and iodosylbinaphthyl analogues.

Alternatively, we turned our attention to widely applied chiral (diacetoxyiodo) arenes derivatives **(*R,R*)-46b** to **(*R,R*)-50b** as promoters for the asymmetric aziridination protocol (**Figure 29**).[46,35]

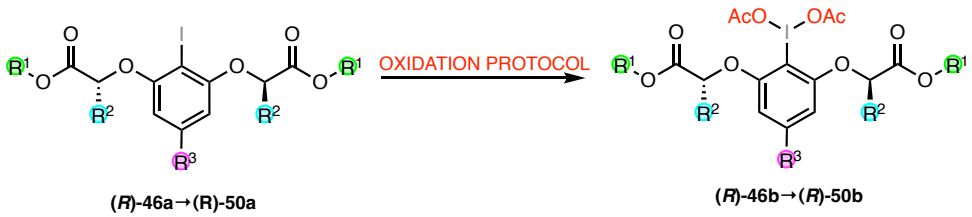


Figure 12. Oxidation of chiral resorcinol-lactate derivatives.

Oxidizing iodoarenes to create hypervalent iodine reagents is a complex process. The requirement for stoichiometric oxidizing agents not only diminishes the sustainability of the process due to the generation of toxic waste but also makes finding the appropriate oxidant challenging because of potential side reactions and by-product formation. Although m-chloroperbenzoic acid (*m*CPBA) is frequently used as an oxidant in modern synthesis, it often results in undesired epoxidation, particularly with electron-rich alkenes, rather than the intended difunctionalization by fluorine or acetate. This problem often necessitates the use of more expensive oxidants, such as Selectfluor. Furthermore, the purification of the final products becomes problematic due to the need to remove large quantities of oxidant by-products, like m-chlorobenzoic acid when *m*CPBA is used. This issue is exacerbated in large-scale reactions, making the process even more cumbersome.[59]

In this study, we compared different protocols for the oxidation of chiral resorcinol-lactate derivatives using the readily available aryl iodide **(*R,R*)-46**. We examined different protocols reported by Thomas Wirth and co-workers (**Table 1**).[46,60]

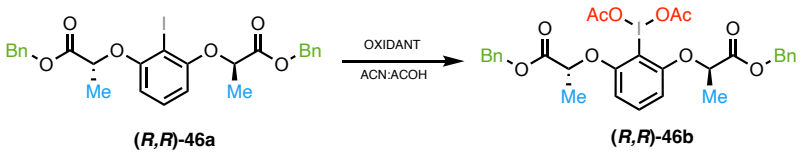
Following the protocols, using Selectfluor as an oxidant showed no significant differences during the reaction itself. These reactions are believed to proceed through the intermediacy of $ArIF_2$, which is either *in-situ* or subsequently treated with the reagent featuring the final ligand in the hypervalent iodine reagent, usually of acidic nature, namely AcOH for the formation of the $ArI(OAc)_2$. However, the work-up process varied. Protocol 1 involved concentrating the reaction under vacuum, adding water to dissolve

residual AcOH and Selectfluor, and washing with DCM, resulting in an 85% yield of the oxidized chiral resorcinol-lactate derivative (***R,R*)-46b**, with 15% remaining as the reduced form (***R,R*)-46a**.

In contrast, protocol **2**, involved concentrating the reaction under vacuum, dissolving the crude product in chloroform, and filtering under an argon atmosphere to remove Selectfluor remnants. The filtrate was then concentrated and washed with a 3:1 mixture of diethyl ether and n-hexane. Surprisingly, this method promoted the reverse reaction, yielding 29% of **(*R,R*)-46b** and 71% of the reduced product **(*R,R*)-46a**. We hypothesize that the reverse reaction was facilitated during the filtration over Celite.

Finally, we tested another protocol for the oxidation of chiral resorcinol-lactate derivative **(*R,R*)-46a** using meta-chloroperbenzoic acid as the oxidant while maintaining the same conditions as protocol **1**. This approach did not result in the identification of **(*R,R*)-46b**; instead, we observed a mixture of oxidized compounds that we were unable to identify.

Table 1. Oxidation protocols for chiral resorcinol-lactate based model **(*R,R*)-46a.**[a]



(*R,R*)-46a (*R,R*)-46b

Protocol	Oxidant	MeCN:AcOH	Conversion[b]
1	Selectfluor (5 equiv.)	76:24	85%
2	Selectfluor (5.5 equiv.)	75:25	29%
3	*m*-CPBA (2equiv.)	75:25	-

[a] General conditions: 1 equiv of **(*R,R*)-46a**, room temperature; 0.012 M [b]Determined by ^{1}H NMR by a relation between protons of the **(*R,R*)-46a** and **(*R,R*)-46b**.

The reactions were monitored using ^{1}H NMR. We confirmed the presence of the oxidized form by observing a new peak corresponding to acetate ligands at 1.90 ppm. Additionally, new signals in the aromatic region, slightly low-field shifted with respect to those of the starting iodoarene, were observed. Specifically, H4 and H6 were used as identification peaks, which showed chemical shifts of 6.31 ppm for **(*R,R*)-46a** and 6.49 ppm for **(*R,R*)-46b**, respectively **(Figure 13)**. Furthermore, due to the sensitive nature of the oxidized reagent **(*R,R*)-46b**, we quantified the conversion amount in the crude mixture by determining the ratio between the protons H4 and H6 of **(*R,R*)-46a** and **(*R,R*)-46b** without using an internal standard and used the crude mixture in the aziridination step without any further purification.

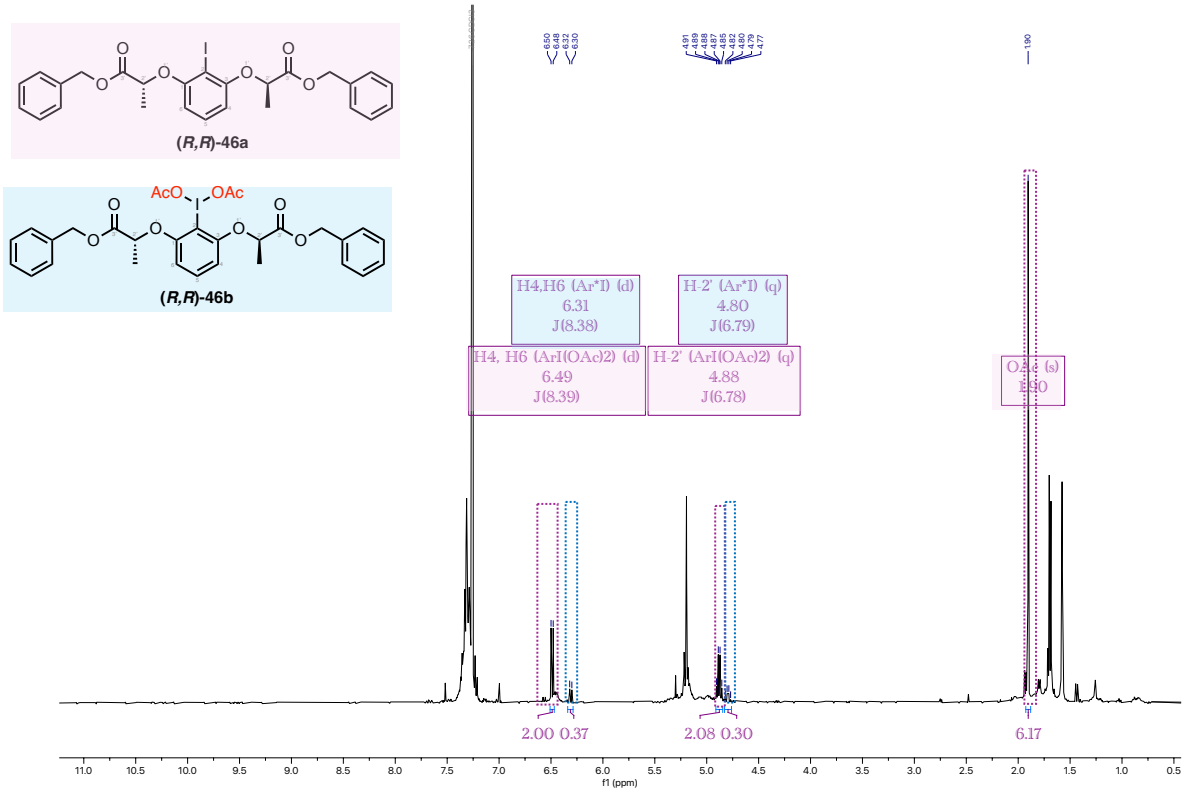


Figure 13. 1H NMR spectra of the mixture of ***(R,R)*-46a** and ***(R,R)*-46b**.

In conclusion, we selected protocol 1 utilizing Selectfluor as the oxidant because of its efficient work-up procedure and the high yield it produces.

3.5. Preliminary studies on the asymmetric aziridination of model dienyl carbamate using chiral iodine-(III) reagents.

3.5.1. Asymmetric Aziridination-ring opening using chiral iodine (III) reagents.

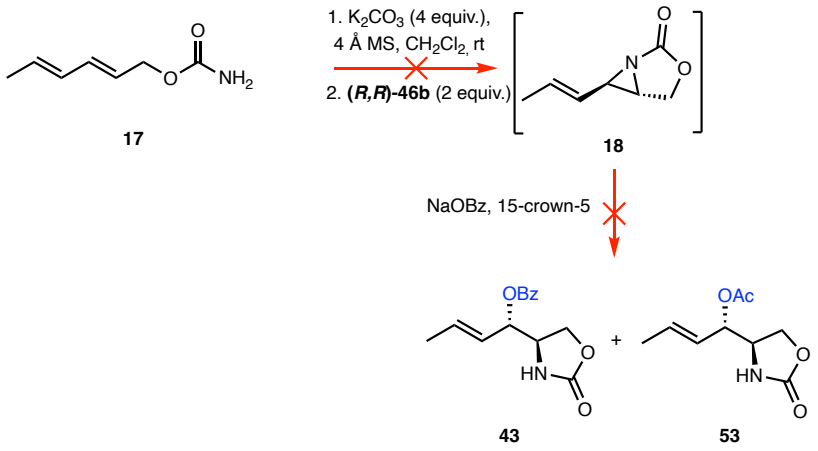
After selecting the oxidation protocol for chiral resorcinol-lactate derivatives, we began our initial trials for asymmetric aziridination using previously optimized conditions for $PhI(OAc)_2$-mediated intramolecular diene aziridination.

During this optimization, Gimenez-Nueno reported that the use of Lewis or Bronsted acids, such as boron trifluoride diethyl etherate ($BF_3{\cdot}Et2O$), triflic acid (TfOH), commonly used for the activation of diacetoxylated hypervalent iodine catalysts, promoted complete conversion of the starting material, but unfortunately., the desired oxazolidinone was never detected.

Fortunately, when K_2CO_3 was used as a basic additive for the intramolecular aziridination of carbamate **17**, oxazolidinone **(±)-18** was generated, but only in low yields. An external nucleophile was also required for the ring-opening step. It became evident that a basic reaction medium was necessary for the model

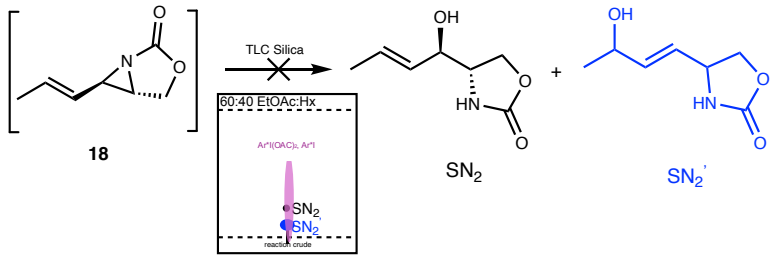
carbamate **17** to be effectively transformed into the key iminoiodane intermediate **55**. Consequently, four different inorganic bases were tested under optimized conditions: MgO, acetate salts, Cs_2CO_3, and potassium salts. Unfortunately, only cesium salts provided results similar to those obtained with K_2CO_3, with oxazolidinone **(±)-53** again formed in low yields. Thus, base screening did not yield improved results, and K_2CO_3 remained the base of choice for $PhI(OAc)_2$-mediated aziridination/ring-opening experiments.

Although reaction with $PhI(AcO)_2$ typically proceeds at 35 ºC, , dienyl carbamate **17** was treated with 2 equivalents of ***(R,R)*-46b** in dry CH_2Cl_2 at room temperature in order to favor enantioinduction (**Scheme 21**).[54]



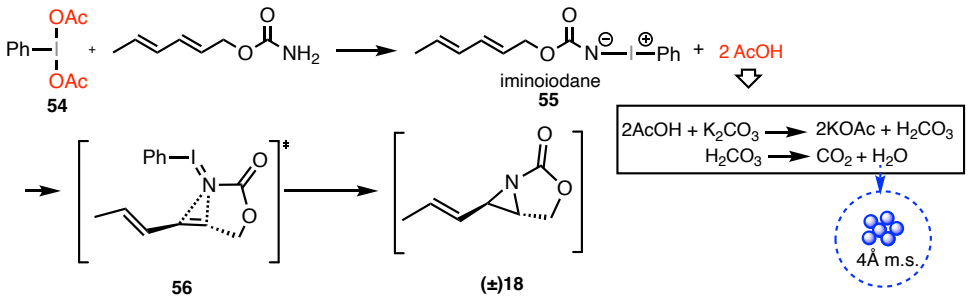
Scheme 21. Starting reaction conditions for asymmetric aziridination/ring-opening of model dienyl carbamate **17**.

Monitoring the progress of the reactions by TLC was challenging due to a massive spot caused by the hypervalent iodine reagent, which extended from the base up to an Rf of 0.65 on the plate. This hindered the identification of the aziridine intermediate, which should have appeared at the base. However, indirect evidence of aziridine formation was suggested by the appearance of two spots at approximately Rf 0.05 and Rf 0.1. These spots correspond to the silica gel-promoted ring-opening of the aziridine intermediate with water under S_N2 and S_N2' conditions. In addition to the desired product **43**, we expected to observe sub-product **53**, arising from the ring-opening of the aziridine caused by the acetate released by the hypervalent reagent (**Scheme 22**). Surprisingly, after 24 hours of stirring, we did not observe the formation of the desired oxazolidinone **43** or by-product **53**. Additionally, vinyl aziridine **18** was not detected by TLC, consistent with previous reports.



Scheme 22. Reaction and TLC analysis of the asymmetric aziridination crude indicating the formation of aziridine through the presence of S_N2 and S_N2' oxazolidinones resulting from the reaction of compound 18 with TLC silica.

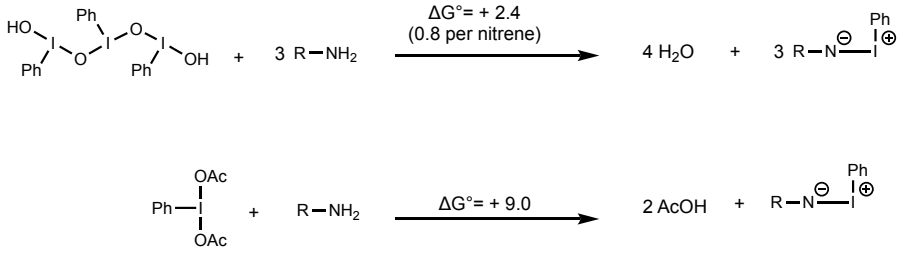
As described in the optimization of $PhI(OAc)_2$-mediated intramolecular diene aziridination, using K_2CO_3 as a basic additive is essential. It is expected to facilitate the formation of iminoiodane **55**, which subsequently promotes aziridine formation through a mechanism previously proposed by our group. Furthermore, the results obtained with K_2CO_3 in combination with molecular sieves can be explained by the shift in the unfavorable acid/base equilibrium, resulting in the formation of carbonic acid, which decomposes into CO_2 and water (**Scheme 23**).



Scheme 23. Proposed mechanism for the formation of aziridine from the iminoiodinane intermediate and the acid-base reaction of AcOH and K_2CO_3.

On the other hand, the role of the base can be better understood by referring to previous DFT calculations conducted in collaboration with Professor Maseras's research group. These calculations suggested that the conversion of the carbamate into the iminoiodane using $PhI(OAc)_2$ is significantly more endergonic ($\Delta G°$=+9.0 kcal/mol) compared to the analogous process using PhIO ($\Delta G°$=+2.4 kcal/mol, 0.8 kcal mol^{-1}/nitrene) using a trimer model for the iodosobenzene reagent (**Scheme 24**).[54]

These results align with the lower experimental reactivity observed for $PhI(OAc)_2$ compared to PhIO. We attribute this behavior to the low basicity of the corresponding acetate moiety in the PIDA.

