A BRIEF STUDY ON HALO-SPIROKETALIZATION : METHODOLOGY, TOTAL SYNTHESIS AND CATALYST DEVELOPMENT

By

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ABSTRACT

This dissertation consists of an account focused on the development of spiroketal: a key pharamacophoric unit for the drug discovery. Chapter I is further subdivided into three sections: the first section discusses the development of a novel diastereoselective protocol for the synthesis of mono-bromospiroketal. The development of this methodology builds on our previously developed concepts of *HalA* and NAAA utilizing the potent power of a weakly nucleophilic ketone towards halo-functionalization and further entrapment of the carbocation through a pendant alcohol. Fine tuning the protection on the alcohol was instrumental in the development of a highly diastereoselective process. The second section is dedicated to the asymmetric development of the same reaction which delves deep into the development of a new class of Brønsted acidic catalyst. This acccount portrays a structure-guided approach for the optimization of VANOL-derived imidodiphosphorimidates as catalysts for the halonium-ion-induced spiroketalization reaction. Fine tuning of the catalyst active site, alongside enhanced acidity, were required to achieve high catalytic activity for the spiroketalization reaction. A wide range of substrates were well tolerated yielding halogenated spiroketals in high yields, diastereoselectivities, and enantioselectivities. The third section is dedicated to the development of benzannulated spiroketals through desymmetrization. Initial attempts were successful in the development of a highly diastereoselective protocol. Current efforts are focused on the development of an asymmetric variant utilizing our previously developed VANOL/VAPOL based catalyst.

Chapter II describes an application of the previously discovered methodology towards the total synthesis of the natural product Obtusin. The enabling role of the protecting group on the nucleophilic oxygen atom presents a unique discovery that can improve the reaction outcome.

Chapter III depicts the development of three independent methodologies from a critical observation during the mono-bromospiroketalization reaction. Variation of reaction condition enables the shifting of the equilibrium either towards the formation of macrocyclic ether or towards the formation of double anomeric or single anomeric products leading to the generation of cores that are biologically active. A wide range of substrates were well tolerated yielding halogenated macrocyclic ethers and spiroketals in high yields and excellent diastereoselectivities.

Dedicated to my father, my mother, my late grandfather and my late grandmother for their constant love and support

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LIST OF SYMBOLS AND ABBREVIATIONS

Ar	aromatic
ax	axial
ACN	acetonitrile
AcOH	acetic acid
α	angle of rotation
Å	angstrom
$BF_3{\bullet}OEt_2$	boron trifluoride diethyl ether
Bn	benzyl
BnBr	benzyl bromide
BnCl	benzyl chloride
BINOL	1,1’-Bi-2-naphthol
VAPOL	2,2′-Diphenyl-3,3′-(4-biphenanthrol)
VANOL	3,3′-Diphenyl-2,2′-bi-1-naphthalol
$CHCl_3$	chloroform
cm	centimeter
cm^{-1}	wavenumber
d	doublet
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DFT	density functional theory

DMAP	4-dimethylaminopyridine
ESI	electrospray Ionization
Et_3N	triethylamine
EtOAc	ethyl acetate
ee	enantiomeric excess
er	enantiomeric ratio
Et_2O	diethyl ether
equiv	equivalents
eq	equatorial
M	molar
mM	millimolar
mg	milligram
mmol	millimole
>	larger than
<	less than
DMF	*N*,*N*-dimethylformamide
HRMS	high resolution mass spectrometry
$[a]_D$	specific rotation
g	gram(s)
h	hour(s)
HPLC	high pressure liquid chromatography
Hz	hertz

HMPA	hexamethylphosphoramide
i-Pr	isopropyl
IR	infrared
J (NMR)	coupling constant
LAH	lithium aluminum hydride
m	multiplet
mCPBA	3-chloroperoxybenzoic acid
MeOH	methanol
min	minute
µg	micro gram
MHz	megahertz
MS	mass spectrometry
m/z	mass to charge ratio
mp	melting point
mbar	millibar
$MgSO_4$	magnesium sulfate
NaOH	sodium hydroxide
NMR	nuclear magnetic resonance
nm	nanometer
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl

q	quartet
s	singlet
$CDCl_3$	deuterated chloroform
X	mole fraction
NH_4Cl	ammonium chloride
Na_2SO_4	sodium sulfate
CH_2Cl_2	dichloromethane
EtOH	ethanol
DIBAL-H	diisobutylaluminium hydride
DHP	dihydropyran
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
dr	diastereomeric ratio
PPTS	pyridinium p-toluenesulfonate
PPh_3	triphenylphosphine
TsCl	4-toluenesulfonyl chloride
HCl	hydrochloric acid
NaHMDS	sodium bis(trimethylsilyl)amide
DMSO	dimethyl sulfoxide
Me_3Al	trimethylaluminium
NOSEY	nuclear Overhauser effect spectroscopy
nOe	nuclear Overhauser effect
NAAA	nucleophile assisted alkene activation

n.a.	not applicable
n.d.	not determined
NaH	sodium hydride
HalA	halenium affinity
MOM	methoxymethyl acetal
TES	triethylsilane
PMB	4-methoxybenzyl ether
rt	room temperature
rb	round bottom
DBDMH	1,3-dibromo-5,5-dimethylhydantoin
DCDMH	1,3-dichloro-5,5-dimethylhydantoin
BCDMH	1-bromo-3-chloro-5,5-dimethylhydantoin
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
TBCO	2,4,4,6-tetrabromo-2,5-cyclohexadienone
t	triplet
TBS	tert-butyl dimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride
TMS	trimethylsilyl

OTf	triflate
OTs	tosylate
t-BuLi	tert-butyllithium
n-BuLi	n-butyllithium
TLC	thin layer chromatography

CHAPTER I: DEVELOPMENT ON HALO-SPIROKETALIZATION : A METHODOLOGY AND CATALYST DEVELOPMENTAL APPROACH

INTRODUCTION

The spiroketal framework adorns a plethora of marine and terrestrial natural products,[1] and often ordains the overall shape of the molecule. This unique spiroketal framework dictates the 3-dimensionality of the structure in a manner to generate amphiphilic faces central to their biological activity.[1-4] The spiroketal moiety is key to the function and properties of these molecules, while recognized as a privileged pharmacophore for drug discovery (Figure I-1).[1-5]

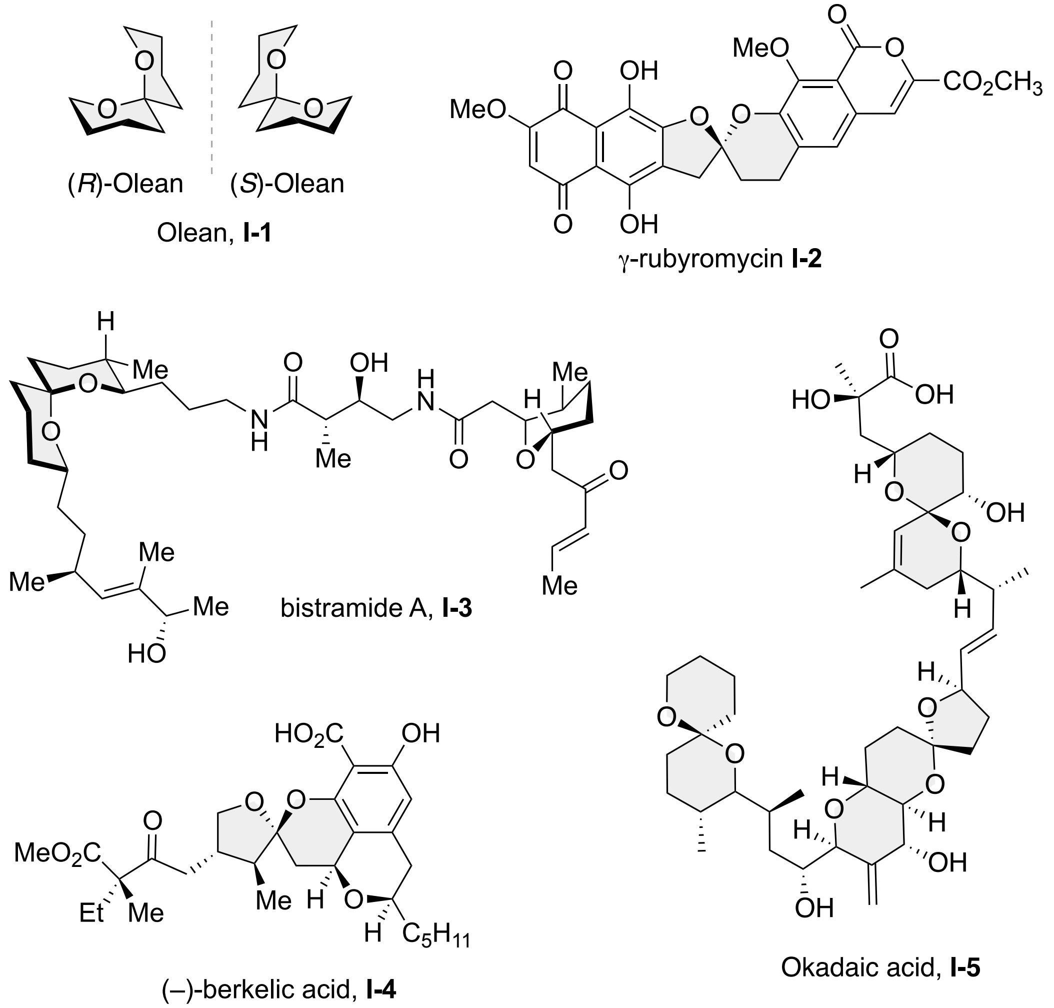
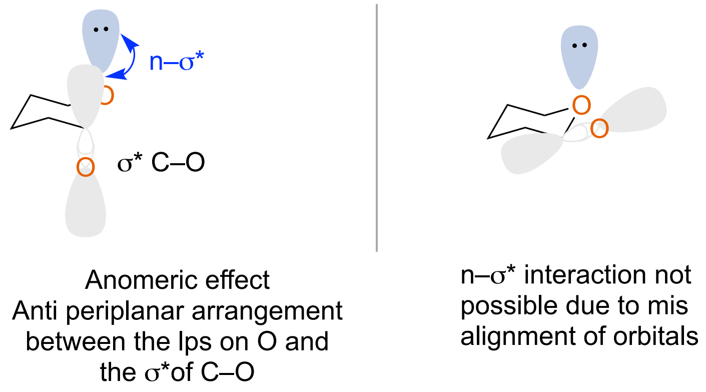


Figure I-1: Natural products containing spiroketal cores.

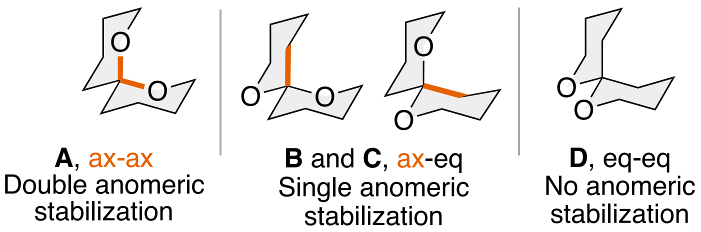
The majority of spiroketal-containing natural products and bioactive molecules are either [6,6], [6,5], or [5,5]- spiroketals. These range from the simplest [6,6] spiroketal found in Olean **I-1**[6] [the major female produced sex-pheromone of the olive fruit fly (*Bactrocera oleae*)] to the more complex structures found in γ-rubyromycin **I-2**[7] [inhibitor of HIV-1 reverse transcriptase], Bistramide A **I-3**[8] [inhibits actin polymerization, depolymerizes filamentous F-actin], (–)-berkelic acid **I-4**[9] [inhibition towards human ovarian cancer cell line OVCAR-3], okadaic acid **I-5** [10] [inhibitor of protein phosphates] etc (Figure I-1).

Spiroketals belongs to the class of molecules broadly recognized as acetals. These are molecular substructure that contain two carbon oxygen single bond at the same carbon atom. This special structural arrangement leads to a unique set of reactivity patterns arising from the “anomeric effect”, a behavior mostly observed in carbohydrates. The term “anomeric effect” refers to the tendency of an electronegative group at the anomeric center (C1) of a pyranose ring to occupy the axial rather than the equatorial position, despite unfavorable 1,3-diaxial (steric) interactions (Figure I-2a).[11, 12] As illustrated in Figure I-2, anomeric stabilization finds its origin in the interaction between one of the lone pairs on the oxygen atom and the σ^* orbital of the C–O bond. The stabilization enjoyed as a result of the latter process is ~2 kcal/mol (1.4-2.4 kcal/mol).[13, 14, 15 ,16] The maximum overlap to achieve this arrangement occurs only when the two oxygen atoms are antiperiplanar with respect to each other; an arrangement that is possible only if they are bis-axially disposed in a spiroketal (double anomeric). Despite the presence of this type of favorable interactions in a system, sometimes steric congestion or solvent stabilization or a combination of both might override the anomeric effect leading to the formation of the less stable mono-anomeric products (see Chapter III for a detailed discussion). Based on the orientation of the C-O across a 6-membered ring, for a [6,6]-spiroketal there are four possible anomeric structures possible (Figure I-2b). **A** with its bis-axially substituted oxygen atoms is most stable. The bis-equatorially substituted **D** is the least stable, while **B** and **C**, with one axially disposed oxygen atom are intermediate in stability.[17] For a 5-membered ring these effects are not that significant because of the inability to attain a conformationally stable chair form, instead forms a

a. Stabilization through Anomeric Effect:



b. Anomeric structures possible for [6,6]-spiroketals



c. Anomeric effect in [6,5] and [5,5]-spiroketal

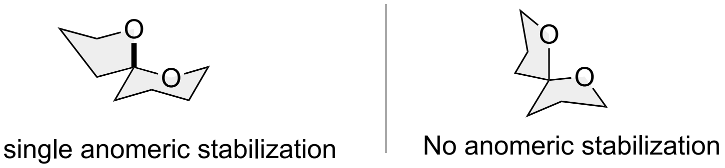


Figure I-2: a. Principle of anomeric stabilization, b. Anomeric structures in [6,6], [6,5], [5,5] system.

skewed conformer. Hence, [5,5]-spiroketal are the least stable spirocyclic system while [6,5] / [5,6]- spiroketals enjoys more stabilization through anomeric effects. These spiroketals formations are most often governed by the steric interactions present in the substrate.

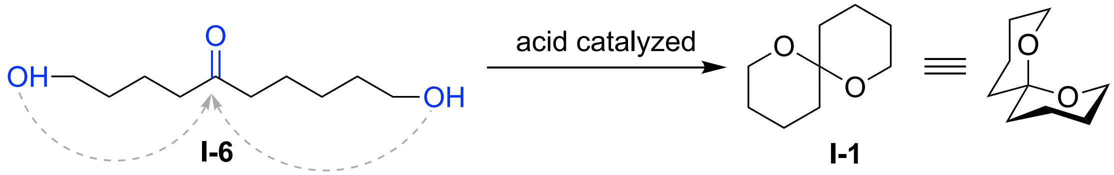
The interest in this structural motif has garnered the attention of organic chemists to develop strategies for its synthesis,[6,18-34] although the paucity of methods to generate diastereoselective and enantioselective spiroketals remains an issue to be addressed. Piqued by our interest for the halofunctionalization of olefins to generate an array of diverse carbocyclic cores, we aimed to develop a diastereoselective and an enantioselective protocol for the preparation of halogenated spiroketals.

I.I. Synthetic approaches towards the synthesis of Spiroketal

I.I.1. Dynamic diastereoselective spiroketalization

Since the spiroketal motif is a sub-class of the acetal family; the most generic approach to access these motifs involves acid catalyzed acetal formation by a pendant diol onto an incipient ketone **I-6** (Figure I-3a). This acid catalyzed acetalization approach is generally the thermodynamic pathway and hence generates the most stable doubly anomeric spiroketal core as the major product (sometimes these cyclizations are influenced by the substituents present along the chain). Most naturally occurring compounds contain a double anomeric spiroketal moiety, hence the aforementioned acid catalyzed dehydration approach has been extensively utilized to access numerous natural products.[1, 6, 30, 31, 35]

a. Generalized approach towards the formation of spiroketal



b. Schreiber and coworkers - Diastereoselective Spiroketalization

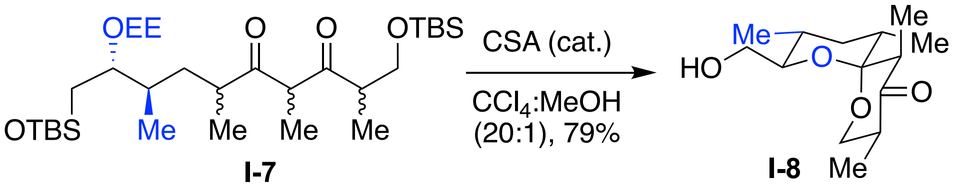


Figure I-3: Synthetic approaches towards the formation of spiroketal cores.

Figure I-3 demonstrates the utility of this methodology through two prominent studies found in the literature. During the total synthesis of 6-deoxyerythronolide B, Schreiber *et al*. demonstrated a thermodynamically controlled spiroketalization of a diastereomeric mixture of diol **I-7** with three epimerizable stereocenters (Figure I-3b).[35, 36] The reversibility associated with the acid catalyzed 6-exo cyclization (and/or enolization) allows for thermodynamic control, furnishing **I-8** as a single diastereomer. In this reaction the stereodefined centers (highlighted in blue in I-7), determine final stereochemistry of the spiroketal.

I.I.2. Hemi-ketalization followed by Michael addition

Figure I-4 describes a unique approach developed by the Tan & Liu group for the diastereoselective formation of benzannulated spiroketal core through a domino of hemi-ketalization-dehydration-Michael addition-ketalization cascade reactions.[37] The crux of their approach was driven by the formation of the allylideneoxonium intermediate **I-13**. In this approach, as illustrated in Figure I-4, formation of the hemi-ketal **I-12** from the α,β-unsaturated carbonyl system **I-9** followed by the extrusion of water generated the oxacarbenium intermediate **I-13**, which would then undergo a Michael addition generating

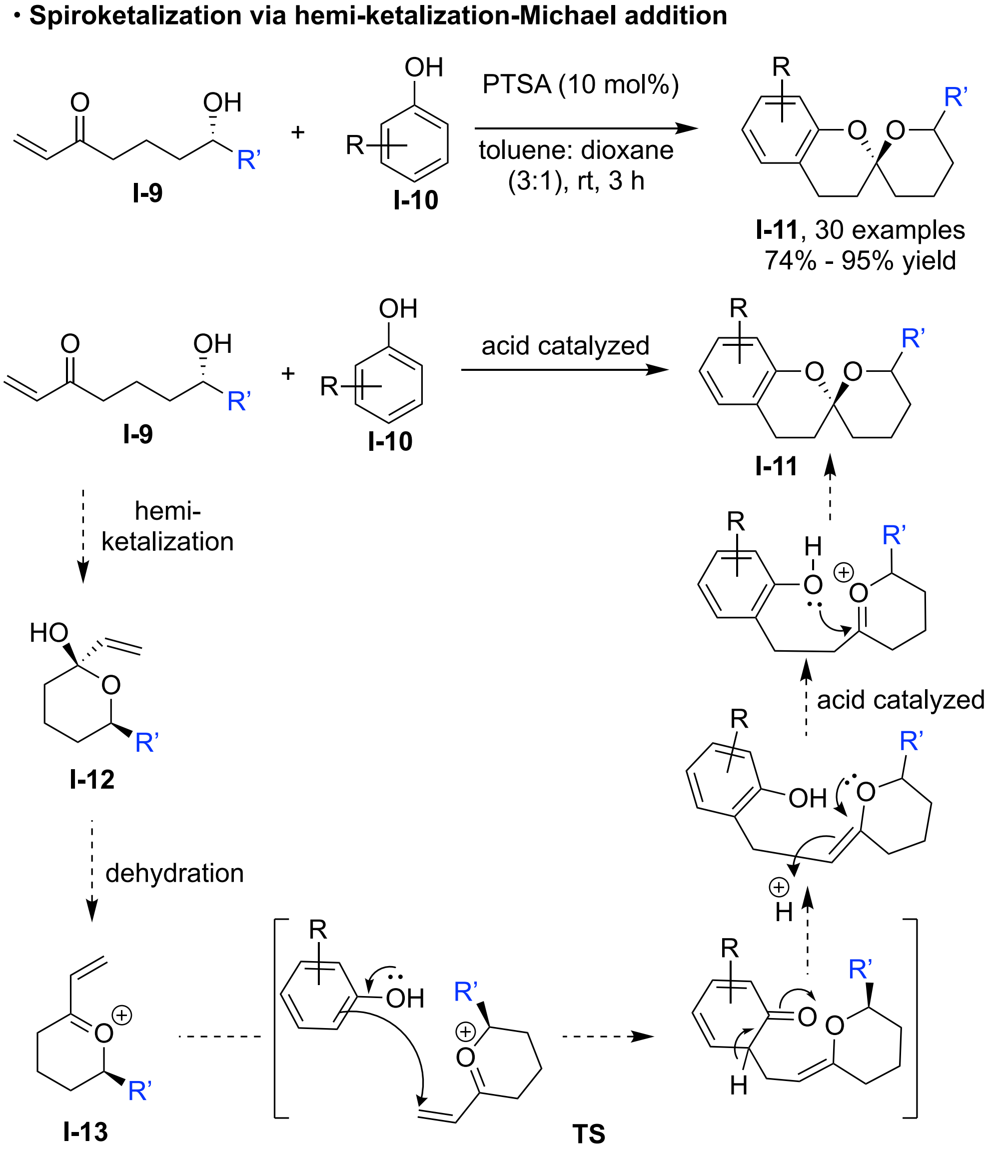
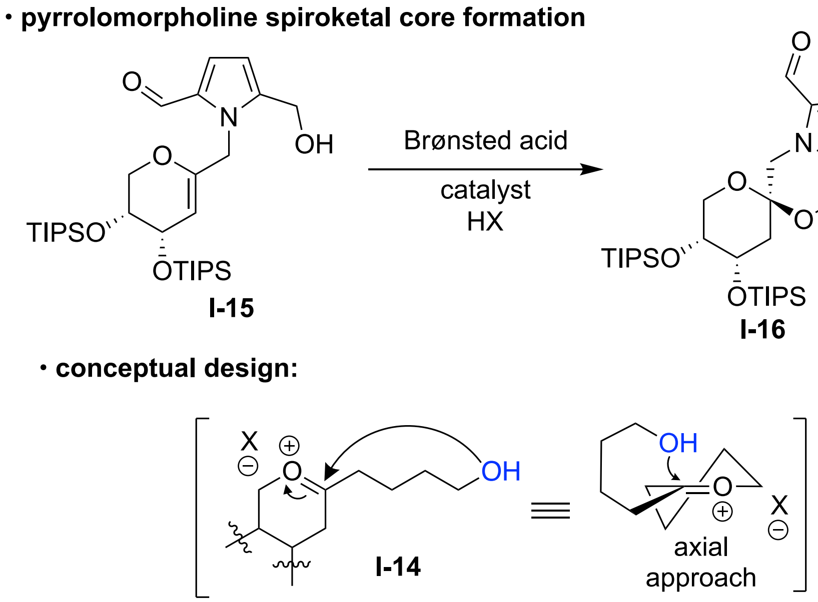


Figure I-4: Spiroketal core through hemi-ketalization-Michael addition approach.

the spiroketal core **I-11** in 83% yield. Due to simplicity of the methodology a wide array of natural products could be accessed from readily available phloroglycinol **I-10** and hydroxy vinyl ketones **I-9**.

I.I.3. Spiroketalization through the Dihydropyranyl core

The formation of an oxacarbenium intermediate can also be achieved following the protonation of a dihydropyranyl moiety. As illustrated in Figure I-5, in this approach developed by the Tan group, the generated oxacarbenium intermediate (**I-14**) remains embedded in a well-defined 6-membered ring system that guides the trajectory of the incoming nucleophile towards the incipient oxonium ion mostly from the axial face (unless over-ridden by steric effects). This results in the formation of the spiroketal with high diastereoselection. The oxacarbenium intermediate is trapped by a tethered alcohol leading to the formation of the double anomeric spiroketal (Figure I-5).[6, 30] A similar


• pyrrolomorpholine spiroketal core formation

• conceptual design:

Figure I-5: Spiroketal synthesis from DHP core.

strategy was utilized for the formation of a pyrrolomorpholine spiroketal framework where the protonation of the DHP core of **I-15** with preset pyrrole-hydroxy motif was able to diastereoselectively generate **I-16** as a single diastereomer.[38]

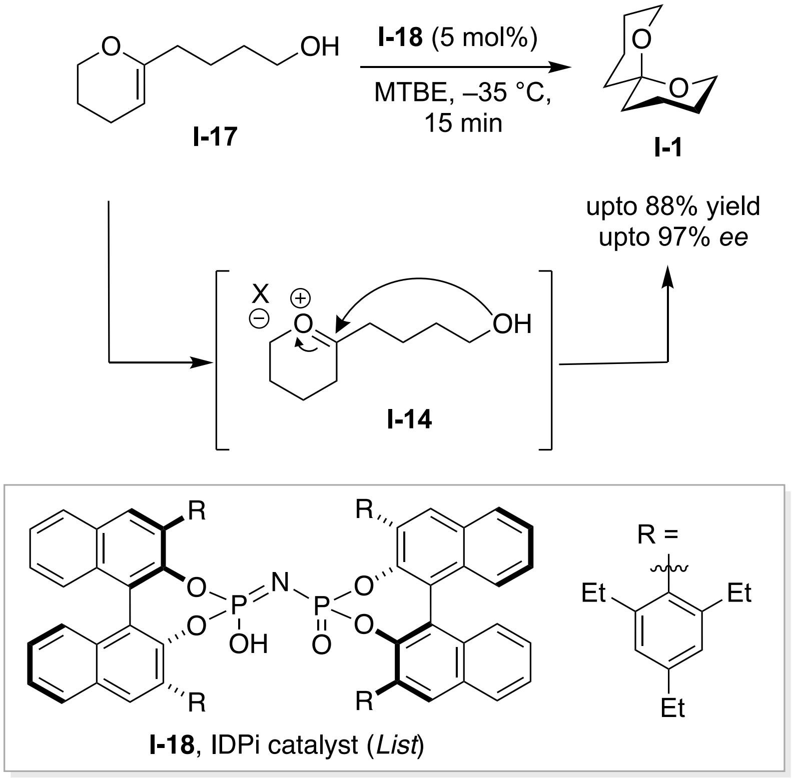
I.II. Asymmetric Spiroketalization Approaches

Taking inspiration from these elegant highly diastereoselective strategies, it was realized that the major steps towards spiroketalization was the formation of the oxa-carbenium intermediate; the subsequent trapping of this carbocationic species inside the chiral pocket of the embedding catalyst would thus lead to the formation of the asymmetric spiroketals. Different groups have thus far devised elegant synthetic strategies towards the development of these enantio-enriched spiroketals.

I.II.1. Generation of the chiral-oxacarbenium intermediate through BINOL based Bronsted Acidic Catalyst:

List's Approach: List research group in 2012 reported the first novel approach to the synthesis of spiroketals in a catalytic enantioselective manner via the protonation of the dihydropyranyl moeity (Figure I-6).[6] In this strategy, dihydropyrans bearing a pendant alcohol underwent diastereo and enantioselective spiroketalization in presence of imidodiphosphoric acid catalyst **I-18** gave the desired product **I-1** in excellent yield and asymmetric induction. The use of chiral Brønsted acidic catalyst **I-18** resulted in the formation of the oxacarbenium intermediate contained in a highly constrained binding pocket, that resulted in the formation of the spiroketal in excellent enantioselectivity during the spiroketalization event. Further investigation revealed that the same catalyst is capable of overriding the thermodynamic preference leading to the formation of

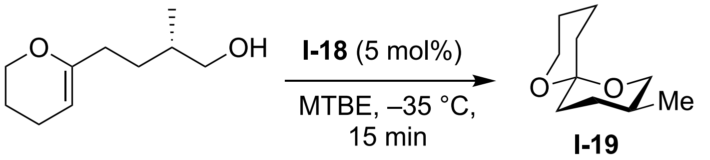
a. List's Approach:



upto 88% yield
upto 97% *ee*

I-18, IDPi catalyst (*List*)

b. Formation of the kinetic spiroketal:



upto 70% yield
>50:1 *dr*

Figure I-6: Asymmetric Spiroketal synthesis by protonation of the DHP core.

spiroketal; therefore, several substrates such as **I-19** bearing a chiral center underwent a kinetically controlled spiroketalization and generated a non-thermodynamically stable spiroketal in excellent diastereoselectivity (Figure I-6).

Nagorny's Approach: The Nagorny group in 2012, has also reported a similar approach of forging an enantioselective spiroketal framework using the dihyropyranyl moiety **I-21** as a precursor utilizing a monomeric BINOL-based chiral phosphoric acid **I-20** (Figure I-7).[30] A tertiary alcohol intercepts the generated oxacarbenium intermediate *en route* to the spiroketal formation (Figure I-7). They have further investigated the mechanism of their spiroketalization reaction as well as the origin of the selectivity through experimental and computational studies. Their results revealed a highly diastereoselctive

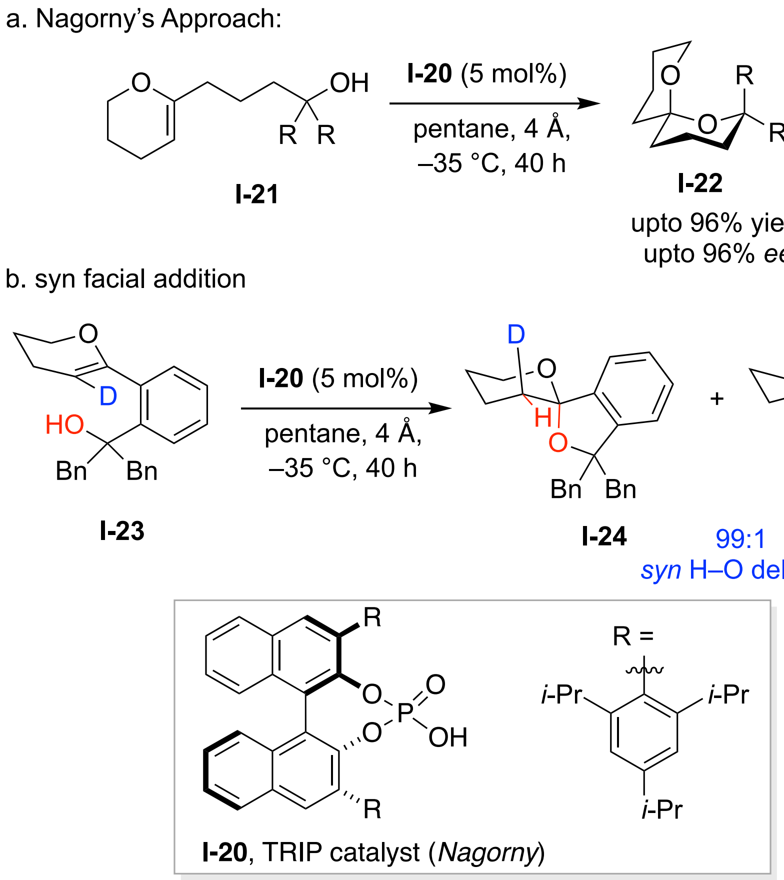


Figure I-7: Asymmetric Spiroketalization approach by Nagorny.

syn-facial protonation and subsequent nucleophilic addition (predominantly favoring the formation of **I-24**) mechanism during the course of spiroketalization (Figure I-7).[31]

I.II.2. Carreira's Approach*:* An elegant strategy to forge a vinyl substituted spiroketal **I-27** framework has been reported by the Carreira group in 2017.[32] This approach, proceeds through the formation of a π-allyl complex catalyzed by the iridium–(P, olefin) complex **I-28** (Figure I-8). The ketone is in equilibrium with its hemiacetal moiety **I-29** (through its interaction with the pendent hydroxyl group), exposes a nucleophilic face for interception of the metal-π allyl complex, consequently forming the spiroketal framework

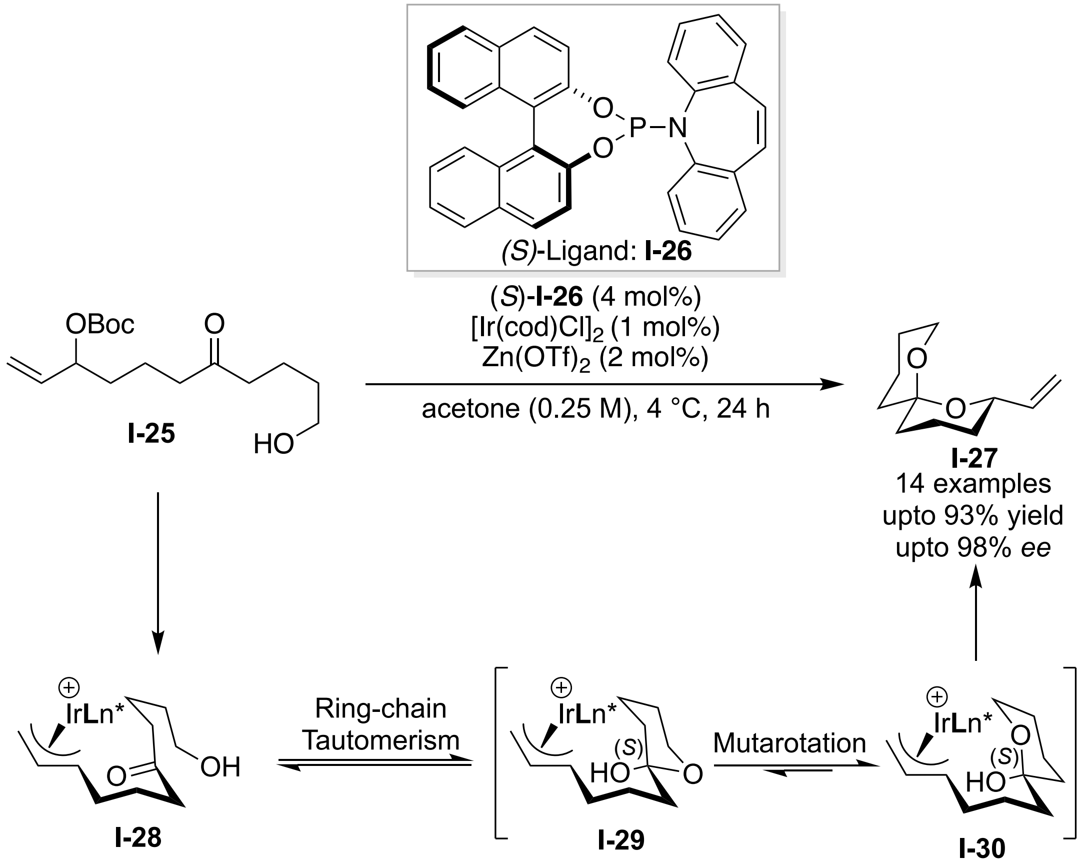


Figure I-8: Carriera's approach towards enantioselective spiroketalization.