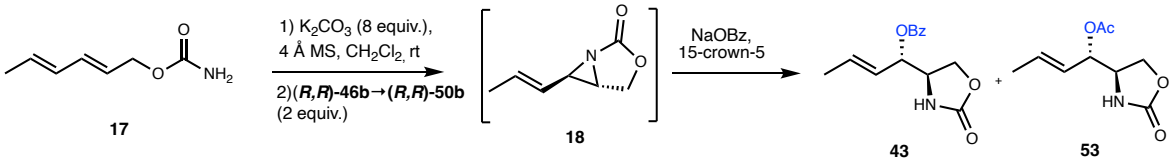


Scheme 24. Thermodynamics of the iminoiodinane formation from PhIO trimeric structure and $PhI(OAc)_2$. Free energies in kcal mol^{-1}.

We next performed the asymmetric aziridination reaction with a large excess of K_2CO_3 (8 equivalents). To our delight, after 24 hours of reaction, TLC analysis indicated the formation of aziridine, although some starting dienyl carbamate was still present. Consequently, we allowed the reaction to continue until the starting material disappeared, which took a total of 52 hours. Then, we applied the ring-opening protocol with sodium benzoate and 15-crown-5, obtaining a 25% isolated yield of **43** and a 15% isolated yield of the acetoxy ring-opening product **53**. Due to the small quantity of product relative to the chiral iodine (III) reagent used, we were unable to perform a quantitative NMR analysis on the crude product.

Afterward, we analyzed the enantiomeric mixture using HPLC-UV under previously optimized conditions, revealing a 69:31 **(*R,S*)-43:(*S,R*)-43** enantiomeric ratio (**Table 2, Entry 1**). Additionally, it is noteworthy that we successfully recovered 25% of the initial chiral resorcinol-lactate derivative **(*R,R*)-46a** after purification.

Table 2. Asymmetric aziridination of model dienyl carbamate **17** using lactate-based iodine (III) compounds **(*R,R*)-46b** to **(*R,R*)-50b**.[a]



Entry	Iodine (III) reagent	Yield (%) 43 [b]	Yield (%) 53 [c]	er [d]
1	(*R,R*)-46b	25	15	69:31
2	(*R,R*)-47b	7	15	68:32
3	(*R,R*)-48b	-	18	-
4	(*R,R*)-49b	6	28	73:27
5	(*R,R*)-50b	5	30	72:28

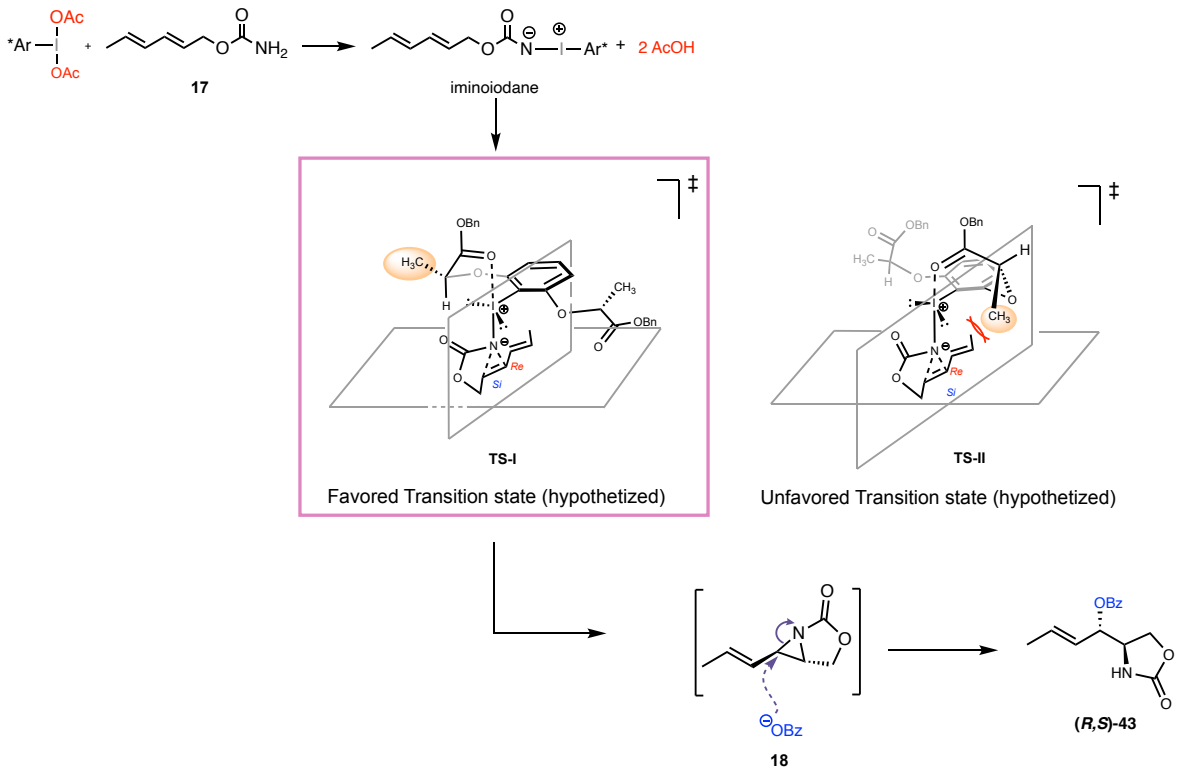
[a] Carbamate **16** (1 equiv.), K2CO3 (8 equiv.), 4Å M.S. (100 mg per 0.1 mmol carbamate 16), **(*R,R*)-46b → (*R,R*)-50b** (2 equiv.), CH_2Cl_2 (0.04M), r.t. Ring-opening: NaOBz(5 equiv.)/15-crown-5 (1equiv.)(6 drops:1.5 mL). [b], [c] Isolated yield. [d] Enantiomeric ratio **(*R,S*)-43**: **(*S,R*)-43** determined by chiral HPLC-UV.

At this stage of the asymmetric study, we aimed to evaluate the efficiency of other chiral lactate-based iodine (III) reagents (***R,R*)-46b** to (***R,R*)-50b** under our reaction conditions. To achieve this, we oxidized previously synthesized chiral resorcinol-lactate derivatives **(*R,R*)-46a** to **(*R,R*)-50a** using Selectfluor and $AcOH/CH_3CN$ following the established protocol **1**.[46]

As a result, we obtained oxazolidinone **43** in slightly improved enantioselectivities for reagents **(*R,R*)-49b** and **(*R,R*)-50b** (Table 2, entries 4 and 5), featuring slightly more bulky alkyl groups at the α-position of the ester moiety (R2) , namely a benzyl and an isopropyl group and unhindered alkoxy moieties (R1). However, very low yields were observed. This might be attributed to the low reactivity of these lactate-based iodine reagents, possibly due to their high steric hindrance, compared to the reference $PhI(AcO)_2$ reagent. Additionally, reduced electrophilicity of the reagent due to the presence of alkoxy ligand in the arene moiety could not be discarded. The enantioselectivity outcome in the formation of sub-product oxazolidinone **53** was not determined due to its UV-inactivity**.** An alternative strategy to prevent the formation of mixtures of reaction products would involve the use of sodium acetate as a nucleophile for the ring-opening step. However, since this compound is not UV-visible and HPLC-UV could not be used, this strategy would require hydrolysis of acetate **53** to the corresponding alcohol, followed by derivatization of the latter with a UV-active acyl chloride, such as benzoyl chloride, to furnish a UV-active product amenable for analysis by HPLC-UV. However, we did not undertake this process due to time constraints.

Furthermore, since the configuration of the major enantiomer was previously determined via kinetic resolution as **(*R,S*)-43**, we hypothesized a transition state to understand how these hypervalent iodine (III) reagents induce chirality in the formation of the aziridine intermediate. The formation of an iminoidane is hypothesized arising from ligand exchange of one acetate ligand by the carbamate ligand followed by departure of the second acetate ligand, as a consequence of the moderately high *trans* influence of the carbamate ligand, destabilizing the intermediate acetoxy-*N*-dienyloxy-carbonyl-iodane. As previously reported by many authors, we envisioned that the iminoiodane could be stabilized through coordination of the carbonyl moiety in the lactate side chain *trans* to the carbamate ligand. Additionally, intramolecular $n-\sigma^*$ [36] secondary interactions between the electron-deficient hypervalent iodine (suitable from σ* of C-I) and the lone pair of the carbonyl group of the carbamte could not be discarded, in a similar ways to that described for N-trifluoroacetyl-iminoiodanes.[39] As shown in **Scheme 25**, preferential formation of enantiomer **(*R, S*)-43** involves the nitrene addition through the Si face of carbon 2 and the Re face of carbon 3.

The chiral helicity created by these centers provides an ideal environment for achieving enantioselective oxidations. The terminal functional group on the ester sidechain can influence this chiral environment through its steric bulkiness and electronic interactions. Thus, favoring this enantiomer, also modifying these terminal functional groups effectively tunes the stereoselectivity in oxidative transformations. Taking into account that in our case increasing the bulkiness of the side chain on R2, a slight increase in the enantioselectivity was observed a speculative model for the transition state was devised. The purportedly preferred transition state (TS-I) would involve the interaction of the ester side chain with iodine moiety leading to minimal steric interactions with the carbamoyl moiety, so that the alkyl group in the α-position of that ester pointing away from it. Additionally, TS-I would be also benefited by π-stacking interactions of the distal double bond with the aryl moiety. Participation of the other lactate side chain interacting on the top face would alternatively lead to a sterically more hindered TS (TS-II), likely to be less stable in energy. (**Table 2, entries 4 and 5**).



Scheme 25. Proposed transition state for the facial selectivity of lactate-based hypervalent iodine (III) reagents.

3.5.2. In situ oxidation/asymmetric aziridination-ring opening using chiral iodines (III) reagents

After observing the sensitive nature of hypervalent iodine (III) reagents and noting the presence of both the chiral resorcinol-lactate derivative **(*R,R*)-46a** and its oxidized form **(*R,R*)-46b** after work-up using

oxidation protocol **1**, we opted to proceed with the oxidation of the chiral iodide without further purification. In this approach, 2 equivalents of the iodine(I) precursor **(*R,R*)-46a** were oxidized using 5 equivalents of Selectfluor in an AcOH/CH_3CN solvent system. Upon confirming complete conversion to the chiral iodine (III) reagent **(*R,R*)-46b** and the disappearance of Selectfluor by ^1H NMR, we utilized the product directly after solvent removal, thereby avoiding the need for further purification and circumventing the work-up protocol.

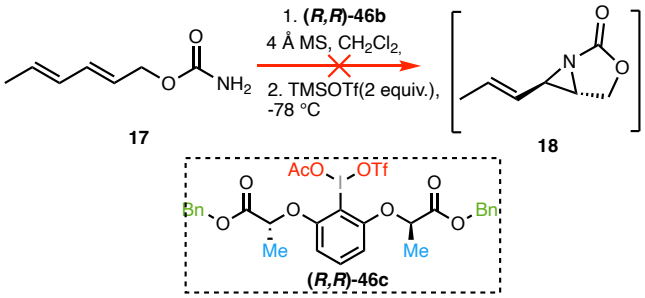
After applying this protocol for the asymmetric reaction, we achieved complete conversion of the starting material **17**. However, we did not observe the formation of the aziridine intermediate **18** or the oxazolidinones **43** and **53**. We hypothesized that the remaining reduced form of Selectfluor might be interacting with carbamate **17**, thereby promoting the decomposition of the starting material.

Also, to minimize waste of the chiral iodine reagent, we adjusted the concentration of **(*R,R*)-46b** to 1.1 equivalents. Unfortunately, despite this adjustment, we still did not observe the formation of the intermediate **18** or the oxazolidinone products **43** and **53**.

3.5.3. Enhancing oxidative capacity of chiral iodine (III) reagents by Ligand interchange

Following the promising results obtained from the asymmetric aziridination using chiral iodine (III) reagents, one notable disadvantage was the lengthy reaction time of 52 hours. To address this, we aimed to increase the oxidative capacity of these reagents by replacing the moderately electron-withdrawing OAc ligands with electron-withdrawing OTf ligands. Generally, less nucleophilic ligands result in greater oxidative capacity due to the more electron-poor iodine center.

Following the protocol established by Thomas Wirth and colleagues for stereoselective metal-free oxyaminations using chiral hypervalent iodine reagents, TMSOTf was used as additive in order to boost the reactivity of the hypervalent iodine reagent through the postulated *in-situ* formation of the more reactive **(*R,R*)-46c**. In this case, we avoided using K_2CO_3 to prevent a neutralization reaction with TMSOTf. Unfortunately, after 12 hours of reaction, we did not observe the formation of the dienyl aziridine **18**. Even after 72 hours, **18** did not form, and we found the model carbamate **17** and the chiral hypervalent iodine reagent **(*R,R*)-46b** intact (**Scheme 26**). In contrast to the studies described by Wirth successfully using of this additive starting from tosyl amides, the presence of a basic carbamate moiety in our substrate might led to the formation of a Lewis acid-base complex with the additive, thus preventing the formation of (***R,R*)-46c**.



Scheme 26. Asymmetric aziridination of a model dienyl carbamate by promoting the formation of **(*R*)-46c** *in situ*.

Subsequently, we added an excess of 8 equivalents of K_2CO_3 to neutralize the reaction and promote aziridine formation via the iminoiodinane intermediate **55**. After 48 hours, we observed the formation of **18**. Then, we performed the ring-opening protocol, followed by purification and HPLC-UV analysis, achieving a 73:27 enantiomeric ratio of **(*R,S*)-43**:**(*S,R*)-43**.

These results corroborate that the reaction is favored under basic conditions, which are crucial for the reaction to proceed and for the formation of the iminoiodinane intermediate **55**. Activation of the hypervalent iodine reagent through ligand exchange under protonolysis conditions proved incompetent using dienyl carbamates as substrates, probably due to the basic nature of carbamate functionality in comparison to tosyl amides.

4. CONCLUSIONS

We established a protocol for the oxidation of resorcinol-lactate-based reagents (I) and successfully developed a new asymmetric method for preparing enantioenriched vinylaziridine intermediates. This method builds on the previously reported optimization of one-pot $PhI(OAc)_2$-mediated aziridination/ring-opening of model dienyl carbamate, where the use of K_2CO_3 as a basic additive proved pivotal in promoting the formation of oxazolidinone.

The essential role of K_2CO_3 in the $PhI(OAc)_2$-mediated intramolecular diene aziridination is highlighted by its ability to facilitate the formation of iminoiodane **55**, subsequently promoting aziridine formation. This effect is attributed to the shift in the unfavorable acid/base equilibrium, resulting in the formation of carbonic acid, which decomposes into CO_2 and water.

Applying the protocol to lactate-based resorcinol-lactate reagents (III) **(*R,R*)-46b** to **(*R,R*)-50b** demonstrated promising enantiocontrol but resulted in poor reaction yields. This was mainly due to the formation of oxazolidinone **53** from the ring-opening of the aziridine by acetate released from the hypervalent reagent. Additionally, the reduced reactivity of these lactate-based iodine reagents is likely due to high steric hindrance and decreased electrophilicity caused by an alkoxy ligand in the arene moiety.

Furthermore, based on the major enantiomer's configuration, determined as **(*R,S*)-43**, we hypothesized a transition state to explain how hypervalent iodine (III) reagents induce chirality in aziridine intermediate formation. Nitrene addition occurs through the Si face of carbon 2 and the Re face of carbon 3, with intramolecular $n-\sigma^*$ interactions between the hypervalent iodine and the carbonyl group's lone pair of electrons on the lactate. In this sense, the chiral helicity provided by these centers creates an ideal environment for enantioselective oxidations. The ester side chain's terminal functional group influences this chiral environment through its steric bulkiness and electronic interactions, favoring one enantiomer. Adjusting these terminal functional groups effectively tunes stereoselectivity. Increasing the side chain bulkiness on R2 and decreasing it on R1 in the lactate-based hypervalent iodine (III) reagents improved selectivity.

Finally, initial attempts to enhance the oxidative capacity of chiral iodine (III) reagents were unsuccessful. However, these results helped corroborate that the reaction is favored under basic conditions, which are crucial for the reaction to proceed and for the formation of the iminoiodinane intermediate **55**. Activation of the hypervalent iodine reagent through ligand exchange under protonolysis conditions proved ineffective using dienyl carbamates as substrates, likely due to the basic nature of the carbamate functionality compared to tosyl amides.

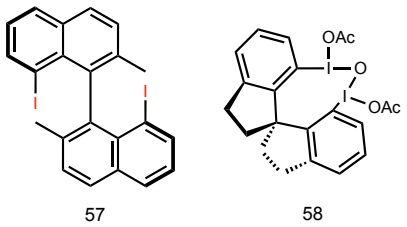
5. FUTURE PROSPECTS

An alternative strategy to improve the reaction yield of this asymmetric aziridination-ring opening of dienyl carbamates using chiral iodine (III) reagents is to prevent the formation of mixtures resulting from the ring-opening reaction by using sodium acetate as a nucleophile for the ring-opening step. However, since sodium acetate is not UV-visible, we can collaborate with the mass-spectrometry facility at ICIQ to use HPLC-TOF for analysis.

Another strategy to improve the reaction yield involves the hydrolysis of acetate **53** to the corresponding alcohol, followed by derivatization with a UV-active acyl chloride, such as benzoyl chloride, to produce a UV-active product suitable for analysis by HPLC-UV.

Additionally, solvent screening can be employed to increase the enantiomeric ratio and yield. Adjusting the terminal functional groups of lactate-based chiral iodine (III) reagents can effectively tune stereoselectivity. Specifically, increasing the side chain bulkiness on R_2 and decreasing it on R1 in the lactate-based hypervalent iodine (III) reagents has shown improvements in selectivity.

Also, we can use other hypervalent iodine (III) reagents (**Figure 14**) reported by Kita, which have shown promising results in asymmetric hypervalent iodine(III) oxidation. These reagents can also be applied to the asymmetric aziridination-ring opening of dienyl carbamates.



57 58

Figure 14. hypervalent iodine (III) reagents reported by Kita and co-workers.

6. EXPERIMENTAL SECTION

A. General Information

Proton nuclear magnetic resonance (1H NMR) spectra were obtained using Varian Mercury VX400 or Varian NMR System 400 spectrometers, operating at 400 MHz and 100 MHz, respectively, with CDCl3 as the solvent. Chemical shifts (δ) were calibrated using internal standards in CDCl3 (7.26 ppm for 1H)

High-performance liquid chromatography with diode-array detection (HPLC-DAD) spectra were recorded using an Agilent 1200 liquid chromatograph paired with a G1315D Diode Array Detector from Agilent Technologies.

Reactions were monitored via thin-layer chromatography (TLC) on 0.25 mm Merck® silica gel 60 F254 aluminum plates, with the developed plates visualized under short-wave UV light (254 nm) and by heating after immersion in a solution of p-anisaldehyde in ethanol/H2SO4/AcOH (90:3:1).

Liquid chromatography-mass spectrometry was conducted using a Thermo Scientific™ Exploris mass spectrometer equipped with an HESI interface, paired with a Vanquish UHPLC Liquid Chromatograph. For MS detection, the heated electrospray ionization parameters were configured for both positive and negative ionization modes as follows: source voltage at 3.5 kV (positive) and 2.8 kV (negative); sheath gas (N2) flow rate at 45 a.u.; auxiliary gas (N_2) flow rate at 15 a.u.; sweep gas (N_2) flow rate at 1 a.u.; s-lens RF level at 60%; SCAN mode; resolution set to 60000 (at m/z 200); AGC target set to standard mode; maximum injection time of 180 ms; and scan range from 100 to 600 m/z. Xcalibur 4.4 software (Thermo Scientific) was utilized for instrument control and data processing.

All reactions conducted under anhydrous conditions utilized oven-dried equipment and were performed in an argon atmosphere. Brine refers to a saturated sodium chloride solution. Anhydrous sodium sulfate (Na_2SO_4) was employed as a drying agent during reaction work-up as specified. All reagents were sourced from Sigma Aldrich, Apollo Scientific, and Fluorochem chemical companies.

B. General Procedures

General procedure for one-pot PhIO mediated Aziridination/Ring- Opening.[10] A flame-dried Schlenk flask containing a magnetic stirring bar was charged with activated 4Å molecular sieves (100 mg per 0.1 mmol carbamate) in distilled DCM (0.04 M) under an argon atmosphere. Dienyl carbamate (0.1 mmol) and PhIO (0.2 mmol) were added, and the heterogeneous mixture was stirred at 35°C until TLC indicated complete consumption of the starting material, unless specified otherwise in the procedure. A nucleophile was then added, and the reaction mixture was stirred overnight. The crude solution was filtered over celite, thoroughly washed with DCM, and concentrated under reduced pressure. The yield over the two steps was determined after purification by column chromatography purification. Initially, the crude reaction mixture was purified through a short column chromatography (8-10 cm) to prevent product decomposition from prolonged contact with silica gel.

General procedure for the preparation of lactate-based chiral aryliodide precursors.[62] To a solution of 2-iodobenzene-1,3-diol or 2-iodo-5-methylbenzene-1,3-diol (8.0 mmol), Ph_3P (18.4 mmol), and a chiral lactate derivative (16.8 mmol) in THF (80 mL) at 0°C, DIAD (18.4 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. Once the starting material was completely consumed, the solvent was removed under reduced pressure, and Et_2O (40 mL) was added. The triphenylphosphine oxide was removed by filtration, the filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography.

General procedure for the oxidation of lactate-based chiral aryliodide precursors (protocol 1).[63] Lactate-based chiral aryliodide (191.7 mg, 0.25 mmol) and Selectfluor (885 mg, 2.5 mmol) were dissolved in ACN (16 mL) and glacial acetic acid (5 mL) under argon atmosphere. The reaction mixture was stirred at room temperature overnight. After that, the mixture was concentrated under vacuum, and water (25 mL) was added to the residue. The aqueous phase was extracted with ACN (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield the oxidized lactate-based chiral aryliodide.

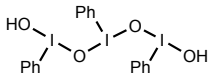
Procedure for the oxidation of lactate-based chiral aryliodide precursors (protocol 2).[60] Lactate-based chiral aryliodide (237.7 mg, 0.4 mmol) and Selectfluor (836.8 mg, 2.4 mmol) were dissolved in ACN (14 mL) and glacial acetic acid (4 mL) under an argon atmosphere. Upon completion of the reaction, the solvents were evaporated under vacuum, and the resulting product was dissolved in $CHCl_3$. The solution was then filtered under a nitrogen atmosphere, the filtrate was concentrated under reduced pressure, and the residue was washed with a 3:1 mixture of Et_2O/n-hexane to yield the pure product.

Procedure for the oxidation of lactate-based chiral aryliodide precursors (protocol 3). Lactate-based chiral aryliodide (213 mg, 0.4 mmol) and mCPBA(138 mg, 0.8 mmol) were dissolved in ACN (14 mL) and glacial acetic acid (4 mL) under an argon atmosphere. The reaction mixture was stirred at room temperature overnight. After that, the mixture was concentrated under vacuum, and water (25 mL) was added to the residue. The aqueous phase was extracted with DCM (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield the oxidized lactate-based chiral aryliodide.

General procedure for one-pot Ar*I(OAc)$_2$ mediated Aziridination/Ring- Opening. A flame dried Schlenk containing a magnetic stirring bar was charged with oven dried K_2CO_3 (0.8 mmol), activated 4A° M.S. (100 mg / 0.1 mmol carbamate), carbamate (0.1 mmol) and Ar*I(OAc)$_2$ in deoxygenated DCM (0.04 M) under argon atmosphere. ArI(OAc)$_2$ (0.2 mmol) was added and the crude mixture was left at room temperature until TLC showed complete consumption of the carbamate (c.a. 72 hours). The ring-opening step was then performed using sodium benzoate (0,5 mmol), and the reaction mixture was stirred overnight. The crude solution was filtered over celite, thoroughly washed with DCM, and concentrated under reduced pressure. The yield over the two steps was determined after purification by column chromatography purification. Initially, the crude reaction mixture was purified through a short column chromatography (8-10 cm) to prevent product decomposition from prolonged contact with silica gel.

C. Compound characterization

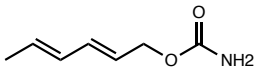
Iodosylbenzene (PhIO).[64]



PhIO

A sodium hydroxide solution (3N, 20 mL) was gradually added over 10 minutes to finely ground recrystallized (diacetoxyiodo)benzene (4.0 g, 12.4 mmol) in a 100 mL beaker with vigorous stirring. The reaction mixture was kept at room temperature until completion, approximately 45 minutes. Then, water (15 mL) was added, and the resulting solid iodosylbenzene was filtered using a Büchner funnel. The wet solid was returned to the beaker, triturated with water (25 mL), filtered again using the Büchner funnel, washed with water, and dried overnight under vacuum. The final purification involved triturating the dried solid with chloroform (10 mL) in a beaker, filtering it, and drying under vacuum, yielding 2.0 g (75% yield) of iodosylbenzene as a yellow powder.

(2*E*,4*E*)-hexa-2,4-dien-1-yl carbamate (17).[61,10]

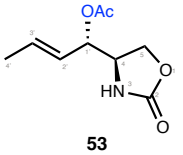


17

Trichloroacetyl isocyanate (TAI) (0.25 mmol, 0.3 mL) was added dropwise to a stirred solution of commercially available (2E,4E)-hexa-2,4-dien-1-ol (0.27 mL, 2.39 mmol) in dry dichloromethane (5 mL) at 0°C. The mixture was allowed to stir at room temperature until TLC indicated the starting alcohol was fully consumed. Subsequently, a 20 mol% solution of K_2CO_3 in MeOH (3 mL per mmol of alcohol) was added, and the mixture was stirred at room temperature for 3 hours. After evaporating the solvent, the residue was dissolved in a 1:1 mixture of diethyl ether and brine. The aqueous phase was extracted with diethyl ether, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified via column chromatography using a solvent gradient of 30:70 → 50:50 AcOEt/hexanes. Compound **17** was then recrystallized by slow diffusion of pentane into a THF solution of the carbamate, yielding 0.26 g (76% yield) as a white powder.

Rf = 0.20 (30:70 AcOEt/Hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.25 (dd, *J* = 15.2, 10.36 Hz, 1H, H-3), 6.05 (ddd, *J* = 15.12, 10.36, 1.78 Hz, 1H, H-4), 5.76 (dq, *J* = 14.2, 6.7 Hz, 1H, H-5), 5.62 (dt, *J* = 15.2, 6.6 Hz, 1H, H-2), 4.65 (brs, 2H, NH_2), 4.56 (d,d *J* = 6.61, 1,24 Hz, 2H, H-1), 1.76 (dd, *J* = 6.7, 1.6 Hz, 3H, H-6). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 156.8 (C=O), 134.8 (C-3), 131.3 (C-5), 130.5 (C-4), 124.1 (C-2), 65.7 (C-1), 18.3 (C-6). The spectroscopic data are in agreement with a previous report.[10]

u-4-[(*E*)-1-acetoxybut-2-en-1-yl]-oxazolidin-2-one (53).

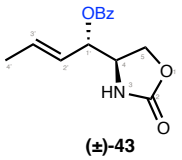


53

The title compound is a by-product resulted from the ring-opening of the aziridine caused by the acetate released by the hypervalent reagent, and it was synthesized using a **(*R,R*)-46b** mediated aziridination and ring-opening procedure, starting with carbamate **17** (32mg, 0.227 mmol) and Ar*I$(OAc)_2$ (300 mg, 0.453 mmol). A mixture of solid sodium benzoate (164mg, 1.135 mmol) and 15-crown-5 (45 μL, 0.227 mmol) was used as the nucleophile. The crude solution was filtered over celite, washed with DCM and concentrated under reduced pressure. The product was purified by column chromatography (100 → 40:60 Hexanes/AcOEt), yielding 15 mg (15% yield) of oxazolidinone **53** as a yellowish oil. For hypervalent reagents (***R,R*)-47b**, **(*R,R*)-48b**, **(*R,R*)-49b**, and **(*R,R*)-50b**, yields of 15%, 18%, 28%, and 30% were obtained, respectively.

Rf = 0.66 (AcOEt). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 5.91 (dq, *J* = 15.3, 6.6 Hz, 1H, H-3'), 5.56 (brs, 1H, NH), 5.37 (ddq, *J* = 15.3, 7.7, 1.7 Hz, 1H, H- 2'), 5.23 (dd, *J* = 7.7, 4.7 Hz, 1H, H-1'), 4.43 (t, *J* = 8.9 Hz, 1H, H-5a), 4.22 (dd, *J* = 9.0, 5.0 Hz, 1H, H-5b), 3.99 (dt, *J* = 8.8, 4.9 Hz, 1H, H-4), 2.08 (s, 3H, OAc), 1.74 (dd, *J* = 6.6, 1.7 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 170.1 (C=O OAc), 159.0 (C=O), 134.3 (C-3'), 123.6 (C-2'), 74.8 (C-1'), 66.3 (C-5), 54.7 (C- 4), 21.2 (OAc), 18.1 (C-4'). The spectroscopic data are in agreement with a previous report.[10]

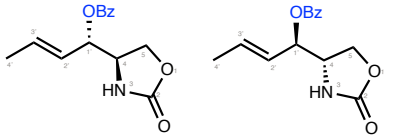
u-4-[(E)-1-Benzoyloxybut-2-en-1-yl]-oxazolidin-2-one ((±)-43).[9]



(±)-43

The title racemic compound was synthesized using a PhIO-mediated aziridination and ring-opening procedure, starting with carbamate **1** (169.4mg, 1,2 mmol) and **PhIO** (528 mg, 2.4 mmol). A mixture of solid sodium benzoate (865 mg, 6 mmol) and 15-crown-5 (238 μL, 1.2 mmol) was used as the nucleophile. The crude solution was filtered over celite, washed with DCM and concentrated under reduced pressure. The product was purified by column chromatography (100 → 40:60 Hexanes/AcOEt), yielding 105 mg (34% yield) of oxazolidinone (±)-**4** as a yellowish oil.

(*R*)-4-[(1*S*,2*E*)-1-Benzoyloxybut-2-en-1-yl]-oxazolidin-2-one ((*R,S*)-43) and **(*S*)-4-[(1*R*,2*E*)-1-Benzoyloxybut-2-en-1-yl]-oxazolidin-2-one ((*R,S*)-43) and (*R*)-4-[(1*S*,2*E*)-1-Benzoyloxybut-2-en-1-yl]-oxazolidin-2-one ((*S,R*)-43).**[9]

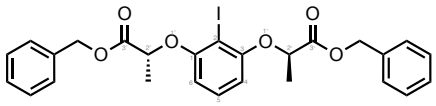


(R,S)-43 **(S,R)-43**

The title compound was synthesized using a **(*R*)-46b** mediated aziridination and ring-opening procedure, starting with carbamate **17** (32mg, 0.227 mmol) and Ar*I(OAc)$_2$ (300 mg, 0.453 mmol). A mixture of solid sodium benzoate (164mg, 1.135 mmol) and 15-crown-5 (45 μL, 0.227 mmol) was used as the nucleophile. The crude solution was filtered over celite, washed with DCM and concentrated under reduced pressure. The product was purified by column chromatography (100 → 40:60 Hexanes/AcOEt), yielding 15 mg (25% yield) of oxazolidinone (±)-**3** as a yellowish oil. For hypervalent reagents **(*R,R*)-47b**, **(*R,R*)-49b**, and **(*R,R*)-50b**, yields of 7%, 6%, and 5% were obtained, respectively.