I-27. The chirality of the phosphoramidite based ligand **I-26** determines the facial selectivity of the asymmetric allylic substitution. Mutarotation of the equilibrating hemiacetal **I-30** intermediate provides a mechanism for setting up the stereochemistry on the acetal center under the influence of the chiral ligand (Figure I-8).

I.II.3. Denmark's Approach*:* A recent contribution from Denmark and coworkers illustrates the use of chiral Lewis basic selenophosphoramide catalysts **I-32** to achieve delivery of an aryl thiiranium along with capture of the incipient oxonium with a latent hydroxyl group (Figure I-9) to generate thio-spiroketals **I-33** in great yields and excellent *er*.[20] In a structurally related study to spiroketals, Yeung and coworkers demonstrated

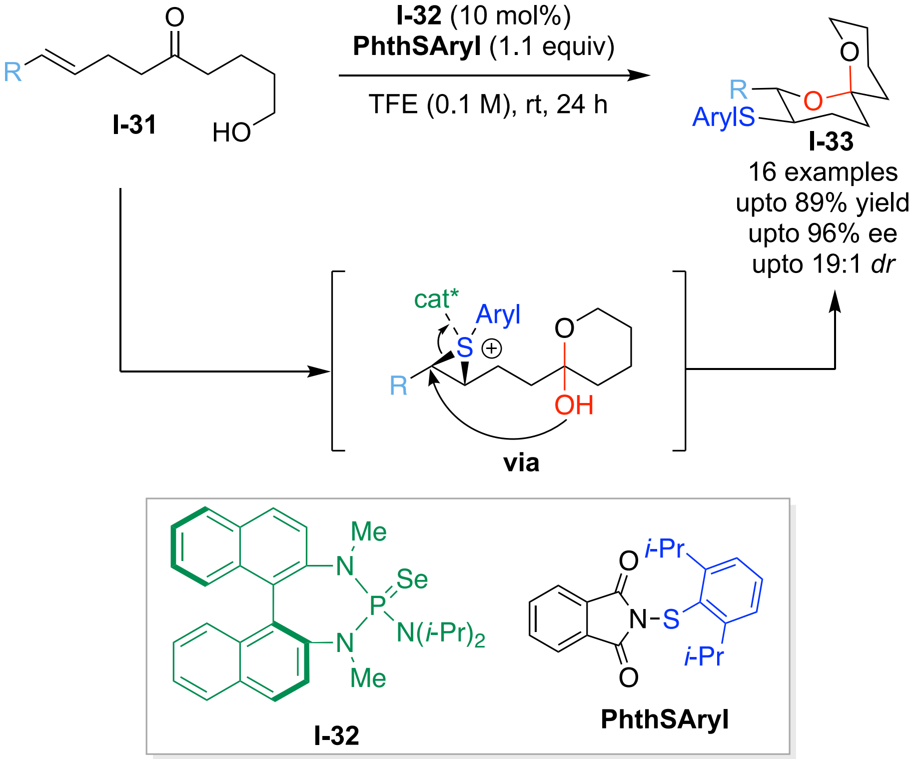
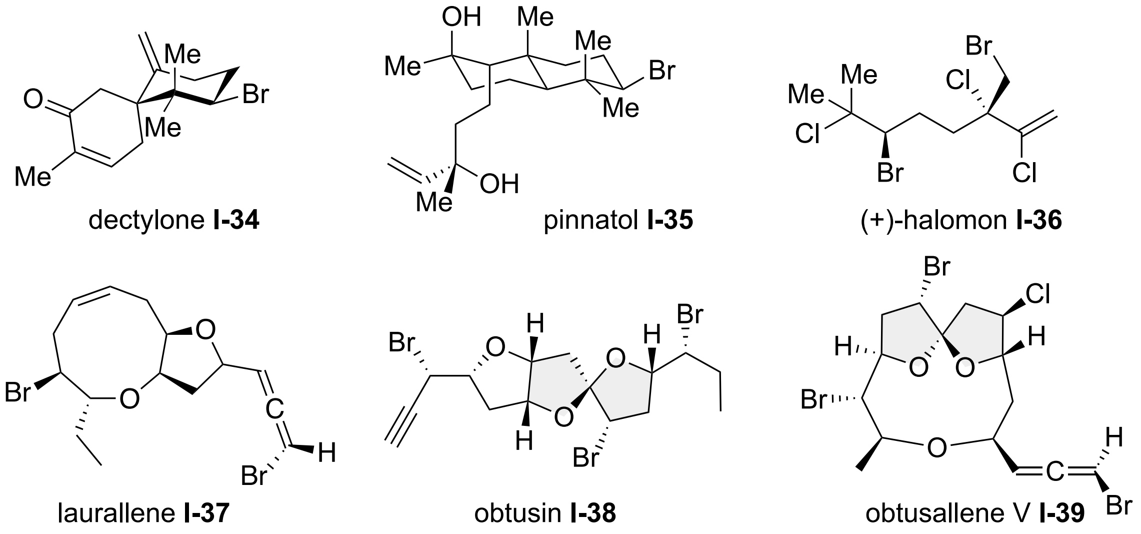


Figure I-9: Denmark's Approach towards enantioselective spiroketal.

enantioselective spirolactonization of vinylsubstituted benzophenone carboxylic acids using their thiourea based chiral catalysts.[28]

I.III. Halenium assisted spiroketalization (our approach)

Despite excellent advances in the spiroketalization reaction, synthesis of halogenated spiroketals is not well explored. Halogenated natural products are frequently encountered. In fact, more than 5000 halogenated natural products had been discovered as of 2011. Some of these halogenated natural products contain the spiroketal moiety in their skeleton (Figure I-10).[5, 39, 40] A robust and diastereoselective synthesis of halogenated spiroketals can provide a route towards the total synthesis of these compounds.



dectylone **I-34**　pinnatol **I-35**　(+)-halomon **I-36**

laurallene **I-37**　obtusin **I-38**　obtusallene V **I-39**

Figure I-10: Natural product core containing halogens [halogenated natural products with spiroketal core have been shaded].

I.III.1. Development of halenium assisted spiroketalisation

The carbon-carbon double bond is arguably one of the most versatile functional groups in organic chemistry. An enormous body of literature is devoted to the transformation of alkenes into diverse and versatile functionalities.[41] The enantioselective

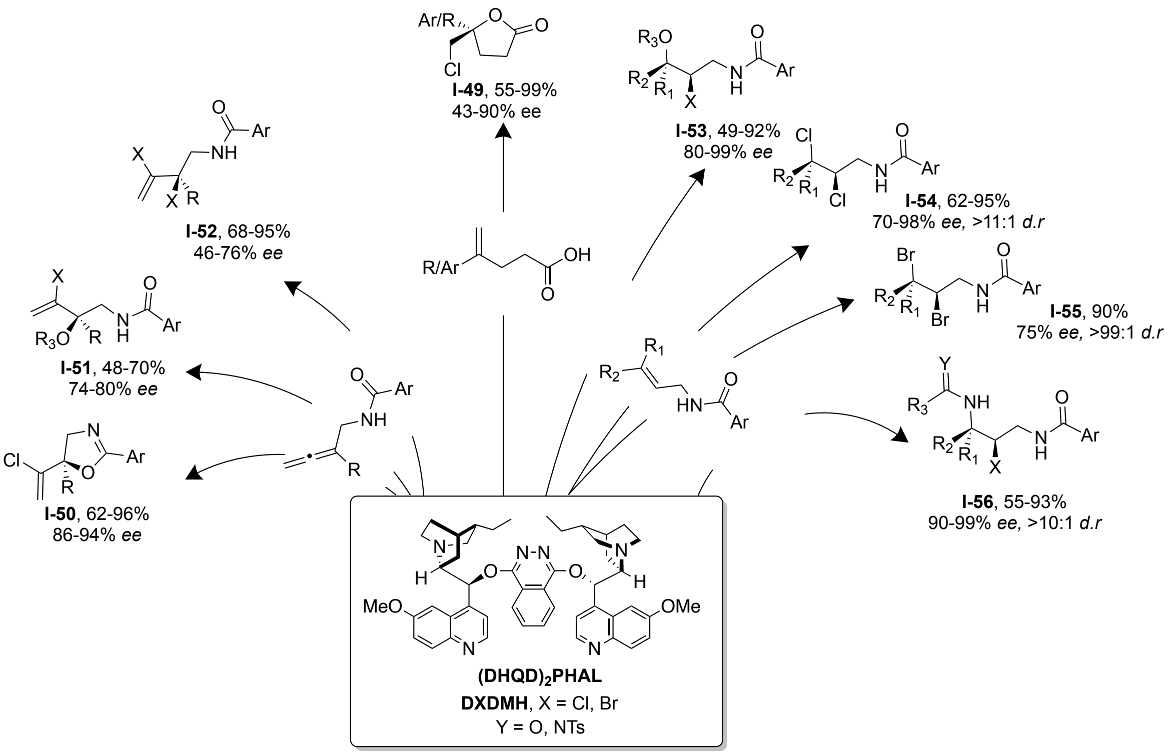


Figure I-11: Development of halofunctionalization protocols by our group over the years.

functionalization of alkenes has witnessed a sustained interest for the best part of the last five decades.[42, 43] Our group has been intensely engaged with catalytic asymmetric halofunctionalization of alkenes. Our first report in this area dates back to 2010 when we disclosed the first catalytic and highly enantioselective chlorolactonization reaction of alkenoic acids.[44] Subsequently, numerous groups have reported on asymmetric halofunctionalization reactions.[45-49, 50-52] Our own contributions to this field have since focused on reaction discovery and mechanistic studies. This has led to the development of protocols for the asymmetric halocyclizations of alkenes with various functional groups, kinetic resolution of allyl amides, intermolecular halofunctionalizations with allyl and

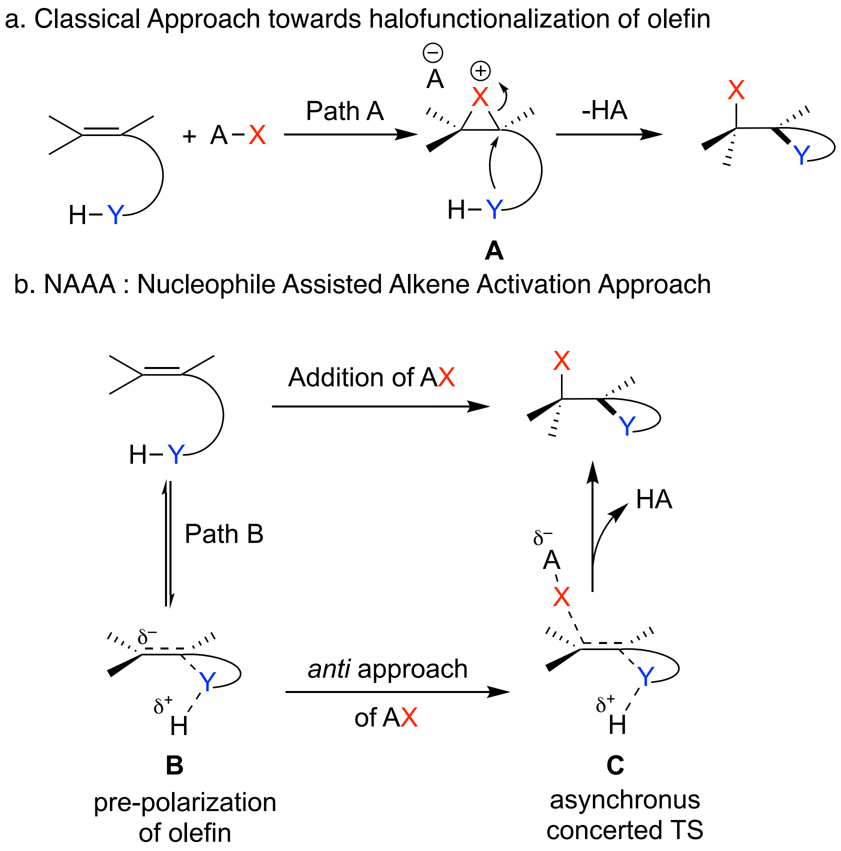


Figure I-12: Conceptual demonstration of NAAA via traditional approach.

allenyl amides, including the first Ritter-based asymmetric transformation, as well as catalytic asymmetric dihalogenations. [44, 53-66] We have also pursued structure-enantioselectivity studies of the catalyst and mechanistic investigations for a better understanding of factors that lead to the observed stereochemical outcomes in these reactions. The crux of these reactions has generally been through the initiation of an active halenium source that adds to olefins, rendering further functionalization through the nucleophilic attack of multiple functional groups (Figure I-11). [60, 64, 65]

With our first successful report in 2010, on the enantioselective chlorolactonization of unsaturated carboxylic acids **I-49**, we soon realized the empowering effect of the dimeric cinchona alkaloid chiral catalyst [$(DHQD)_2$PHAL]. The use of nucleophiles other than carboxylic acids served to significantly improve the scope of this transformation and allow for the synthesis of a wide variety of chiral heterocycles. The relative and absolute selectivity in chlorolactonization **I-49**, chloroamidation **I-50** to **I-56** and chloro-carbamate cyclization reactions were examined with the help of deuterated substrates with surprising results.[60, 64, 65] First, the chlorenium is delivered to the same face of the olefin with high selectivity irrespective of the substrate. Second, the nature of the nucleophile and reaction conditions dictate whether the relative stereochemistry of addition is *syn* or *anti*.

<u>HalA</u>: During the development of these multiple halofunctionalization reactions, we realized the need for the introduction of a parameter that defines the affinity of various

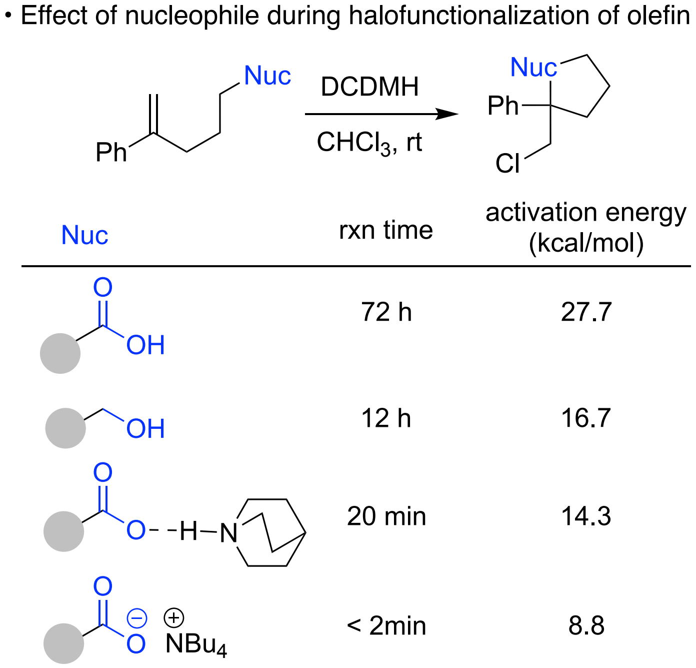


Figure I-13: Nucleophilic activation during halofunctionalization.

functional groups towards a halogen. A new scale that defines the propensity of a given nucleophile to capture the halenium ion was introduced. The halenium affinity (*HalA*- akin to proton affinity) scale ranks various acceptors (olefins for instance) embedded in a molecule based on their ability to stabilize a "free halenium ion", thus providing a means for prediction the pathway of the reactions and product distributions.[55] The *HalA* values enable a rapid and quantitative determination of the propensity of various functional groups (alkenes as the central theme) to react with the halenium sources. Parametrization for the affinity of olefins towards the halenium capture led to a revised mechanistic understanding of halofunctionalization of olefins.

<u>NAAA:</u> In the classical assumptions the role of the nucleophile in the halofunctionalization of olefins is neglected. However, empowered by *HalA*, our group was able to demonstrate that the halenium affinity of an olefin can be dramatically affected by the role of the pendent nucleophile during the course of the reaction. It was suggested that the substrate

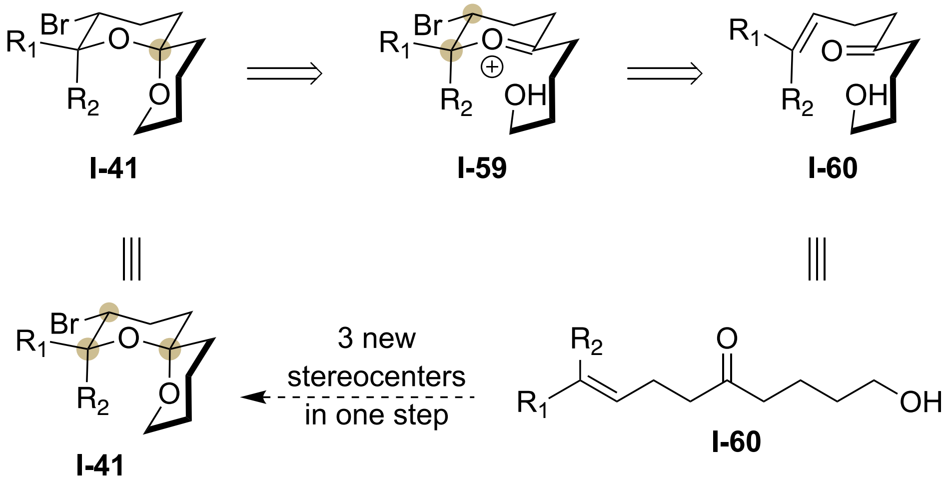


Figure I-14: Our retro synthetic approach for the synthesis of halogenated spiroketal.

re-organizes (structurally) before participation in the reaction. The aforesaid pre-organization occurs via the interaction between the non-bonding orbital of the nucleophile and the π* of alkene which pre-activates the alkene and sets it up for further transformation. As a result, an asynchronous concerted mechanism was proposed for the halofunctionalization of olefin (Path B, Figure I-12). The term nucleophile-assisted alkene activation (*NAAA*) was used to describe this phenomenon to accentuate the importance of the nucleophilic partner during the halofunctionalization of the olefins (Figure I-12).[56] We noted a direct and strong correlation between the rate of halofunctionalization and the strength of the nucleophile (Figure I-13): the stronger the nucleophile (carboxylate anion in this instance), the greater will be the accumulation of the charge density on the olefin, and the faster will be the capture of the halenium ion. We proposed nucleophile assisted alkene activation (*NAAA*), in which the preorganization of the olefin with the tethered nucleophile facilitates the halofunctionalization reaction (Figure I-13).[56]

I.III.1. Halenium assisted diastereoselective mono-bromospiroketalization

A. Reaction development and Optimization Studies

We sought to investigate the halofunctionalization with a ketone as the tethered nucleophile. The latter reaction would result in formation of oxocarbinium species that can lead to spiroketals if intercepted by a tethered alcohol moiety.

Spiroketalization was envisioned through two logical disconnections. Firstly, the formation of an oxa-carbenium intermediate **I-59** and then the subsequent trapping of the intermediate with an adjacent alcohol. Thus, the overall process involved two nucleophilic attacks: the weaker nucleophilic partner ketone and an alcohol as a stronger nucleophilic

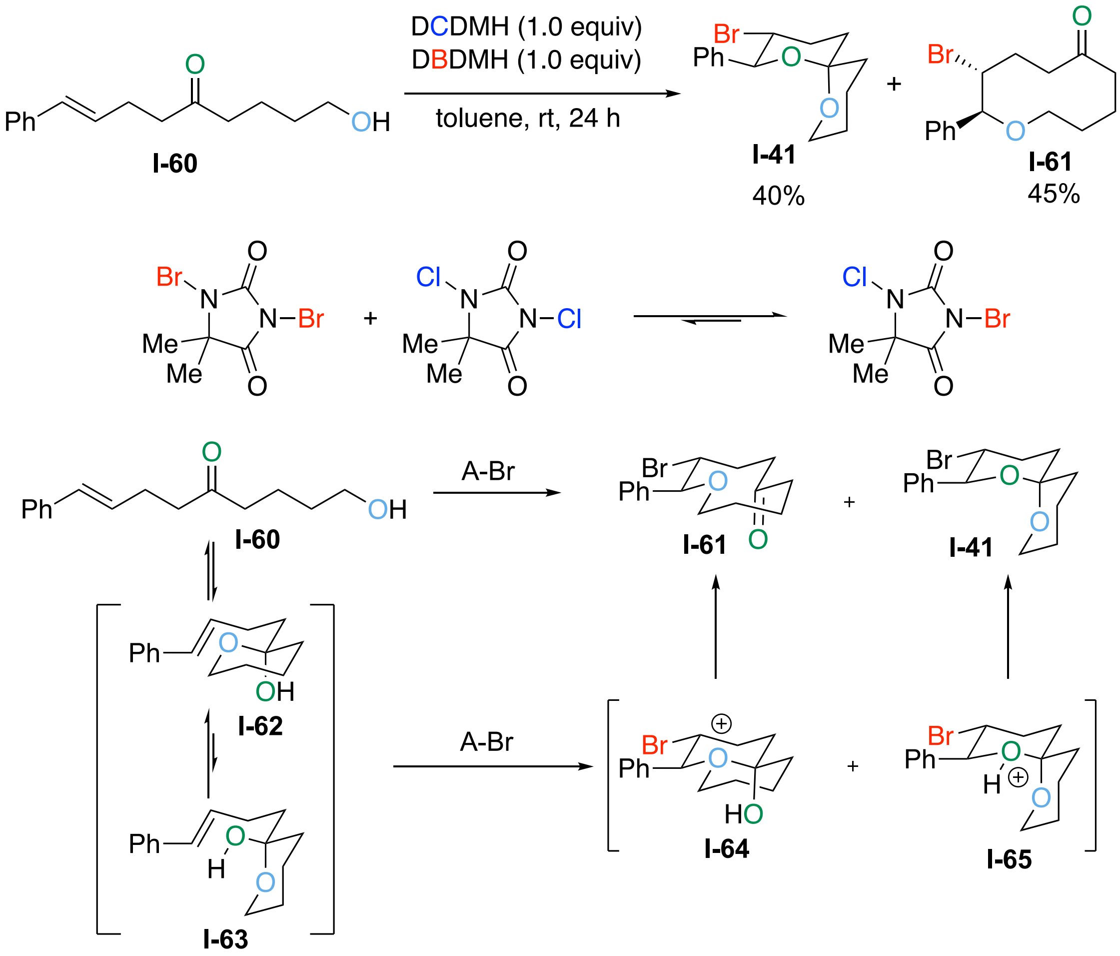


Figure I-15: Bromo-spiroketalization through the free OH **I-60** generating the macroether as a major product.

component. General substrate keto-alken-ol **I-60** bearing both alcohol and olefin was envisioned to undergo halenium (bromenium) capture with the aid of the ketone generating an oxocarbenium intermediate that can be intercepted by the tethered alcohol to furnish the spiroketal. This transformation led to the generation of three stereocenters, with complete control of diastereoselectivity (Figure I-14).[53]

Initial screening of the bromonium sources proved the incompetence of NBS and DBDMH in delivering the spiroketal **I-41**. Further optimization revealed 3-bromo-1-chloro-5,5-dimethylhydantoin (BCDMH) as the optimum halonium source which was generated *in situ* by reacting an equimolar mixture of DCDMH and DBDMH. Surprisingly, the desired spiroketal **I-41** was isolated as a minor product along with the macrocycle **I-61** as the major product after reacting the substrate **I-60** with BCDMH as the halonium source

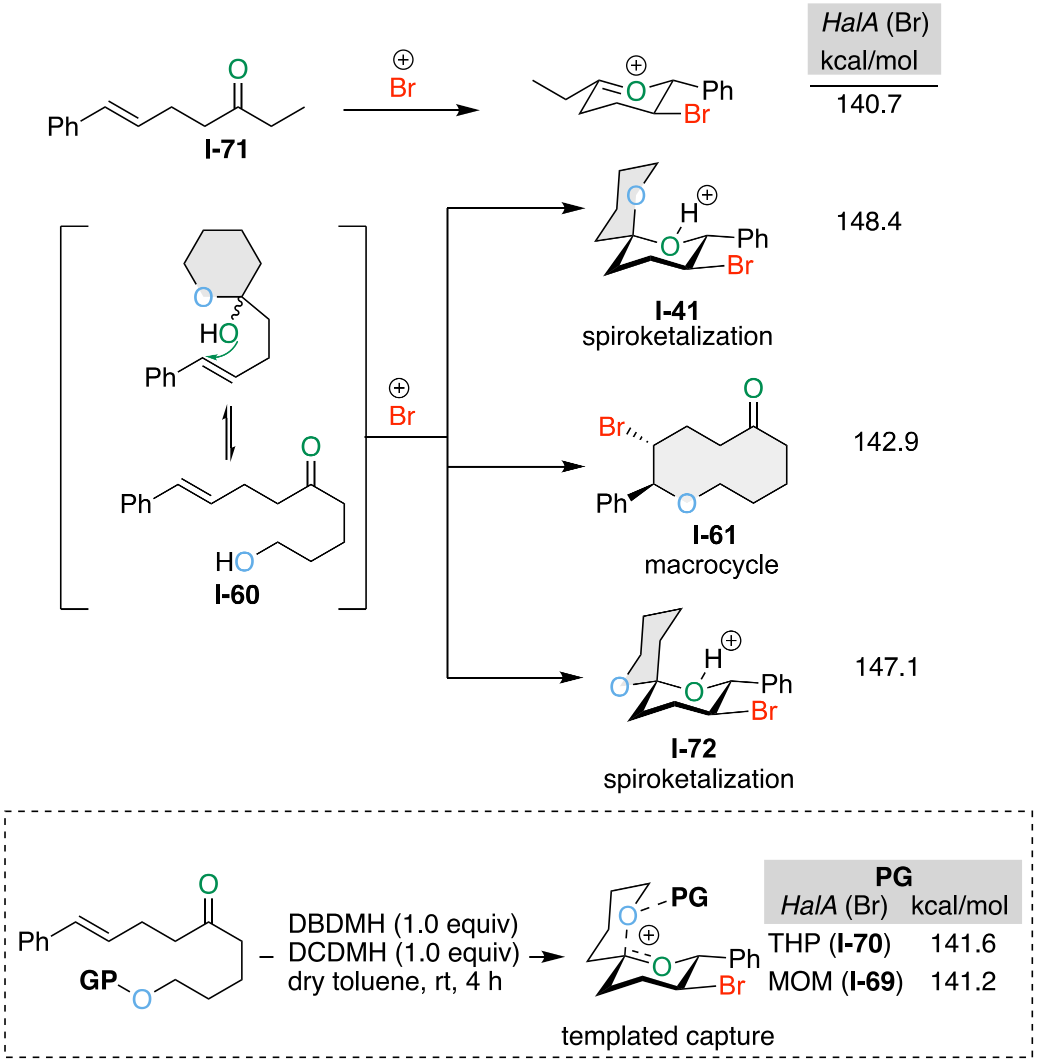
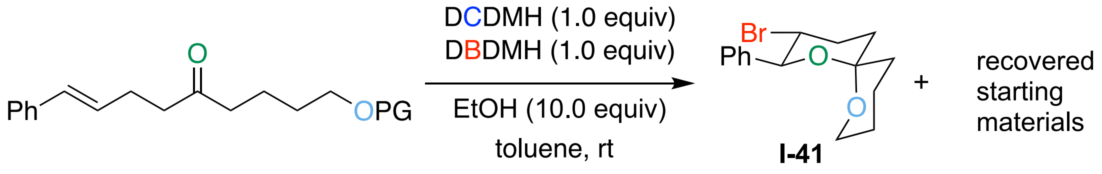


Figure I-17: Computed *HalA* values; templation effect to generate the desired spiroketal.

(Figure I-15). This product distribution indicated an existing equilibrium between substrate **I-60** and its hemiacetal forms **I-62** and **I-63**. The interception of the hydroxy group in bromo functionalization in hemiacetal **I-65** produced the desired spiroketal **I-41** while the interception of the oxygen moiety embedded in the six-membered ring, **I-64**, yielded the macrocycle **I-61**. Presence of the hemiacetal is in agreement with Carreira's report shown in Figure I-7.[32] In order to circumvent this side product, we sought to protect the tethered alcohol, to prevent the formation of hemiacetal intermediates that lead to the macrocyclic product.

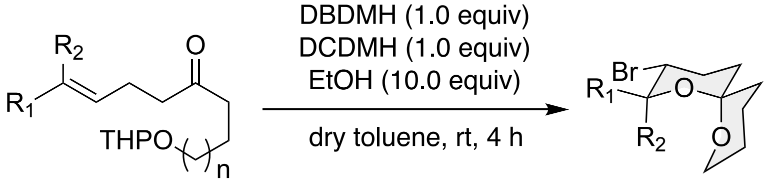
The protection of the pendant hydroxy moiety was considered to suppress the macrocyclization of substrate **I-60** and different protecting groups such as TBS, TES, and PMB were evaluated; however, only trace amounts of the desired spiroketal was observed (Figure I-16). Interestingly, protecting the free alcohol with MOM protecting group (**I-69**) gave spiroketal **I-41** in 20-35% yield. Finally using THP as the protecting



entry	PG	yield of **I-41** (%)	*dr*	recovered SM (%)
1.	TBS (**I-66**)	<2	n.d	>95
2.	TES (**I-67**)	<2	n.d	>95
3.	PMB (**I-68**)	<2	n.d	>95
4.	MOM (**I-69**)	20-35	n.d	10-18
5.	THP (**I-70**)	99	>98:2	n.d

Figure I-16: Bromo-spiroketalization with protected alcohol.

Table I-1: General substrate scope for the bromo-spiroketalization.



Entry[a]	R_1	R_2	Substrate Label	n	Yield (%)[b]	*dr*[c]
1	Ph	H	**I-41**	2	99	>98 : 2
2	Ph	H	**I-73**	1	73	>98 : 2
3	α-naphthyl	H	**I-74**	2	88	>98 : 2
4	β-naphthyl	H	**I-75**	2	93	>98 : 2
5	*p-Me*-C_6H_4	H	**I-76**	2	87	>98 : 2
6	*o-Me*-C_6H_4	H	**I-77**	2	80	>98 : 2
7	*p-F*-C_6H_4	H	**I-78**	2	84	>98 : 2
8	*p-Ph*-C_6H_4	H	**I-79**	2	83	>98 : 2
9[d]	*p-OMe*-C_6H_4	H	**I-80**	2	73	>98 : 2
10	Ph	Me	**I-81**	2	77	>98 : 2
11[e]	Ph	H	**I-82**	2	82	>98 : 2
12	H	*n*-Bu	**I-83**	1	88	1.6 : 1

[a] Reactions were performed using 0.1 mmol of substrate. [b] isolated yields. [c] *dr* were estimated by ^{1}H NMR analysis. [d] 1.1 equiv of NBS was used as the bromenium source. [e] reaction was performed at rt using 1.1 equiv of NIS as halenium source.

group **I-70** generated the desired spiroketal **I-41** in excellent yield and diastereoselectivity. Addition of ethanol was crucial for this reaction as it facilitates removal of the THP group from intermediate, furnishing the desired spiroketal. This result was corroborated by our *HalA* calculations, the ketone is a weak nucleophile and hence is incompetent to participate and effect the desired transformation.[53] The presence of a free pendant alcohol makes it extremely reactive through the formation of hemi-acetal (*HalA* 142.9 kcal/mol) and hence leads to the formation of the undesired macro-ether. Hence, templating the free alcohol with –OTHP **I-70** and –OMOM **I-69** enhances the *HalA* by 0.9 kcal/mol and 0.5 kcal/mol, respectively, in order to tune the reaction towards the formation of the spiroketal (Figure I-19). The methyl ketone that shows the lowest *HalA* value resembles substrates with protecting groups such as TES, TBS and PMB (Figure I-19) that were incompetent to furnish spiroketalization. Once the desired templating effect was established, the THP-protected ketoenol **I-70** was subjected to 1.0 equiv. of DCDMH and DBDMH, leading to the desired bromospiroketal which was obtained in great yield and excellent diastereoselectivity (Table I-1, entry 1). Similar reactivity was also observed when the chain length was shortened, as the formed spiroketal was obtained in good yield and excellent diastereoselectivity (>98:2) (Table I-1, entry 2). With this protocol in hand, the iodinated version of this methodology was able to generate the iodo-spiroketal in good yield and excellent *dr* (Table I-1, entry 11). But the chlorinated and fluorinated version were not successful.

After the successful development of this methodology, in order to showcase the generality a brief substrate scope was developed.[53] Table I-1 summarizes the results for a handful of keto-alkenols that were subjected to the optimized conditions for mono-bromospiroketalization. Most of these substrates, irrespective of their electronic properties, were well tolerated and generated the desired product in good yield and excellent diastereoselection. The relative stereochemistry in these halogenated spiroketals was established unequivocally by the crystal structure of the products **I-73** and **I-74**. Both [6,6] and [6,5]-spiroketals were formed in good to excellent yield with *dr* > 98:2, but [5,5] spiroketal **I-83** that lack the anomeric stabilization due to formation of the skewed 5-membered spiroketal ring, generated the corresponding spiroketal in good yield but with low diastereoselectivity of 1.6:1 (Table I-1, entry 12).

Summary: We have demonstrated the application of Halenium Affinity (*HalA*) as a guiding tool towards modulation of nucleophilic strength, leading to a diastereoselective spiroketalization. Unaided ketones were found to be inefficient nucleophiles towards olefin activation; however, the tethered alcohol provided a handle to modulate the ketone's nucleophilic strength. Calculation of the *HalA* values revealed the effect of tethered alcohol on the halogen affinity of the olefin. THP protected tethered alcohol proved to be optimal for the spiroketalization reaction.

I.III.2. Asymmetric mono-bromospiroketalization: Reaction development and Optimization Studies

With an excellent diastereoselective spiroketalization reaction in hand, our next goal was to develop the enantioselective version of this transformation.[59] We had previously shown the exceptional performance of cinchona alkaloid dimers in delivering enantioenriched halogenated products, both intra- and intermolecularly. Nonetheless, a thorough exploration of reaction conditions for the bromenium ion-induced spiroketalization of **I-70** in an asymmetric fashion failed to deliver products with substantial selectivity. This was not unexpected since allyl amides are privileged substrates for halenium mediated reactions catalyzed by cinchona alkaloid dimers. It became clear that a new catalytic system was necessary for this transformation.

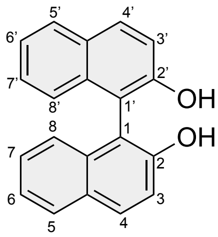
As we contemplated the appropriate choice for an asymmetric catalyst, we envisaged garnering control of the reaction through the interaction of the catalyst with the bromenium source, such that modification in its *HalA* would facilitate the reaction with the olefin in the presence of an asymmetric catalyst. Recently, we have demonstrated that Brønsted acid catalysts are capable of modulating the *HalA* value of the halonium source via protonation, leading to its higher reactivity.[65] It was envisioned that BINOL [67-69,70] and VANOL/VAPOL[71-76] derived Brønsted acid catalysts may catalyze the asymmetric bromonium ion-initiated spiroketalization.