Rf =0.20 (50:50AcOEt/Hexanes).**^{1}HNMR**(400MHz,CDCl3,δinppm):δ = 8.02 (dd, *J* = 8.4, 1.4 Hz, 2H, Ar), 7.57 (tt, *J* = 7.44, 1.4 Hz, 1H, Ar), 7.44 (t, *J* = 7.7 Hz, 2H, Ar), 6.10 (brs, 1H, NH), 6.02-5.91 (m, 1H, H-3'), 5.51-5.43 (m, 2H, H-2', H- 1'), 4.48 (t, *J* = 8.9 Hz, 1H, H-5a), 4.34 (dd, *J* = 9.0, 4.8 Hz, 1H, H-5b), 4.11-4.07 (m, 1H, H-4), 1.74 (dd, *J* = 6.6, 1.1 Hz, 3H, H-4'). **^{13}C NMR** (100 MHz, CDCl3, δ in ppm): δ = 165.6 (C=O), 159.7 (C=O), 134.1 (C-3'), 133.5 (Ar), 129.8 (Ar), 129.6 (Ar), 128.6 (Ar), 123.6 (C-2'), 75.4 (C-1'), 66.3 (C-5), 54.9 (C-4), 18.1 (C-4'). The spectroscopic data are in agreement with previously report.[9] **HPLC** Chiralpak IC column (80:20 hexanes:ethanol, 1.0 mL/min, 220 nm), major enantiomer(R,S) t_r = 14 min, second enantiomer (S,R)t_r = 16 min. **ESI-TOF** $[M+H]^+$ cal for $C_{14}H_{15}NO_4$: 262.10; found: 262.1060; $[M+Na]^+$ calc for C14H15NNaO4: 284.08, found: 284. 0878.

Dibenzyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))-(2R,2'R)-dipropionate ((*R,R*)-46a).[62]

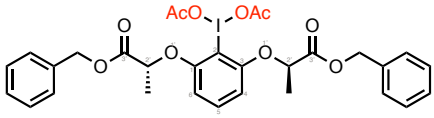


(*R,R*)-46a

The title compound was synthesized using the general procedure for preparing chiral aryliodides, starting with 2-iodobenzene-1,3-diol (0.85 g, 3.6 mmol), Ph_3P (2.3 g, 8.3 mmol), benzyl-(S)-lactate (1 g, 7.6 mmol), and DIAD (1.6 mL, 8.3 mmol). The crude product was purified by column chromatography (5:95 AcOEt/hexanes), yielding 1.02 g (52% yield) of chiral aryliodide precursor **(*R,R*)-46a** as a sticky white solid.

Rf = 0.22 (10:90 AcOEt/Hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.36-7.27 (m, 10H, Bn), 7.01 (t, *J* = 8.3 Hz, 1H, H-5), 6.31 (d, *J* = 8.3 Hz, 2H, H-4, H-6), 5.18 (d, *J* = 2.1 Hz, 4H, CH_2-Bn), 4.80 (q, *J* = 6.8 Hz, 2H, H-2'), 1.71 (d, *J* = 6.8 Hz, 6H, Me-2'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 171.6 (C=O), 158.3 (C-1, C-3), 135.4 (Bn), 129.6 (C-5), 128.7, 128.5, 128.3 (Bn), 107.1 (C-4, C-6), 80.8 (C-2), 74.3 (C-2'), 67.0 (CH_2-Bn), 18.7 (Me-2'). The spectroscopic data are in agreement with previously report.[62]

Dibenzyl 2,2'-((2-(diacetoxy-λ^3-iodaneyl)-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate ((*R,R*)-46b).

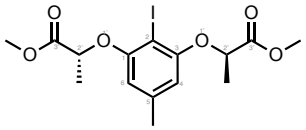


(*R,R*)-46b

The title compound was synthesized using the general procedure for the oxidation of lactate-based chiral aryliodide precursor, starting with **(*R,R*)-46a** (0.22 g, 0.4 mmol), Selectfluor (0.766 g, 2 mmol), ACN (26 mL), and AcOH (8 mL). The reaction yielded 0.24 g (97%), comprising 90% **(*R,R*)-46b** and 10% **(*R,R*)-46a**. The resulting mixture was a sticky yellowish solid and it was used without any further purification.

Rf = 0.22 (10:90 AcOEt/Hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.36-7.27 (m, 10H, Bn), 7.22 (t, *J* = 8.3 Hz, 1H, H-5), 6.49 (d, *J* = 8.4 Hz, 2H, H-4, H-6), 5.20 (d, *J* = 0,46 Hz, 4H, CH_2-Bn), 4.88 (q, *J* = 6.8 Hz, 2H, H-2'), 1.90 (s, 6H, OAc) 1.69 (d, *J* = 6.8 Hz, 6H, Me-2').

Dimethyl 2,2'-((2-iodo-5-methyl-1,3-phenylene)bis(oxy))-(2R,2'R)- dipropionate ((*R,R*)-47a).[60]



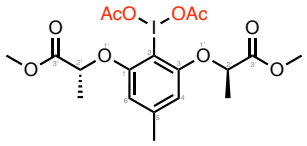
(*R,R*)-47a

The title compound was synthesized following the general procedure for chiral aryliodide preparation starting from 2-iodo-5-methylbenzene-1,3-diol (1.0 g, 4.0 mmol), Ph_3P (2.4 g, 9.2 mmol), methyl-(*S*)-lactate (0.8 mL, 8.4 mmol) and DIAD (1.8 mL, 9.2 mmol). The crude was purified by column chromatography (10:90 to 20:80 AcOEt/hexanes) to afford 1.2 g (74% yield) of chiral aryliodide precursor **(*R,R*)-47a** as a white solid.

Rf = 0.12 (10:90 AcOEt/Hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 6.20 (s, 2H, H-4, H-6), 4.75 (q, *J* = 6.8 Hz, 2H, H-2'), 3.76 (s, 6H, Me), 2.25 (s, 3H, Me-5), 1.69 (d, *J* = 6.8 Hz, 6H, Me-2'). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 172.4 (C=O), 158.1 (C-1, C-3), 140.3 (C-5), 108.3 (C-4,

C-6), 76.9 (C-2), 74.3 (C-2'), 52.5 (Me), 22.0 (Me-4), 18.8 (Me-2'). spectroscopic data are in agreement with previously report.[60]

Dimethyl 2,2'-((2-(diacetoxy-λ3-iodaneyl)-5-methyl-1,3 phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate ((*R,R*)-47b). [63]

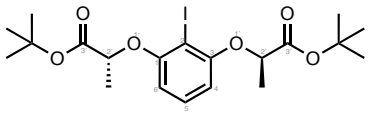


(*R,R*)-47b

The title compound was synthesized using the general procedure for the oxidation of lactate-based chiral aryliodide precursor, starting with **(*R,R*)-47a** (0.30 g, 0,71 mmol), Selectfluor (1,923g, 5,4 mmol), ACN (32 mL), and AcOH (10 mL). The reaction yielded 0.326 g (85 %), comprising 50% **(*R,R*)-47b,** 18% **(*R,R*)-47a** and 32% of mixture of oxidized species. The resulting mixture was a sticky yellowish solid and it was used without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): δ = 6.37 (s, 2H, H-4, H-6), 4.85 (q, *J* = 6.7 Hz, 2H, H-2'), 3.77 (s, 6H, Me), 2.36 (s, 3H, Me-5), 1.97 (s, 6H, OAc), 1.69 (d, *J* = 6.8 Hz, 6H, Me-2'). The spectroscopic data are in agreement with previously report.[63]

Di-tert-butyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))-(2R,2'R)-dipropionate ((*R,R*)-48a).[65]

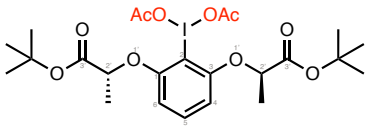


(*R,R*)-48a

The title compound was synthesized following the general procedure for chiral aryliodide preparation starting from 2-iodobenzene-1,3-diol (1.4 g, 6.1 mmol), Ph_3P (3.7 g, 13.9 mmol), *tert*-butyl-(*S*)-lactate (1.9 g, 12.7 mmol) and DIAD (2.7 mL, 13.9 mmol). The crude was purified by column chromatography (2:98 AcOEt/hexanes) to afford 1.2 g (41% yield) of chiral aryl iodide precursor **(*R,R*)-48a** as a sticky white solid.

R_f = 0.60 (30:70 AcOEt/Hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.12 (t, *J* = 8.3 Hz, 1H, H-5), 6.36 (d, *J* = 8.3 Hz, 2H, H-4, H-6), 4.64 (q, *J* = 6.8 Hz, 2H, H-2'), 1.66 (d, *J* = 6.8 Hz, 6H, Me-2'), 1.42 (s, 18H, CH_3-^{t}Bu) . **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 171.0 (C=O), 158.5 (C-1, C-3), 129.3 (C-5), 106.7 (C-4, C-6), 82.0 (C-^{t}Bu), 80.6 (C-2), 74.6 (C-2'), 28.1 (CH_3-^{t}Bu), 18.6 (Me-2'). The spectroscopic data are in agreement with previous report.[65]

(2,6-bis(((R)-4,4-dimethyl-3-oxopentan-2-yl)oxy)phenyl)-λ3-iodanediyl diacetate ((*R,R*)-48b).

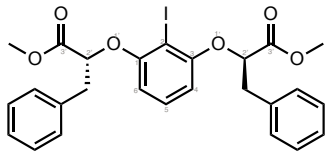


(*R,R*)-48b

The title compound was synthesized using the general procedure for the oxidation of lactate-based chiral aryliodide precursor, starting with **(*R,R*)-48a** (0.506 g, 1 mmol), Selectfluor (1,923g, 5 mmol), ACN (32 mL), and AcOH (10 mL). The reaction yielded 0.62 g (99 %), comprising 98% **(*R,R*)-48b** and 2% **(*R,R*)-48a.** The resulting mixture is a sticky yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): δ = 7.37 (t, *J* = 8.3 Hz, 1H, H-5), 6.54 (d, *J* = 8.4 Hz, 2H, H-4, H-6), 4.71 (q, *J* = 6.8 Hz, 2H, H-2'), 1.95 (s, 6H, OAc), 1.64 (d, *J* = 6.8 Hz, 6H, Me-2'), 1.43 (s, 18H, CH_3-^{t}Bu). The resulting mixture was a sticky yellowish solid and it was used without any further purification.

Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))-(2R,2'R)-bis(3-phenyl propanoate) ((*R,R*)-49a).[66]

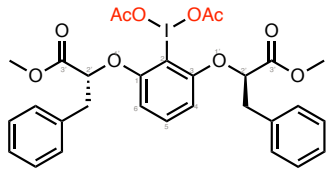


(*R,R*)-49a

The title compound was synthesized following the general procedure for chiral aryliodide preparation starting from 2-iodobenzene-1,3-diol (2.0 g, 8.5 mmol), Ph_3P (5.1 g, 19.5 mmol), methyl (2*S*)-2-hydroxy-3-phenylpropanoate (3.2 g, 17.8 mmol) and DIAD (3.8 mL, 19.5 mmol). The crude was purified by column chromatography (7:93 AcOEt/hexanes) to afford 2.2 g (46% yield) of chiral aryliodide precursor **(*R,R*)-49a** as a white solid.

Rf = 0.27 (20:80 AcOEt/Hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$, δ in ppm): δ = 7.44-7.41 (m, 4H, Bn), 7.33- 7.23 (m, 6H, Bn), 7.04 (t, *J* = 8.3 Hz, 1H, H-5), 6.21 (d, *J* = 8.3 Hz, 2H, H-4, H-6), 4.81 (dd, *J* = 8.0, 4.5 Hz, 2H, H-2'), 3.67 (s, 6H, Me), 3.36 (dd, *J* = 14.0, 8.0 Hz, 2H, $(CH_2)_a$-Bn), 3.28 (dd, *J* = 14.0, 4.5 Hz, 2H, $(CH_2)_b$-Bn). **^{13}C NMR** (100 MHz, $CDCl_3$, δ in ppm): δ = 171.1 (C=O), 158.3 (C-1, C-3), 136.2, 130.0 (Bn), 129.6 (C-5), 128.5, 127.2 (Bn), 106.0 (C-4, C-6), 79.5 (C-2), 79.0 (C-2'), 52.4 (Me), 39.3 (CH_2-Bn). The spectroscopic data are in agreement with previous report.[66]

Dimethyl 2,2'-((2-(diacetoxy-λ^3-iodaneyl)-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-bis(3-phenylpropanoate) ((*R,R*)-49). [66]

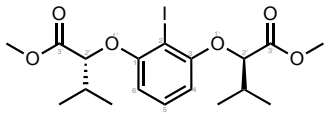


(*R,R*)-49b

The title compound was synthesized using the general procedure for the oxidation of lactate-based chiral aryl iodide precursor, starting with **(*R,R*)-49a** (0.564 g, 1 mmol), Selectfluor (1,923g, 5 mmol), ACN (32 mL), and AcOH (10 mL). The reaction yielded 0.62 g (97 %), comprising 95% **(*R,R*)-49b** and 5% **(*R,R*)-49a**. The resulting mixture is a sticky yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): δ = 7.20-7.34 (m, 11H), 6.43 (d, *J* = 8.4 Hz, 2H, H-4, H-6), 4.9 (dd, *J* = 6.8, 5.6 Hz, 2H, H-2'), 3.67 (s, 6H, Me), 3.30 (d, *J* = 3.30 Hz, 2H, $(CH_2)_a$-Bn), 3.29 (s, 2H, $(CH_2)_b$-Bn), 1.89 (s, 6H, OAc). The spectroscopic data are in agreement with previous report.[66]

Dimethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))-(2R,2'R)-bis(3-methyl butanoate) ((*R,R*)-50a).[67]

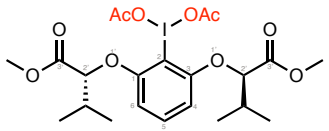


(*R,R*)-50a

The title compound was synthesized following the general procedure for chiral aryliodide preparation starting from 2-iodobenzene-1,3-diol (850.4 mg, 3.6 mmol), Ph_3P (2.2 g, 8.3 mmol), methyl (2*S*)-2-hydroxy-3-methylbutanoate (1.0 g, 7.6 mmol) and DIAD (1.6 mL, 8.3 mmol). The crude was purified by column chromatography (5:95 to 6:94 AcOEt/hexanes) to afford 539.1 mg (32% yield) of chiral aryliodide precursor **(*R,R*)-50a** as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): δ = 7.11 (t, *J* = 8.3 Hz, 1H, H-5), 6.24 (d, *J* = 8.3 Hz, 2H, H-4, H-6), 4.44 (d, *J* = 4.8 Hz, 2H, H-2'), 3.73 (s, 6H, Me), 2.41-2.29 (m, 2H, CH-^{i}Pr), 1.17 (d, *J* = 6.9 Hz, 6H, CH_3-^{i}Pr), 1.13 (d, *J* = 6.9 Hz, 6H, CH_3-^{i}Pr). The spectroscopic data are in agreement with previously report.[67]

Dimethyl 2,2'-((2-(diacetoxy-λ^3-iodaneyl)-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-bis(3-methylbutanoate) ((*R,R*)-50b).[67]



(*R,R*)-50b

The title compound was synthesized using the general procedure for the oxidation of lactate-based chiral aryl iodide precursor, starting with **(*R,R*)-50a** (0.561 g, 1 mmol), Selectfluor (1,923g, 5 mmol), ACN (32 mL), and AcOH (10 mL). The reaction yielded 0.62 g (93 %), comprising 96% **(*R,R*)-50b** and 4% **(*R,R*)-50a**. The resulting mixture is a sticky yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): δ = 7.37 (t, *J* = 8.3 Hz, 1H, H-5), 6.50 (d, *J* = 8.3 Hz, 2H, H-4, H-6), 4.58 (d, *J* = 4.8 Hz, 2H, H-2'), 3.73 (s, 6H, Me), 2.36 (m, 2H, CH-^{i}Pr), 1.97 (s, 6H, OAc), 1.10 (d, *J* = 6.9 Hz, 12H, CH_3-^{i}Pr). The spectroscopic data are in agreement with previously report.[67]

7. REFERENCES

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ERASMUS MUNDUS JOINT MASTER DEGREE IN SUSTAINABLE CATALYSIS

ENANTIOSELECTIVE AZIRIDINATION OF DIENYL CARBAMATES EN ROUTE TO SPHINGOLIPID MIMICS

MASTHER THESIS

SUPPORTING INFORMATION

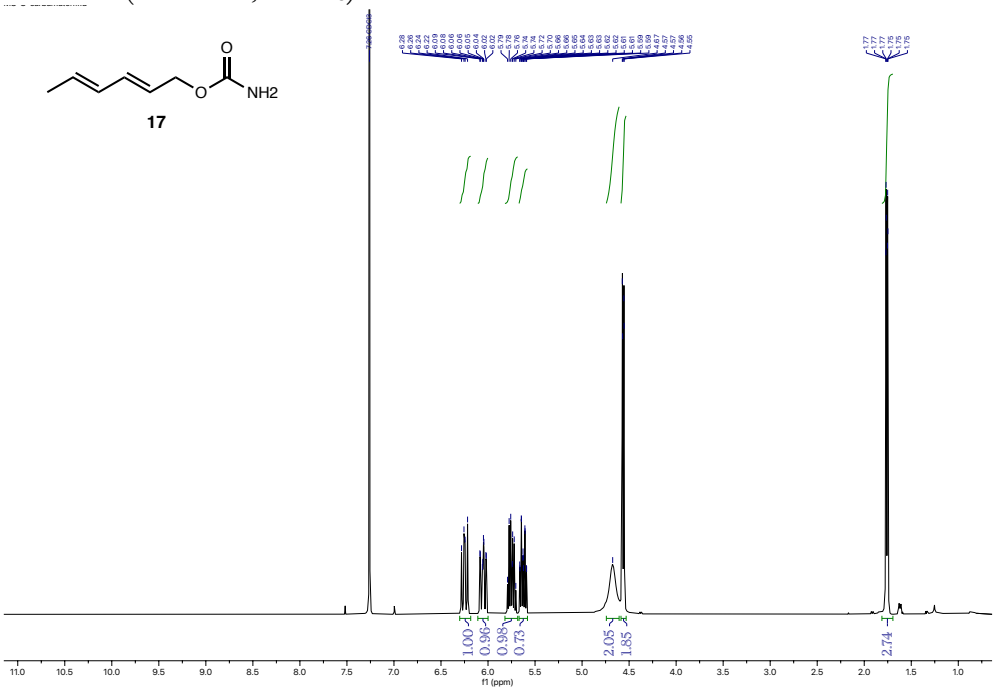
Author:
Marisa Sánchez

Supervisor:
Yolanda Díaz, PhD.