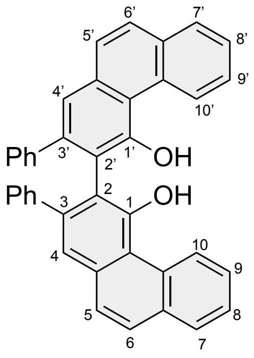
The success of this project hinged on achieving 2 major goals: I. Design and develop a robust catalytic system for the asymmetric bromo-spiroketalization reaction, II.

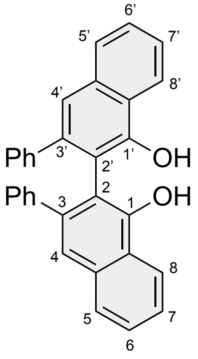
Synthesis and development of a library of VANOL/VAPOL based Bronsted acidic catalysts.

Catalyst Nomenclature:

The catalysts described in the manuscript are structurally related, and thus, we utilized a numbering scheme that identifies different domains of the catalyst with


BINOL : **1**


VAPOL : **2**


VANOL : **3**

	C3,3' BINOL or C7,7' VAPOL/VANOL
a	H
b	TRIP
c	9-anthracenyl
d	*t*-Bu
e	2-naphthyl
f	Phenyl
g	3,5-$(CF_3)_2$-C_6H_3-
h	9-phenanthryl
i	-$(CH_2)_3Ph$
j	*i*-Pr
k	TBDPS
l	Adamantyl
m	Br

	C3,3' VAPOL/VANOL
α	4-(OMe),3,5-(t-Bu)$_2C_6H_2$
γ	4-(t-Bu)C_6H_4

	C6,6' VAPOL/VANOL
Δ	2-naphthyl

Figure I-18: Catalyst nomenclature.

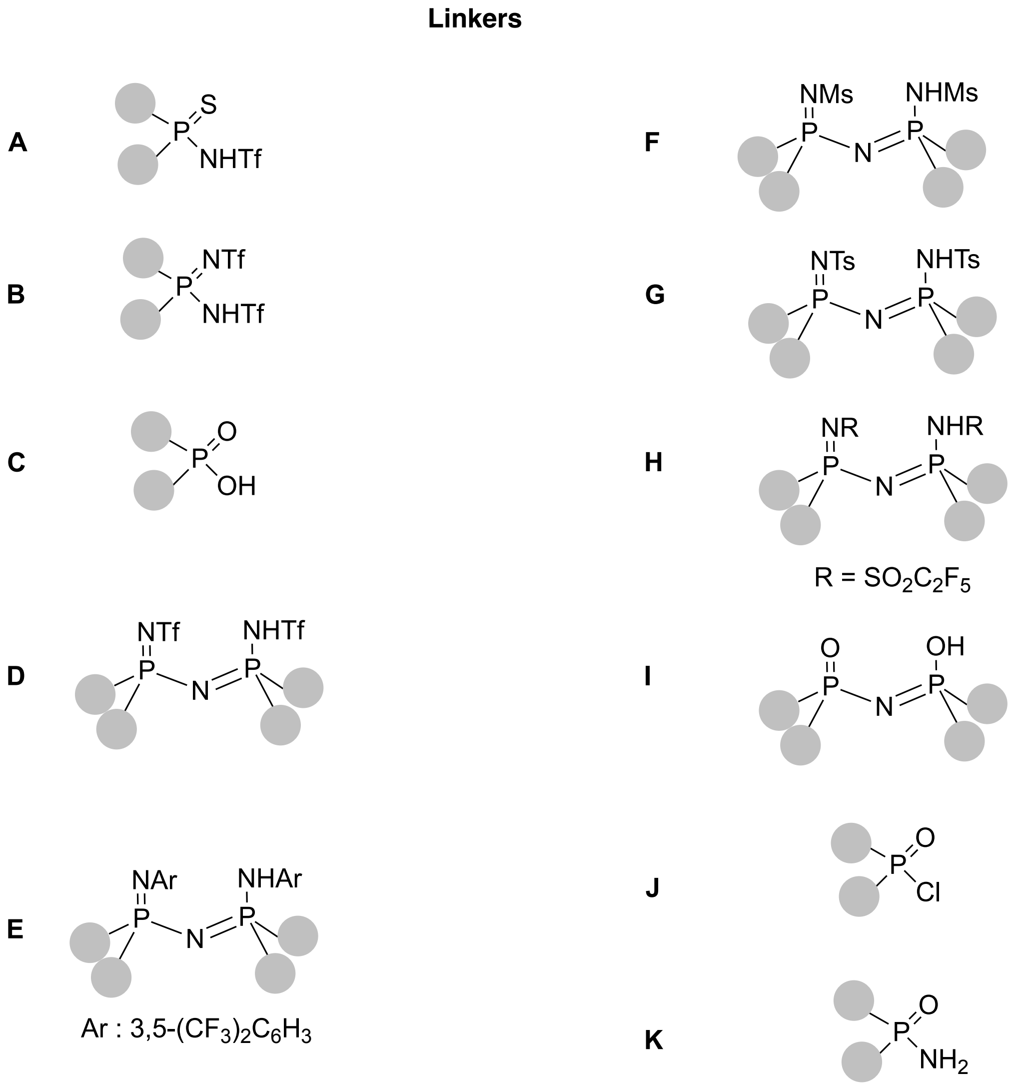
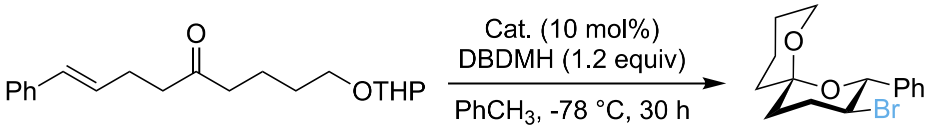


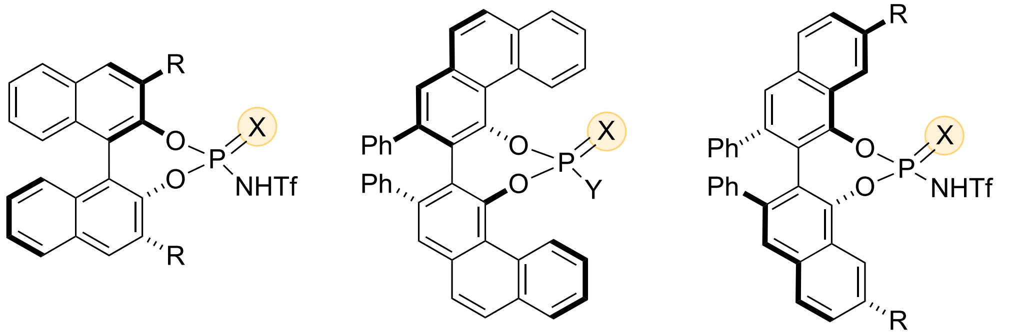
Figure I-19: Linker nomenclature.

alphanumerical designations. Parent designators **1**, **2**, and **3** are used for BINOL, VAPOL, or VANOL respectively. Lower case letters that follow the number indicate the nature of the substituent at C3 for BINOL, and C7 for VAPOL and VANOL (these are the typical sites of substitution for each series of catalysts). Table I-2 below illustrates the structures of the cores (1, 2, and 3) with their respective carbon numbering, as well as the key that correlates substituents to the lower-case alphabet. For example, catalyst **2a** has a hydrogen atom at C7 (VAPOL), while **3f** indicates phenyl substitution at C7 of VANOL.

Table I-2: Initial screening of monomeric catalyst for asymmetric bromospiroketalization.



I-70 **I-41**



(*R*)-**1b-A**, R: TRIP, X: S
(*R*)-**1c-B**, R: 9-anthryl X: NTf

(*S*)-**2a-A**, X: S, Y: NHTf
(*S*)-**2a-B**, X: NTf, Y: NHTf
(*S*)-**2a-C**, X: O, Y: OH

(*R*)-**3d-A**, R: *t*-Bu, X: S
(*R*)-**3d-B**, R: *t*-Bu X: NTf
(*S*)-**3e-B**, R: 2-naphthyl, X: NTf

Entry[a]	Catalyst	X	Yield (%)[b]	*er*[c]
1	(*R*)-**1b-A**	S	72	50:50
2	(*R*)-**1c-B**	NTf	60	48:52
3	(*S*)-**2a-A**	S	32	53:47
4	(*S*)-**2a-B**	NTf	60	55:45
5[d]	(*S*)-**2a-C**	O	48	58:42
6	(*R*)-**3d-A**	S	70	45:55
7	(*R*)-**3d-B**	NTf	93	42:58
8	(*S*)-**3e-B**	NTf	80	71:29

[a] All reactions were performed with 0.1 mmol of **I-70** at 0.1 M. [b] Isolated yield. [c] Enantiomeric ratios were determined by HPLC analysis. [d] Reaction was carried out for 12 h at rt.

Lower case Greek symbols are used for any substitutions other than hydrogen at C3, while upper case Greek symbols indicate C6 substitutions other than hydrogen atom.

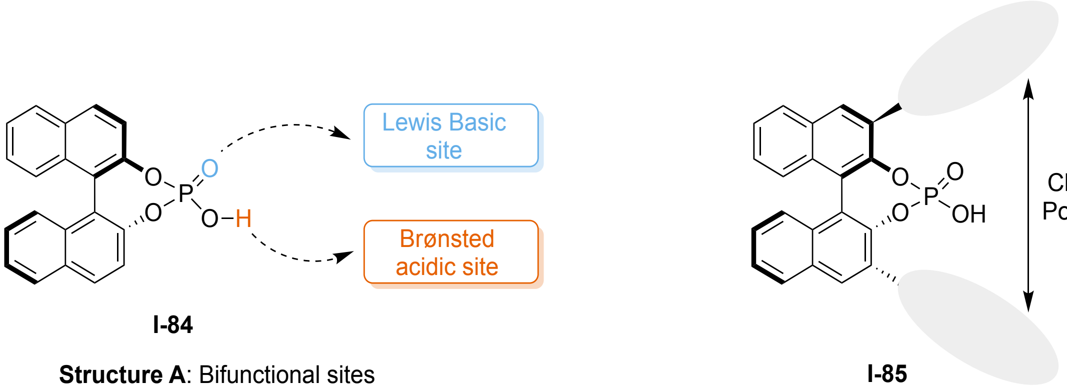
Dimeric catalysts are composed of two identical units connected through a substituted diphosphorimidate. The linker that connects to the core structures (as monomer or dimer) are denoted by the use of capital letters. For example, **$(\mathbf{3d})_2$-D** denotes the C7-substituted *t*-butyl VANOL catalyst dimerized with bistriflyl-imidodiphosphorimidate linker. The table below lists the set of linkers used in this study. Note that the subscript indicates the dimeric catalyst containing two units of **3d**.

Initial Catalyst Screening: First, the BINOL derived thio-phosphorimide **1b-A** and N-triflyl phosphoramidimidate **1c-B** were investigated. Both catalysts generated the desired product in good yields; however, in poor enantiomeric ratio (Table **I-2**, entry 1-2). Similarly, exploring a battery of conditions with VAPOL and VANOL based Brønsted acid catalysts led to the desired product with low enantioselectivity (Table **I-2**, entries 3-8). VAPOL phosphoric acid **2a-C** (entry 5) was even less selective, and also less active requiring higher temperatures for completion, indicating that the acidity of the catalyst is influential on the progress of the reaction. Change in the steric nature of the 7,7'-positions on the VANOL altered enantioinduction, although not significantly to warrant further optimization. VANOL N-triflyl phosphoramidimidate **3e-B** bearing 2-naphthyl as the substituent in 7,7'-positions produced the brominated spiroketal in good yield but in a moderate enantiomeric ratio (Table **I-2**, entry 8).[59]

Quickly we realized that the monomeric BINOL, VANOL, and VAPOL derivatives (both thiophosphoramide and phosphoramidimidate) although were efficient in delivering the final spiroketal in good yields and high diastereoselectivity, are not able to significantly alter the enantioselectivity of the reaction.

Rational design and synthesis of imidodiphosphorimidate catalyst:

Imidodiphosphoric acid catalyst: The active site of the chiral phosphoric acid catalyst consists of both Bronsted acidic (O-H) and Lewis basic (O) sites; hence these classes of molecules are often referred to as bifunctional catalysts (Figure I-18). These catalysts have been successful in imparting asymmetry due to 2 major reasons: one, because of its ability to be bifunctional and secondly, because these active sites can stabilize the transition state of a specific asymmetric transformation. Introducing substituents in 3,3'-

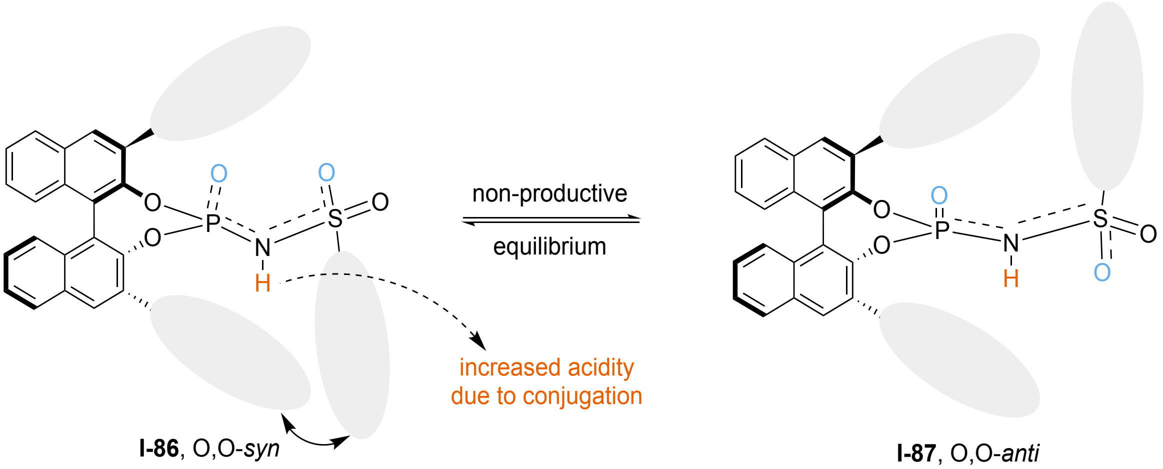


I-84

Structure A: Bifunctional sites

I-85

Structure B: Substituents at 3,3'-position controls the chiral pocket



I-86, O,O-*syn*

Structure C: Additional steric control around the chiral pocket

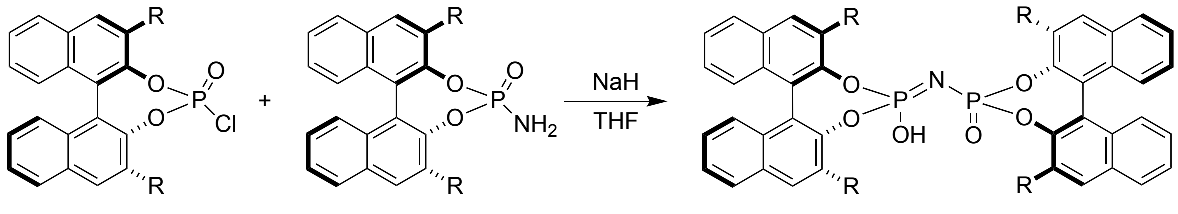
I-87, O,O-*anti*

Structure D

Figure I-20: Dual functionality of BINOL phosphoric acid and phosphoamides.

positions of BINOL ligand creates chiral space around the active site of the chiral phosphoric acid; however, these substituents are pointing away from the active site (structure B). N-triflyl BINOL phosphoramide bearing substituents on sulphur creates a better chiral environment around the active site by bringing further steric demand close to it (structure C); however the free rotation around the N–S bond enables the catalyst (structure C) to adopt two distinct isomers: O,O-*syn* and O,O-*anti* (structure D) which provides flexibility to the relative position of the Brønsted acid and Lewis base components of the catalyst and leads to a reduced selectivity.

These considerations led the List research group to design a new class of highly efficient BINOL Brønsted acid catalysts of the type **I-91** (Figure I-19).[6] These imidodiphosphoric acid catalysts were synthesized by reacting equimolar amounts of phosphoramide **I-89** and phosphoryl chloride **I-90** in the presence of a strong base such as NaH. The structure of this catalyst was unequivocally determined to be a dimeric species via X-ray structural analysis.[6] The crystal structure also revealed that the catalyst exists exclusively as the *O,O-syn* isomer presumably because of steric hindrance

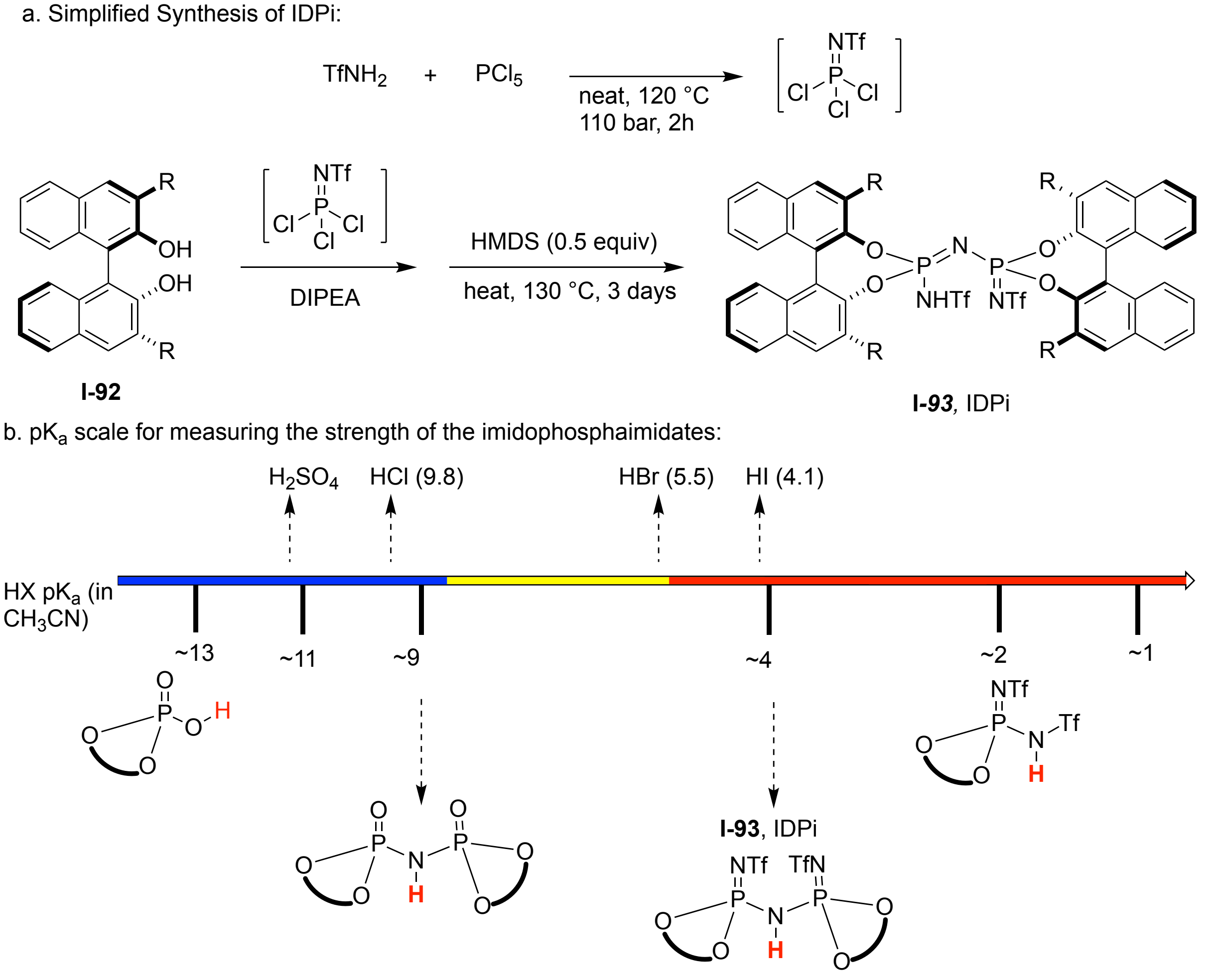


I-89

I-90

I-91

Figure I-21: Formation of O,O-*syn* imidodiphosphoric acid **I-91.**



a. Simplified Synthesis of IDPi:

b. pK_a scale for measuring the strength of the imidophosphaimidates:

Figure I-22: Synthesis and acidic strength of IDPi (**I-93**) catalyst.

imposed by BINOL subunits in 3,3'-positions. It was assumed that the rigidity of the chiral microenvironment around the active site caused by the unique structure of this catalyst improved the performance of the catalyst. The utility of BINOL imidodiphosphoric acid catalyst was explored in numerous asymmetric transformations including enantioselective sulfoxidation, asymmetric acetalization, resolution of chiral diols, asymmetric carbonyl-ene reaction and asymmetric vinylogous Prins cyclizations (not shown). [77-81]

Inspired by Yamamoto's strategy in increasing the acidity of the phosphoric acid catalyst, an oxo group of the imidodiphosphoric acid catalyst was replaced with the strong electron withdrawing NSO_2CF_3. The synthesis of ((trifluoromethyl)sulfonyl)phosphorimidoyl trichloride ($TfNPCl_3$) enabled List to access the synthesis of extremely active Brønsted acid catalyst (Figure I-20). [82] The oxo (O) and hydroxy (OH) groups in imidodiphosphoric acid were replaced with NTf as the strong electron-withdrawing group. Introduction of these groups makes the catalyst **I-93** extremely acidic (stronger than sulphuric acid or HCl), and these possess a pK_a of ~ 2 - 4 in MeCN [the acidity of HI in MeCN is 4.1] (Figure I-20).

Inspired by the work of List and coworkers with BINOL derived IDP*i*,[82-88] BINOL imidodiphosphorimidate catalyst **(1e)$_2$-D** was synthesized and its performance was investigated in our model reaction (Figure I-21). Two important factors drove this decision; 1. The increased acidity of the imidodiphosphorimidate as compared to the corresponding phosphoramidimidate could lead to a stronger interaction between the catalyst and the

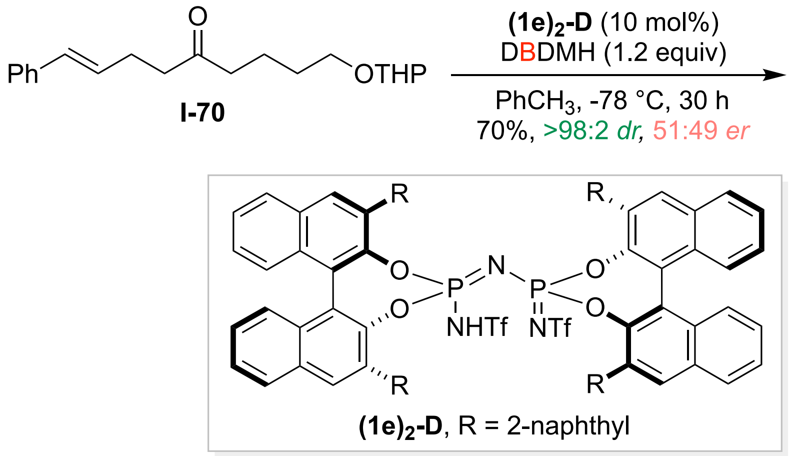


Figure I-23. Bromospiroketalization catalyzed by BINOL IDPi catalyst **(1e)$_2$-D.**

bromenium donor, or even, result in the transfer of the bromenium to the catalyst prior to its reaction with the olefin, and 2. The dimer would likely generate a more defined asymmetric binding cavity that might better suit a 'floppy' substrate such as **I-70**. Nonetheless, BINOL IDP*i* catalyst **(1e)$_2$-D** proved ineffective, delivering the desired halogenated spiroketal **I-41** devoid of enantio-induction (Figure I-21).

Realizing a choreographed arrangement of the catalyst, substrate, and bromenium donor is likely required for achieving high selectivity, we opted to investigate the vaulted

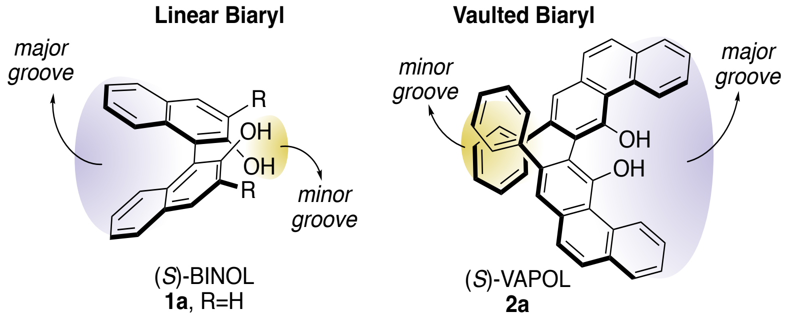
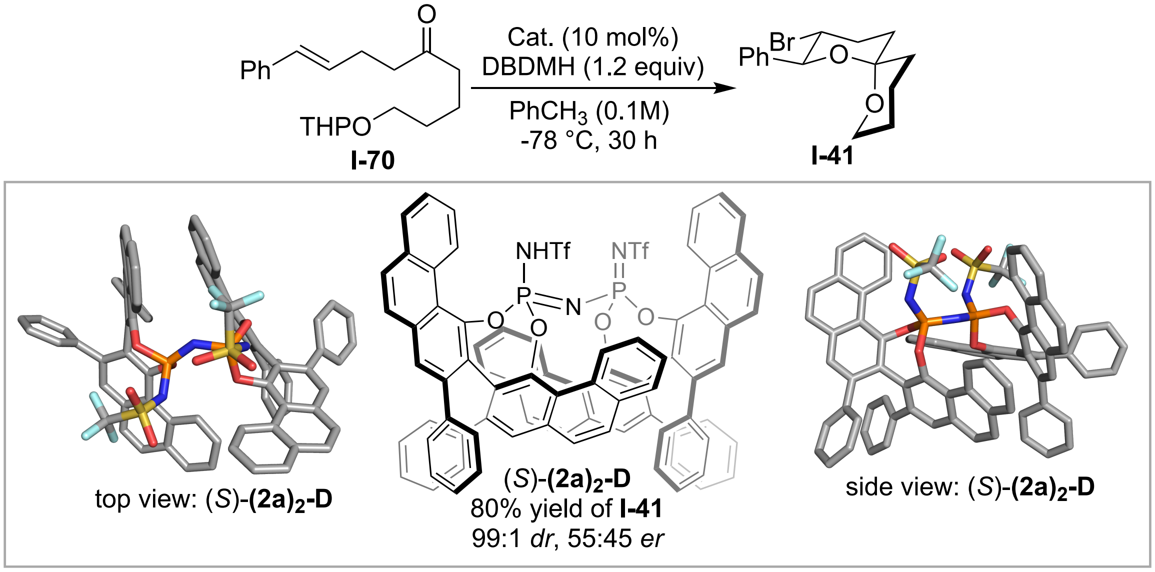


Figure I-24. Comparison of linear vs. vaulted biaryls. In contrast to linear biaryls, the major groove of vaulted biaryls encompass the hydroxyl groups.

biaryl framework. As depicted in Figure I-22, the 'major groove' of the vaulted systems resides in the center of the molecule. We anticipated the activation of the halenium source via proton delivery from the triflimide occurs in this region, and thus surmised a larger binding cavity might allow for a more structured arrangement of the reaction components.[71-76, 89-92]

VAPOL imidodiphosphorimidate **(2a)$_2$-D** was prepared from VAPOL and (triflyl)phosphorimidoyl trichloride following reported procedures[82] and was evaluated as



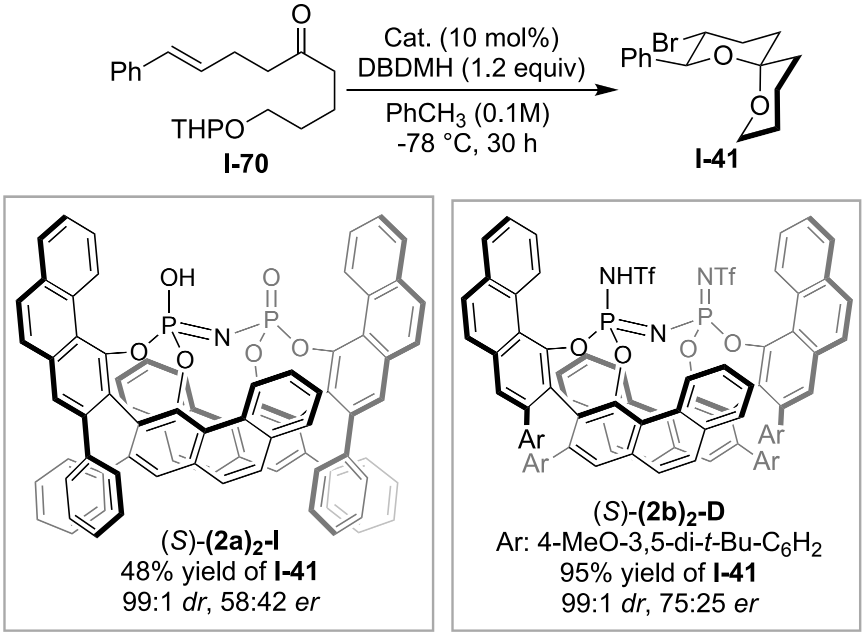
top view: (*S*)-**(2a)$_2$-D**

(*S*)-**(2a)$_2$-D**
80% yield of **I-41**
99:1 *dr*, 55:45 *er*

side view: (*S*)-**(2a)$_2$-D**

Figure I-25. Bromo spiroketalization of **I-70** with VAPOL derived catalysts (*S*)-**(2a)$_2$-D**. Crystal structure of (*S*)-**(2a)$_2$-D** illustrates an exposed, open active site and a π-stacked interaction of the phenanthrene rings.

the catalyst for the bromo-spiroketalization of **I-70**. The desired product **I-41** was obtained in good yield but low *er* (Figure I-23). X-ray structural analysis of catalyst **(2a)$_2$-D** confirmed a well-defined C$_2$ symmetric active site had formed, yet the two phenanthrene subunits from each VAPOL ligand were positioned over the active site in a manner which may in fact restrict access to the inner active site of the catalyst. We speculated that this might be the reason for the observed low enantioselectivity. Two other VAPOL analogs were synthesized for analysis. The phosphoric acid derived dimer (*S*)-**(2a)$_2$-I** performed similarly poor in delivering enantioenriched products (Figure I-24). Furthermore, the yield of the reaction suffered with this catalyst, presumably as a result of its reduced acidity. Catalyst (*S*)-**(2b)$_2$-D** performed best in the VAPOL series. The enhanced acidity maintained the high yield for the reaction, while the bulky aryl substituent led to higher *er*.



(S)-**$(2a)_2$-I**
48% yield of **I-41**
99:1 *dr*, 58:42 *er*

(S)-**$(2b)_2$-D**
Ar: 4-MeO-3,5-di-*t*-Bu-C_6H_2
95% yield of **I-41**
99:1 *dr*, 75:25 *er*

Figure I-26. Results for VAPOL derivatives during asymmetric spiroketalization of **I-70** with catalysts (S)-**$(2a)_2$-I** & (S)-**$(2a\alpha^3)_2$-I.**

The effect of the aryl substituent is most probably related to steric interactions that lead to a more well-defined catalytic pocket, as will be demonstrated in the VANOL family of analogs (*vida infra*). The synthesis of a library of substituted VAPOL derivatives is likely to require a lengthier synthesis that will need to be individually crafted for each position on VAPOL which is in contrast to the synthesis of the VANOL derivatives and hence we decided to focus more on the VANOL family. [89, 92, 93]

Optimization of the reaction condition:

Two important factors led us to evaluate VANOL imidodiphosphorimidates as potential catalysts. First, of the imidophosphates examined initially, the VANOL derived catalyst (S)-**3e-B** showed the best selectivity (Table I-2, entry 8). Second, we presumed success

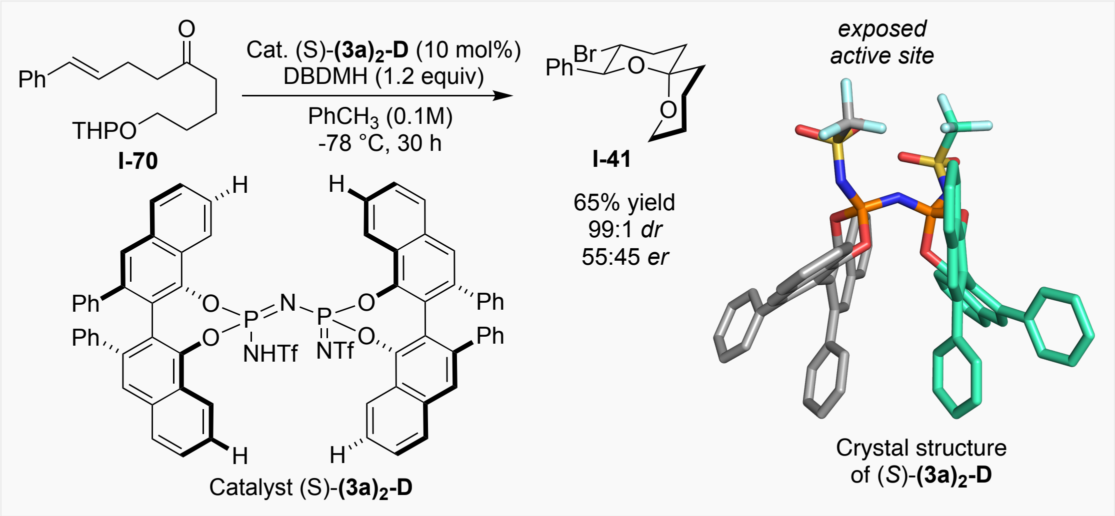


Figure I-27. VANOL IDPi catalysts for bromospiroketalization of **I-70** with (*S*)-**(3a)$_2$-D.**

will hinge on one simple fact: changes in the substitution pattern on the chosen core should be synthetically accessible. With this in mind, the crystalline nature of the VANOL-based VIP catalysts was instrumental for initiating a ‘structure-guided’ design. The search commenced with the synthesis and evaluation of the simplest VIP catalyst **(3a)$_2$-D,** although the desired product **I-41** was obtained in low enantioselectivity (Figure I-25). The crystal structure of catalyst **(3a)$_2$-D** was illuminating, as the four naphthalene units that comprise the two VANOL ligands adopt a severely p-stacked orientation, leading to an active site that is devoid of any asymmetrically disposed steric handles. Not surprisingly, the ‘open’ active site results in low asymmetric induction.

The streamlined synthesis of VANOL facilitates substitutions at the 6,6’ and 7,7’ positions with relative ease. We envisage imposing steric interactions to alter the geometry observed with catalyst **(3a)$_2$-D** by substitutions at these sites. VIP catalyst **(3aΔ)$_2$-D,** bearing

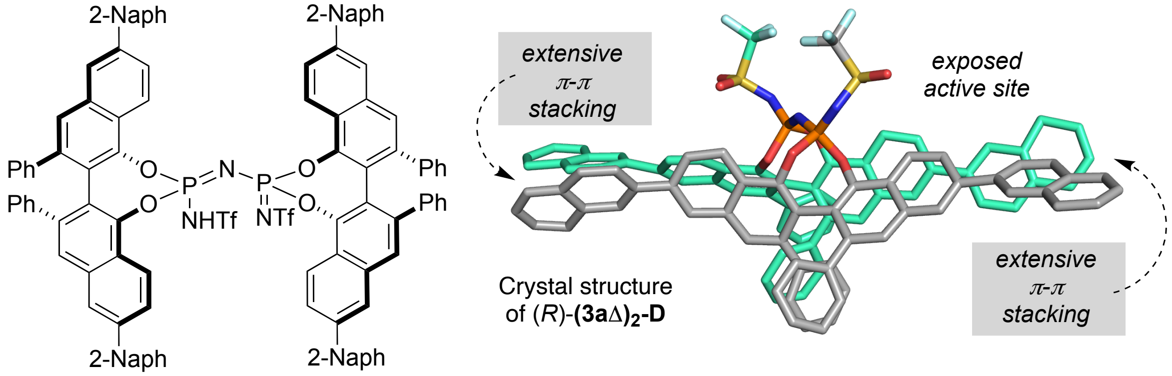
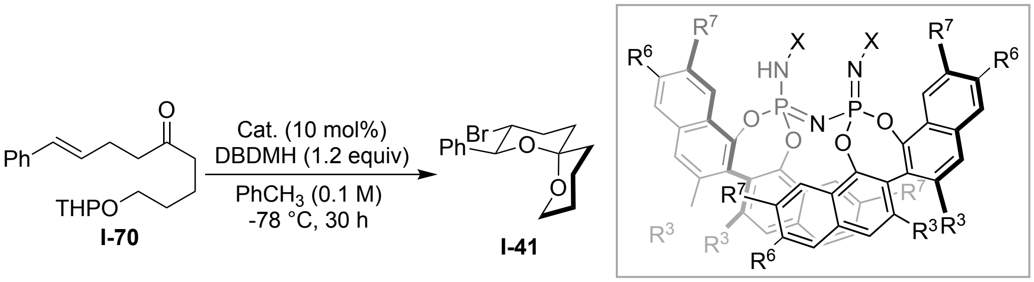


Figure I-28. Crystal Structural information reveal an open chiral pocket with extensive π-π stacking interaction for catalyst (*S*)-**(3aΔ)$_2$-D.**

2-naphthyls in the 6,6'-positions was synthesized and subsequently examined. Nonetheless, while maintaining a good yield of product, the observed selectivity was again disappointingly low (56:44 *er*). Analysis of its crystal structure showed an even more open active site as compared to that observed for catalyst **(3a)$_2$-D** (Figure I-26). The addition of the 2-naphthyl rings at the 6,6'-positions not only did not interrupt the p-stacking, but in fact seem to have enhanced this interaction (Figure I-26). Although unexpected, the result was informative in avoiding the 6,6'-positions for future optimizations of the catalyst structure.

The 7,7'-positions are less symmetrically situated relative to the structure of the molecule, and potentially could affect and perturb the high tendency for p-stacking observed with the latter two catalysts. As such, we directed our efforts towards the synthesis of the VIP catalysts bearing 7,7'-phenyl and 3,5-$(CF_3)_2C_6H_3$ substituents (catalysts **(3f)$_2$-D** and **(3g)$_2$-D**, respectively, Table I-3). To our delight, these two catalysts showed a marked improvement in delivering product **I-41** in good yields and much improved selectivities (80:20 and 78:22 *er* for catalysts **(3f)$_2$-D** and **(3g)$_2$-D**, respectively)

Table I-3: Screening of VANOL derived IDPi catalysts for the asymmetric bromospiroketalization reaction.



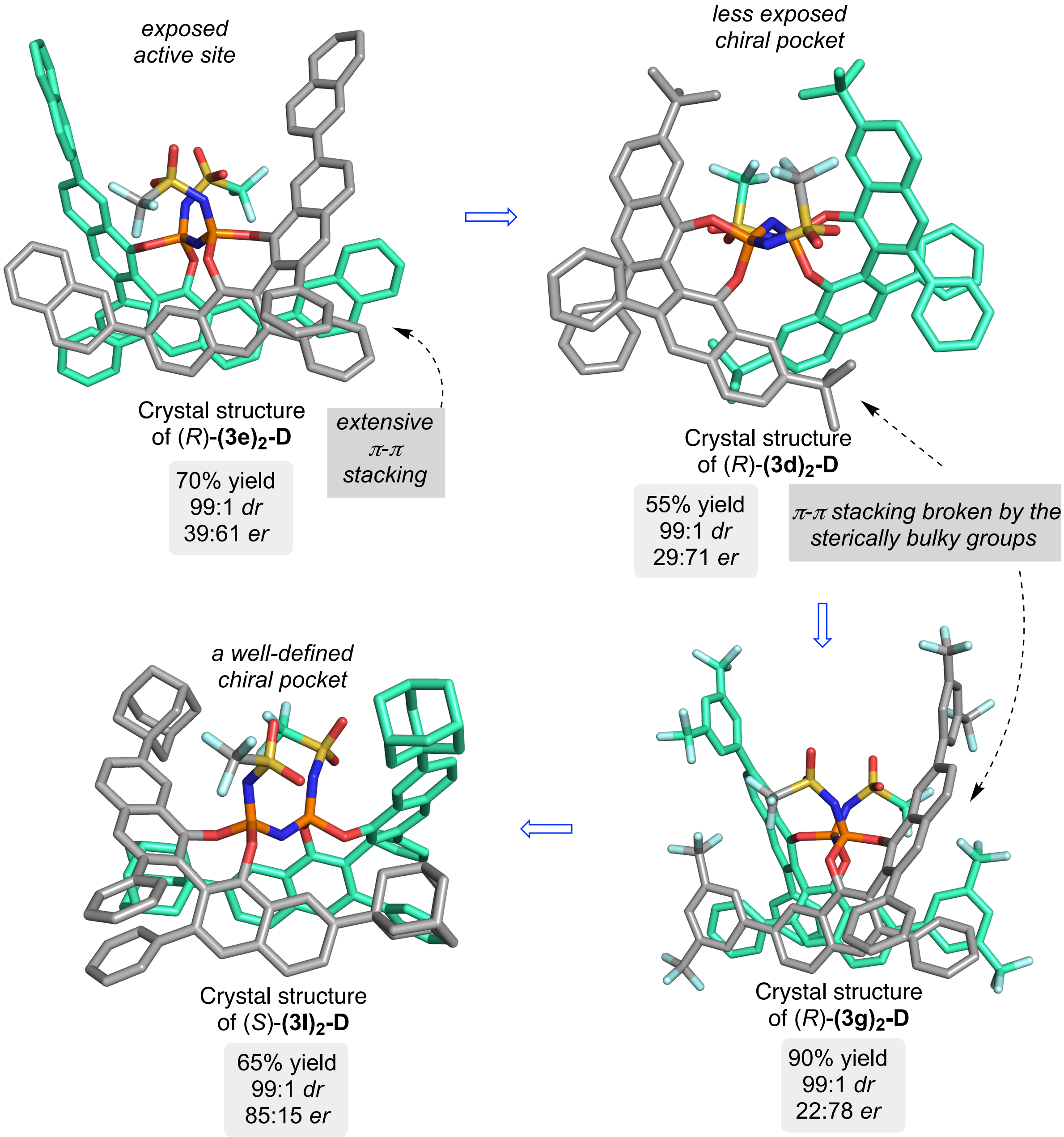
Entry[a]	Cat.	R^3	R^6	R^7	X	Yield (%)[b]	*dr*[c]	*er*[d]
1	(*S*)-**(3a)$_2$-D**	Ph	H	H	Tf	65	99:1	55:45
2	(*R*)-**(3aΔ)$_2$-D**	Ph	2-Naph	H	Tf	70	99:1	44:56
3	(*R*)-**(3f)$_2$-D**	Ph	H	Ph	Tf	82	99:1	20:80
4	(*R*)-**(3g)$_2$-D**	Ph	H	3,5-$(CF_3)_2C_6H_3$	Tf	90	99:1	22:78
5	(*R*)-**(3e)$_2$-D**	Ph	H	2-Naph	Tf	70	99:1	39:61
6	(*R*)-**(3eγ)$_2$-D**	4-*t*-BuC_6H_4	H	2-Naph	Tf	85	99:1	39:61
7	(*S*)-**(3h)$_2$-D**	Ph	H	9-Phen	Tf	50	99:1	56:44
8	(*S*)-**(3h)$_2$-E**	Ph	H	9-Phen	3,5-$(CF_3)_2C_6H_3SO_2$	71	99:1	65:35
9	(*R*)-**(3i)$_2$-D**	Ph	H	$(CH_2)_3$Ph	Tf	73	99:1	35:65
10	(*R*)-**(3j)$_2$-D**	Ph	H	*i*-Pr	Tf	53	99:1	32:68
11	(*R*)-**(3k)$_2$-D**	Ph	H	TBDPS	Tf	74	99:1	22:78
12	(*R*)-**(3d)$_2$-D**	Ph	H	*t*-Bu	Tf	55	99:1	29:71
13	(*S*)-**(3l)$_2$-D**	Ph	H	Ad	Tf	65	99:1	85:15

[a] All reactions were performed with 0.1 mmol of **I-70** at 0.1 M. [b] Isolated yield. [c] diastereomeric ratio was determined from ^{1}H nmr. [d] Enantiomeric ratio was determined by HPLC analysis.

(Table I-3, entry 3-4). As can be seen from the crystal structure of catalyst **(3g)$_2$-D** (Figure I-27), the substitutions at the 7,7' have drastically altered the conformation of the molecule as compared to the two prior catalysts. The bulk of the two 7-aryl substituents at the bottom face of the catalyst leads to a confined and well-defined chiral pocket, presumably by disrupting the π-stacking that had led to a flattened structure for catalysts **(3a)$_2$-D** and **(3aΔ)$_2$-D** (Table I-3).

Our efforts continued with exploration of the 7,7’-positions, with the aim to generate Structure-Enantioselectivity Relationships (SER) that would guide further improvements. Although the ultimate goal is to optimize catalyst structure to deliver products with high selectivity, an SER model requires a range of performing catalysts (from bad to good). At this point, we had surmised that the 7,7’ substitutions reduce p-stacking that flattened the overall structure of the catalyst, and thus, changing the bulk and nature of these substituents could have a significant effect on the structure of the catalyst. Prior to the synthesis of catalyst **(3e)$_2$-D**, it was not clear if the 2-naphthyl substituents at the 7,7’-positions would enhance the sterics to 'break' the p-stacking, or conversely, regress because their flat extended ring system would contribute to the stacked arrangement. Interestingly, catalyst **(3e)$_2$-D** led to reduced *er* for product **I-41** (61:39). Nonetheless, its crystal structure shows a more defined pocket as compared to catalysts **(3a)$_2$-D** and **(3aD)$_2$-D** (Figure I-27), but more open in comparison to the structure obtained for catalyst **(3g)$_2$-D**. Not surprisingly, the *er* of the product reflects the qualitative description of the active site pocket.

Substitution of the 7,7’-positions with the 9-phenanthryl group led to catalyst **(3h)$_2$-D**. Although it has an extended aryl cross-sectional area, we surmised that the conformational restriction that should result from its rotation about the C7/C7’-Ar bond would alter the geometry from that observed in catalyst **(3e)$_2$-D** with the 2-naphthyl substitutions. Nonetheless, the observed selectivity for product **I-41** decreased with catalyst **(3h)$_2$-D** (56:44 *er*). In an attempt to increase the bulk closer to the presumed site of bromenium transfer, catalyst **(3h)$_2$-E**, having the same skeletal build as **(3h)$_2$-D**, yet differing only in the imidodiphosphorimidate linker, led to slightly improved *er* (65:35). Not surprisingly, the crystal structure of catalyst **(3h)$_2$-E** is similar to that observed for catalyst **(3h)$_2$-D**, although with some changes to the dimensions of the 'catalytic pocket' (Figure I-28).



exposed active site

Crystal structure of (*R*)-**(3e)$_2$-D**

70% yield
99:1 *dr*
39:61 *er*

extensive π-π stacking

less exposed chiral pocket

Crystal structure of (*R*)-**(3d)$_2$-D**

55% yield
99:1 *dr*
29:71 *er*

π-π stacking broken by the sterically bulky groups

a well-defined chiral pocket

Crystal structure of (*S*)-**(3l)$_2$-D**

65% yield
99:1 *dr*
85:15 *er*

Crystal structure of (*R*)-**(3g)$_2$-D**

90% yield
99:1 *dr*
22:78 *er*

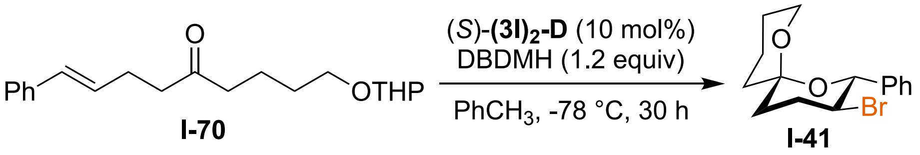
Figure I-29. Comparision of the crystal structures highlighting the space of the catalytic site.

Up to this point, the 3,3' positions were substituted with a phenyl group. The synthetic strategy for the preparation of VANOL analogues was easily modified to bulk-up the phenyl groups, generating catalyst **(3eg)$_2$-D** bearing 4-*t*-butylPh substituents. We predicted that the added bulk should alter the interactions of the p-stacked aromatics and add to the data that could correlate structure to function. Catalyst **(3eg)$_2$-D** delivered the spiroketal **I-41** with a similar selectivity as catalyst **(3e)$_2$-D**, albeit with a slightly higher yield (72% vs 85%). This catalyst was also crystalline, with a structure that likewise shows a more characteristic pocket for catalysis. Along the same lines to 'break' the stacked arrangements of the aryl groups, catalyst **(3d)$_2$-D**, with *t*-butyl substitution of the 7,7' positions were prepared. We surmised that steric interactions that result from the larger alkyl substitution would not allow strong π-π stacking and the catalyst would thus adopt a more 'twisted' conformation. This is borne out by inspecting its crystal structure (Figure I-27), leading to a slight improvement in the product *er* (71:29).

With a number of crystal structures of the VIP catalysts within the same family on hand, i.e.; variation of substitution at one location (7,7'-substitutions, catalysts **(3a)$_2$-D**, **(3g)$_2$-D**, **(3e)$_2$-D**, **(3h)$_2$-D**, **(3h)$_2$-E**, and **(3d)$_2$-D**), we searched for structural clues that could be correlated with the observed enantio-inductions. Two points emerged: 1. Substituents at the 7,7' position affect the trajectory of the biaryl groups relative to each other, altering the geometric constraints of catalytic pocket; and more instructively; 2. Although there is a loose association between the observed enantio-induction and the dihedral angle that is defined between the substituents at 7,7'-positions of each VANOL ligand (Figure 6a, R^2 <0.2), it is clear that more than one structural descriptor is required to correlate measurable attributes with the *er* of the products.

Synthesis of catalysts **(3i)$_2$-D**, **(3j)$_2$-D**, and **(3k)$_2$-D**, with varied substituents at the 7,7'-position was pursued. While **(3i)$_2$-D** and **(3j)$_2$-D** possess smaller substituents at the 7,7'-position as compared to **(3d)$_2$-D** (*t*-butyl), TBDPS-substituted catalyst **(3k)$_2$-D** is larger. Interestingly, the observed trend in higher product enantioselectivity mirrors the increasing bulk of the non-aryl 7,7'-substituents (Table I-3). Unfortunately, these catalysts did not succumb to crystallization, but did provide the impetus to synthesize the 7,7'-adamantyl

Table I-4: Optimization of the reaction conditions for the asymmetric bromospiroketalization.



Entry[a]	X-Br	T (°C)	Solvent	Yield (%)[b]	*er*[c]
1[d]	DBDMH	–78	Toluene	0	—
2	DBDMH	–78	Toluene	65	85:15
3[e]	NBS	–78	Toluene	52	75:25
4	DBDMH	–78	Toluene	72	78:22
5	DBDMH	–50	Toluene	85	94:6
6	DBDMH	–25	Toluene	55	80:20
7	DBDMH	–50	Pentane	60	80:20
8	DBDMH	–50	Ether	81	70:30
9[f]	DBDMH	–50	Toluene	55	74:26
10[g]	DBDMH	–50	Toluene	40	80:20

[a] All reactions were performed with 0.1 mmol of **I-70** at 0.1 M. [b] Isolated yield. [c] Enantiomeric ratios were determined by HPLC analysis. [d] No catalyst was used. [e] 5 mol% catalyst was used. [f] 0.6 equiv DBDMH was used. [g] 2.5 equiv DBDMH was used.

substituted catalyst **(3l)$_2$-D** to further increase the bulk of the alkyl substituent. Spiroketalization of **I-70** with catalyst **(3l)$_2$-D** led to product **I-41** with the highest *er* (85:15) amongst the catalysts tested thus far. Furthermore, **(3l)$_2$-D** could be crystallized (Table I-3, entry 13) and analyzed via the previously described multiple linear regression. Illustrated in Figure 6b (line 2), catalyst **(3l)$_2$-D** follows the predictions derived with other members of the same catalyst family, suggesting that the alterations to the orientation are predicted by the four different descriptors as described above.

Optimization of Reaction Conditions with Cat (3l)$_2$-D:

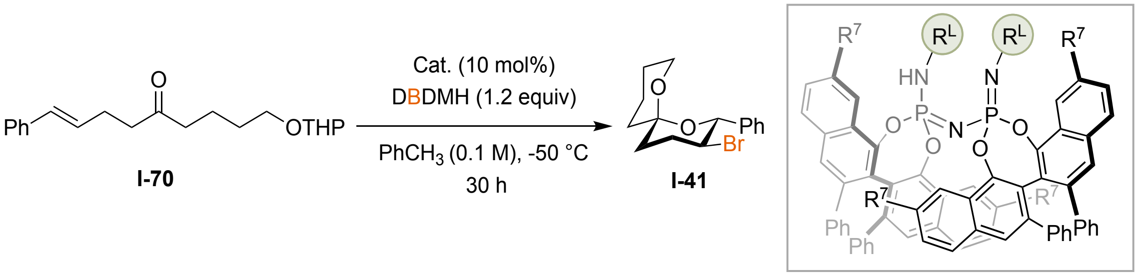
With a structurally optimized catalyst in hand, we set out to investigate other reaction parameters. Table I-4 Illustrates a brief overview of the optimization studies. The reaction does not proceed in the absence of the catalyst, even after 72 h, suggesting its presence is necessary for the activation of the bromonium ion (Table I-4, entry 1). Lowering the catalyst loading led to the decrease in yield and *er* of the product (entries 2-3). Similarly, a weaker bromonium source (NBS vs. DBDMH) substantially decreased the *er* of the final product (entry 4). The reaction is temperature dependent, with -50 °C as the optimal choice (entry 5), as colder and warmer conditions (entries 2 and 6) led to the deterioration of yield and *er*. Although speculative, a bell-shaped dependence on temperature could suggest either solubility issues at low temperatures or change in catalyst structure/aggregation state. The test reaction with catalyst **(3l)$_2$-D** exhibited a correlation with the dielectric constant of the solvents examined. Toluene was chosen as the optimal solvent, with diminished yield and stereoinduction with either more polar or more nonpolar media (entries 7-8). Finally, a lower stoichiometry of the bromenium source resulted in incomplete conversion to the product without benefit to the *er*, while increasing the equivalence led to the formation of side products (entries 9-10). Ultimately, the best conditions for the conversion of **I-70** to the bromo-spiroketal **I-41** led to the isolation of the product in 85% yield and 94:6 *er* (Table I-4, entry 5).

Exploring the Imidodiphosphorimidate Structure:

With the optimized condition in hand, we explored one final component of the catalyst structure to interrogate its effects on the test reaction. Alterations of the catalyst structures (Table I-3) centered on changes to the 3,3' (R^3), 6,6' (R^6), and 7,7' (R^7) positions. Nonetheless, access to different R^L substituents of the imidodiphosphorimidate linker is easily achieved by changing the requisite sulfonamide that eventually yields the final catalyst. The nature of the imidodiphosphorimidate linker could be pivotal, since it not only plays a role in defining the catalytic pocket, but also electronic perturbations of the R^L substituent can affect its acidity. In fact, we had observed a change in the stereoinduction of the product as a result of altering R^L in catalyst **(3h)$_2$-D** vs. **(3h)$_2$-E** (*er* 56:44 vs 65:35), where a 2.5 fold increase of *ee* was observed (Figure I-28), albeit with a less selective catalyst framework. Highlighted in Table I-5, a new set of catalysts with R^L groups that have different steric and electronic properties were synthesized. Note, the new catalysts have the same VANOL skeleton as catalyst **(3l)$_2$-D**.

Catalyst **(3l)$_2$-E** was to mimic the change of R^L represented in catalyst **(3h)$_2$-E** as compared to **(3h)$_2$-D**. Interestingly, changing the R^L substituent in catalyst **(3l)$_2$-D** to the 3,5-bistrifluoromethylphenyl sulfonyl group (catalyst **(3l)$_2$-E**) delivered the bromospiroketal in poor enantioselectivity (Table I-5, entry 3). Although the trend with the

Table I-5: Screening the linker subunit of the catalyst for asymmetric bromospiroketalization.



Entry[a]	Catalyst	R^7	R^L	Conv. (%)	Yield (%)[b]	*er*[c]
1	(*S*)-**$(3l)_2$-D**	Ad	CF_3SO_2 (Tf)	99	92	94:6
2	(*S*)-**$(3h)_2$-D**	9-Phen	CF_3SO_2 (Tf)	99	50	56:44
3	(*S*)-**$(3h)_2$-E**	9-Phen	3,5-$(CF_3)_2C_6H_3SO_2$	99	71	65:35
4	(*R*)-**$(3l)_2$-E**	Ad	3,5-$(CF_3)_2C_6H_3SO_2$	99	61	33:67
5	(*R*)-**$(3l)_2$-F**	Ad	CH_3SO_2 (Ms)	58	50	9.5:90.5
6	(*R*)-**$(3l)_2$-G**	Ad	4-$CH_3C_6H_4SO_2$ (Ts)	75	70	44:56
7	(*R*)-**$(3l)_2$-H**	Ad	$C_2F_5SO_2$	99	80	7:93

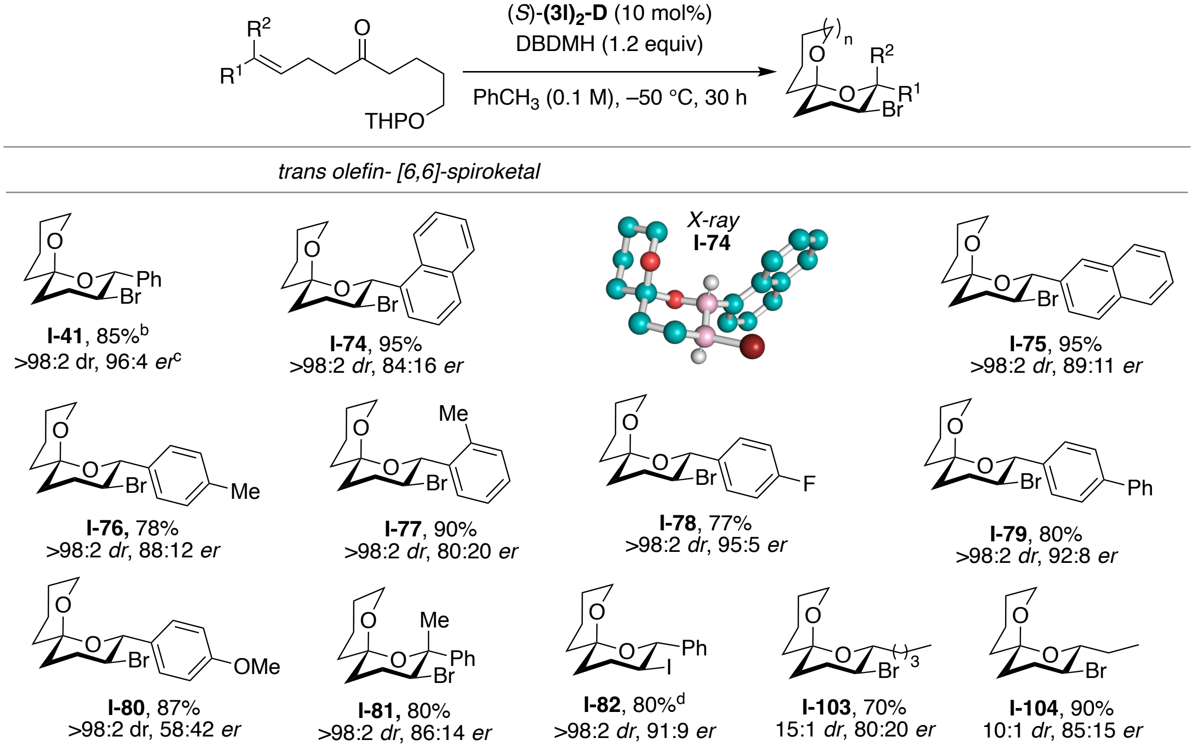
[a] All reactions were performed with 0.1 mmol of **I-70** at 0.1 M. [b] Isolated yield. [c] Enantiomeric ratio was determined by HPLC analysis.

9-anthracenyl substituted catalysts were not observed here, this is not surprising, since as described above, structural factors that likely control high selectivity are multifaceted. Changes to R^L can also result in structural perturbations that are not favorable for achieving high selectivity. This was further probed by examining the *p*-toluyl sulfonyl group (catalyst **$(3l)_2$-G**), which also led to poor enantioselection (56:44 *er*, entry 6). Reverting to the smaller methyl sulfonyl group (catalyst **$(3l)_2$-F**) rescued enantio-induction *(*90.5:9.5 *er*, entry 5), yet the reaction was sluggish with a lower yield and substantially diminished conversion. Presumably, in comparison to the trifluorosulfonyl group in catalyst **$(3l)_2$-D**, the depressed acidity of catalyst **$(3l)_2$-F** leads to lower reactivity. Catalyst

$(3l)_2$-H was prepared to preserve the small size of the R^L substituent, while maintaining high acidity of the imidodiphosphorimidate functionality. The latter catalyst performed nearly as well as catalyst **$(3l)_2$-D**, delivering the product in high yield and *er*.

Changes to R^L suggest that increasing the bulk within the catalytic pocket (e.g., by the introduction of phenyl group) dramatically decreases *er*. Whereas the Ms group, although not as electron withdrawing to promote high acidity, and thus, reactivity, delivered the product with high *er*. Hypothetically, accessing the bromospiroketal in high enantioselectivity requires fine-tuning of the catalyst active site with an interplay of steric and electronic parameters. Electronics are reflected in the acidity of the Imidodiphosphorimidate group, leading to activation of the bromenium ion, while sterics alter the geometry of the catalyst as required for high selectivity.

Substrate Scope*:* The generality of the bromospiroketalization reaction was examined with various keto-alkenols (Figure I-29). *Trans*-disubstituted substrates with different *p*-substituted arenes were well tolerated, providing products **I-41**, **I-74** to **I-82**, **I-103** & **I-104** in high yields (>75%), excellent *dr* (>98:2), and a good *er*s, except for the electron rich substrate **I-80**. Presumably electron rich systems do not require nucleophilic activation of the olefin for bromenium capture, and thus circumvent the templated orientation dictated by *NAAA* required for selectivity. Ortho-substituted aryl substrate **I-77** performed well with catalyst **$(3l)_2$-D**, yielding product in good yield and enantioselection. The slight decrease in the *er* might be due to added effect of the electron donating methyl group in **I-76** through inductive effect as well as the increase of the steric bulk at the active site. The 1- and 2-naphthyl substituted substrates respectively, were also successfully

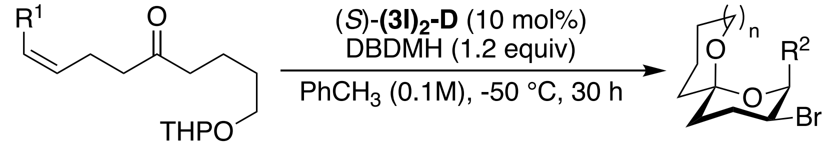


[a]Unless otherwise specified, all reactions were performed in toluene, –50 °C for 30 h with 0.1 mmol of substrate at 0.1 M and 1.2 equiv DBDMH. [b]Isolated yield. [c]Enantiomeric ratios were determined by HPLC analysis. [d]NIS (1.2 equiv) was used instead of DBDMH.

Figure I-30. Substrate Scope for the *trans* substituted olefins generating [6,6]-spiroketal.

transformed to their corresponding [6,6]- bromospiroketal **I-74** and **I-75**. Fortuitously, the formed product **I-74** was crystalline, enabling assignment of its absolute stereochemistry, which was used to infer the assignment of absolute configuration of the other products in Figure I-29.

The conversion of the tri-substituted alkene to its corresponding product **I-81** was uneventful, as were the reaction of substrates bearing alkyl substituted olefins **I-103** and **I-104**. Under similar conditions, with the change of the halenium source to NIS, the iodospiroketalization proceeds with similar efficiency, yielding **I-82** in good yield with 91:9 *er*. As with other substrates, the iodo variant did not suffer in diastereoselection. Shortening



cis olefin- [6,6]-spiroketal

I-109, 60%^{a,b}
5:1 *dr,* 85:15 *er*^{c}

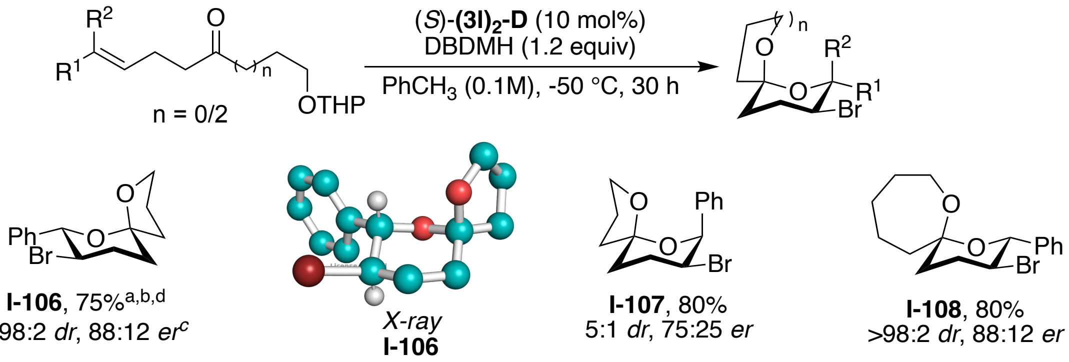
I-110, 40%
2:1 *dr*, 69:31 *er*

[a]Unless otherwise specified, all reactions were performed in toluene, -50 °C for 30 h with 0.1 mmol of substrate at 0.1 M and 1.2 equiv DBDMH. [b]Isolated yield. [c]Enantiomeric ratios were determined by HPLC analysis.

Figure I-31. Substrate Scope for the *cis* substituted olefins generating [6,6]-spiroketal.

the chain delivered the [5,6]-bromospiroketal **I-106**, retaining the high yield and diastereoselection, with good enantioinduction. Noteworthy, this transformation was catalyzed with (*R*)-**(3I)$_2$-D**, providing the enantiomeric product, which succumbed to crystallography and verified the inferred stereochemistry of the products assumed based on the crystal structure obtained for **I-106**. Extending the chain by one carbon led to the [7,6]-bromospiroketal **I-108**, which was also obtained with similar yields and stereoselectivities.

We next examined *cis*-olefins, these substrates were transformed to the corresponding product with reduced diastereomeric selection as well as the depressed enantioinduction. Presumably, these substrates suffer from 1,3-*syn* diaxial interaction in the transition state that leads to the bromospiroketal product. Although **I-109** was obtained with acceptable *er*, the enantioselecion of the alkyl variant **I-110** suffered and moderate enantioenrichment of



[a]Unless otherwise specified, all reactions were performed in toluene, -50 °C for 30 h with 0.1 mmol of substrate at 0.1 M and 1.2 equiv DBDMH. [b]Isolated yield. [c]Enantiomeric ratios were determined by HPLC analysis.[d](*R*)-**$(3I)_2$-D** catalyst was used instead of the (*S*)-**$(3I)_2$-D**.

Figure I-32. Substrate scope for spiroketalization with different ring sizes.

69:31 *er* was observed. Similarly, the [5,6]-bromospiroketal **I-107** was obtained with less selectivity as compared to its *trans* variant **I-106**.

Further mechanistic nuances predicted by *NAAA* were explored using the much stronger EWG, *p*-CF_3 in substrate **I-S-111** (Figure I-30). As anticipated, destabilization of a developing charge on the benzylic position yields near equal ratios of the [6,6]- and the

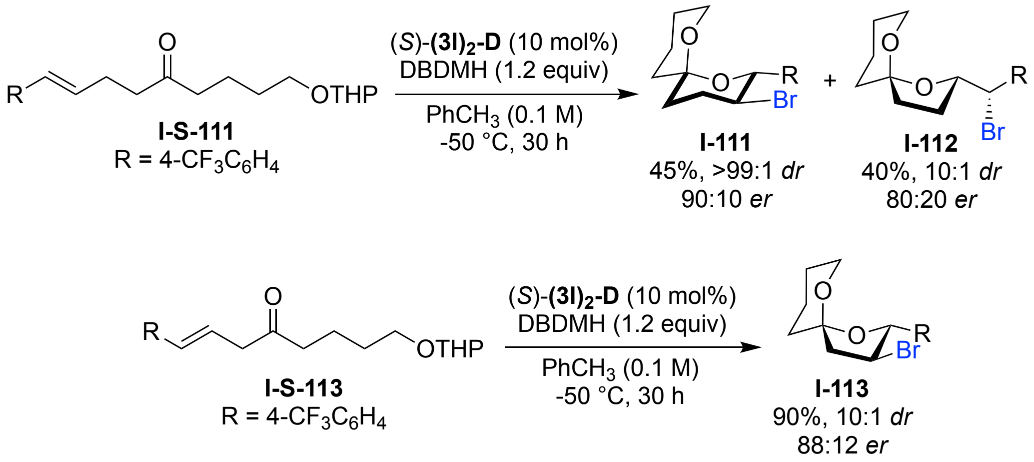


Figure I-33. Regioselection in the bromospiroketalization of electron deficient aryl substrates.