Tarragona, July 2024

ANNEX A: NMR SPECTRA

^{1}H NMR (400 MHz, $CDCl_3$)



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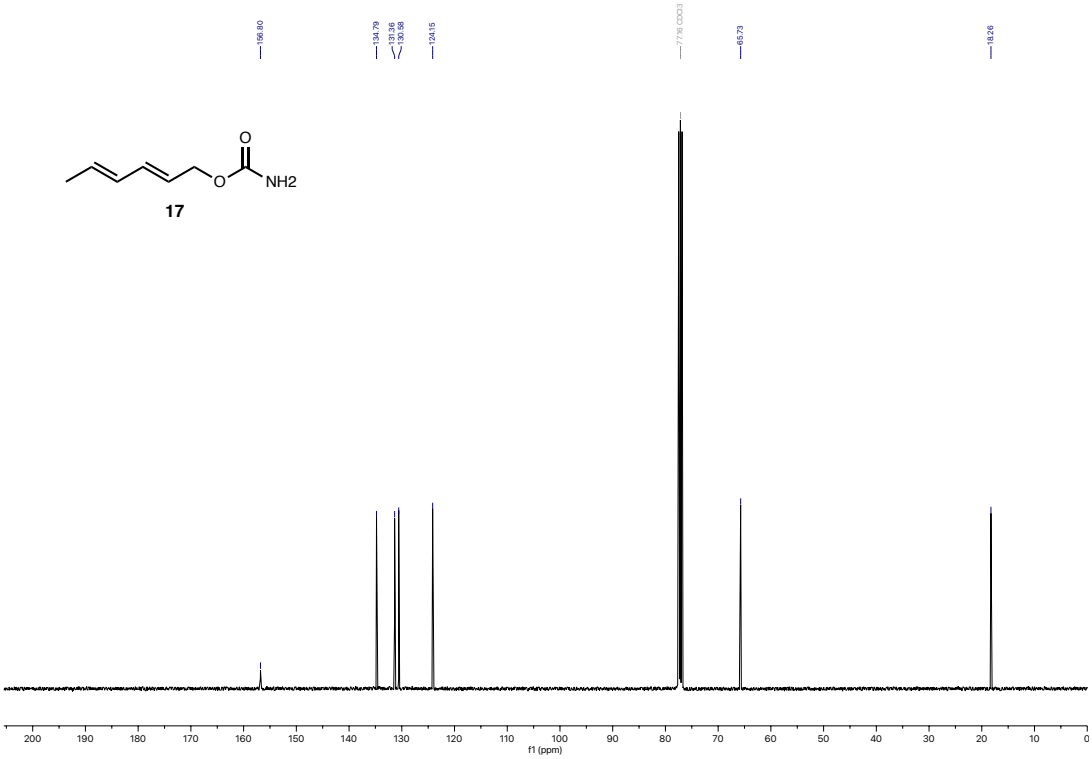

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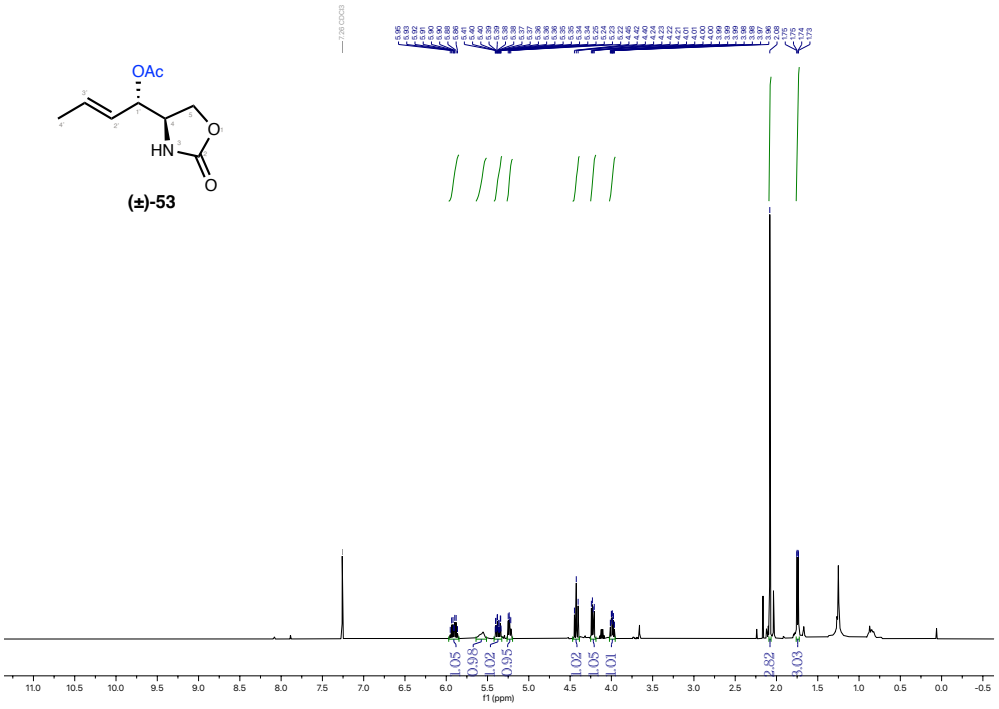

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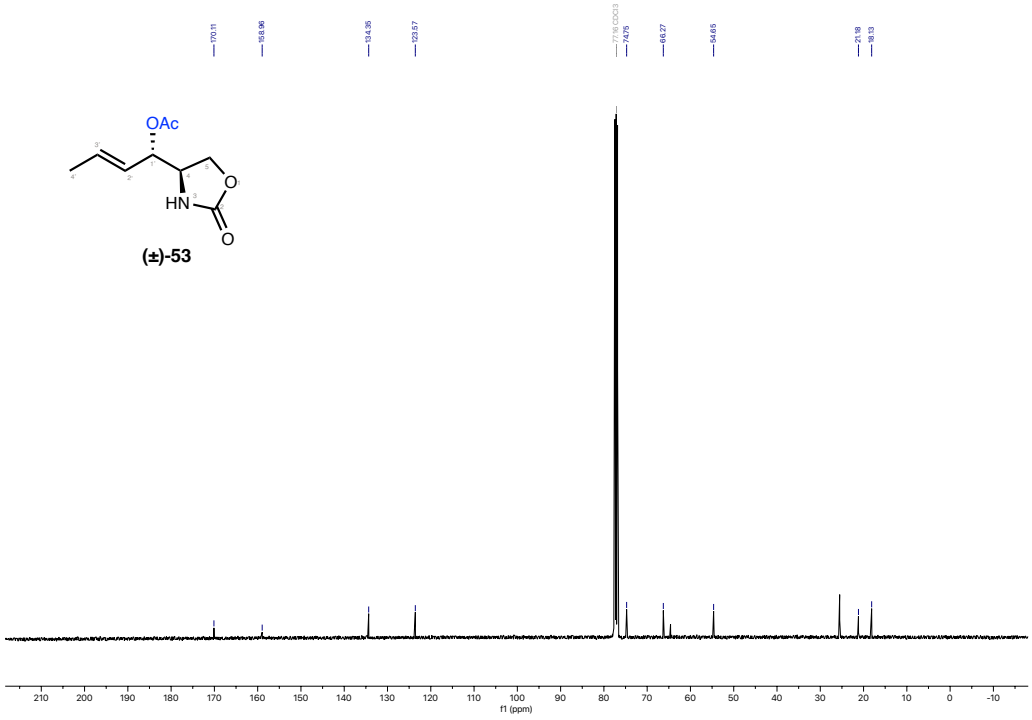

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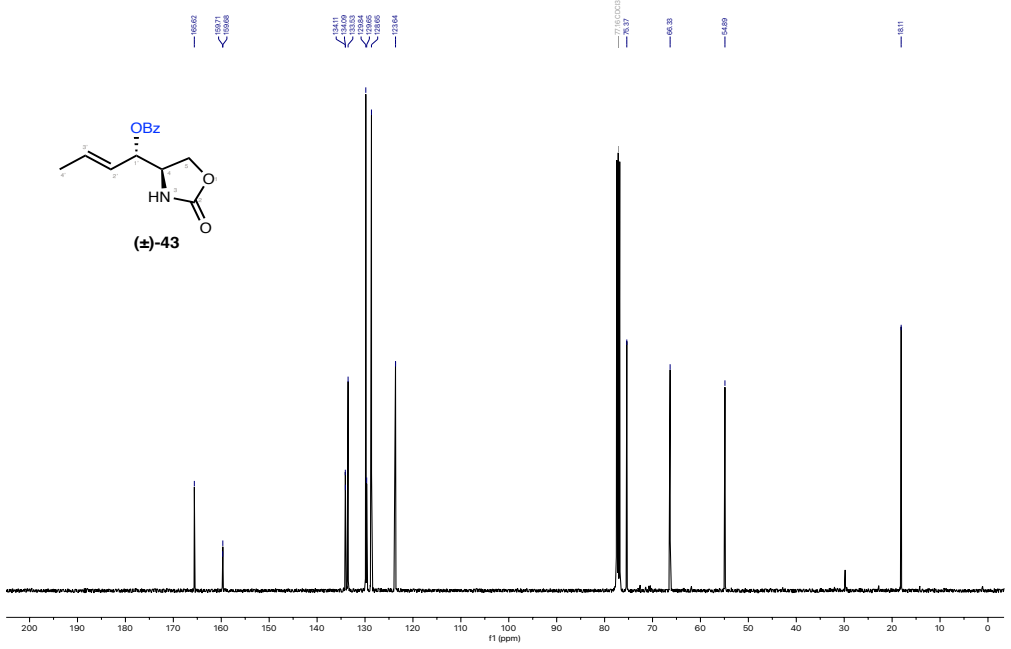

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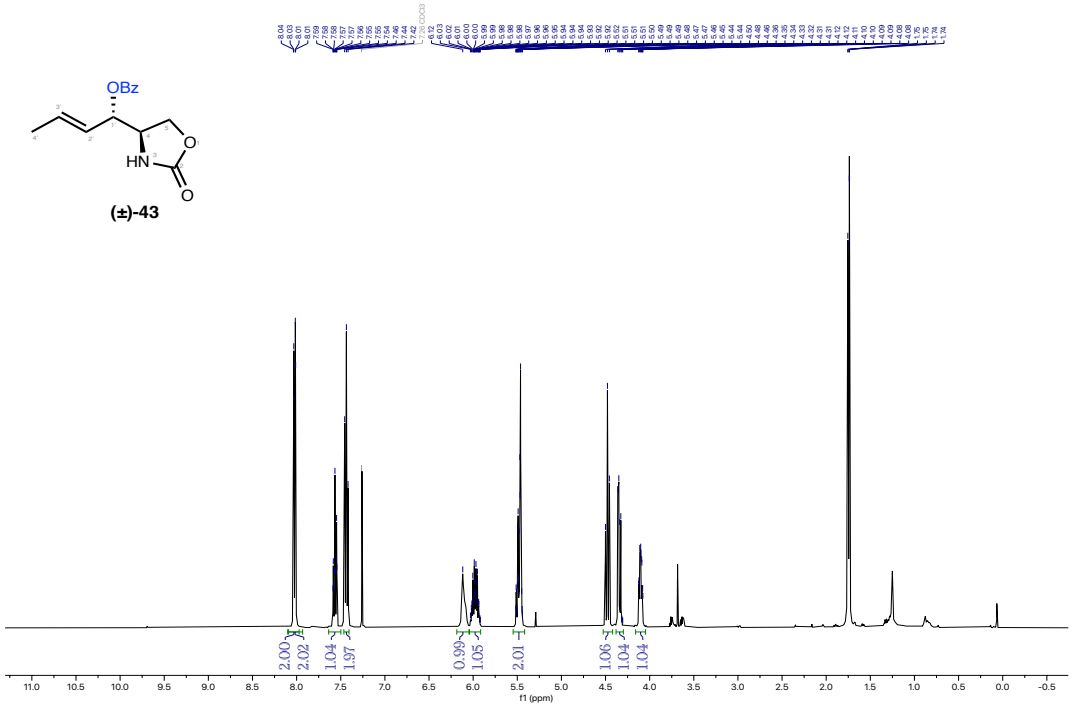

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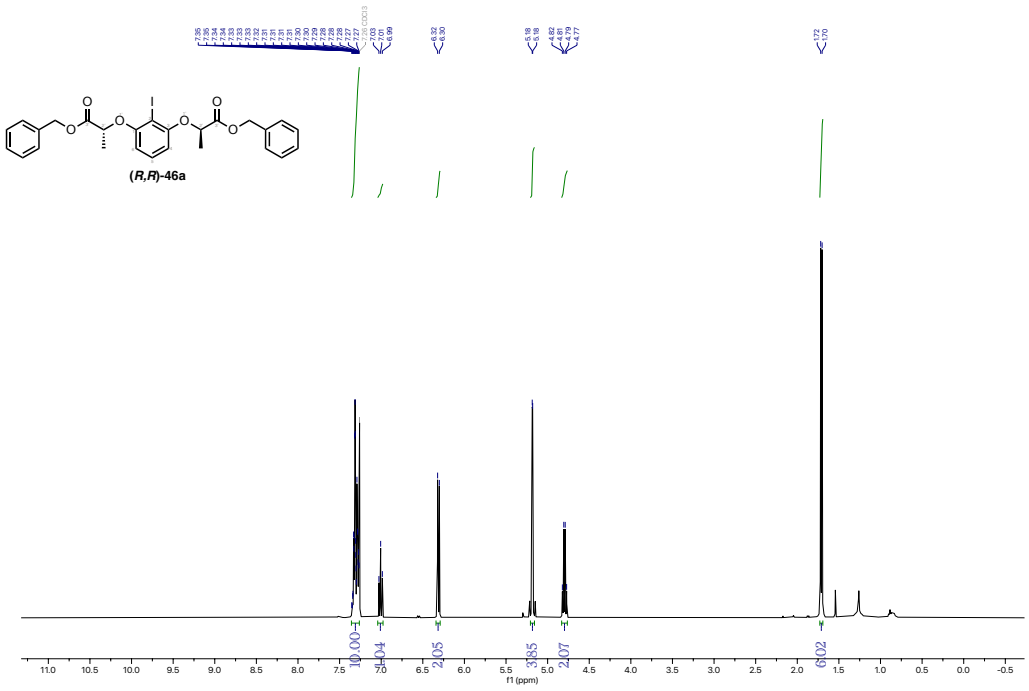