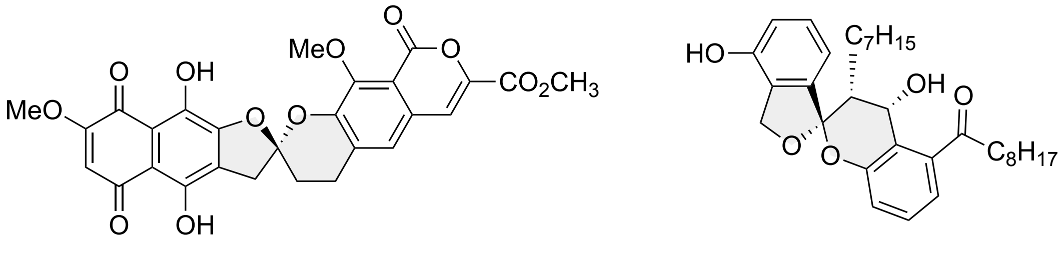
[5,6]-bromospiroketal products **I-111** and **I-112**, respectively. The [6,6]-spirocycle **I-111** was obtained as a single diastereomer (90:10 *er*), while the [5,6]-product **I-112** was isolated as a 10:1 mixture of diastereomers with moderate enantioselectivity for the major product (80:20 *er*). Shortening the chain alleviated the production of regioisomeric mixtures as demonstrated with substrate **I-S-113**. Its reaction under the same conditions led to spiroketal **I-113** as a single product in 90% yield and 88:12 *er*. Presumably, formation of the 4-membered ring containing product is not observed because of the higher strain associated with its transition state.

Gram-scale reaction of **I-70** with catalyst **$(3I)_2$-D** under the optimized conditions proceeded similarly, furnishing product **I-41** in 75% yield, as a single diastereomer, and comparable *er* (88:12). Recovery of the catalyst was also examined, with routine isolation of 85-95% of the material. Reuse of the recovered catalyst led to the comparable yields (80% yield for **I-41**) and selectivities (>98:2 *dr*, 94:6 *er*) observed with freshly produced batches.

Summary: We have presented a highly efficient catalytic system for the halonium ion-induced spiroketalization reaction. The crystalline nature of the VIP motifs allowed us to follow a novel structure-guided catalyst design in the synthesis of VIP catalysts. The success to achieve a high level of enantio-induction hinged on the synthesis of a VIP catalyst bearing an optimum dihedral angle (the defined angle between the substituents at 7,7'-positions on each VANOL ligands of the VIP catalyst), and the magnitude of such an angle depends on the nature of the substituents in 7,7'-positions on VANOL ligand. Our approach led us to design an efficient VIP catalyst that catalyzed the spiroketalization reaction and yielded the desired brominated products in excellent yields and enantioselectivities. In this reaction, the VIP catalyst acts as a Brønsted acid/Lewis base catalyst and such a dual function activates the halonium source (DBDMH) via decreasing its *HalA* and facilitate its transfer to the substrate.

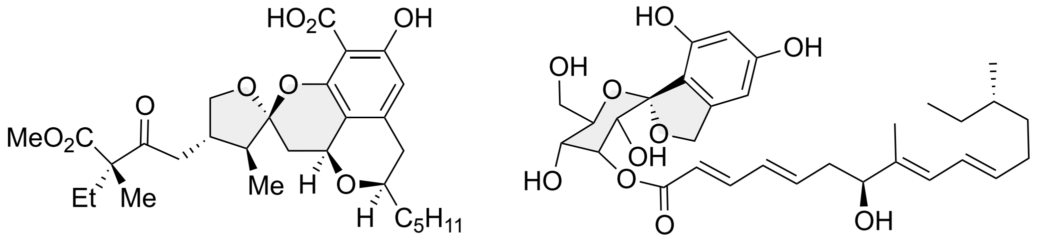
I.III.3. Desymmetrization of alkyne-diol: A swift and rapid way to access [5,6]-halogenated-spiroketal

Introduction*:* Spiroketal framework is often central to the biological activity of multiple natural products. Spiroketal cores have been widely found in insects, plants, bacteria, and marine organisms. [1, 2] Among these, benzannulated [5,6]-spirocyclic cores are most prevalent and are often found as core structure in natural products like paecilospirone **I-114** [inhibitor of microtubule assembly], [94] γ-rubromycin **I-2** [inhibitor of HIV-1 reverse transcriptase], [7] (–)-berkelic acid **I-4** [inhibition towards human ovarian cancer cell line OVCAR-3],[9] papulacandin D **I-115** [antifungal activities through inhibition of the β-1,3-D-glucan synthase][95] etc and plays a central role associated to its pharmacophoric properties (Figure I-31). These natural products besides possessing a spiroketal core are



γ-rubyromycin **I-2**

paecilospirone **I-114**



(–)-berkelic acid, **I-4**

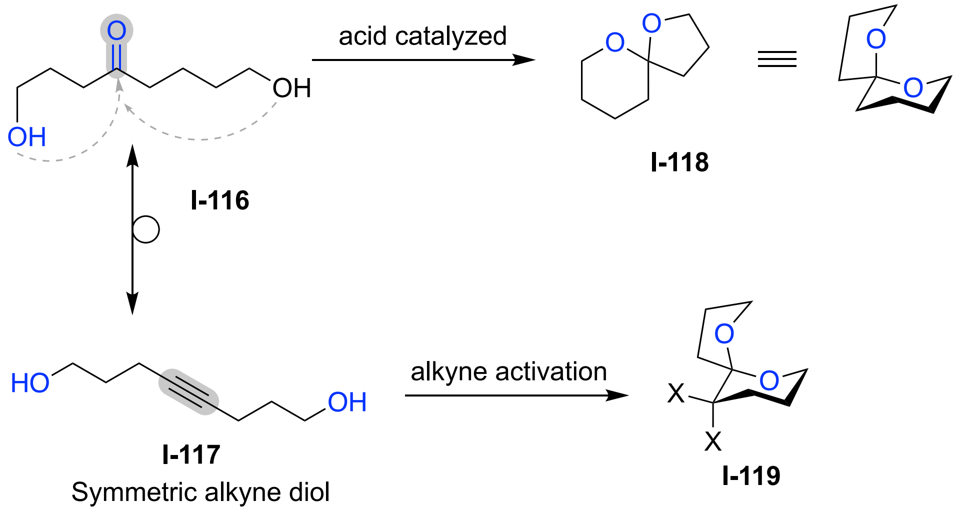
papulacandin D **I-115**

Figure I-34. Natural product core decorated with [5,6]-spiroketal.

also seen to be centrally attached to two benzylic moieties on either side of the spirocycle, thus making it a challenging [6-5-6-6] core.

As discussed previously, since spiroketals are a sub-class of the acetal family; the most generic approach to access such a motif involves acid catalyzed acetal formation by a pendant diol onto an incipient ketone **I-116** (Figure I-32a). [1, 6, 30] The alkyne unit has the same oxidation state as the -CH_2C(O)- unit of a typical carbonyl compound. Thus, classical carbonyl chemistry could be accessed through alkynes. This immediately renders the possibility for the formation of spiroketal from the same starting point with a

a. Generalized approach towards the formation of spiroketal



b. Desymmetrization of alkynediol to generate benzannulated spiroketal

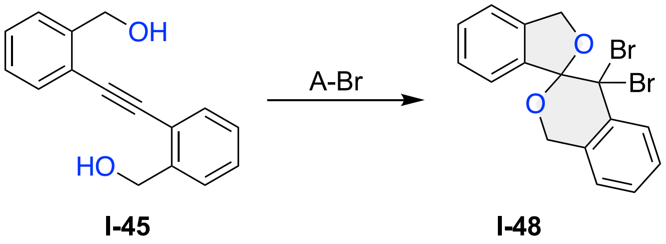
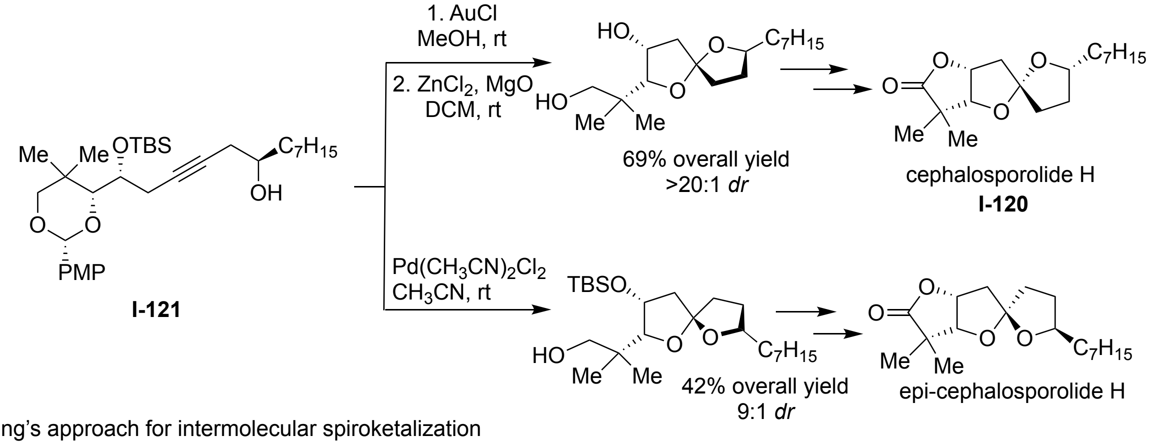


Figure I-35. Rational design at the synthesis of [5,6]-spiroketal from alkyne-diols.

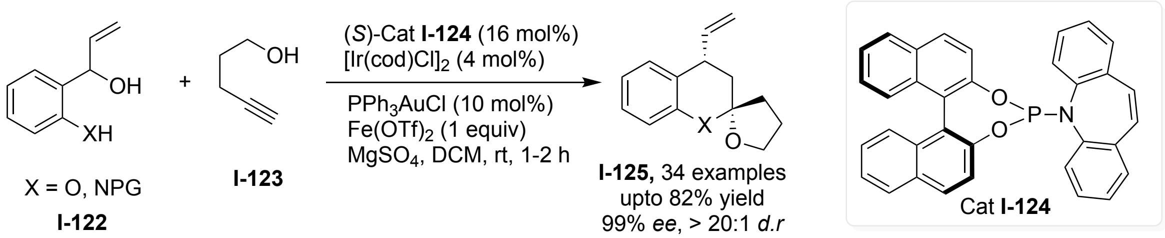
subtle replacement of the carbonyl functional group with that of the alkyne **I-117** functionality (Figure I-32a). This powerful technique provides an atom economical and redox neutral approach in the late stage spiroketalization.

Recently benzannulated spiroketals have garnered tremendous attraction due to the range of promising pharmacophoric properties. [96, 97] When the CO in **I-116** is replaced with C≡C (**I-117**), a symmetric alkynediol subunit is obtained, which would harbor the synthesis of the spiroketal through desymmetrization (Figure I-32b).

a. Dudley's intramolecular bishydroxylation of alkynes



b. Deng's approach for intermolecular spiroketalization



c. Reisman's approach during the total synthesis of Ritterazine B

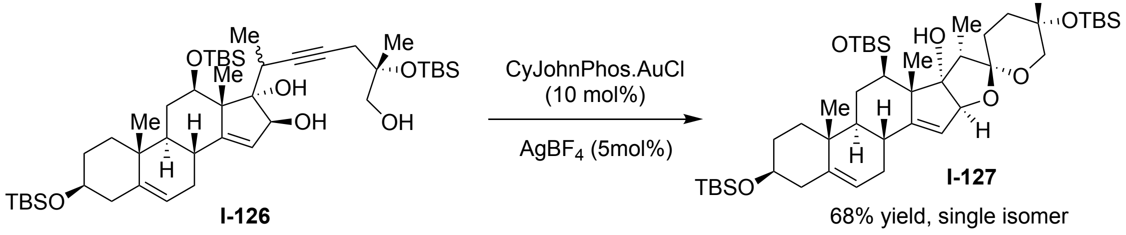


Figure I-36. Previous approaches towards accessing the [5,6]-spiroketal.

Enantioselective desymmetrization presents a powerful technique which enables the conversion of a relatively simple achiral starting materials to high-value stereochemically enriched products. Enantioinduction through desymmetrization has

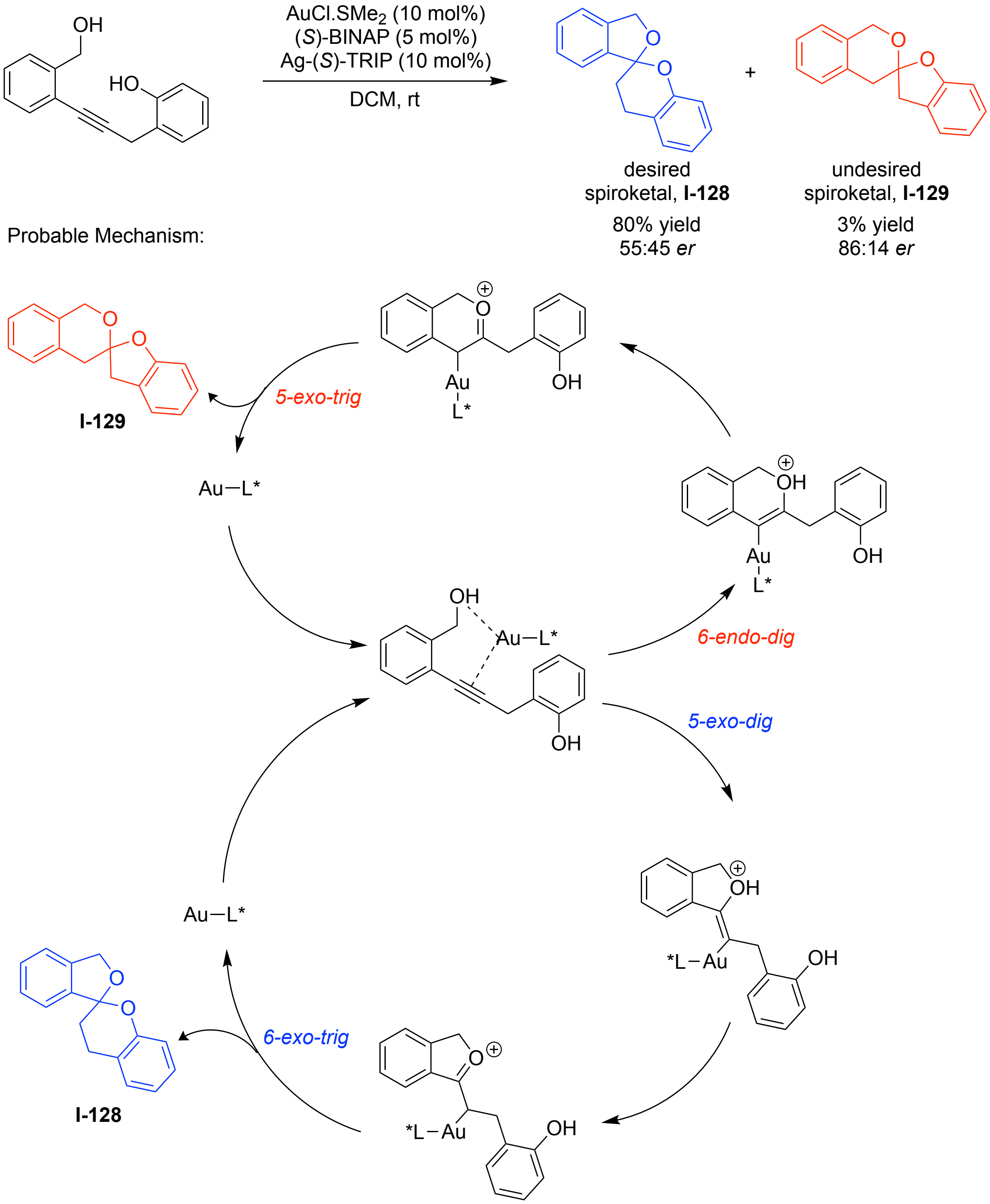


Figure I-37. Brimble's approach towards alkyne dihydroxylation.

been a go to option for chemists over the last 30 years.[98-102] Organocatalyzed desymmetrization of alkenes have been widely known strategy and has been effectively utilized to create diverse functionalization in a molecule. But organocatalyzed desymmetrization of alkynes has found limited application due to the higher reactivity of the alkynyl motif. Most strategies that have been developed involving alkyne are based on the use of the π-acidic catalysts based on transition metal catalyst like Au, Ag, Pd. [103-108] In 2010, Dudley and co-workers reported the synthesis of cephalosporolide H **I-120**, an anti-inflammatory agent containing a [5,5]-spiroketal system. A key spiroketal forming step in the synthetic route towards this natural product was accomplished through an Au(I) catalyzed hydroxylation of an alkyne precursor **I-121** (Figure I-33a).[109] In a recent report by the Deng group, the formation of a spiroketal has been reported where they have utilized iridium-gold catalyzed system to perform enantioselective cascade reaction between racemic 2-(1-hydroxyallyl)phenol **I-122** and alkynol **I-123** (Figure I-33b). [110] Reisman *et.al*. has also utilized a similar strategy to join during the total synthesis of Ritterazine B (Figure I-33c). [111] In this strategy, a combination of Au-Ag catalyst has been used to forge two separate fragments containing the spiroketal **I-127** starting from a chiral diol **I-126**. The two spiroketals were synthesized following similar methodology that were later stitched together to give the final natural product. The preset stereochemistry in the molecule was utilized to generate the [5,6]-spiroketal core in good yield and excellent diastereocontrol. In 2013, Brimble *et al*. described an elegant strategy to synthesize the benzannulated spiroketals **I-128** and **I-129** cores through the use of chiral Au-phosphine complex, [97] although the products were obtained with an enantioinduction of 10% *ee*. The chiral Au complex co-ordinates with the alkyne and that induces the more nucleophilic benzylic alcohol to attack thus forming a trans-alkenyl gold complex. The oxonium ion thus generated, is susceptible to the nucleophilic attack of the less nucleophilic phenol. Protodeauration then regenerates the gold complex and the spiroketal product (Figure I-34). A 5-exo-dig cyclization followed by a 6-exo-trig cyclization thus generates the paecilospirone spiroketal core **I-128**. However, a 6-endo-dig cyclization followed by a 5-exo-trig cyclization would furnish the isomeric spiroketal **I-129**.

Halenium assisted spiroketalization (our approach): After the successful development of the diastereoselective and enantioselective protocol towards accessing halogenated spiroketal (mainly focused on [6,6]-spiroketals), using our previously developed concepts of *HalA* and *NAAA* we wanted to develop a protocol: firstly, for the [5,6]-spirocyclic system that are synthetically more challenging than the [6,6]-system (due

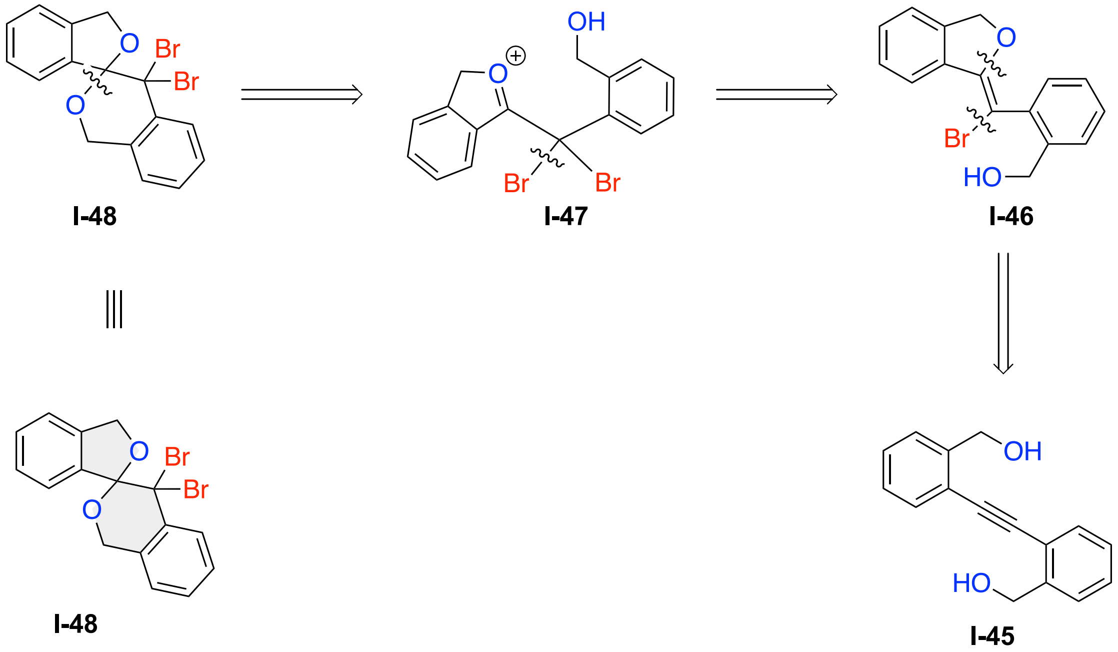


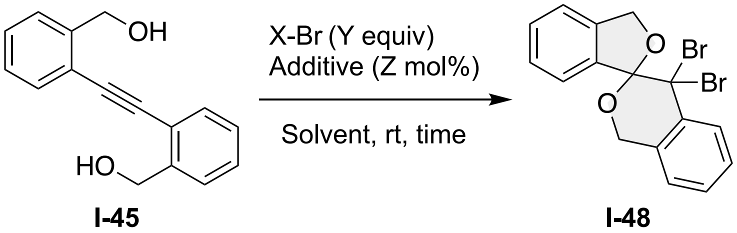
Figure I-38. Retro-synthetic analysis towards arriving at the benzannulated 5,6-spiroketal.

to the lack of anomeric stability) and secondly, we wanted to use the more reactive alkyne sub-unit for core functionalization. The alkyne unit has the same oxidation state as the -$CH_2C(O)$- unit of a typical carbonyl compound. This equivalence is readily illustrated by the fact that alkynes are converted to aldehydes/ketone via hydration through well-known reactions of Markovnikov/ anti-Markovnikov additions. Thus, “classical carbonyl chemistry” can be accessed through alkynes, hence, the logical disconnection of the spiroketal (**I-48**) to the oxa-carbenium intermediate **I-47**. This oxa-carbenium intermediate **I-47** can equilibrate to its enol-ether form **I-46**, which can be formed from the alkyne-diol **I-45** (Figure I-35). Alkynes are more reactive (have higher *HalA*) towards halogens and hence difficult to modulate their reactivity. Also a few literature reports are available for diversification on halo-functionalization of alkynes. Thus, at the onset we envisioned to achieve three major goals for this project: 1. The development of a highly diastereoselective halogenated [5,6]-spiroketal from alkyne. 2. Extending this protocol to synthesize 6-5-6-6 carbocyclic core structure analogous to the natural products like paedilospirone, γ-rubyromycin etc. 3. Develop this protocol into an enantiselective diastereoselctive methodology towards accessing halogenated [5,6]-spirocycle.

Reaction development and Optimization Studies for the diastereoselective dibromospiroketal:

With the alkyne-diol **I-45** in hand, we envisioned the dibromo-spiroketal **I-48** formation through the nucleophilic activation of the hydroxy onto the alkynyl carbon. Thus, employing NBS (bromonium ion) under basic condition did generate the desired product

Table I-6. Optimization condition for dibromospiroketalization.

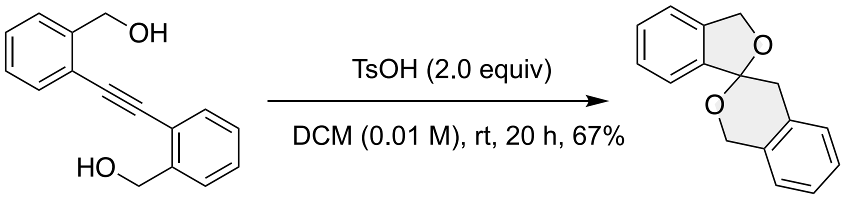


Entry[a]	X-Br (equiv)	Additive (mol%)	Solvent	Time (h)	Yield (%)[b]
1	NBS (2.0)	NaOH (100)	EtOAc	48	24
2	NBS (3.0)	NaOH (100)	EtOAc	48	35
3	DBDMH (3.0)	NaOH (100)	EtOAc	48	32
4	NBS (3.0)	NaOH (100)	Toluene	48	20
5	NBS (2.0)	–	EtOAc	24	60
6	NBS (2.0)	1 M HCl (10)	EtOAc	1	80
7	NBS (2.2)	1 M HCl (10)	EtOAc	1	96
8	NBS (2.5)	1 M HCl (10)	EtOAc	1	96
9	DBDMH (2.2)	1 M HCl (10)	EtOAc	1	96
10	NBAc (2.2)	1 M HCl (10)	EtOAc	1	90
11	NBS (2.2)	1 M HCl (50)	EtOAc	0.25	96
12	NBS (2.2)	1 M HCl (10)	DCM	1	95
13[c]	NBS (2.2)	1 M HCl (10)	EtOAc	1	96
14[d]	NCS (2.2)	1 M HCl (50)	EtOAc	0.25	87
15[e]	NIS (2.2)	1 M HCl (50)	EtOAc	17	67

[a] All reactions were performed with 0.1 mmol of **I-45** at 0.1 M. [b] Isolated yield. [c] Reaction was performed with 1 g of **I-45** [d,e] Chloro/iodo-spiroketal was formed as the final product

but only in 24% yield (Table I-6, entry 1). A slight increase in the yield was observed with higher equivalence of the brominating agent (entries 2, 3). In general, under basic conditions, the reaction was sluggish and starting material was recovered after 48 h. When the reaction was carried out in the absence of base, the reaction generated the desired product in 60% yield in 48 h. This initial hit motivated us to screen multiple different reaction conditions. Addition of catalytic amount of acid not only increased the yield of the final product to 80% but also led to complete conversion of the reaction in an hour (entry 6). After fine tuning the reaction conditions the desired dibromo spiroketal **I-48** was obtained as a white crystalline solid in 96% isolated yield (Table I-6, entry 11). The structure of **I-48** was confirmed through X-ray crystallography. Other brominating agents were equally efficient and led to the formation of the dibromo product in high yields (entries 9,10). The major factor that was responsible for the formation of this product was the addition of catalytic amount of the acid. Acid was used to activate the bromonium source NBS (modulate the *HalA* value) [$HalA_{(NBS)}$ = 197 kcal/mol, $HalA_{(NBS+HCl)}$ = 166.6 kcal/mol] but the conjugate base might have also helped to deprotonate and generate **I-46**. Formation of **I-46** was the most crucial step (slow step), because it generates the enol-ether which instantaneously reacts with a second equivalent of bromine to generate the oxa-carbenium **I-47**, which gets trapped by the pendent alcohol sub-unit. Table I-6 lists multiple solvent systems, and halogenating agents that were successful in delivering the final spiroketal in high yields and diastereoselectivity (entries 9, 10, 12). With NCS, dicholospiroketal **I-130** was obtained in excellent yield and disatereoselectivity (Table I-6, entry 14). Similarly, NIS was able to generate the iodo-variant **I-131** in good yield and diastereoselection (Table I-6, entry 15).

After a successfully synthesizing the di-halo variants of the [5,6]-spirocyclic motifs we investigated the preparations of a dihydro variant. Slight modification in the optimized conditions was good enough to generate **I-132** in great yields (Figure I-36). Although molecule I-132 is well known in the literature but most strategies that have been developed are based on the use of the π-acidic catalysts based on transition metal catalyst like Au, Ag. [103-108] Thus, this methodology provides a organo-catalysed route to access the benzannulated spiroketals.



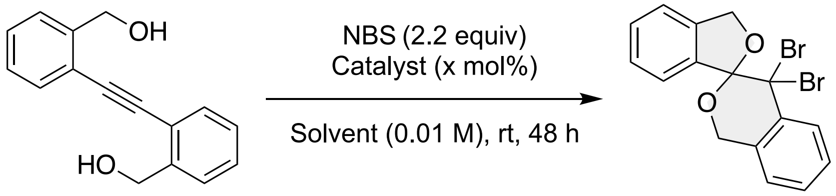
I-45 **I-132**

Figure I-39. Synthesis of dihydrospiroketal.

Reaction development and Optimization Studies for the enantioselective dibromospiroketal:

With a successful diastereoselective protocol in hand, we pursued the development of an enantioselective version for the synthesis of [5,6]-spiroketal. Table I-7 illustrates the efforts towards the enantioselective desymmetrization of alkyne diol **I-45**. Our asymmetric protocols in the past had developed around cinchona alkaloid family. So, we began our asymmetric screening by reacting **I-45** with NBS (2.2 equiv) and quinine (20 mol%) in toluene at rt for 48 h. Dibromospiroketal **I-48** was formed in 28% yield with a slight enantioenrichment [*er* = 52:48] (Table I-7, entry 1). Switching the solvent inceased both yield and the enantioinduction (entry 2). Increasing the catalyst loading had no effect on the enantioenrichment (Table I-7, entry 3). With very little success with quinine, we

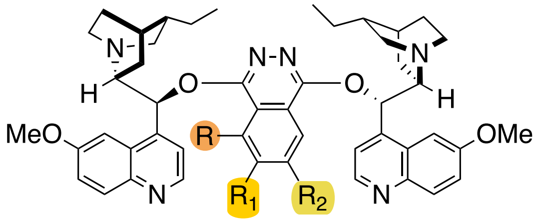
Table I-7. Optimization condition for asymmetric dibromospiroketalization.



I-45 **I-48**

Entry[a]	Catalyst	Loading (mol%)	Solvent	Yield (%)[b]	*er*[c]
1	Quinine	20	Toluene	28	52:48
2	Quinine	20	EtOAc	40	54:46
3	Quinine	50	EtOAc	48	54:46
4	$(DHQD)_2PHAL$	20	Toluene	22	52:48
5	$(DHQD)_2PHAL$	20	DCM	35	55:45
6	$(DHQD)_2PHAL$	20	EtOAc	40	58:42
7	$(DHQD)_2PHAL$	50	EtOAc	55	58:42
8	$(DHQD)_2AQN$	20	EtOAc	42	56:44
9	$(DHQD)_2Pyr$	20	EtOAc	35	52:48
10	$(DHQD)_3PHAL$-I	20	EtOAc	40	50:50
11	$(DHQD)_3PHAL$-II	20	EtOAc	45	50:50
12	$(DHQD)_4PHAL$-III	20	EtOAc	40	52:48

[a] All reactions were performed with 0.1 mmol of **I-45** at 0.1 M. [b] Isolated yield. [c] *er* was determined using chiral HPLC



$(DHQD)_{3/4}PHAL$

cat I R = DHQD, R_1 = H , R_2 = H

cat II R = H, R_1 = DHQD , R_2 = H

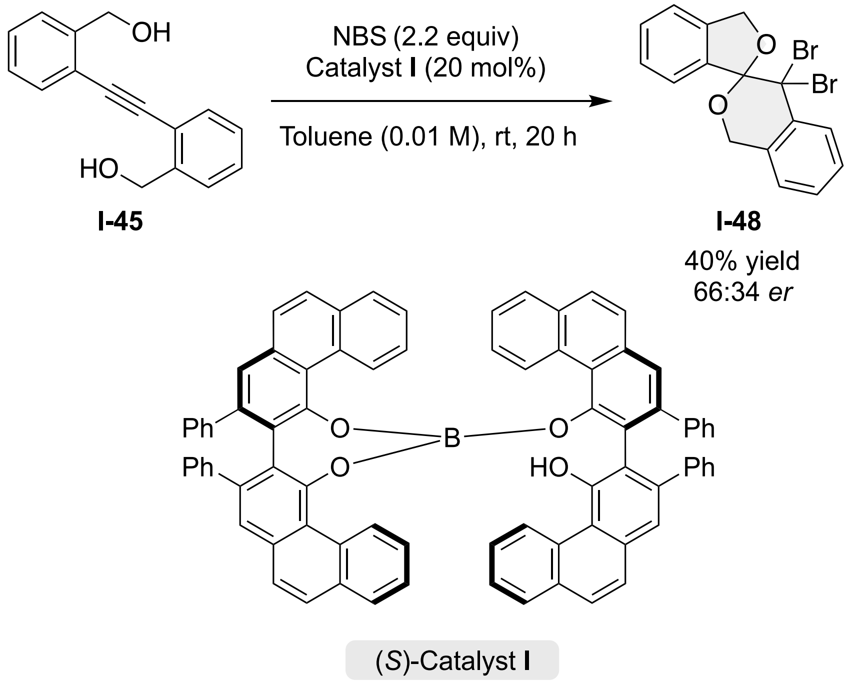
cat III R = H, R_1 = DHQD , R_2 = DHQD

switched to the dimeric $(DHQD)_2PHAL$ catalyst. When the chiral catalyst was switched to

$(DHQD)_2PHAL$ the enhancement of enantioinduction was observed (Table I-7, entry 4-6) with maximum *ee* of 16% when EtOAc was used as the solvent (entry 6). Further optimization of the reaction conditions was not fruitful in increasing the enantioselectivity. Despite our best efforts, there was no change in the observed enantioinduction of **I-48** with $(DHQD)_2PHAL$. Several other catalysts based on $(DHQD)_2PHAL$ with different linkers like anthraquinone and diphyenylpyrimidienyl, were tried but were not as useful in inducing enantioenrichment as the pthalazine linker (entries 8,9). Other variations of the catalyst like shown as **cat I**, **Cat II** and **Cat III** that were synthesized by inclusion of an addition quinine unit in the pthalazine linker. These C1 catalyst were envisioned to add steric congestion and hence help in boosting the enantioselectivity. But these were also not successful in delivering the spiroketal with increased *er* (entries 10-12).

During the optimization for the dibromo-spiroketalization we observed that the introduction of catalytic amount of acid rapidly increased the yield and the speed of the reaction. Hence, we sought to use the same analogy, instead of Bronsted acids we started pursuing Lewis acidic catalyst. Professor Wulff and coworkers have successfully developed BOROX based catalyst using VANOL/VAPOL ligands. [89, 90, 92, 93] These catalysts have been tremendously successful in coordinating with N,O-nucleophiles and delivering enantio-enriched products. [90, 112-116] When VAPOL-Borox was used as a catalyst the desired dibromospiroketal was formed with an enantioenrichment of 66:34 (*ee* of 32%) (Figure I-37). Further screening is currently underway in our lab to enhance the enantioinduction. Future work will include screening of the VANOL/VAPOL based IDPi catalysts that have already been developed in collaboration with the Wulff research lab (Section I.III.2.).

Summary: We have demonstrated the utilization and application of alkynes as potential surrogate for carbonyls and used their potential to form the [5,6]-spiroketal core. Through this recent protocol we can generate the [6,5,6,6] carbocycle swiftly and conveniently. The developed protocol is highly diastereoselective and furnished the desired product in excellent yield. Current efforts are underway to develop an enantioselective version of the same.



I-45

I-48
40% yield
66:34 *er*

(*S*)-Catalyst **I**

Figure I-40. Asymmetric dibromospiroketal using (*S*)-VAPOL-Borox catalyst.

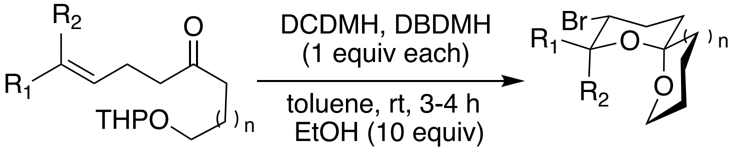
General Remarks

All reactions were performed in flame-dried glassware under an atmosphere of nitrogen gas unless otherwise indicated. Unless otherwise specified, all solvents were strictly dried before use: dichloromethane was distilled over calcium hydride under a stream of nitrogen gas; tetrahydrofuran, and toluene were distilled from sodium and benzophenone. Hexanes and ethyl acetate were ACS grade and were used as purchased. Varian Unity Plus 500 MHz spectrometer was used to record the ^{1}H NMR and ^{13}C NMR spectra using $CDCl_3$ as solvent. The residual peak of $CDCl_3$ or TMS was used as the internal standard for both ^{1}H NMR ($\delta = 7.26$ ppm for $CDCl_3$ or $\delta = 0$ ppm for TMS) and ^{13}C NMR ($\delta = 77.0$ ppm). Chemical shifts were reported in parts per million (ppm). Analytical thin-layer chromatography (TLC) was performed on Silicycle silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, or by staining with phosphomolybdic acid in ethanol. Column chromatography was performed with silica gel 60 (230 – 450 mesh). HPLC analyses were performed using Agilent 1100 or 1260 HPLC system with CHIRALCEL® OD-H and Pirkle D-Phenylglycine and OT(+) columns. HPLC grade hexanes (mixture of isomers) and 2-propanol were used for HPLC analyses. Optical rotations were obtained at a wavelength of 589 nm (sodium D line) using a 1.0 decimeter cell with a total volume of 1.0 mL. Specific rotations are reported in degrees per decimeter at 20 °C and the concentrations are given in gram per 100 mL in spectral grade $CHCl_3$ unless otherwise noted. High Resolution Mass Spectrometry was performed in the Department of Chemistry at Michigan State University Mass Facility.

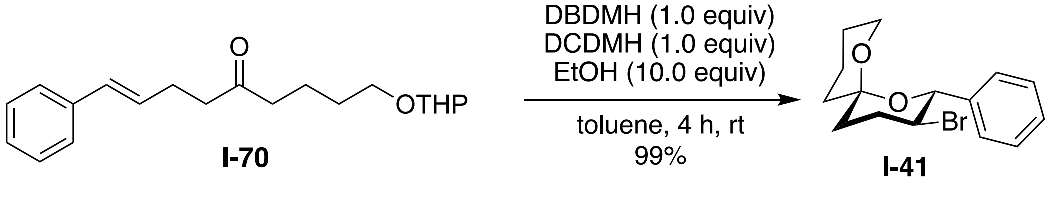
Experimental Section

I.III.1. Diastereoselective mono-bromospiroketalization

Bromo spiroketalization of THP-protected keto-alkenol–General Procedure I (GPI):



To the THP-protected keto-alkenol (1.0 equiv) in dry toluene (0.1 M) was added dry ethanol (10.0 equiv) and a mixture of 1,3-dibromo-5,5-dimethylhydantoin, DBDMH (1.0 equiv) and 1,3-dichloro-5,5-dimethylhydantoin, DCDMH (1.0 equiv). The reaction mixture was stirred at room temperature and followed by TLC. The initial colorless solution changed to orange solution during the reaction and become clear along with precipitation of hydantoin. This clear solution was the indication for the completion of the reaction, which took 3-4 h. The reaction mixture was diluted with hexanes (2 mL) followed by addition of aq. Na_2SO_3 (2 mL) The organic layer was separated, and the aqueous layer was extracted with hexanes (3 x 2 mL). Combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure at room temperature to give the crude product. Crude ^{1}H NMR was used to determine the diastereoselectivity of the reaction. The crude product was then purified by column chromatography (silica, ethyl acetate/hexanes = 3%) leading to the pure bromo spiroketal products.



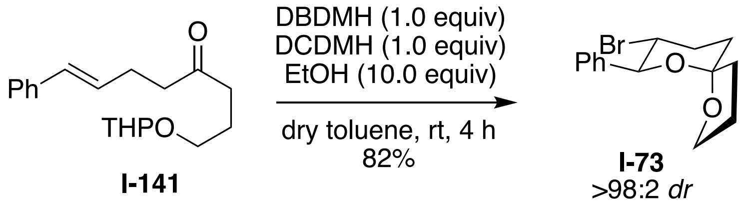
According to GP I, spiroketalization reaction on ketone **I-70 (**1.0 mmol), led to the formation of monobromospiroketal **I-41** in 99% yield (307.0 mg) as a white film. Reaction on a 0.1 mmol scale of **I-70** gave similar results.

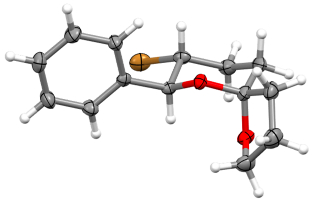
Analytical data for bromospiroketal I-41: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.44 – 7.39 (m, 2H), 7.38 – 7.30 (m, 3H), 4.66 (d, J = 10.4 Hz, 1H), 4.00 (ddd, J = 12.0, 10.3, 4.5 Hz, 1H), 3.72 – 3.60 (m, 2H), 2.50 (tdd, J = 12.9, 12.0, 5.0 Hz, 1H), 2.26 (dtd, J = 13.0, 4.5, 2.9 Hz, 1H), 1.82 – 1.63 (m, 4H), 1.63 – 1.54 (m, 1H), 1.52 – 1.41 (m, 3H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 139.7, 128.3, 128.1, 128.0, 96.0, 76.3, 60.8, 52.4, 37.6, 34.9, 31.2, 25.0, 18.3.

IR: 3065, 2900, 1440, 1263, 1176, 1081 cm^{-1}.

HRMS: TOF MS ES$^+$ (C$_{15}$H$_{20}$BrO$_2$): Calc. [M + H]$^+$: 311.0647, Found [M + H]$^+$: 311.0645.





X-ray structure of **I-73**

Following GP I, spiroketalization on ketone **I-141** (30.0 mg, 0.1 mmol) produced **I-73** (24.3 mg, 82% yield) as a white solid. Compound **I-73** was crystalized from a solution of DCM/hexanes by slow evaporation; the collected crystals were used for X-ray data collection.

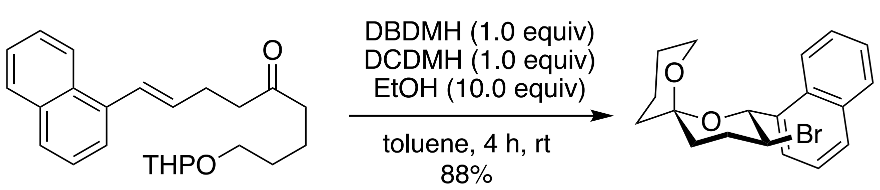
Analytical data for bromospiroketal I-73: ^{1}H NMR (500 MHz, CHCl$_3$): δ 7.41 – 7.30 (m, 5H), 4.83 (d, *J* = 10.4 Hz, 1H), 4.03 (ddd, *J* = 12.0, 10.3, 4.6 Hz, 1H), 3.99 – 3.86 (m, 2H), 2.51

(tdd, *J* = 13.4, 12.0, 4.3 Hz, 1H), 2.40 (dtd, *J* = 12.9, 4.6, 2.8 Hz, 1H), 2.09 (td, *J* = 13.6, 4.5 Hz, 1H), 2.04 – 1.93 (m, 2H), 1.90 – 1.81 (m, 2H), 1.77 – 1.69 (m, 1H).

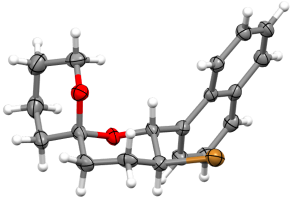
^{13}C NMR (125 MHz, CDCl$_3$): δ 139.73, 128.32, 128.14, 127.92, 106.16, 67.37, 52.06, 37.19, 35.21, 32.71, 23.63.

IR: 3054, 3030, 2920, 2869,1435, 1368, 1272, 1197, 1073, 1048, 968, 763 cm^{-1}.

TOF MS ES$^+$ ($C_{14}H_{18}BrO_2$): Calc. [M + H]$^+$: 297.0490, Found [M + H]$^+$: 297.0482.



I-134 **I-74**



X-ray structure of **I-74**

Following GP I, spiroketalization on ketone **I-134** (36.0 mg, 0.1 mmol) led to **I-74** as a white solid (31.8 mg, 88% yield).

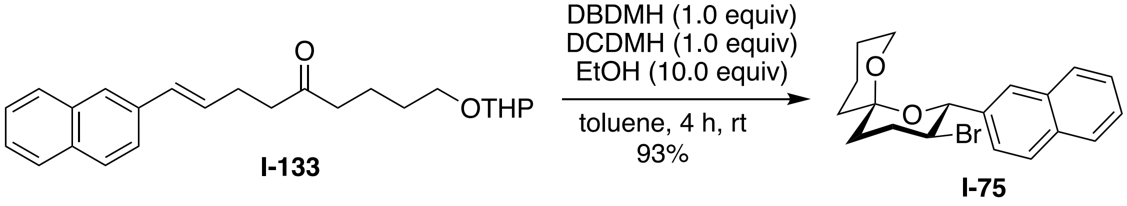
Analytical data for bromospiroketal I-74:

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.37 (d, J = 8.6 Hz, 1H), 7.85 (dd, J = 16.0, 8.1 Hz, 2H), 7.67 – 7.56 (m, 1H), 7.49 (dq, J = 15.4, 7.4 Hz, 3H), 5.49 (br, 1H), 4.36 (br, 1H), 3.82 – 3.54 (m, 2H), 2.62 (qd, J = 12.1, 7.5 Hz, 1H), 2.34 (dq, J = 12.6, 4.0 Hz, 1H), 1.92 – 1.83 (m, 2H), 1.75 – 1.61 (m, 2H), 1.54 (pd, J = 12.3, 5.8 Hz, 2H), 1.43 (dd, J = 26.1, 9.7 Hz, 2H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 139.2, 133.8, 131.8, 128.9, 128.8, 125.8, 125.4, 125.2, 96.2, 60.9, 52.5, 37.8, 35.0, 31.6, 25.0, 18.3.

IR: 3055, 2911, 2850, 1439, 1376, 1267, 1225, 1175, 1132, 970, 705 cm^{-1}.

HRMS: TOF MS AP$^+$ ($C_{19}H_{22}BrO_2$): Calc. [M + H]$^+$:361.0803, Found [M + H]$^+$: 361.0803.



Following GP I, spiroketalization on ketone **I-133** (35 mg, 0.1 mmol) led to **I-75** as a white solid (33.5 mg, 93% yield).

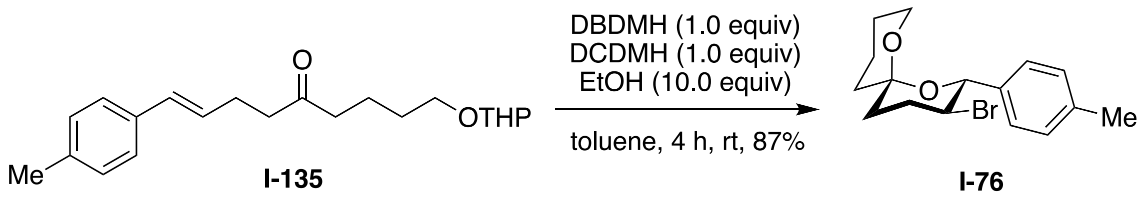
Analytical data for bromospiroketal I-75:

^{1}H NMR (500 MHz, CHCl$_3$): δ 7.89 – 7.81 (m, 4H), 7.56 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.50 – 7.46 (m, 2H), 4.85 (d, *J* = 10.4 Hz, 1H), 4.14 (ddd, *J* = 12.0, 10.3, 4.5 Hz, 1H), 3.75 – 3.69 (m, 2H), 2.64 – 2.50 (m, 1H), 2.32 (dtd, *J* = 12.9, 4.4, 3.1 Hz, 1H), 1.88 – 1.80 (m, 2H), 1.78 – 1.68 (m, 2H), 1.65 – 1.57 (m, 1H), 1.54 – 1.43 (m, 3H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 137.04, 133.40, 132.98, 128.16, 127.89, 127.71, 127.55, 126.04, 125.38, 96.08, 76.55, 60.87, 52.27, 37.69, 34.89, 31.29, 25.01, 18.36.

IR: 3054, 2939, 2869, 1448, 1375, 1349, 1270, 1080 cm^{-1}.

HRMS: TOF MS AP$^+$ ($C_{19}H_{22}BrO_2$): Calc. [M + H]$^+$:361.0803, Found [M + H]$^+$: 361.0803.



Following GP I, spiroketalization on ketone **I-135** (33.0 mg, 0.1 mmol) led to the formation of **I-76** as a white foam (28.2 mg, 87% yield).

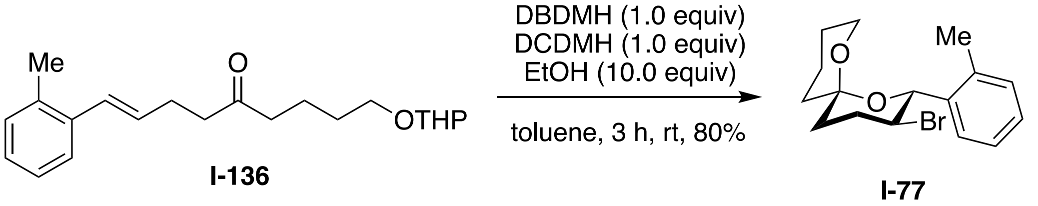
Analytical data for bromospiroketal I-76:

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30 (d, J = 8.0, 2H), 7.16 (d, J = 8.0 Hz, 2H),, 4.63 (d, J = 10.3 Hz, 1H), 4.00 (ddd, J = 12.0, 10.3, 4.5 Hz, 1H), 3.72 – 3.59 (m, 2H), 2.56 – 2.43 (m, 1H), 2.35 (s, 3H), 2.26 (dtd, J = 12.9, 4.4, 2.9 Hz, 1H), 1.81 – 1.62 (m, 4H), 1.60 – 1.41 (m, 4H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 138.0, 136.7, 128.8, 127.8, 95.9, 76.1, 60.74, 52.5, 37.6, 34.8, 31.2, 25.0, 21.2, 18.3 ppm.

IR: 3010, 2939, 2869, 1517, 1440, 1380, 1274, 1175, 1040, 998, 968, 811cm^{-1}.

HRMS: TOF MS AP$^+$ ($C_{16}H_{22}BrO_2$): Calc. [M + H]$^+$: 325.0803, Found [M + H]$^+$: 325.0803.



Following GP I, spiroketalization of ketone **I-136** (49.0 mg, 0.15 mmol) led to **I-77** as a white solid (39.0 mg, 80% yield). mp = 47 – 50°

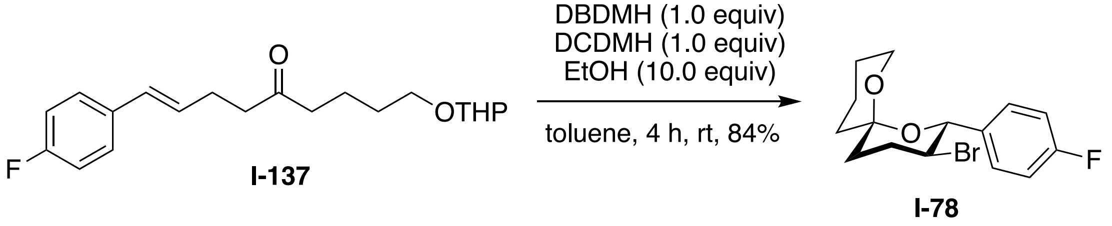
Analytical data for bromospiroketal I-77:

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.46 – 7.39 (m, 1H), 7.32 – 7.15 (m, 3H), 5.06 (d, J = 10.4 Hz, 1H), 4.11 (ddd, J = 12.1, 10.4, 4.4 Hz, 1H), 3.76 – 3.63 (m, 2H), 2.59 – 2.52 (m, 1H), 2.51 (s, 3H), 2.29 (dtd, J = 13.0, 4.3, 2.8 Hz, 1H), 1.87 – 1.65 (m, 4H), 1.62 – 1.42 (m, 4H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 138.4, 136.5, 130.1, 128.0, 127.1, 126.1, 96.0, 71.7, 60.7, 53.1, 37.8, 35.0, 31.4, 25.0, 20.2, 18.3.

IR: 3001, 2939, 2869, 1487, 1300, 1274, 1175, 1080, 998, 96 cm^{-1}.

HRMS: TOF MS AP$^+$ ($C_{16}H_{22}BrO_2$): Calc. [M + H]$^+$: 325.0803, Found [M + H]$^+$: 325.0803.



Following GP I, spiroketalization on ketone **I-137** (49.0 mg, 0.15 mmol) led to the formation of **I-78** as a white foam (41.0 mg, 84% yield),

Analytical data for bromospiroketal I-78:

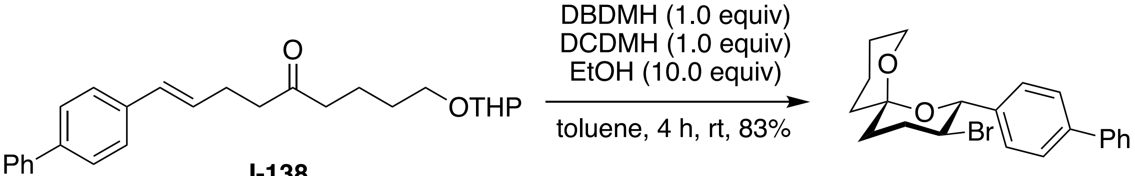
^{1}H NMR (500 MHz, CDCl$_3$) δ 7.43 – 7.34 (m, 2H), 7.09 – 6.99 (m, 2H), 4.64 (d, J = 10.3 Hz, 1H), 3.93 (ddd, J = 12.1, 10.3, 4.5 Hz, 1H), 3.68 (ddt, J = 11.0, 5.0, 1.8 Hz, 1H), 3.64 – 3.57 (m, 1H), 2.49 (tdd, J = 13.1, 12.0, 4.8 Hz, 1H), 2.25 (dtd, J = 13.0, 4.4, 2.8 Hz, 1H), 1.83 – 1.62 (m, 4H), 1.60 – 1.43 (m, 4H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 162.6 (d, $J_{C\text{-}F}$ = 246.1 Hz), 135.6 (d, $J_{C\text{-}F}$ = 3.3 Hz), 129.6 (d, $J_{C\text{-}F}$ = 8.1 Hz), 115.0 (d, $J_{C\text{-}F}$ = 21.4 Hz), 96.0, 75.6, 60.8, 52.5, 37.6, 34.8, 31.2, 25.0, 18.3.

^{19}F NMR (470 MHz, CDCl$_3$) δ -113.86 – -113.95 (m).

IR: 2941,2870, 1605, 1510, 1450, 1379, 1271, 1177, 1080, 999, 892 cm^{-1}. HRMS: TOF MS ES$^+$ ($C_{15}H_{19}BrFO_2$): Calc. [M + H]$^+$: 329.0552, Found [M + H]$^+$: 329.0544.

Synthesis of bromospiroketal I-79: Following GP I, spiroketalization on ketone **I-138** (39.0 mg, 0.1 mmol) led to the formation of **I-79** as a white foam (32.0 mg, 83% yield).



I-138

I-79

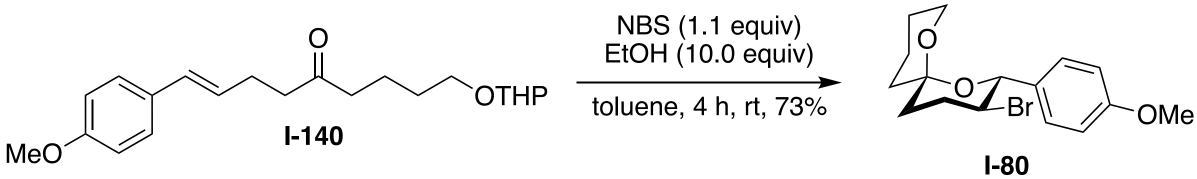
Analytical data for bromospiroketal I-79:

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.62 – 7.57 (m, 4H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.46 – 7.41 (m, 2H), 7.37 – 7.32 (m, 1H), 4.73 (d, *J* = 10.4 Hz, 1H), 4.06 (ddd, *J* = 12.0, 10.3, 4.5 Hz, 1H), 3.78 – 3.59 (m, 2H), 2.60 – 2.48 (m, 1H), 2.30 (dtd, *J* = 12.9, 4.4, 2.9 Hz, 1H), 1.86 – 1.74 (m, 3H), 1.73 – 1.67 (m, 1H), 1.63 – 1.56 (m, 1H), 1.54 – 1.45 (m, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ 141.18, 140.87, 138.68, 128.72, 128.38, 127.27, 127.17, 126.88, 124.81, 96.05, 77.26, 60.84, 52.35, 37.66, 34.88, 31.25, 25.01, 18.37.

IR: 3030, 2924, 2869, 2853, 1448, 1263, 1176, 1079, 1045, 999, 968, 747 cm^{-1}.

HRMS: TOF MS AP$^+$ ($C_{21}H_{24}BrO_2$): Calc. [M + H]$^+$:387.0915, Found [M + H]$^+$: 387.0960.



I-140

I-80

Following GP I, but instead using NBS (1.1 equiv) as the bromonium source, spiroketalization on ketone **I-140** (34.0 mg, 0.1 mmol) led to the formation of **I-80** as a white foam (25.0 mg, 73% yield).

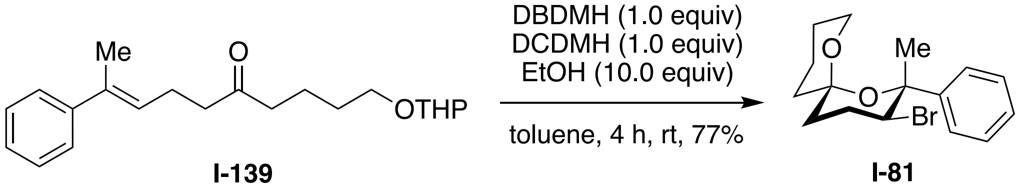
Analytical data for bromospiroketal I-80:

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.33 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.61 (d, J = 10.4 Hz, 1H), 3.99 (ddd, J = 12.0, 10.3, 4.5 Hz, 1H), 3.80 (s, 3H), 3.71 – 3.60 (m, 2H), 2.49 (tdd, J = 12.9, 12.0, 4.9 Hz, 1H), 2.25 (dtd, J = 12.9, 4.4, 2.9 Hz, 1H), 1.80 – 1.62 (m, 4H), 1.60 – 1.42 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 132.0, 129.0, 113.4, 96.0, 75.8, 60.8, 55.2, 52.8, 37.6, 34.9, 31.3, 25.0, 18.3, 14.1.

IR: 3035, 2905, 2835, 1465, 1378, 1335, 1276, 1145, 1100, 1080, 987, 787 cm^{-1} .

HRMS: TOF MS ES$^+$ ($C_{16}H_{22}BrO_3$): Calc. [M + H]$^+$: 341.0752, Found [M + H]$^+$: 341.0741.



Following GP I, spiroketalization on ketone **I-139** (33.0 mg, 0.1 mmol) produced **I-81** as a white solid (24.5 mg, 77% yield).

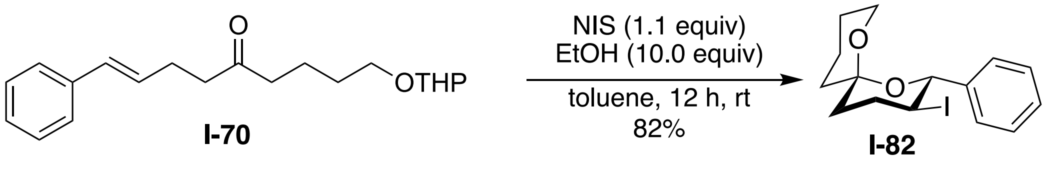
Analytical data for bromospiroketal I-81:

^{1}H NMR (500 MHz, $CHCl_3$): δ 7.71 – 7.61 (m, 2H), 7.43 – 7.35 (m, 2H), 7.34 – 7.28 (m, 1H), 4.71 (dd, *J* = 12.8, 3.7 Hz, 1H), 4.19 (t, *J* = 3.1 Hz, 1H), 3.87 (ddd, *J* = 12.3, 11.2, 3.0 Hz, 1H), 3.69 (ddt, *J* = 11.1, 4.3, 1.9 Hz, 1H), 3.20 (ddd, *J* = 14.3, 12.8, 3.1 Hz, 1H), 2.49 (dt, *J* = 14.3, 3.5 Hz, 1H), 2.32 – 2.21 (m, 1H), 2.04 (s, 3H), 1.75 (qt, *J* = 13.2, 4.1 Hz, 1H), 1.65 – 1.58 (m, 2H), 1.52 (dq, *J* = 12.5, 4.2 Hz, 1H), 1.49 – 1.43 (m, 1H), 1.39 (td, *J* = 13.5, 4.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.77, 127.85, 127.63, 126.24, 96.95, 79.41, 62.90, 57.14, 54.36, 36.76, 36.48, 24.83, 19.58, 19.25.

IR: 2935, 2865, 1575, 1448, 1378, 1310, 1210, 1145, 1100, 1076, 998, 742 cm^{-1}.

HRMS: TOF MS AP$^+$ ($C_{16}H_{22}BrO_2$): Calc. [M + H]$^+$: 325.0824, Found [M + H]$^+$: 325.0803.



Following GP I, but using NIS as iodonium source, spiroketalization reaction on ketone **I-70** (0.1 mmol), led to the formation of **I-82** in 82% yield (29.0 mg) as a white film.

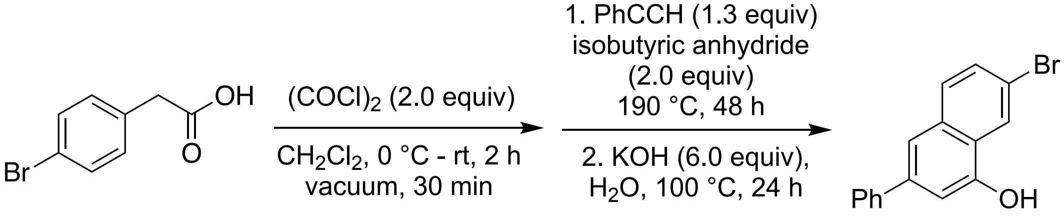
Analytical data for iodospiroketal I-82: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.32 (m, 5H), 4.78 (d, *J* = 10.8 Hz, 1H), 4.18 (ddd, *J* = 12.3, 10.7, 4.3 Hz, 1H), 3.75 – 3.63 (m, 2H), 2.72 (qd, *J* = 13.1, 4.4 Hz, 1H), 2.52 – 2.31 (m, 1H), 1.81 – 1.71 (m, 2H), 1.67 (tdd, *J* = 13.6, 4.3, 2.7 Hz, 3H), 1.51 – 1.41 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.39, 128.40, 128.10, 127.98, 125.96, 96.27, 76.76, 60.77, 38.84, 35.16, 33.61, 32.66, 25.04, 18.25.

IR: 3004, 2909, 1521, 1439, 1305, 1267, 1250, 1175, 1111, 989, 787 cm^{-1}.

I.III.2. Asymmetric mono-bromospiroketalization

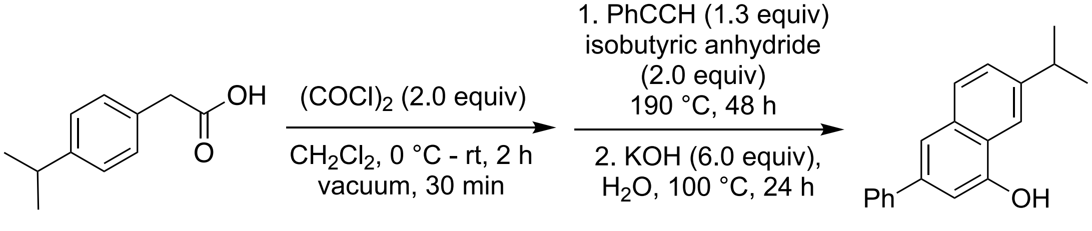
General procedure for the synthesis of 7-substituted-3-phenyl-1-naphthols (GP II):



(3m)$_{1/2}$

Synthesis of 7-bromo-3-phenyl-1-naphthol (3m)$_{1/2}$: A flamed dried 500 mL round bottom flask connected to a bubbler and the bubbler attached to a tube which purged into a beaker filled with saturated solution of NaOH (to neutralize the produced HCl). This flask was charged with 4-bromo-phenylacetic acid (90.0 mmol, 19.4 g) and CH_2Cl_2 (90.0 mL) to obtain a 1 M solution of the starting material. The resulting solution was cooled down to 0 ˚C followed by careful addition of $(COCl)_2$ (180 mmol, 15.4 mL) in a period of 30 min. After stirring the mixture for 1 h at 0 ˚C, the cold bath was removed, and the reaction was allowed to warm up to room temperature and stirred for another hour. The volatiles were removed under reduced pressure and the resulting yellowish liquid was used in the next step without further purification. The resulting acyl chloride in a 500 mL round bottom flask, was fitted with two condensers stacked on top of each with a gentle flow of nitrogen gas across the top of the condenser. To this flask was added phenyl acetylene (117.0 mmol, 12.9 mL) and isobutyric anhydride (180.0 mmol, 29.9 mL). It should be noted that the use of two condensers is crucial in this reaction to achieve full conversion to avoid loss of phenylacetylene. The resulting mixture was stirred at 190 ˚C for 48 h with a continuous flow of nitrogen gas across the top of the condenser. Next, the reaction was cooled down to 60 ˚C followed by the slow addition of a solution of KOH (540.0 mmol, 30.3 g) in H_2O (150 mL). The resulting biphasic mixture was stirred at 100 ˚C for 24 h. The mixture was cooled down to room temperature followed by the addition of ethyl acetate (200 mL) and stirred for 10 min. The aqueous layer was extracted with ethyl acetate (3 X 100 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and filtered through Celite. The resulting black solution was concentrated under reduced pressure and purified via column chromatography (50 X 300 mm, CH_2Cl_2: hexane 1:3 to 1:0), providing the desired product **$(3m)_{1/2}$** as an off-white solid in 60% yield (54 mmol, 16.2 g).

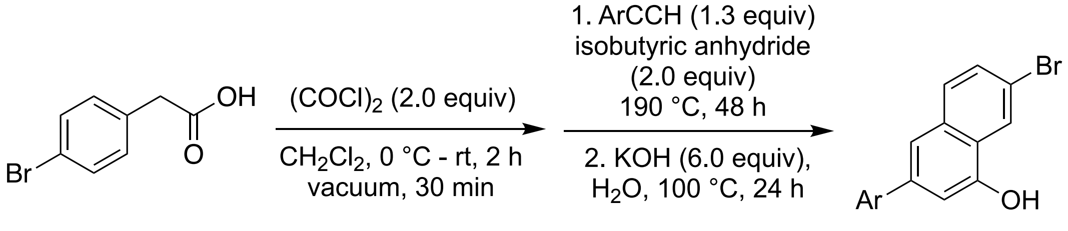
Spectral data for $(3m)_{1/2}$: ^1H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.60 (t, J = 1.2 Hz, 1H), 7.58 (dd, J = 8.7, 2.0 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.42 – 7.37 (m, 1H), 7.09 (d, J = 1.6 Hz, 1H), 5.36 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.00, 140.62, 139.52, 133.48, 130.45, 129.74, 129.05, 127.83, 127.38, 124.78, 124.43, 119.43, 118.72, 109.39. These spectral data are in agreement with literature value. [59,89]



$(3j)_{1/2}$

Synthesis of 7-iso-propyl-3-phenyl-1-naphthol $(3j)_{1/2}$: Compound **$(3j)_{1/2}$** was prepared from 4-isopropylphenylacetic acid (28.1 mmol, 5.01 g), oxalyl chloride (56.2 mmol, 4.82 mL), phenylacetylene (36.5 mmol, 6.10 mL) and isobutyric anhydride (56.2 mmol, 9.41 mL) according to GP II and the crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: CH_2Cl_2 [3:1 – 1:1] as the eluent). The desired compound **(3j)$_{1/2}$** was obtained as a white solid in 52% isolated yield (14.6 mmol, 3.83 g). [59,89]

Spectral data for (3j)$_{1/2}$: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 1.8 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.70 – 7.63 (m, 3H), 7.50 – 7.43 (m, 3H), 7.41 – 7.35 (m, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 5.43 (s, 1H), 3.13 (hept, *J* = 6.9 Hz, 1H), 1.38 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.54, 146.23, 141.12, 138.11, 133.73, 128.92, 128.22, 127.42, 127.36, 126.89, 123.71, 118.70, 117.75, 108.54, 34.60, 24.11. These data are in agreement with the literature values.

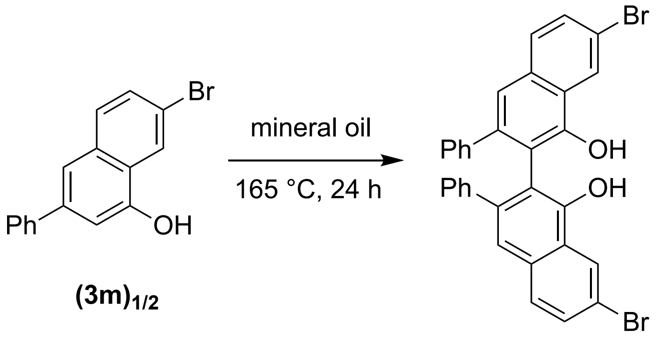


(3mγ)$_{1/2}$

Synthesis of 7-bromo-3-(4-(tert-butyl)phenyl)-1-naphthol (3mγ)$_{1/2}$: Compound **(3mγ)$_{1/2}$** was prepared from 4-bromophenylacetic acid (100.0 mmol, 21.5 g), oxalyl chloride (200.0 mmol, 16.9 mL), 4-*t*-butyl-phenylacetylene (130.0 mmol, 23.4 mL) and isobutyric anhydride (200.0 mmol, 33.0 mL) according to the GP II and the crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: CH_2Cl_2 3:1 – 1:1 as the eluent). The desired compound **(3mγ)$_{1/2}$** was obtained as a white solid in 67% isolated yield (18.5 g), mp 162-164 ˚C.

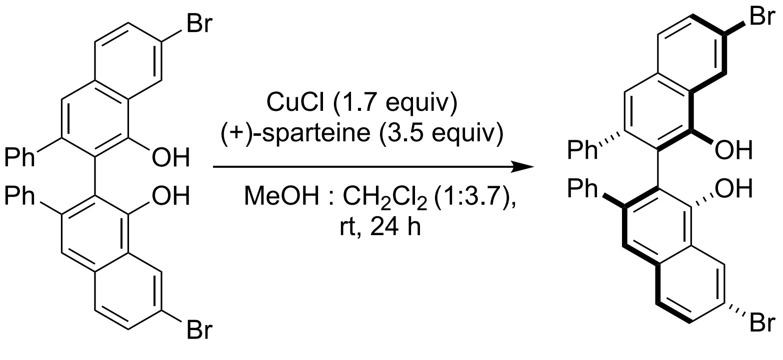
Spectral data for (3mγ)$_{1/2}$: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.0 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.62 – 7.59 (m, 3H), 7.57 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.09 (d, *J* = 1.5 Hz, 1H), 5.35 (s, 1H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 150.95, 150.93, 139.34, 137.64, 133.50, 130.35, 129.70, 126.99, 126.01, 124.67, 124.40, 119.24, 118.42, 109.33, 34.74, 31.48. IR: 3554, 2858, 1586, 1236, 1167, 1086, 826, 548 cm^{-1}. HRMS (ESI-TOF) [C$_{20}$H$_{18}$^{79}BrO] Calc. for [M-H]$^-$: 353.0540, Found: 353.0579.