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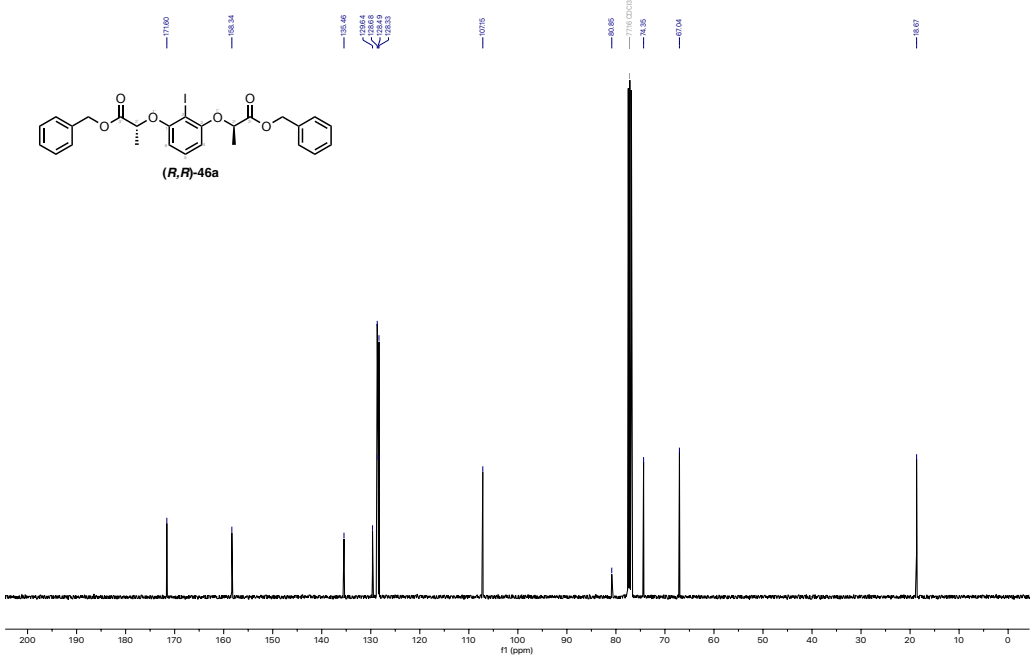

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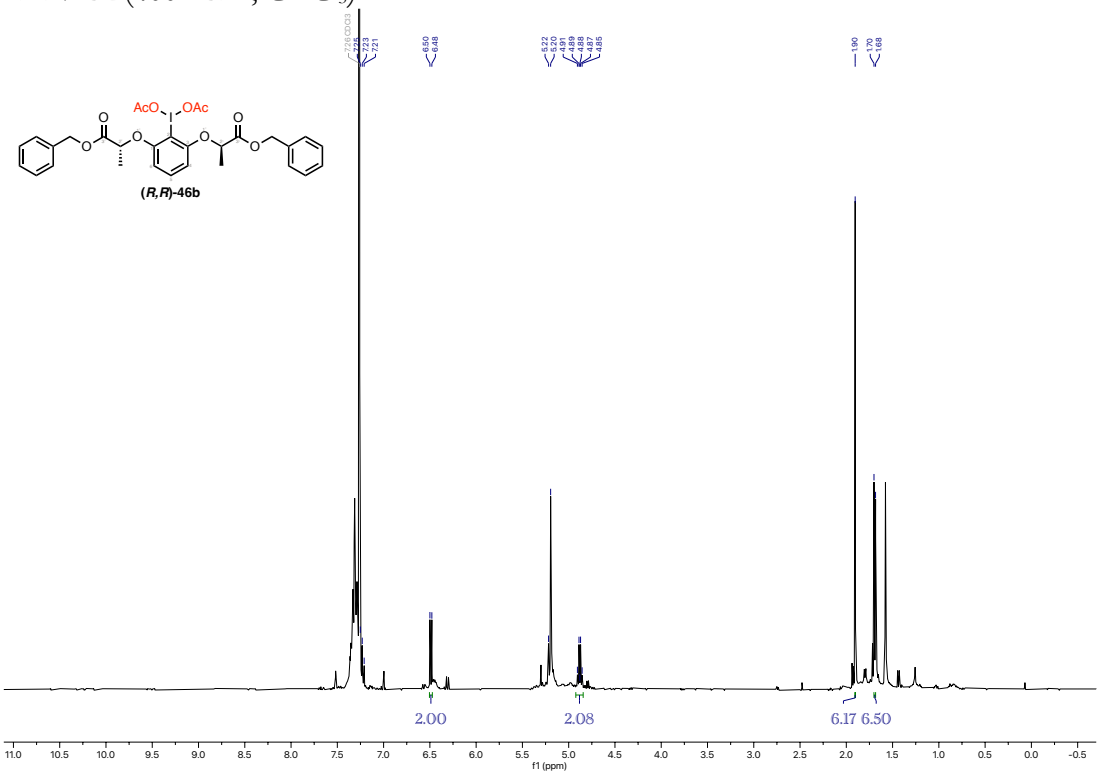

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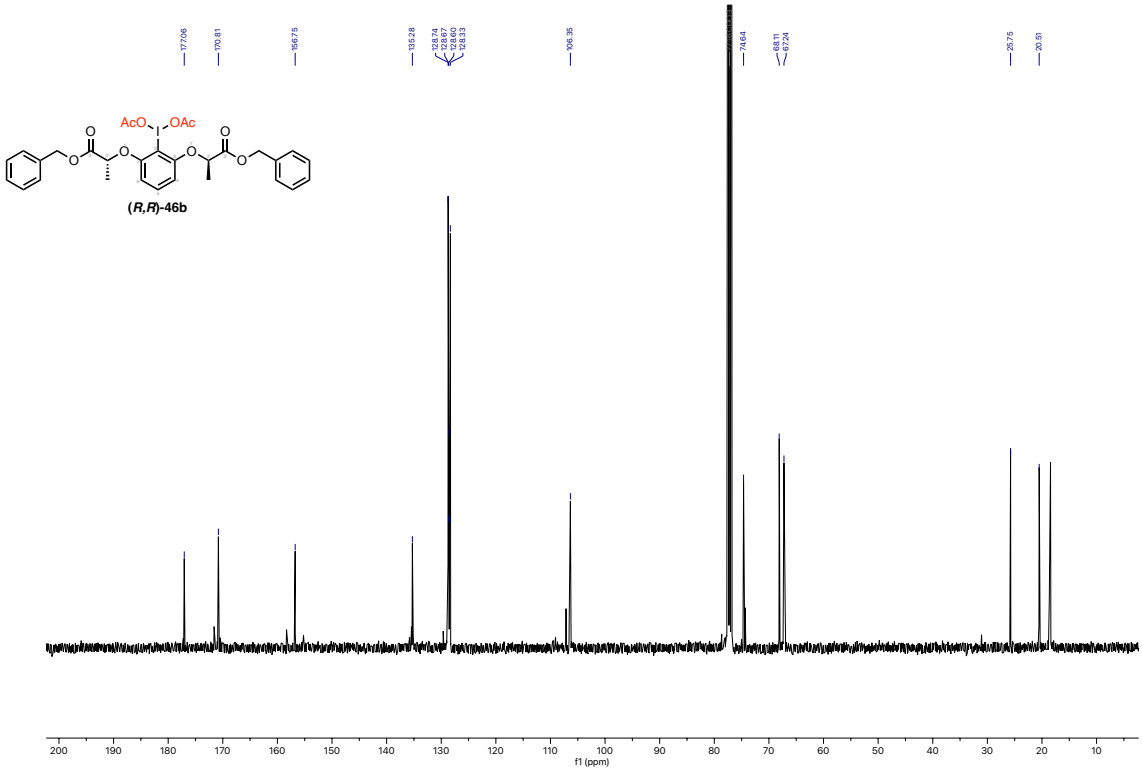

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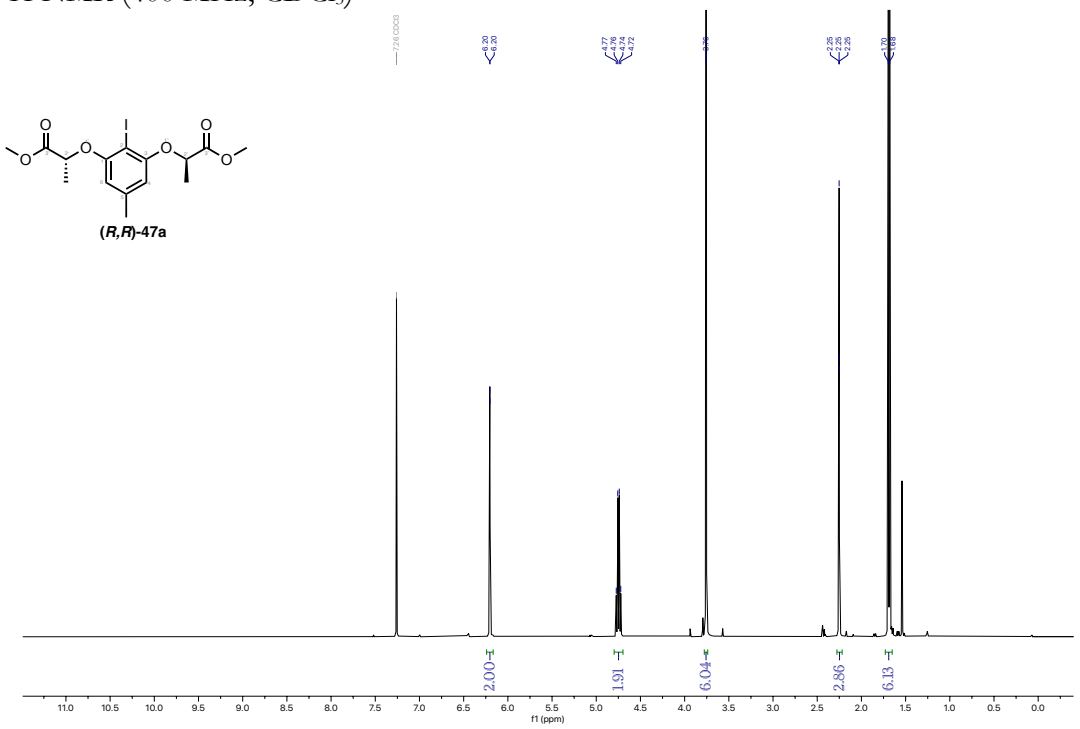

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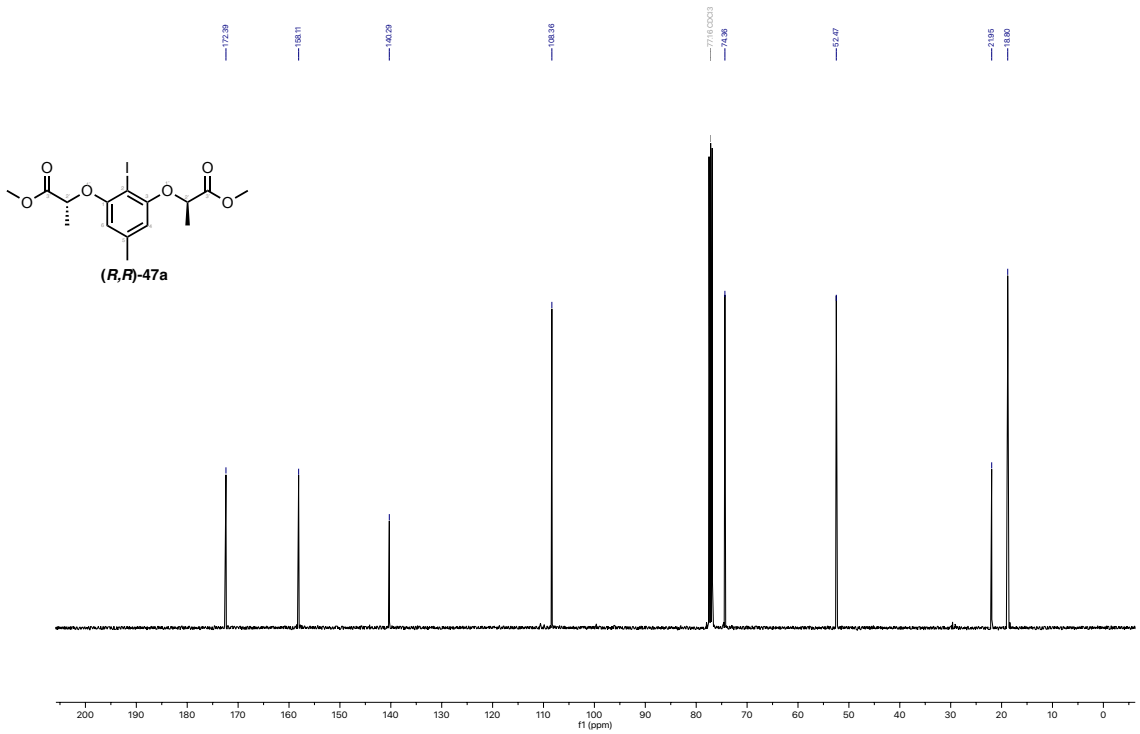

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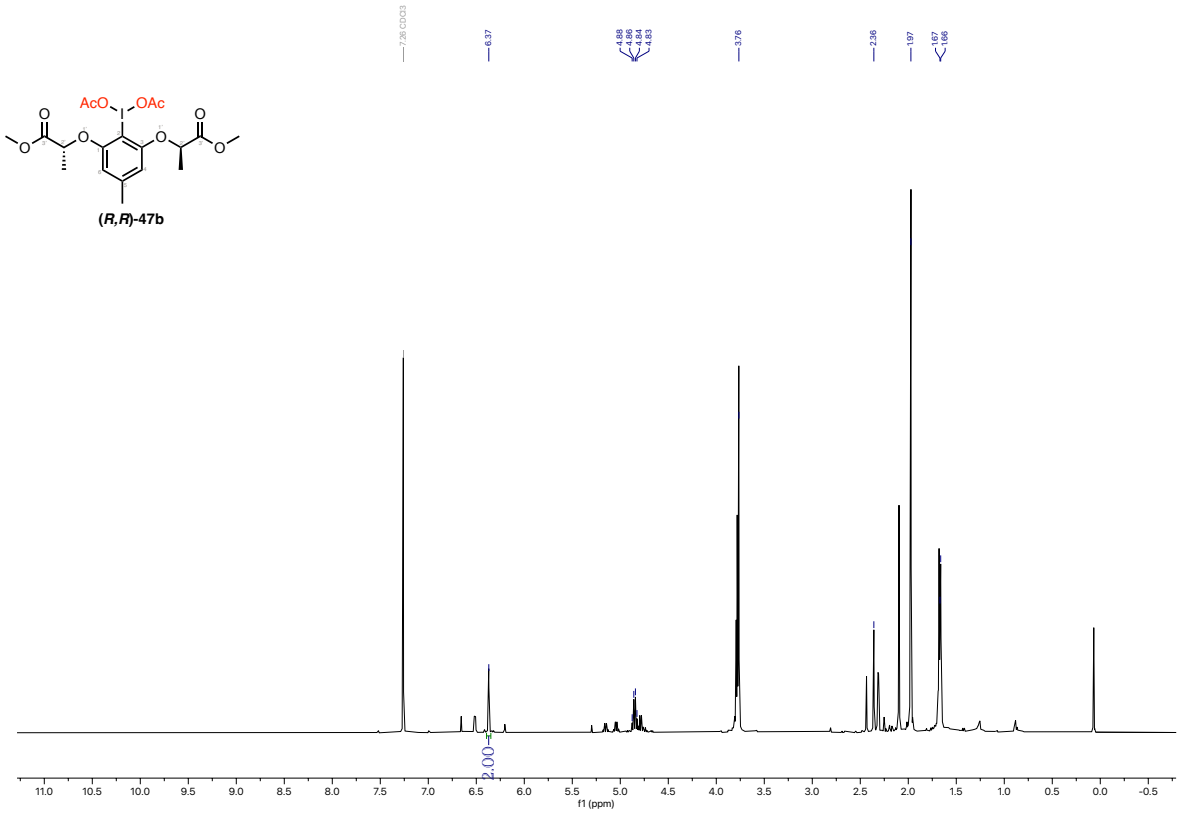