***General Procedure for the synthesis of enantiopure 7,7'-disubstituted-VANOL ligand (GP III)*:**



rac-3m

Oxidative phenol-coupling of compound *rac*-3m: In a 500 mL three neck round bottom flask equipped with a stir bar and cooling condenser was added compound ***rac*-(3m)$_{1/2}$** (47.2 mmol, 14.1 g) and mineral oil (55 mL). A continuous airflow was established one inch above the mixture using a syringe needle. The reaction was stirred at 165 ˚C for 24 h with a continuous air flow over the reaction. The oil bath was removed, and the reaction was allowed to cool down to room temperature followed by the addition of CH$_2$Cl$_2$ (50 mL) and hexane (100 mL). The resulting suspension was stirred at room temperature until all the large chunks were broken followed by cooling down the reaction mixture to -20 ˚C overnight. The resulting solids were collected via filtration and washed with hexane and CH$_2$Cl$_2$, yielding the desired product ***rac*-3m** in 80% isolated yield (37.8 mmol, 11.3 g). The product was pure and used in the next step without further purification.



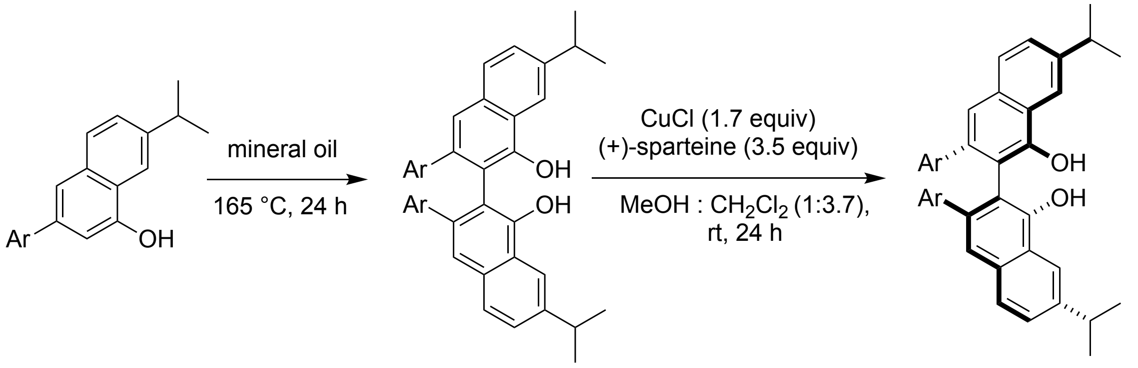
rac-3m **(*R*)-3m**

De-racemization of compound *(R)*-3m: A 500 mL round bottom flask was charged with (+)-sparteine (35 mmol, 8.2 g), CuCl (17.0 mmol, 1.68 g) in MeOH (270 ml); and sonicated under air for an hour. The flask containing the resulting dark green solution was sealed with a septum and purged with argon for another hour.

In a 2 L round bottom flask was added *rac*-7,7'-Br_2VANOL ***rac*-3m** (10.0 mmol. 5.96 g) in CH_2Cl_2 (1020 mL), sealed and purged with argon gas for 60 min. The dark green solution of (+)-sparteine-copper complex in the 500 mL round bottom flask was cannulated to the 2 L round bottom flask containing ***rac*-3m**. The resulting dark green solution was sonicated at room temperature for 15 min. The reaction mixture was then wrapped with aluminum foil and stirred at room temperature overnight. The reaction was quenched by slow addition of satd. aq. solution of $NaHCO_3$ (125 mL) followed by an addition of excess H_2O (400 mL). The resulting suspension was extracted with CH_2Cl_2 (3 X 300 mL), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure resulting in the crude mixture which was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: CH_2Cl_2, 2:1 to 1:1 and 1:2) to afford pure (*R*)-7,7'-Br_2VANOL ***(R)*-3m** as an off-white solid in 73 %

isolated yield (7.3 mmol, 4.3 g). The *ee* was determined to be 99% by HPLC analysis (Pirkle D-Phenylglycine column, 98:2, hexane: *i*-PrOH at 254 nm, flow rate 1 mL/min).

Spectral data for compound *(R)*-3m [59]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.64 – 7.54 (m, 2H), 7.20 (d, *J* = 0.8 Hz, 1H), 7.09 – 7.01 (m, 1H), 6.97 – 6.91 (m, 2H), 6.61 – 6.56 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.02, 141.55, 140.15, 132.89, 130.57, 129.40, 129.02, 127.47, 126.76, 125.50, 124.70, 121.52, 119.49, 115.42. These spectral data are in agreement with the literature value. [89,59]



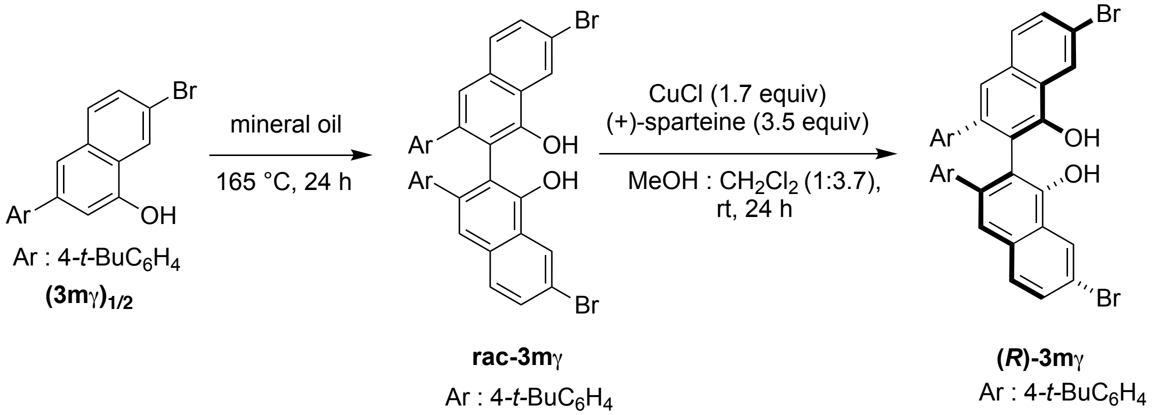
$(3j)_{1/2}$
Ar : 4-*t*-BuC_6H_4

rac-3j
Ar : 4-*t*-BuC_6H_4

(*R*)-3j
Ar : 4-*t*-BuC_6H_4

Synthesis of (*R*)-3j: Compound **(*R*)-3j** was prepared from compound **rac-$(3j)_{1/2}$** (3.83 mmol, 2.01 g) and mineral oil (30 mL) via oxidative coupling followed by deracemization of ***rac*-3j** with CuCl (6.51 mmol, 0.645 g) and (+)-sparteine (13.40 mmol, 3.080 mL) according to GP III. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: CH_2Cl_2, 3:1, 2:1 and 1:1 as the eluent). The desired compound **(*R*)-3j** was obtained as a white solid in 64% isolated yield (2.45 mmol, 1.280 g). The *ee* was determined to be 98% by HPLC analysis (Pirkle D-Phenylglycine column, 99:1, hexane: *i*-PrOH at 254 nm, flow rate 1 mL/min).

Spectral data for (*R*)-3j: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 – 8.16 (m, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.51 (dd, *J* = 8.5, 1.8 Hz, 2H), 7.31 (s, 2H), 7.11 – 7.05 (m, 2H), 6.98 (t, *J* = 7.7 Hz, 4H), 6.68 – 6.59 (m, 4H), 5.85 (s, 2H), 3.18 (hept, *J* = 7.0 Hz, 2H), 1.43 (d, *J* = 6.9 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.17, 146.51, 140.49, 139.97, 133.37, 129.03, 127.88, 127.57, 127.44, 126.55, 123.06, 121.95, 119.20, 112.86, 34.67, 24.18, 24.12. These data are in good agreement with the literature value. [89,59]

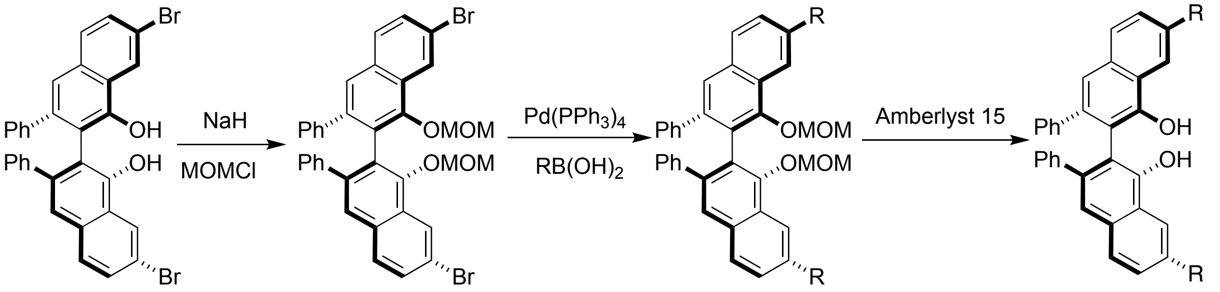


Synthesis of (*R*)-3mγ: Compound **(*R*)-3mγ** was prepared from compound **rac-(3mγ)**$_{1/2}$ (7.0 mmol, 5.0 g) and mineral oil (50 mL) via oxidative coupling followed by deracemization with CuCl (11.9 mmol, 1.18 g) and (+)-sparteine (24.5 mmol, 5.63 mL) according to GP III. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: CH_2Cl_2, 3:1, 2:1 and 1:1 as the eluent). The desired compound **(*R*)-3mγ** was obtained as a white solid in 57% isolated yield (3.99 mmol, 2.83 g). The *ee* was determined to be 99% by HPLC analysis (Pirkle D-Phenylglycine column, 97:3, hexane: *i*-PrOH at 254 nm, flow rate 1 mL/min). mp 73-74 °C.

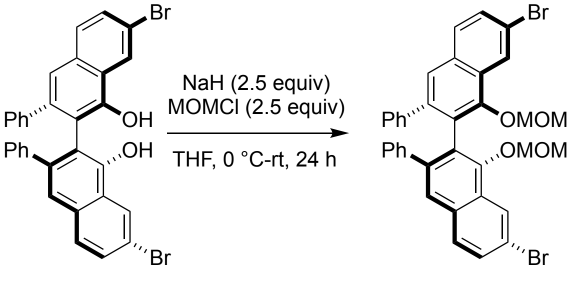
Spectral data for (*R*)-3mγ : ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 1.9 Hz, 2H), 7.71 – 7.61 (m, 4H), 7.31 (d, *J* = 0.9 Hz, 2H), 7.00 – 6.87 (m, 4H), 6.51 – 6.42 (m, 4H), 5.77 (s, 2H), 1.25 (s, 18H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 149.86, 149.44, 141.02, 136.78, 133.18, 131.06, 129.50, 128.39, 125.46, 124.62, 124.07, 121.83, 119.79, 113.74, 34.50, 31.49, 31.41. IR (cm^{-1}): 3491brs, 2965m, 1097m, 873s, 829s, 560s, 541s. HRMS (ESI+TOF) *m/z* 707.1158, [(M+H$^+$); calcd for $C_{40}H_{37}{}^{79}Br{}^{79}BrO_2$: 707.1144]. $[\alpha]^{20}_D$ = 1.22 (c 1.0, CHCl$_3$) on >99% *ee* **(*R*)-3mγ** (HPLC).

General Procedure for MOM-protection, Suzuki coupling and MOM-deprotection- (GP IV):

General Scheme:

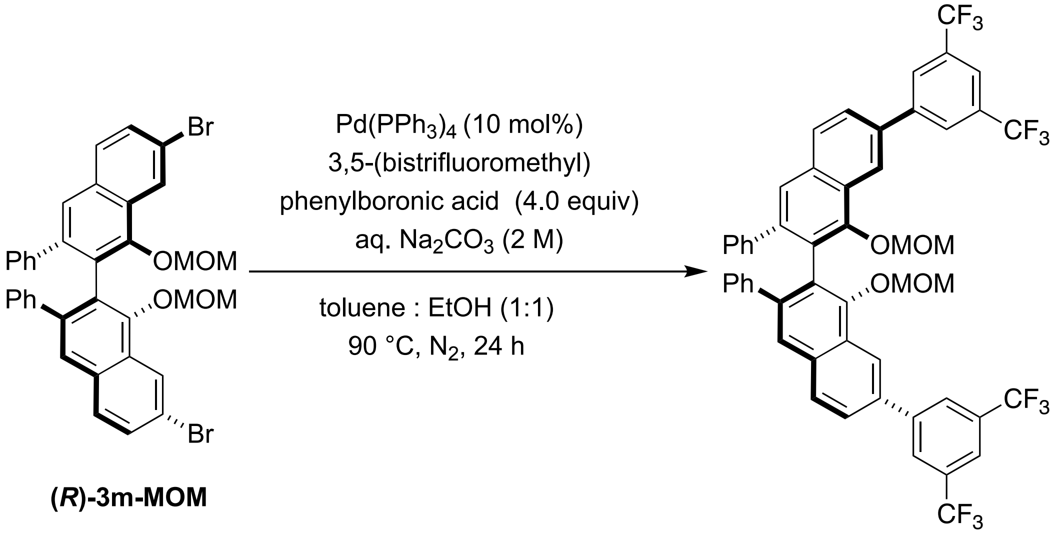


MOM-protection:



(*R*)-3m **(*R*)-3m-MOM**

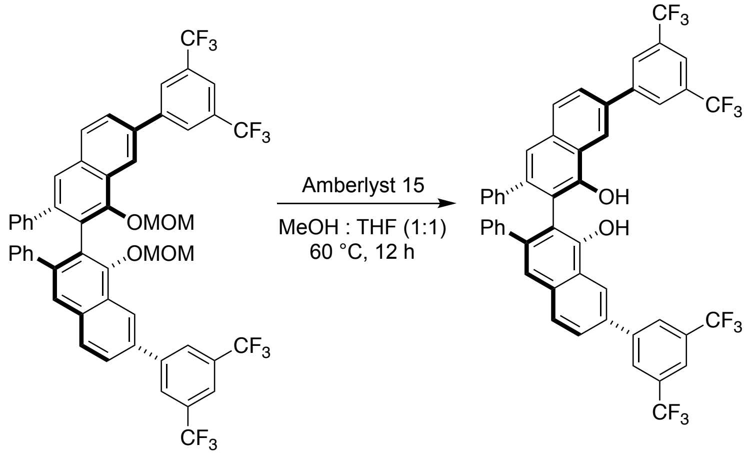
A flame-dried 50 mL round bottom flask was charged with (*R*)-7,7'-Br$_2$VANOL ligand ***(R)*-3m** (1.6 mmol, 0.95 g) in dry THF (12 mL). The mixture was stirred at 0 ˚C for 10 min followed by slow addition of NaH (4.0 mmol, 0.10 g, 60% dispersed in mineral oil). The reaction mixture was stirred at the same temperature for an additional 30 min, the ice bath was subsequently removed, and the flask was allowed to warm up to room temperature and stirred for an additional 30 min. The reaction mixture was then cooled down to 0 ˚C, followed by the addition of MOMCl (4.0 mmol, 0.2 mL) and stirred at room temperature for 24 h. The reaction was quenched by slow addition of saturated aqueous solution of NH_4Cl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was used directly in the next step without further purification.



(*R*)-3m-MOM

(*R*)-3g-MOM

Suzuki coupling: The solids from the previous step ***(R)*-3m-MOM** (1.6 mmol, 1.1 g) were transferred to a 250 mL round bottom flask to which was added tetrakis(triphenylphosphine)palladium (0.16 mmol, 0.19 g), toluene (20 mL) and Na_2CO_3 (2 M aq. solution, 10 mL) was added to the reaction container. 3,5-(Bistrifluoromethyl)phenylboronic acid (6.4 mmol, 1.7 g) in ethanol (10 mL) was added and the resulting solution was refluxed at 90 ˚C overnight with a continuous flow of the nitrogen gas on top of the condenser. The reaction was allowed to cool to room temperature followed by the addition of ethyl acetate (40 mL). The crude reaction mixture was passed through a silica pad to remove the inorganic salts. The aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was used directly in the next step without further purification.

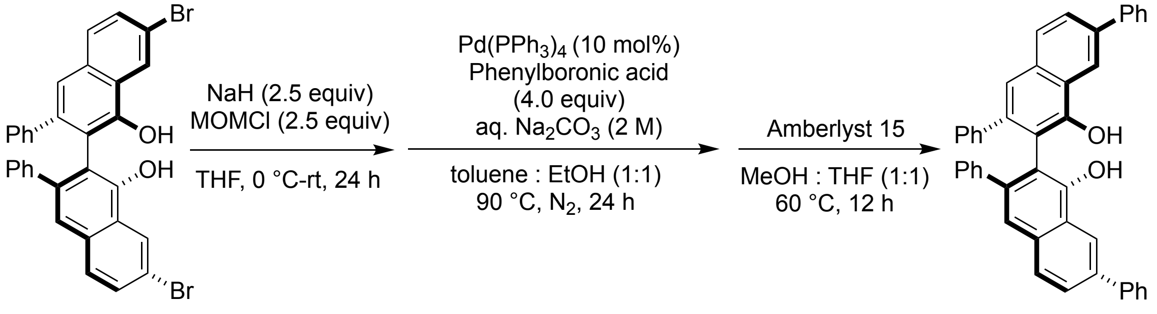


(*R*)-3g-MOM

(*R*)-3g

MOM deprotection: In a 250 mL round bottom flask attached to a condenser was added the crude product from the previous step, Amberlyst 15 (0.83 g) and MeOH:THF (1:1) (60 mL). The solution was stirred at 60 ˚C for 12 h with a continuous flow of nitrogen gas across the top of the condenser. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure and purified via column chromatography [30 mm X 250 mm, hexane:CH_2Cl_2 3:1, 2:1, 1:1 and 1:2] which afforded the desired compound **(*R*)-3g** as a yellow solid with an overall yield of 72% over 3 steps (1.15 mmol, 0.993 g).

Spectral data for (*R*)-3g: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, *J* = 1.9 Hz, 2H), 8.21 (d, *J* = 1.7 Hz, 4H), 7.96 – 7.88 (m, 4H), 7.82 (dd, *J* = 8.5, 1.9 Hz, 2H), 7.36 (s, 2H), 7.10 (t, *J* = 7.2 Hz, 2H), 6.99 (t, *J* = 7.7 Hz, 4H), 6.69 – 6.61 (m, 4H), 5.98 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.87, 143.23, 141.85, 139.81, 135.47, 134.42, 133.15 – 131.74 (m), 129.17, 128.95, 127.73, 127.58 (q, *J* = 3.8 Hz), 127.12, 126.62, 124.64, 123.15, 122.03, 121.76, 121.28 – 120.95 (m), 113.61. These data are in agreement with literature value.[59,89]

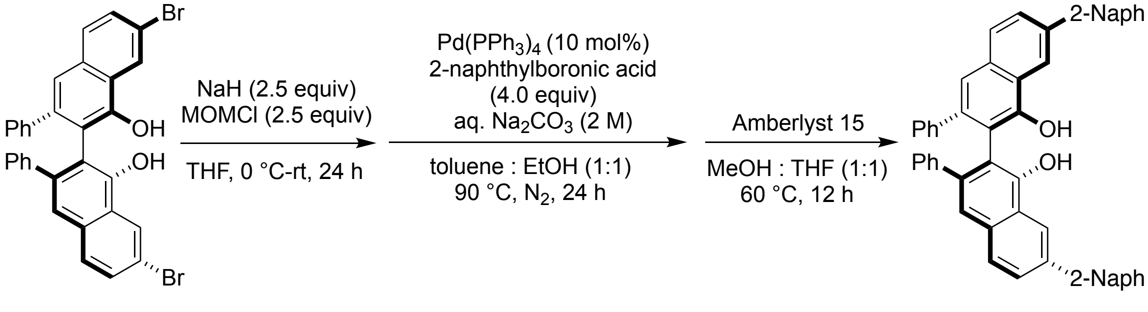


(*R*)-3m

(*R*)-3f

Synthesis of (*R*)-3f: Compound **(*R*)-3f** was prepared from compound **(*R*)-3m** (0.84 mmol, 0.51 g), NaH (2.1 mmol, 84 mg), MOMCl (2.1 mmol, 0.11 mL), phenylboronic acid (3.34 mmol, 0.412 g), tetrakis(triphenylphosphine)palladium (0.084 mmol, 0.097g) and Amberlyst 15 (0.42 g) according to the GP IV. The crude product was purified via column chromatography on silica gel [50 mm X 300 mm, hexane: CH_2Cl_2, 3:1, 2:1 and 1:1 as the eluent]. The desired compound **(*R*)-3f** was obtained as a white solid in 61% isolated yield (0.51 mmol, 0.31 g) overall for 3 steps.

Spectral data for (*R*)-3f: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.0 Hz, 2H), 7.75 – 7.65 (m, 8H), 7.43 – 7.36 (m, 4H), 7.29 – 7.23 (m, 2H), 7.14 (s, 2H), 6.94 (t, *J* = 7.2 Hz, 2H), 6.87 – 6.80 (m, 4H), 6.60 – 6.53 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.17, 141.21, 140.93, 140.61, 137.41, 133.31, 128.93, 128.70, 128.03, 127.13, 127.08, 126.17, 126.14, 126.11, 123.88, 120.81, 120.75, 115.47. One sp^2 carbon is not located. These data are in agreement with the literature value. [89,59]



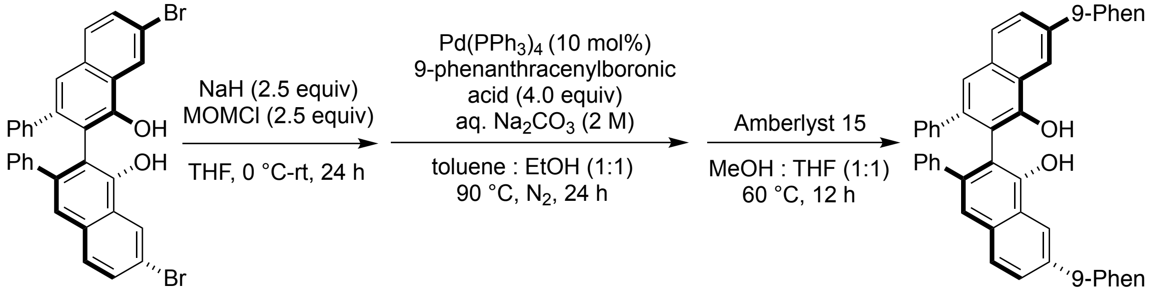
(*R*)-3m

(*R*)-3e

Synthesis of (*R*)-3e: Compound **(*R*)-3e** was prepared from compound **(*R*)-3m** (0.99 mmol, 0.61 g), NaH (2.5 mmol, 0.11 g), MOMCl (2.5 mmol, 0.13 mL), 2-naphthaleneboronic acid (3.99 mmol, 0.691 g), tetrakis(triphenylphosphine)palladium (0.101 mmol, 0.116 g) and Amberlyst 15 (0.5 g) according to GP IV. The crude product was purified via column chromatography on silica gel [50 mm X 300 mm, hexane: CH_2Cl_2, 3:1, 2:1 and 1:1 as the eluent]. The desired compound **(*R*)-3e** was obtained as a white solid in 75% isolated yield (0.75 mmol, 0.52 g) overall for 3 steps.

Spectral data for (*R*)-3e: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 – 8.65 (m, 2H), 8.13 (d, *J* = 1.7 Hz, 2H), 7.87 – 7.78 (m, 8H), 7.76 – 7.71 (m, 4H), 7.43 – 7.31 (m, 4H), 7.14 (s, 2H), 6.96 – 6.89 (m, 2H), 6.83 (t, *J* = 7.6 Hz, 4H), 6.57 (d, *J* = 7.0 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.26, 141.32, 140.59, 138.17, 137.05, 133.50, 133.28, 132.35, 128.89, 128.27, 128.08, 127.99, 127.41, 127.01, 126.14, 126.11, 126.10, 125.75, 125.63, 125.44, 123.96, 121.03, 120.69, 115.68. These data are in agreement with the literature value. [89,59]

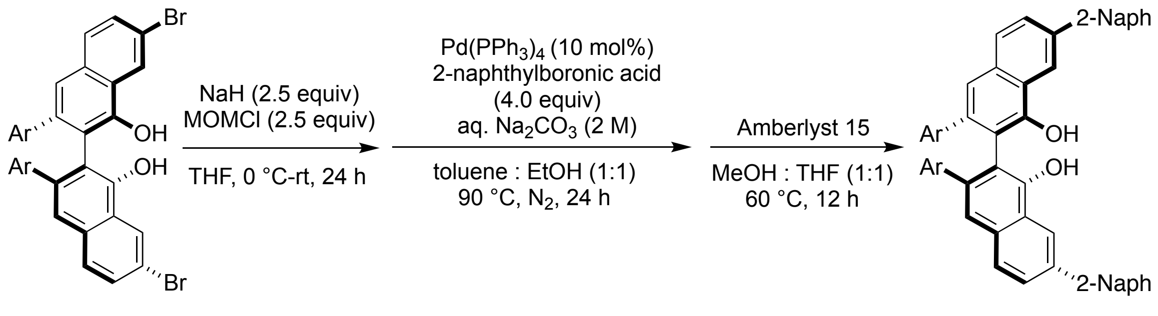
Synthesis of (*S*)-3h: Compound **(*S*)-3h** was prepared from compound **(*S*)-3m** (2.75 mmol, 1.64 g), NaH (6.9 mmol, 0.28 g), MOMCl (6.9 mmol, 0.36 mL), 9-phenanthrecenylboronic acid (11.0 mmol, 1.91 g), tetrakis(triphenylphosphine)palladium (0.275 mmol, 0.319 g) and Amberlyst 15 (1.375 g) according to the GP IV. The crude product was purified via column chromatography on silica gel [50 mm X 300mm, hexane: CH_2Cl_2, 3:1, 2:1 and 1:1 as the eluent]. The desired compound **(*S*)-3h** was obtained as a white solid in 61% isolated yield (1.675 mmol, 1.325 g) overall for 3 steps. mp: 247-248 °C.



(*S*)-3m

(*S*)-3h

Spectral data for (*S*)-3h: ^1H NMR (500 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 8.5, 1.2 Hz, 2H), 8.77 (d, *J* = 8.1 Hz, 2H), 8.61 – 8.57 (m, 2H), 8.06 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.98 – 7.91 (m, 4H), 7.90 (s, 2H), 7.79 (dd, *J* = 8.4, 1.7 Hz, 2H), 7.71 (ddd, *J* = 8.3, 7.0, 3.4 Hz, 4H), 7.66 (dd, *J* = 8.0, 7.0 Hz, 2H), 7.60 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.47 (s, 2H), 7.22 – 7.13 (m, 2H), 7.08 (t, *J* = 7.6 Hz, 4H), 6.80 – 6.73 (m, 4H), 5.99 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.70, 141.08, 140.35, 138.78, 138.49, 133.94, 131.75, 131.30, 130.84, 130.27, 130.21, 129.11, 128.90, 128.26, 127.73, 127.59, 127.12, 127.06, 126.86, 126.84, 126.81, 126.77, 126.69, 123.76, 123.16, 123.15, 122.72, 122.10, 113.34. $[\alpha]^{20}_D$ = -0.68 (c 1.0, $CHCl_3$).



(*R*)-3mγ

(*R*)-3eγ

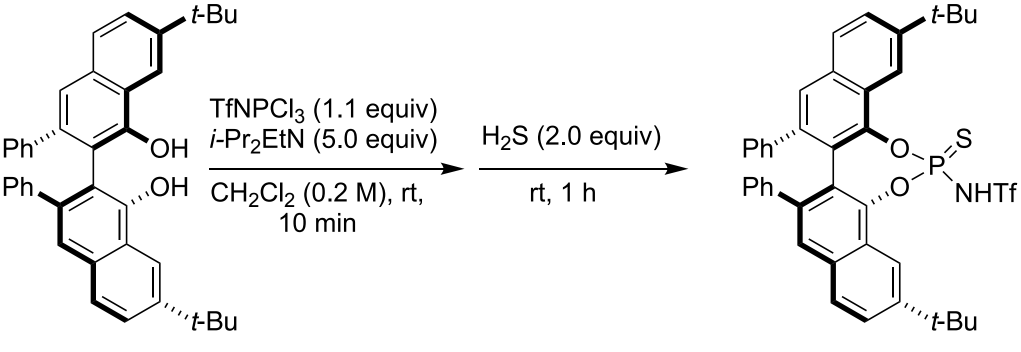
Synthesis of (*R*)-3eg[3]: Compound **(*R*)-3eg** was prepared from compound **(*R*)-3m** (0.75 mmol, 0.61 g), NaH (1.875 mmol, 0.7520 g), MOMCl (1.87 mmol, 0.101 mL), 2-naphthylboronic acid (3.0 mmol, 0.52 g), tetrakis(triphenylphosphine)palladium (0.075 mmol, 0.087 g) and Amberlyst 15 (0.375 g) according to GP IV and the crude product was purified via column chromatography on silica gel [50 mm X 300mm, hexane: CH_2Cl_2, 3:1, 2:1 and 1:1 as the eluent]. The desired compound **(*R*)-3eg** was obtained as a white solid in 68% isolated yield (0.51 mmol, 0.38 g) overall for 3 steps. mp 186-187 °C.

Spectral data for (*R*)-3eg: ^1H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 1.9 Hz, 2H), 8.28 (d, *J* = 1.4 Hz, 2H), 8.04 – 7.88 (m, 12H), 7.59 – 7.49 (m, 4H), 7.44 (s, 2H), 7.02 – 6.97 (m, 4H), 6.61 – 6.53 (m, 4H), 6.00 (s, 2H), 1.28 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.62, 149.57, 140.79, 138.49, 138.25, 137.29, 133.99, 133.92, 132.86, 128.73, 128.55, 128.52, 128.45, 127.83, 127.35, 126.52, 126.29, 126.19, 125.88, 124.61, 123.39, 121.80, 121.24, 113.43, 34.51, 31.46. IR (cm^{-1}): 3510brs, 2958m, 829w, 805s, 743s, 522m. HRMS (ESI+TOF) *m/z* 803.3871, [(M+H^+); calcd for $C_{60}H_{51}O_2$: 803.3889]. $[\alpha]^{20}_D$ = -0.69 (c 1.0, $CHCl_3$).

General Procedure for the synthesis of N-triflylthiophosphorimidates **(GP V):**

Synthesis of ((trifluoromethyl)sulfonyl)phosphorimidoyl trichloride: ((trifluoromethyl)sulfonyl)phosphorimidoyl trichloride was synthesized by reacting $TfNH_2$ (3.0 g, 20 mmol, 1.0 equiv) and PCl_5 (5.5 g, 26 mmol, 1.3 equiv) in a Schlenk tube fitted with a stir bar at 110 °C for an hour. The volatile were removed by connecting the side arm of the tube to a pump set at 110 Torr (~150 mbar). The final product was obtained in 80% yield (4.546 g, 15.96 mmol). [Generally, the different phosphorimidoyl trichloride used for preparing different catalysts were directly taken over to the next step without further purification] [83,59]

Spectral data for ((trifluoromethyl)sulfonyl)phosphorimidoyl trichloride: ^{13}C NMR (126 MHz, $CDCl_3$) δ 119.15 (qd, *J* = 321.3, 10.1 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -78.79. ^{31}P NMR (202 MHz, $CDCl_3$) δ 17.56. These spectral data were in agreement with the literature values. [83,59]



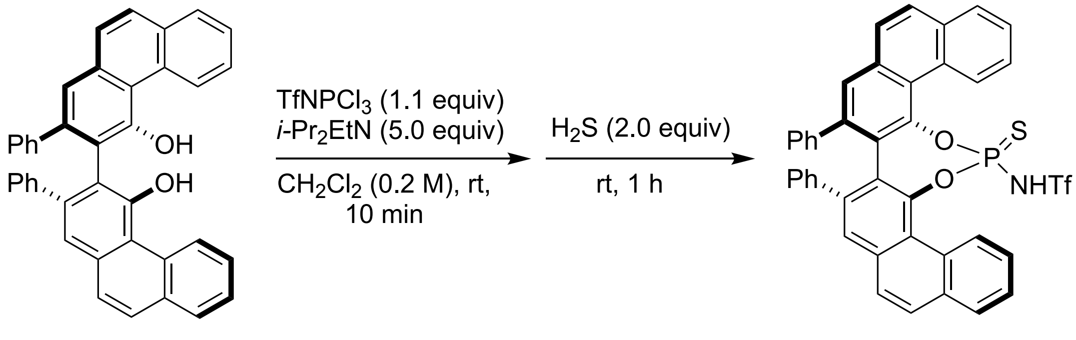
(R)-3d

(*R*)-3d-A

Synthesis of N-triflylthiophosphorimidate (*R*)-3d-A: A flame-dried 25 mL round bottom flask under nitrogen was charged with 7,7' *t*-Bu_2VANOL **(*R*)-3d** (1.0 mmol, 0.55 g), $TfNPCl_3$ (1.1 mmol, 0.32 g) and *i*-Pr_2EtN (5.0 mmol, 0.87 mL) in CH_2Cl_2 (0.2 M, 5 mL). The mixture was stirred at room temperature for 10 min followed by the addition of H_2S

(2.0 mmol, 2.5 mL, 0.8 M in THF). Once the starting material was fully consumed (as judged by TLC), the crude mixture was filtered through a Celite pad, concentrated to dryness under reduced pressure and purified via column chromatography on silica gel (30 mm X 250 mm, pure EtOAc as the eluent), which afforded the desired product as a salt. Compound **(*R*)-3d-A** was obtained in 99% isolated yield (1.0 mmol, 0.76 g) after reacidification with HCl (6.0 M, 5.0 mL) and drying under reduced pressure. mp 182-183 ˚C.

Spectral data for (*R*)-3d-A: Spectral data for **(*R*)-3d-A**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 – 8.32 (m, 2H), 7.84 – 7.71 (m, 4H), 7.53 (s, 2H), 7.11 (q, *J* = 7.3 Hz, 2H), 6.94 (td, *J* = 7.6, 4.5 Hz, 4H), 6.46 (td, *J* = 8.5, 1.3 Hz, 4H), 1.53 (d, *J* = 9.5 Hz, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.40, 150.19, 139.83, 139.75, 139.60, 139.45, 132.80, 132.70, 129.05, 129.02, 127.94, 127.90, 127.62, 127.57, 127.50, 127.48, 127.44, 126.98, 126.77, 126.70, 118.40, 116.82, 77.36, 35.66, 35.42, 31.27. ^{31}P NMR (202 MHz, $CDCl_3$) δ 57.46 (d, *J* = 4.9 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.50 (d, *J* = 2.8 Hz). IR: 2959w, 1201s, 901m, 884s, 765m, 696s, 608s cm^{-1}. HRMS (ESI+TOF) *m/z* 760.2134, [(M+H^{+}); calcd for $C_{41}H_{37}F_3NO_4PS_2$: 760.1932].