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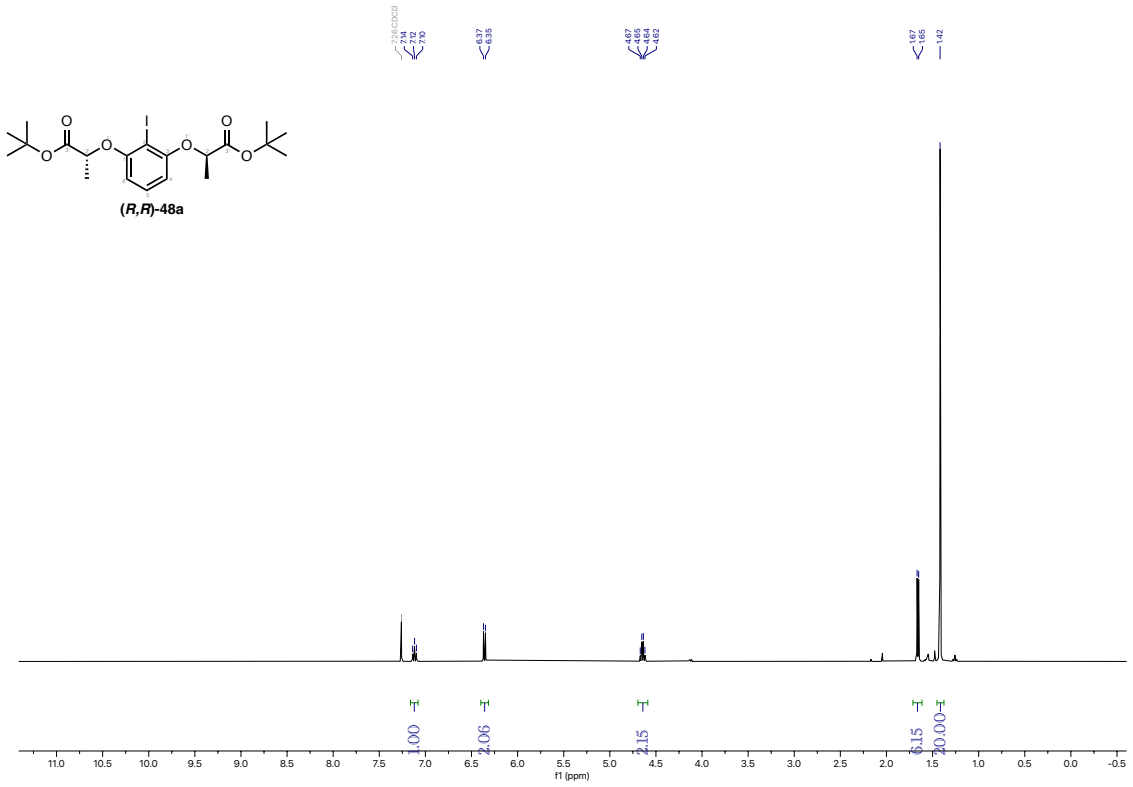
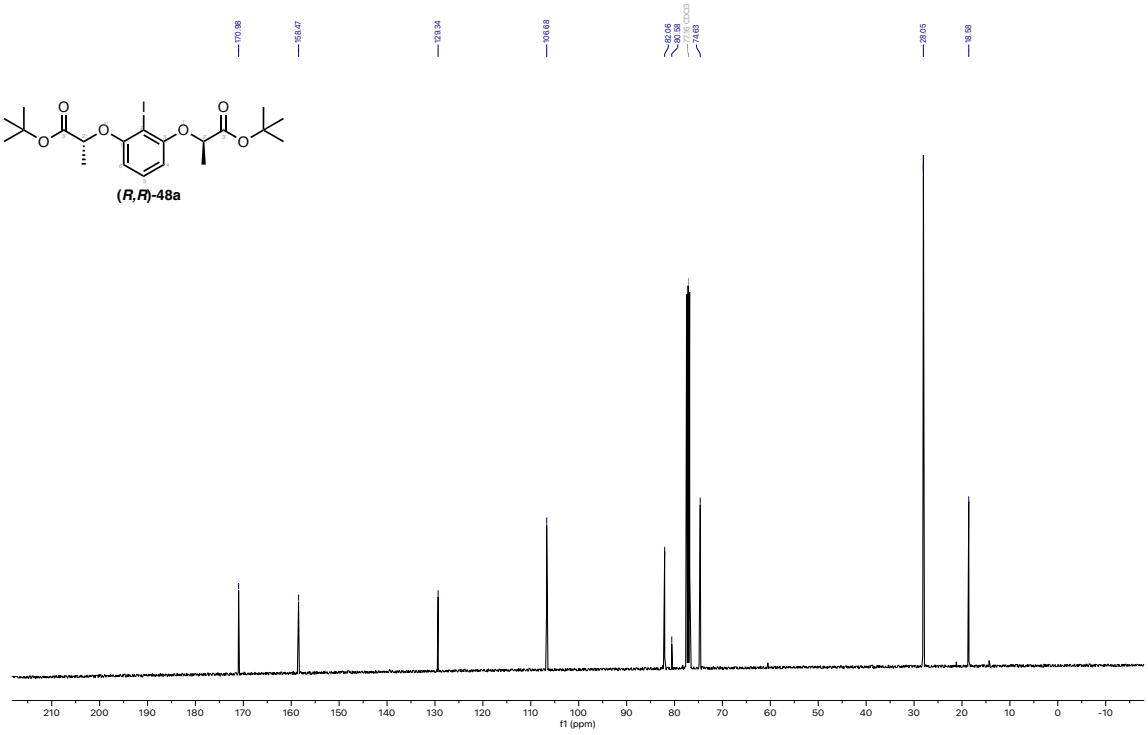
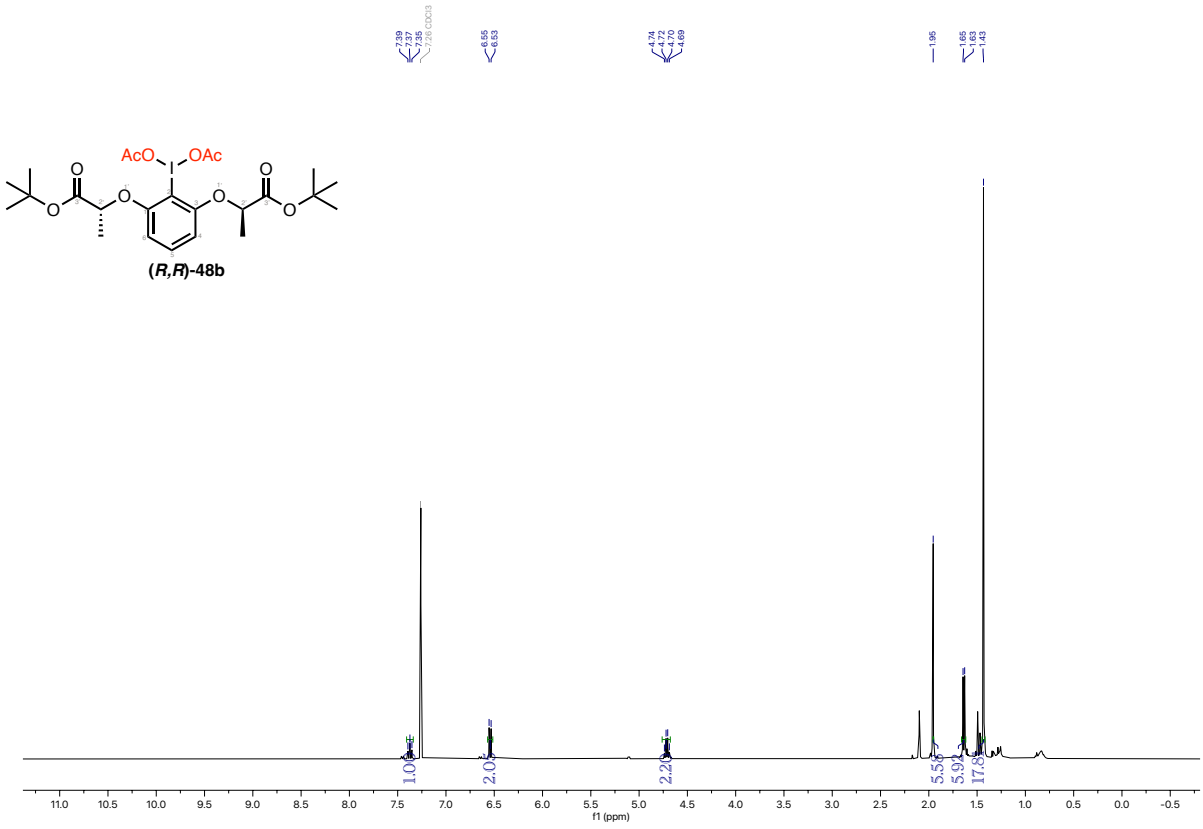


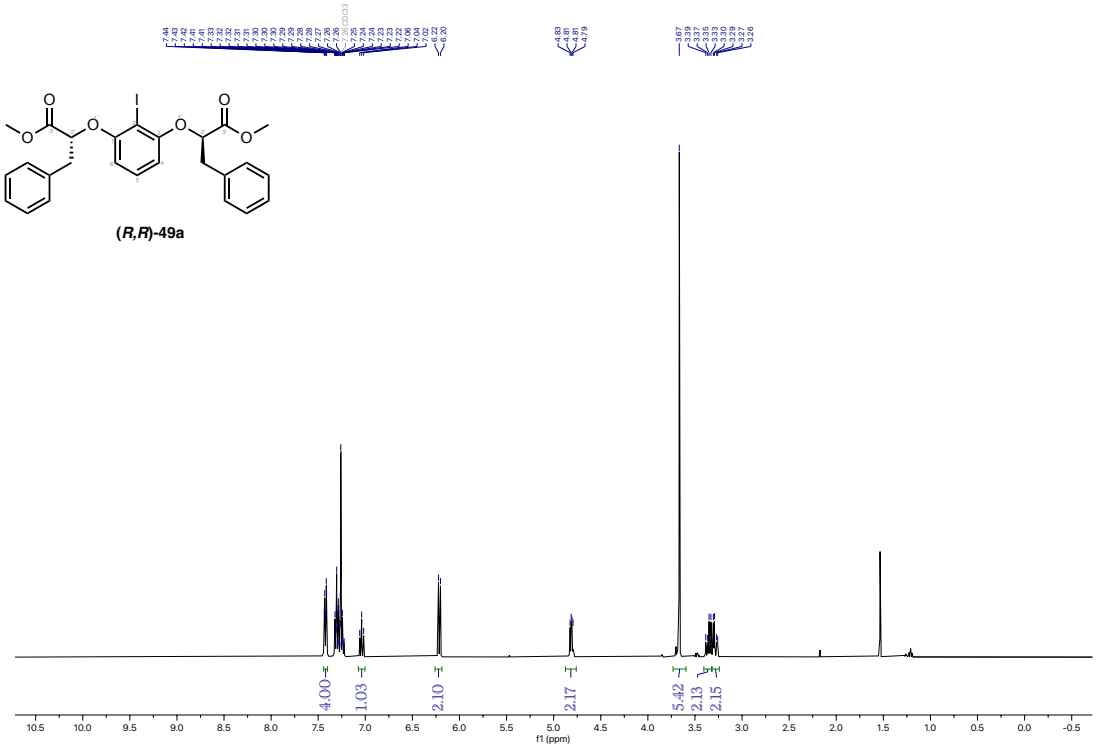
^{13}C NMR (100 MHz, $CDCl_3$)



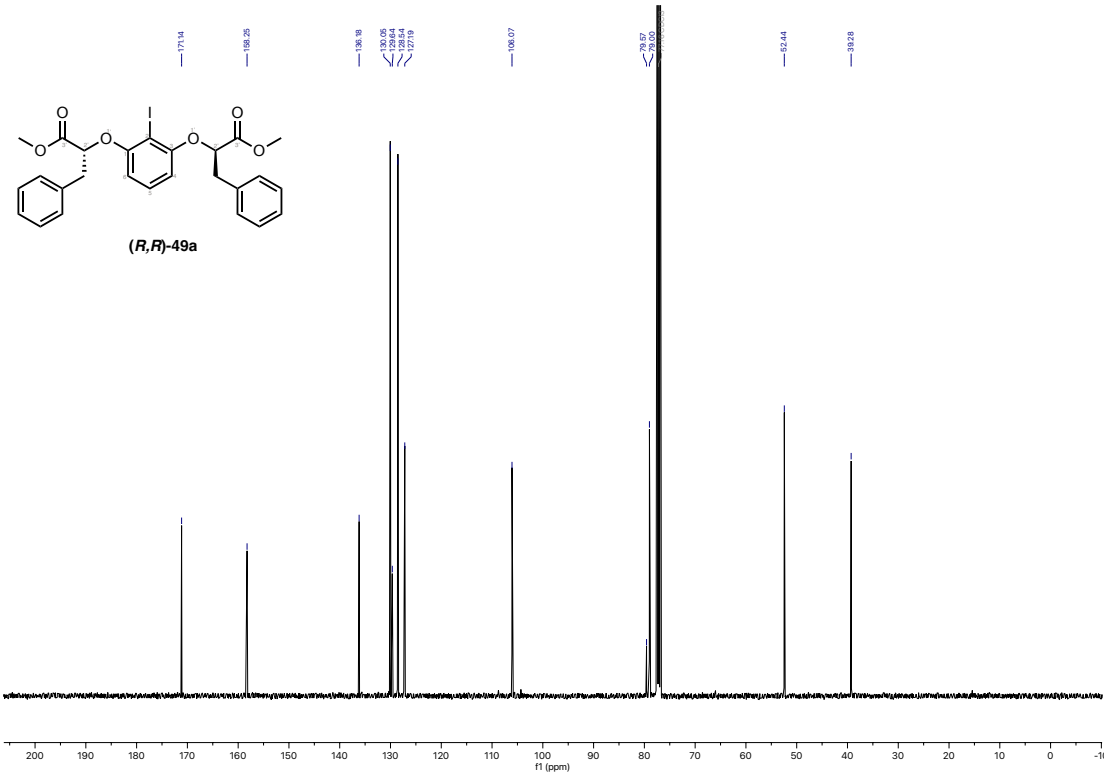
^{1}H NMR (400 MHz, $CDCl_3$)



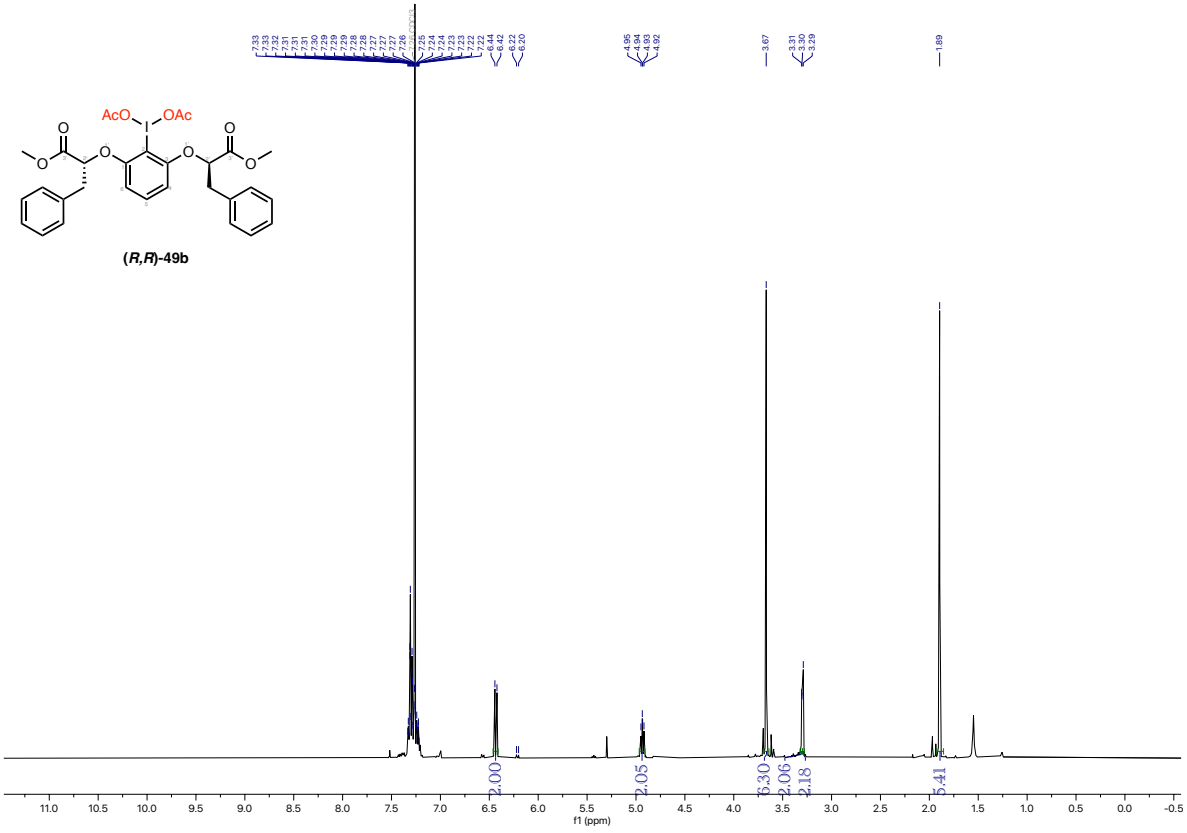
^{1}H NMR (400 MHz, $CDCl_3$)



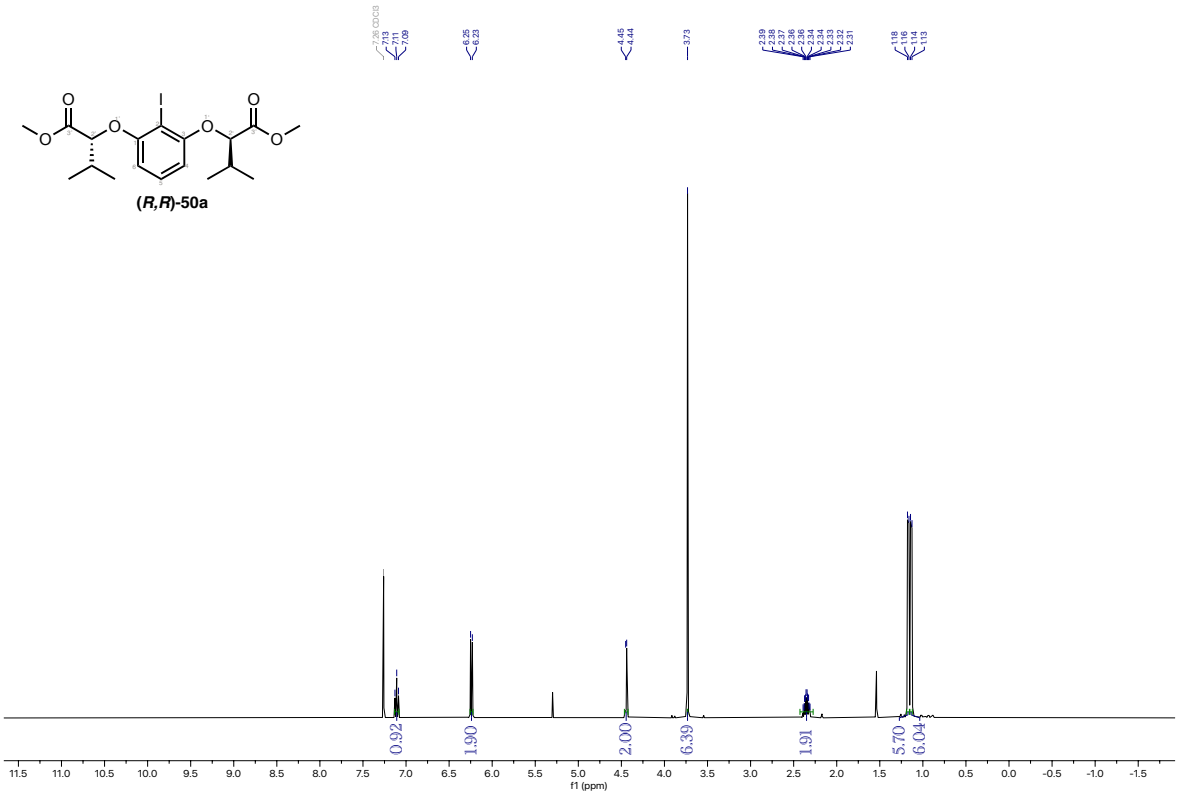
^{13}C NMR (100 MHz, $CDCl_3$)



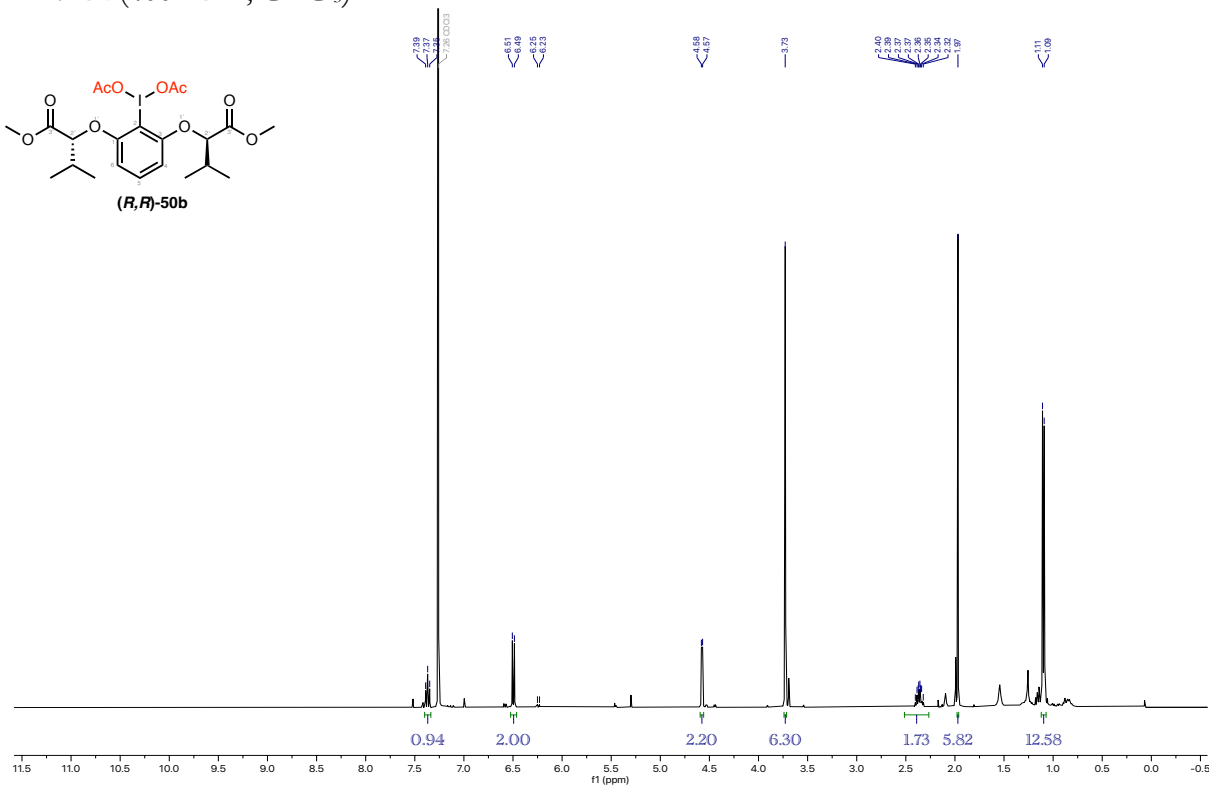
^{1}H NMR (400 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



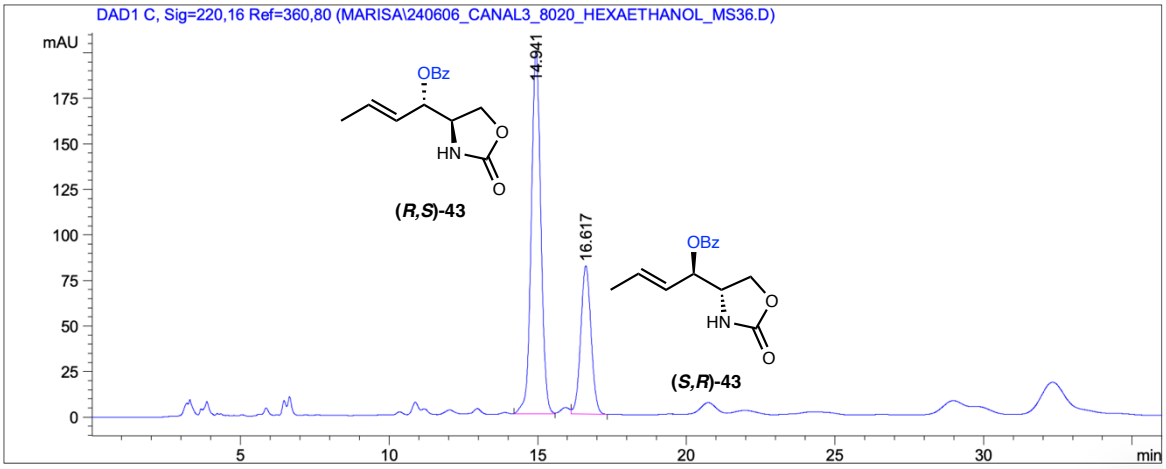
ANNEX B: HPLC-UV CHROMATOGRAMS

To optimize the separation, different chiral columns were tested (**Table 4**). After this, the best conditions were achieved using a Chiralpak IC column with an 80:20 hexanes: ethanol mixture as the mobile phase at a flow rate of 1.0 mL/min and detection at 220 nm. Under these conditions, the enantiomers had a retention time (tr) of 15.1 and 16.8 minutes respectively. These results are in agreement with those previously reported by Irene Gimenez-Nueno in her thesis.[54]

Table 3. Chiral columns and its characteristics

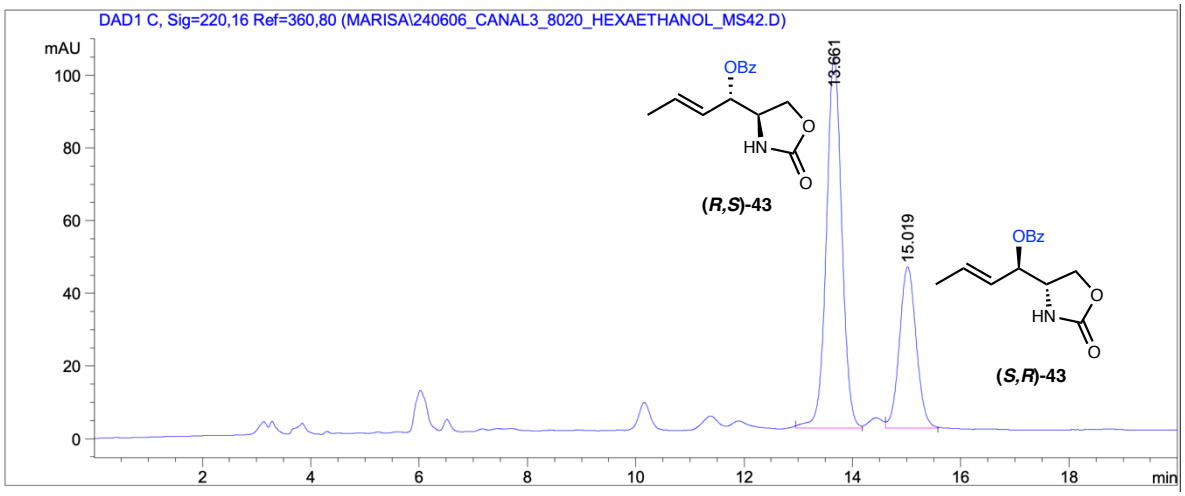
Canal	Column	Characteristics
Canal 1	ID CHIRALPAK	4.6mm x 250mmL x 5mm
Canal 2	ODH CHIRALCEL	4.6mm x 250mmL x 5mm
Canal 3	IC CHIRALPAK	4.6mm x 250mmL x 5mm
Canal 4	4 IA CHIRALPAK	4.6mm x 250mmL x 5mm
Canal 5	IF CHIRALPAK	4.6mm x 250mmL x 5mm
Canal 6	ADH CHIRALPAK	4.6mm x 250mmL x 5mm

Iodine(III) reagent: (*R,R*)-46b



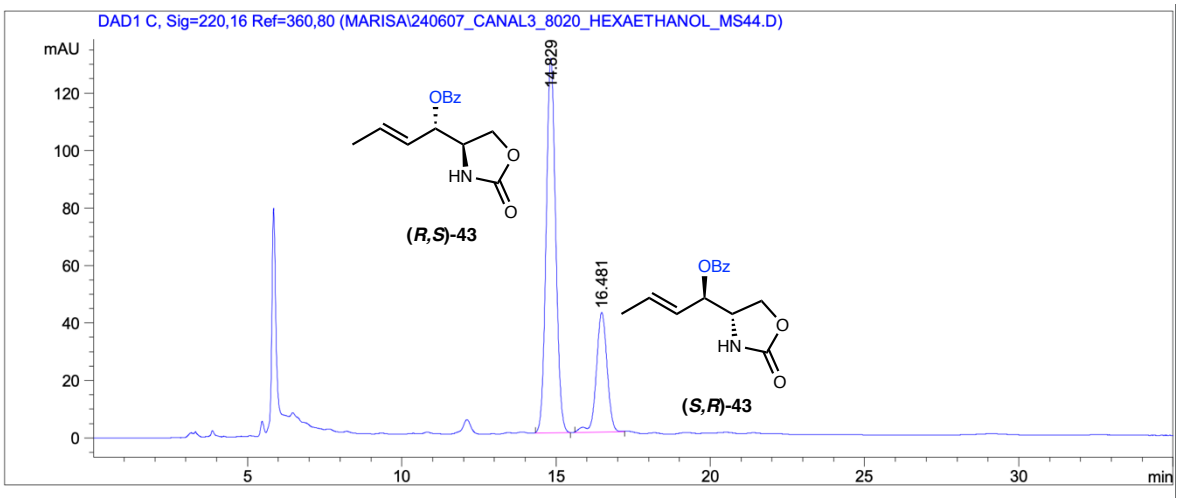
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.941	BB	0.3451	4459.80908	199.28557	69.3066
2	16.617	VB	0.3747	1975.08936	81.51315	30.6934

Iodine(III) reagent: (*R,R*)-47b



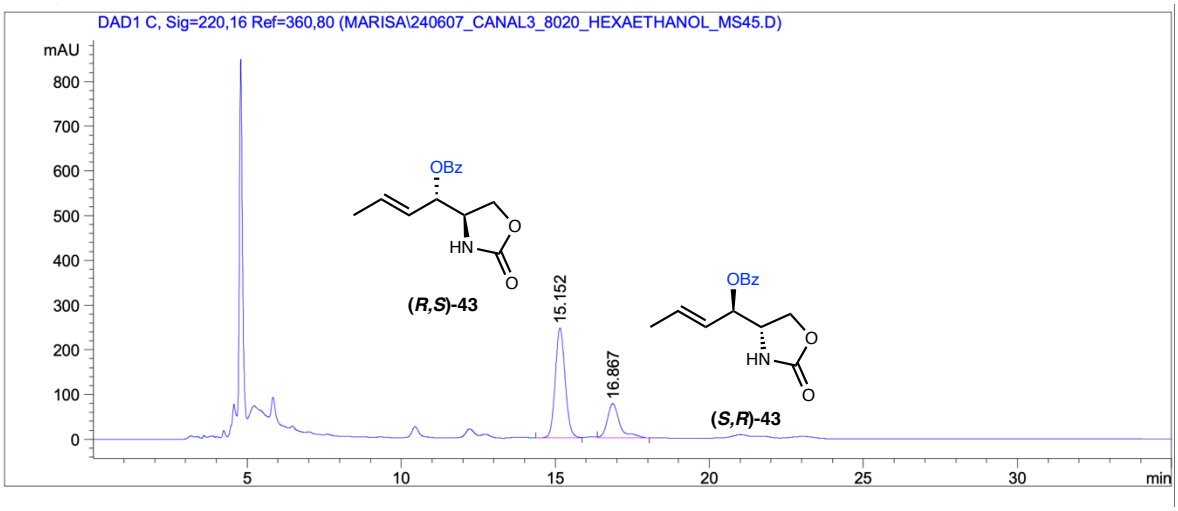
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.661	BB	0.3056	2026.52344	102.06979	68.0168
2	15.019	VB	0.3307	952.92163	44.35343	31.9832

Iodine(III) reagent: (*R,R*)-49b



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.829	BB	0.3311	2786.08521	130.47302	73.3682
2	16.481	BB	0.3735	1011.31647	41.61633	26.6318

Iodine(III) reagent: (*R,R*)-50b



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.152	VB	0.3447	5498.54785	246.05864	71.5315
2	16.867	VB	0.4245	2188.34351	77.25698	28.4685