(*S*)-2a

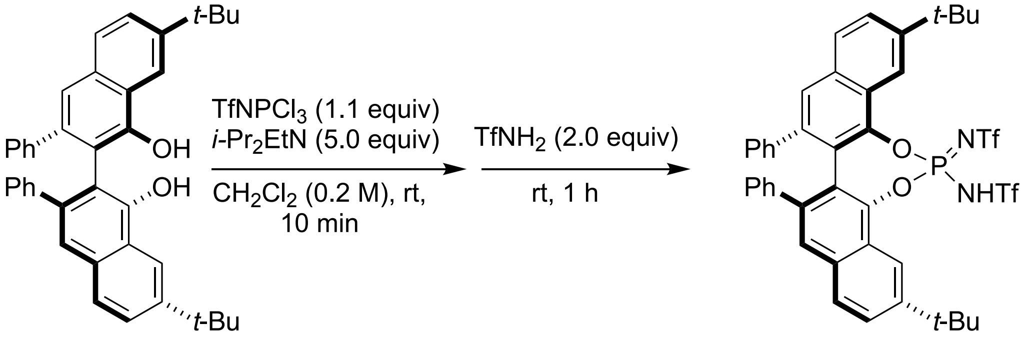
(*S*)-2a-A

Synthesis of VAPOL N-triflylthiophosphorimidate (*S*)-2a-A: Compound **(*S*)-2a-A** was prepared from compound **(*S*)-2a** (1.0 mmol, 0.54 g), $TfNPCl_3$ (1.1 mmol, 0.32 g), *i*-Pr_2EtN (5.0 mmol, 0.87 mL) and CH_2Cl_2 (0.2 M, 5 mL) according to the GP V and the crude product was purified via column chromatography on silica gel (30 mm X 250 mm, pure EtOAc as the eluent). The desired compound **(*S*)-2a-A** was obtained as a white solid in 27% isolated yield (0.27 mmol, 0.21 g). mp 176-177 ˚C.

Spectral data for (*S*)-2a-A: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (dd, *J* = 8.8, 2.3 Hz, 2H), 8.01 (dd, *J* = 22.3, 7.7 Hz, 2H), 7.93 – 7.71 (m, 8H), 7.66 (s, 2H), 7.13 (t, *J* = 7.4 Hz, 2H), 6.97 (td, *J* = 7.7, 5.7 Hz, 4H), 6.60 – 6.55 (m, 2H), 6.52 – 6.49 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 141.86, 141.47, 139.22, 139.19, 134.97, 133.60, 133.47, 129.86, 129.81, 129.62, 129.50, 129.41, 129.06, 129.04, 128.97, 128.84, 128.82, 128.68, 128.63, 128.32, 128.28, 127.91, 127.88, 127.68, 127.57, 127.48, 127.20, 127.10, 127.07, 126.70, 126.67, 126.13, 122.43, 121.20. ^{31}P NMR (202 MHz, $CDCl_3$) δ 52.40. ^{19}F NMR (470 MHz, $CDCl_3$) δ -76.50 (d, *J* = 2.8 Hz). IR (cm^{-1}): 1200s, 891s, 811w, 747m, 696s, 605s. HRMS (ESI+TOF) *m/z* 748.1008, [(M+H$^+$); calcd for $C_{41}H_{25}F_3NO_4PS_2$: 748.0993]. [59]

General procedure for the synthesis of N,N'-bis(triflyl)phosphorimidates-illustrated for the synthesis of 7,7' t-Bu_2VANOL N,N'-bis(triflyl)phosphorimidates (GP VI):

Synthesis of 7,7'-*t*-Bu_2VANOL N,N'-bis(triflyl)phosphoramidimidates *(R)*-3d-B: A flame-dried 25 mL round bottom flask under nitrogen was charged with 7,7' *t*-Bu_2VANOL ***(R)*-3d** (1.0 mmol, 0.55 g), $TfNPCl_3$ (1.1 mmol, 0.32 g), *i*-Pr_2EtN (5.0 mmol, 0.87 mL) and CH_2Cl_2 (0.2 M, 5 mL). The mixture was stirred at room temperature for 10 min followed by the addition of $TfNH_2$ (2.7 mmol, 0.41 g). Once the starting material was fully consumed

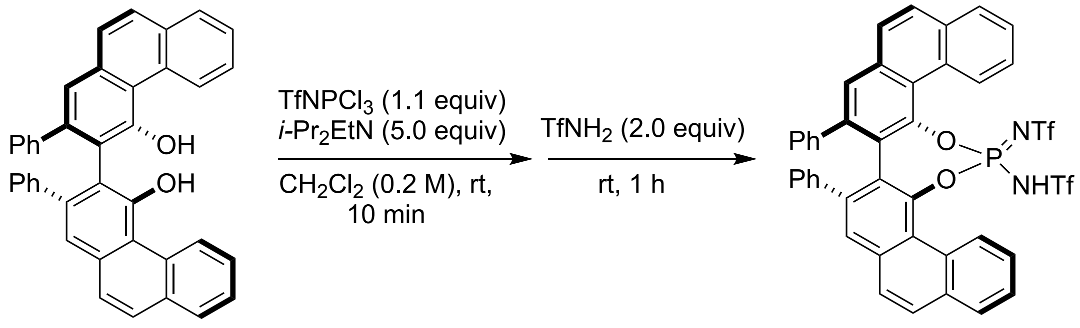


(R)-3d **(*R*)-3d-B**

as judged by TLC, the crude mixture was filtered through a Celite pad, concentrated to dryness under reduced pressure and purified via column chromatography on silica gel (30 mm X 250 mm, pure EtOAc as the eluent), which afforded the desired product as a salt. Compound ***(R)*-3d-B** was obtained in 98% isolated yield (0.98 mmol, 0.86 g) after reacidification with HCl (6 M, 5 mL) and concentrating under reduced pressure. mp 184-185 ˚C. [83,59]

Spectral data for *(R)*-3d-B: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.34 (d, *J* = 2.0 Hz, 2H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.50 – 7.46 (m, 2H), 7.09 (t, *J* = 7.4 Hz, 2H), 6.96 – 6.89 (m, 4H), 6.56 (s, 2H), 6.50 – 6.46 (m, 4H), 1.49 (s, 18H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 150.03, 145.06, 144.97, 140.08, 139.43, 139.42, 132.65, 129.16, 127.78, 127.42, 127.19, 126.83, 126.55, 125.49, 125.46, 122.73, 122.70, 117.80, 35.35, 31.13. ^{31}P NMR (202 MHz, CDCl$_3$) δ -1.41. ^{19}F NMR (470 MHz, CDCl$_3$) δ -78.21 (d, *J* = 8.2 Hz). IR (cm^{-1}): 2959w, 1200s, 910w, 882s, 765m, 696s, 607s, 586w. HRMS (ESI+TOF) *m/z* 875.1804, [(M+H$^+$); calcd for $C_{42}H_{37}F_6N_2O_6PS_2$: 875.1813].

Synthesis of VAPOL N,N'-bis(triflyl)phosphoramidimidates (*S*)-2a-B: Compound **(*S*)-2a-B** was prepared from compound **(*S*)-2a** (0.599 mmol, 0.322 g), TfNPCl$_3$ (0.66 mmol, 0.19 g), *i*-Pr$_2$EtN (3.0 mmol, 0.52 mL), CH$_2$Cl$_2$ (0.12 M, 5 mL) according to the GP VI. The

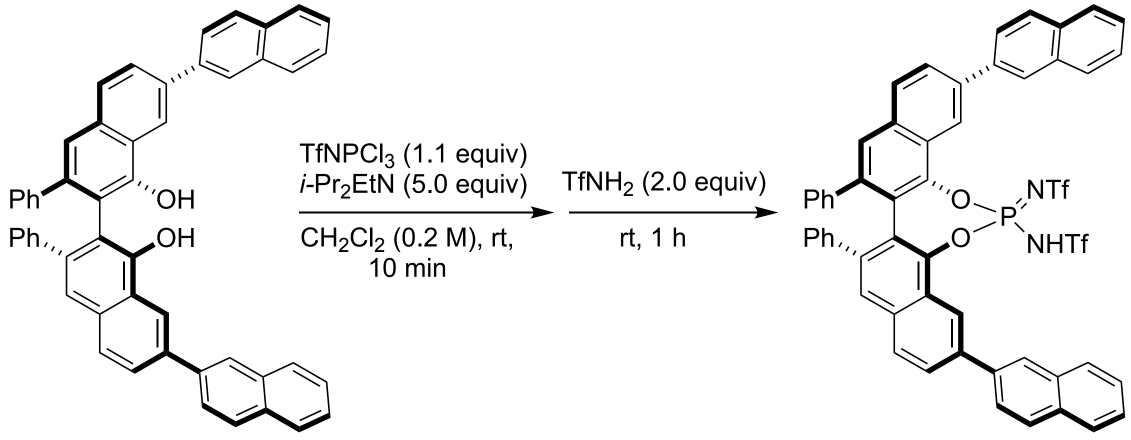


(*S*)-2a **(*S*)-2a-B**

crude product was purified via column chromatography on silica gel (30 mm X 250 mm, pure EtOAc as the eluent). The desired compound **(*S*)-2a-B** was obtained in 91% isolated yield (0.54 mmol, 0.47 g). mp 190 ˚C. [83,59]

Spectral data for (*S*)-2a-B: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (d, *J* = 8.6 Hz, 1H), 9.55 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.66 – 7.52 (m, 5H), 7.46 – 7.39 (m, 2H), 7.32 (s, 1H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.16 (dd, *J* = 8.5, 6.9 Hz, 1H), 7.03 (dt, *J* = 8.8, 7.4 Hz, 2H), 6.84 (t, *J* = 7.6 Hz, 2H), 6.75 (t, *J* = 7.5 Hz, 2H), 6.43 – 6.38 (m, 2H), 6.32 – 6.25 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.91, 146.93, 141.42, 140.91, 139.55, 139.18, 134.57, 134.27, 133.10, 132.99, 129.35, 129.15, 129.02, 128.97, 128.88, 128.83, 128.77, 128.35, 128.21, 127.81, 127.69, 127.51, 127.49, 127.03, 126.87, 126.70, 126.67, 126.47, 125.51, 121.66, 121.54. ^{31}P NMR (202 MHz, $CDCl_3$) δ -0.06. ^{19}F NMR (470 MHz, $CDCl_3$) δ -79.65. IR: 2945w, 1310s, 950w, 892s, 865m, 710s, 635s, 555w. HRMS (ESI+TOF) *m/z* 863.0873 [(M+H$^+$); calcd for $C_{54}H_{34}F_6N_2O_6PS_2$: 863.0878].

Synthesis of 7,7’-naphthyl$_2$VANOL N,N’-bis(triflyl)phosphoramidimidates (*S*)-3e-B: Compound **(*S*)-3e-B** was prepared from compound **(*S*)-3e** (0.599 mmol, 0.415 g), $TfNPCl_3$ (0.66 mmol, 0.19 g), *i*-Pr_2EtN (3.0 mmol, 0.52 mL), CH_2Cl_2 (0.12 M, 5 mL) according to GP VI. The crude product was purified via column chromatography on silica

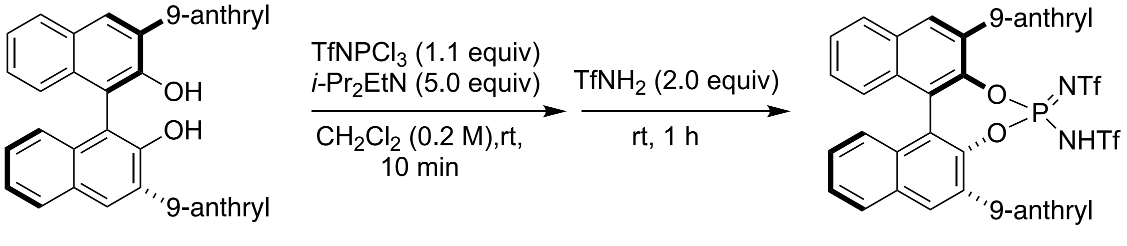


(*S*)- 3e

(*S*)- 3e-B

gel (30 mm X 250 mm, pure EtOAc as the eluent). The desired compound **(*S*)-3e-B** was obtained in 66% isolated yield (0.4 mmol, 0.4 g). mp 205-206 ˚C. [83,59]

Spectral data for (*S*)-3e-B: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 – 8.66 (m, 2H), 8.31 (s, 2H), 8.07 – 7.96 (m, 10H), 7.90 (d, J = 7.8 Hz, 2H), 7.65 (s, 2H), 7.53 (dq, J = 8.2, 6.9 Hz, 4H), 7.17 (t, J = 7.2 Hz, 2H), 7.01 (t, J = 7.7 Hz, 4H), 6.59 – 6.51 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.31, 144.23, 140.64, 140.31, 140.29, 139.40, 137.87, 133.86, 133.67, 133.03, 129.20, 128.93, 128.76, 128.57, 128.43, 128.39, 128.01, 127.80, 127.14, 126.77, 126.63, 126.46, 125.62, 125.47, 125.45, 122.98, 122.96, 119.78, 115.51. ^{31}P NMR (202 MHz, $CDCl_3$) δ -1.20. ^{19}F NMR (470 MHz, $CDCl_3$) δ -78.24. IR (cm^{-1}): 2950w, 1190s, 1072m, 808m, 694m, 606s, 577m. HRMS (ESI+TOF) *m/z* 1015.1487, [(M+H$^+$); calcd for $C_{54}H_3F_6N_2O_6PS_2$: 1015.1500]. $[\alpha]^{20}_D$ = 2.95 (*c* 1.0, $CHCl_3$).

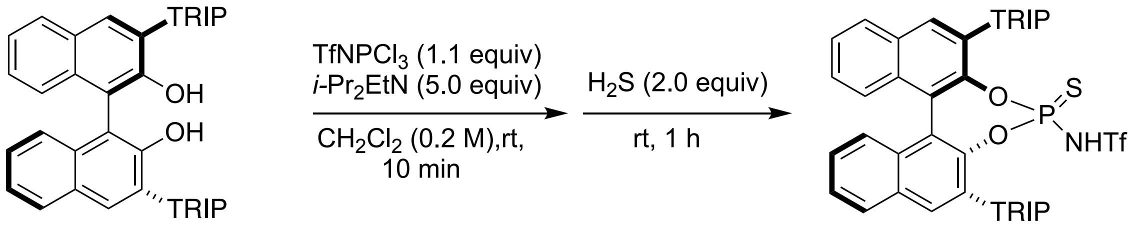


(*R*)- 1c

(*R*)- 1c-B

Synthesis of 3,3'-anthryl$_2$BINOL N,N'-bis(triflyl)phosphoramidimidates (*R*)-1c-B: Compound **(*R*)-1c-B** was prepared from compound **(*R*)-1c** (0.51 mmol, 0.32 g), TfNPCl$_3$ (0.55 mmol, 0.16 g) and *i*-Pr$_2$EtN (2.5 mmol, 0.74 mL), CH$_2$Cl$_2$ (0.1 M, 5 mL), according to GP VI. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, pure EtOAc as the eluent). The desired compound **(*R*)-1c-B** was obtained in 40% isolated yield (0.2 mmol, 0.2 g). mp 215-217 ˚C. [83,59]

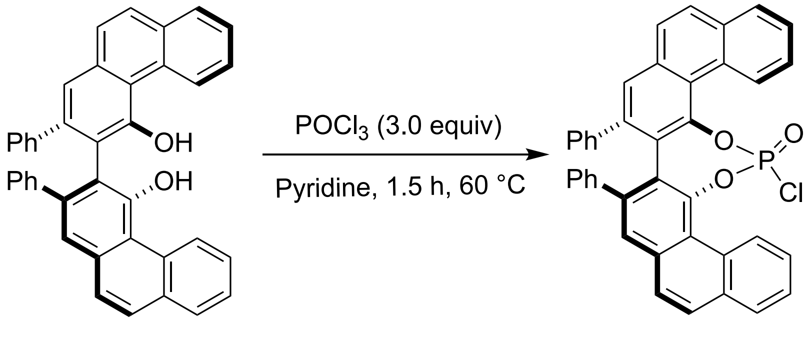
Spectral data for (*R*)-1c-B: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.24 (s, 2H), 8.20 (s, 2H), 8.09 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.74 – 7.61 (m, 8H), 7.57 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.45 – 7.36 (m, 2H), 7.35 – 7.21 (m, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 146.10, 146.01, 134.75, 132.71, 132.69, 131.88, 131.33, 131.06, 130.84, 130.70, 130.67, 130.38, 130.35, 128.87, 128.51, 128.26, 127.93, 127.72, 127.47, 127.21, 126.57, 126.14, 126.01, 125.70, 125.08, 125.05, 125.03, 122.24, 122.22. ^{31}P NMR (202 MHz, CDCl$_3$) δ 2.54. ^{19}F NMR (470 MHz, CDCl$_3$) δ -79.52. IR(cm^{-1}): 1193s, 1097s, 965m, 728s, 607s, 574m. HRMS (ESI+TOF) *m/z* 963.1197, [(M+H$^+$); calcd for $C_{50}H_{29}F_6N_2O_6PS_2$: 963.1187].



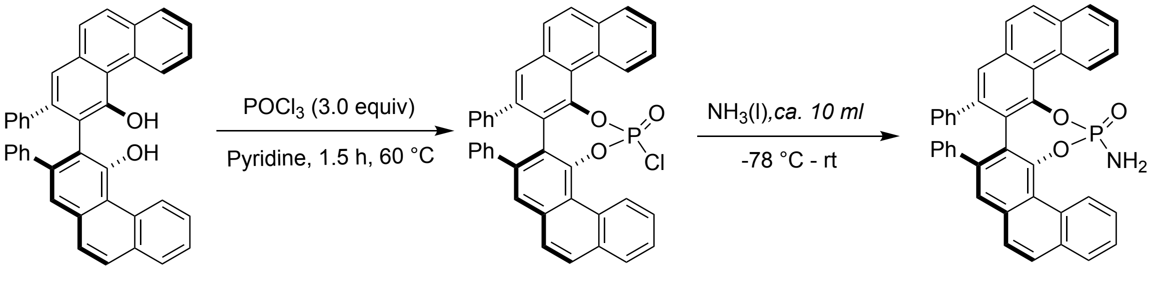
(*R*)- 1b **(*R*)- 1b-A**

Synthesis of 3,3'-TRIP$_2$BINOL N-triflylthiophosphoramides (*R*)-1b-A: Compound **(*R*)-1b-A** was prepared via the reported procedure and the spectral data were in good agreement with the literature values. [83,59]

Synthesis of VAPOL imidodiphosphoric acid catalyst:



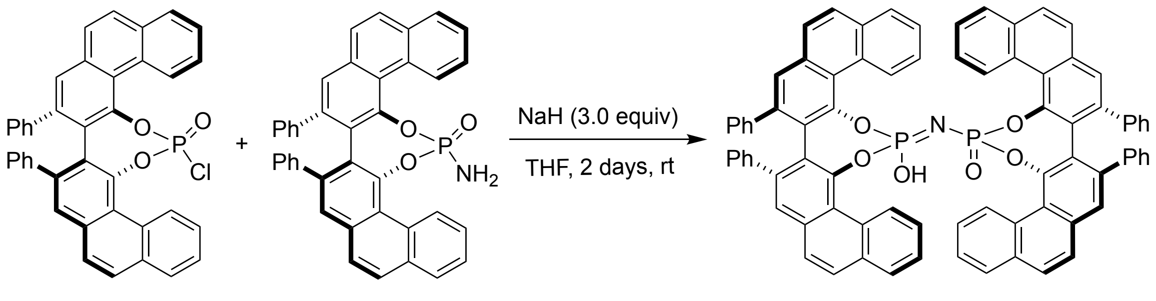
(*S*)- 2a **(*S*)- 2a-J**



(*S*)- 2a **(*S*)- 2a-J** **(*S*)- 2a-K**

A 25 mL round bottom flask was charged with (*R*)-VAPOL **(*S*)-2a** (1.0 mmol, 0.54 g), pyridine (3 mL) and $POCl_3$ (3.0 mmol, 0.28 mL) under nitrogen gas. The resulting solution was stirred at 65 ˚C for 1.5 h. The reaction mixture was concentrated under reduced pressure and the crude mixture was passed through a short pad of silica gel with CH_2Cl_2 as the eluent to give **(*S*)-2a-J**. The product was used in the next step without further purification.

(*S*)-VAPOL **(*S*)-2a** (1.0 mmol, 0.54 g), pyridine (3 mL) and $POCl_3$ (3.0 mmol, 0.28 mL) were added to a 25 mL round flask under nitrogen gas. The resulting solution was stirred at 65 ˚C for 1.5 h, which was then cooled to -78 ˚C followed by the addition of anhydrous ammonia (10 mL). The reaction mixture was warmed up to rt, concentrated under reduced pressure and passed through a short pad of silica gel using pure CH_2Cl_2 as the eluent which affording compound **(*S*)-2a-K** as a white solid, which was taken directly into the next step without further purification.

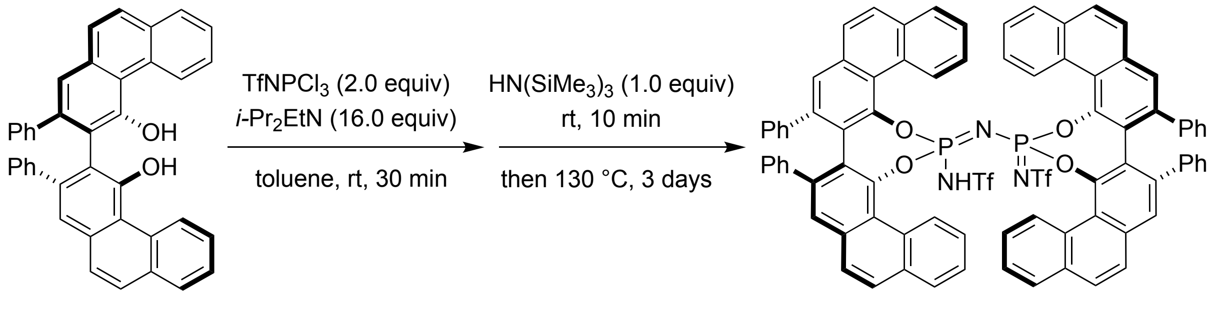


(*S*)- 2a-J **(*S*)- 2a-K** **(*S*)- $(2a)_2$-I**

Synthesis of imidodiphosphoric acid (*S*)-$(2a)_2$-I: To a solution of compounds **(*S*)-2a-J** (0.61 g, 0.99 mmol, 0.99 equiv) and **(*S*)-2a-K** (0.6 g, 1.0 mmol, 1.0 equiv) in THF (0.1 M) at room temperature was added NaH (3.0 mmol, 0.12 g) and the resulting mixture was stirred at rt for 48 h. The reaction was quenched by careful addition of aqueous HCl (1 M, 5 mL) aqueous solution. The organic layer was isolated, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via column chromatography (25 mm X 250 mm, hexane:EtOAc, 3:1 to 1:1) to give a white solid. The solids were dissolved in CH_2Cl_2 (5 mL), and the solution was then acidified with HCl (3 M, 5 mL) and then stirred vigorously at rt for 4 h. The reaction mixture was extracted with CH_2Cl_2 (3 X 3 mL) and then directly concentrated under reduced pressure to afford compound **(*S*)-$(2a)_2$-I** in 40% isolated yield (0.40 mmol, 0.39 g).

Spectral data for (*S*)-$(2a)_2$-I: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (d, J = 8.7 Hz, 2H), 9.29 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 7.9 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H), 7.64 (t, J = 7.4 Hz, 2H), 7.39 (d, J = 8.5 Hz, 4H), 7.29 – 7.22 (m, 6H), 7.21 – 7.14 (m, 5H), 7.09 – 6.97 (m, 8H), 6.86 (t, J = 7.6 Hz, 4H), 6.43 – 6.38 (m, 4H), 6.35 (d, J = 7.6 Hz, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.43, 149.37, 140.67, 139.94, 139.75, 133.77, 133.27, 132.71, 132.04, 129.67, 129.48, 129.45, 128.96, 128.90, 128.51, 128.47, 128.16, 127.83, 127.81, 127.41, 127.38, 127.31, 126.86, 126.61, 126.58, 126.48, 126.40, 125.76, 125.72, 125.46, 121.76, 120.92, 40.09, 40.02, 39.92, 39.85, 39.76, 39.68, 39.59, 39.42, 39.26, 39.09. One sp^2 carbon peak is not located (due to the low solubility of this compound in $CDCl_3$, ^{13}C-NMR was taken in DMSO). ^{31}P NMR (202 MHz, $CDCl_3$) δ -0.84. These data matched with the literature value. [59,117]

General Procedure for the synthesis of imidodiphosphorimidate catalysts (GP VII):



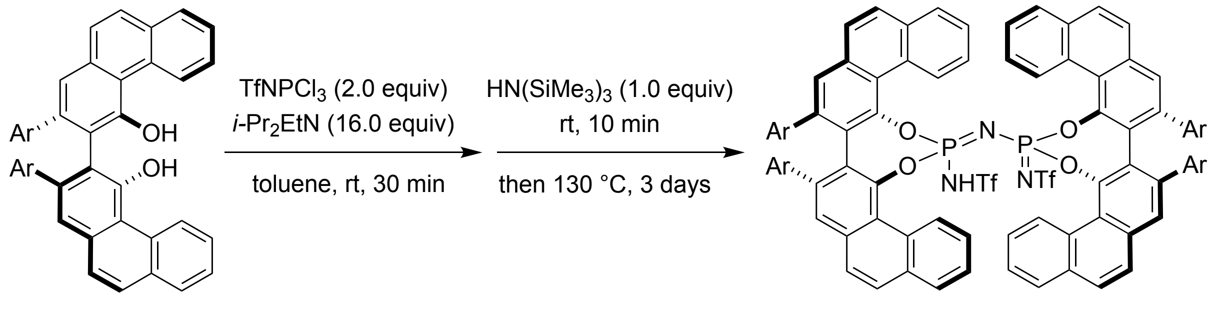
(*S*)-2a

(*S*)-$(2a)_2$-D

Synthesis of VAPOL imidodiphosphorimidate (S)-$(2a)_2$-D: In a clean dry sealed tube was added **(*S*)-2a** (S-VAPOL) (0.90 mmol, 0.49 g), dry toluene (0.11 M, 4.0 mL), *i*-Pr_2EtN (7.20 mmol, 1.25 mL) and $TfNPCl_3$ (0.90 mmol, 0.27 g) and the solution was stirred at room temperature for 30 min. $HN(SiMe_3)_3$ (0.45 mmol, 0.09 mL) was transferred to the reaction and the mixture stirred for an additional 10 min. The reaction mixture was tightly sealed and placed in an oil bath and stirred for three days at 130 ˚C. After cooling the reaction to rt, it was transferred to a 50 mL round bottom flask and concentrated to dryness. The resulting mixture was dissolved in CH_2Cl_2 (5 mL) followed by the addition of HCl (3 N, 3.0 mL) and stirred at rt for 1 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure, and purified via column chromatography (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The resulting off-white solid was dissolved in CH_2Cl_2 (5 mL) and re-acidified with HCl (6 N, 3.0 mL) for 1 h at room temperature. The organic layer was isolated and concentrated to dryness under reduced pressure to afford the desired product as a white solid in 86% isolated yield (0.39 mmol, 0.57 g). mp: 278-279 ˚C. CCDC number: 1818678.

Spectral data for (S)-(2a)$_2$-D: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (d, *J* = 8.4 Hz, 2H), 9.36 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.0 Hz, 2H), 7.99 (dd, *J* = 8.6, 7.0 Hz, 2H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.80 (dd, *J* = 8.0, 6.9 Hz, 2H), 7.74 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.68 (d, *J* = 8.9 Hz, 2H), 7.51 (s, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.29 – 7.19 (m, 8H), 7.02 (dd, *J* = 8.3, 7.3 Hz, 4H), 7.00 – 6.96 (m, 4H), 6.82 – 6.76 (m, 4H), 6.33 – 6.25 (m, 4H), 6.13 (d, *J* = 7.5 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.50, 145.86, 145.86, 141.29, 139.75, 139.41, 139.11, 134.46, 133.55, 133.21, 132.40, 130.09, 129.28, 129.15, 129.01, 128.92, 128.88, 128.71, 128.64, 128.57, 128.07, 128.04, 127.92, 127.88, 127.63, 127.40, 127.34, 127.22, 127.18, 127.14, 126.98, 126.67, 126.64, 126.16, 126.03, 125.30, 121.68, 121.67, 121.22, 121.20. ^{31}P NMR (202 MHz, $CDCl_3$) δ -17.91. ^{19}F NMR (470 MHz, $CDCl_3$) δ -78.47. IR (cm^{-1}): 3049w, 1189s, 1019s, 910m, 746m, 696s, 609s, 568m. HRMS (ESI+TOF) *m/z* 1444.2448, [(M+H$^+$); calcd for $C_{82}H_{49}F_6N_3O_8P_2S_2$: 1444.2418].

Synthesis of imidodiphosphorimidate (*S*)-(2b)$_2$-D: Compound **(*S*)-(2b)$_2$-D** was prepared from compound **(*S*)-2b** (0.50 mmol, 0.32 g), toluene (0.1 M, 5 mL), $TfNPCl_3$ (0.501 mmol, 0.16 g), *i*-Pr_2EtN (4.0 mmol, 0.74 mL) and $HN(SiMe_3)_3$ (0.25 mmol, 26μL) according to GP VII and the crude product was purified via column chromatography on silica gel (30



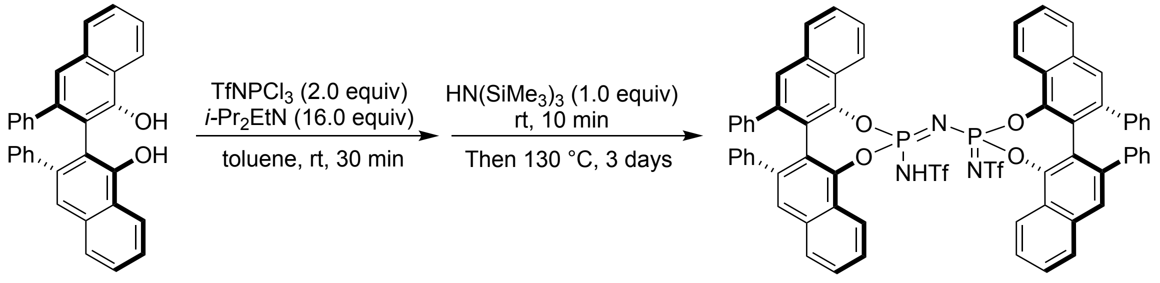
Ar: 4-OMe-3,5-*t*-Bu-C_6H_2
(*S*)- 2b

Ar: 4-OMe-3,5-*t*-Bu-C_6H_2
(*S*)- $(2b)_2$-D

mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*S*)-$(2b)_2$-D** was obtained as a white solid in 84% isolated yield (0.21 mmol, 0.42 g). mp: 266-267 ˚C. [59]

Spectral data for (*S*)-$(2b)_2$-D: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (dd, *J* = 8.7, 4.7 Hz, 4H), 8.02 – 7.93 (m, 4H), 7.87 (d, *J* = 8.9 Hz, 2H), 7.75 (d, *J* = 8.6 Hz, 4H), 7.70 – 7.63 (m, 4H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.36 (s, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.10 (dd, *J* = 19.5, 8.0 Hz, 4H), 6.61 (m, 8H), 3.79 (s, 6H), 3.53 (s, 6H), 1.25 (d, 36H), 0.97 (s, 36H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.97, 158.72, 146.51, 145.60, 142.79, 142.46, 141.20, 139.21, 134.88, 133.68, 133.42, 133.13, 133.07, 132.27, 129.01, 128.80, 128.57, 128.48, 128.27, 128.15, 127.90, 127.64, 127.53, 127.26, 127.08, 126.82, 126.65, 126.52, 126.40, 126.13, 125.60, 121.84, 121.04, 76.90, 64.39, 64.05, 35.50, 35.33, 32.03, 31.82. ^{31}P NMR (202 MHz, $CDCl_3$) δ -16.49. ^{19}F NMR (470 MHz, $CDCl_3$) δ -78.66. IR (cm^{-1}): 2958w, 1198s, 1129m, 1113m, 1014s, 964w, 876s, 808m, 743m, 598s, 568m, 525w cm^{-1}. HRMS (ESI+TOF) *m/z* 2012.7883, [(M+H$^+$); calcd for $C_{118}H_{121}F_6N_3O_{12}P_2S_2$: 2012.7849]. [59]

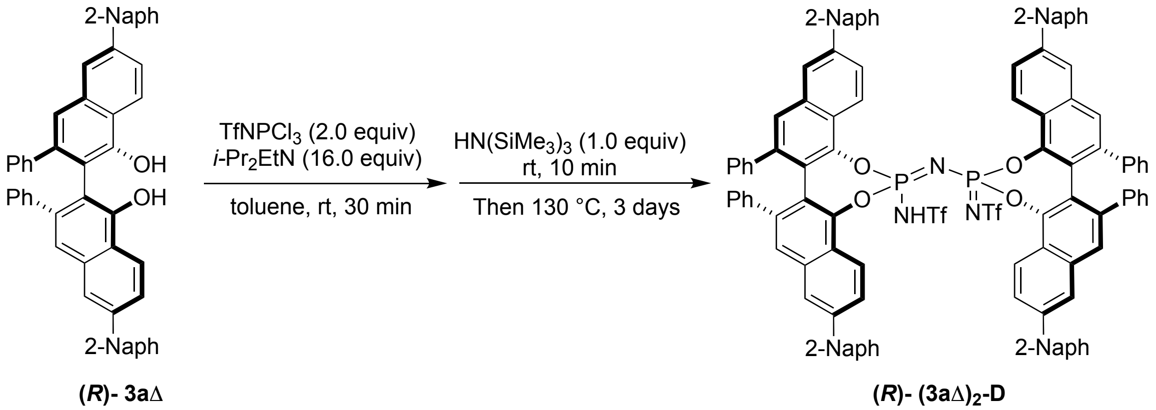
Synthesis of imidodiphosphorimidate (S)-$(3a)_2$-D: Compound **(*S*)-$(3a)_2$-D** was prepared from compound **(*S*)-3a** (1.0 mmol, 0.44 g), toluene (0.1 M, 10 mL), $TfNPCl_3$ (1.01 mmol, 0.31 g), *i*-Pr_2EtN (8.0 mmol, 1.40 mL) and $HN(SiMe_3)_3$ (0.5 mmol, 105 *μ*L)



(*S*)- 3a **(*S*)- (3a)$_2$-D**

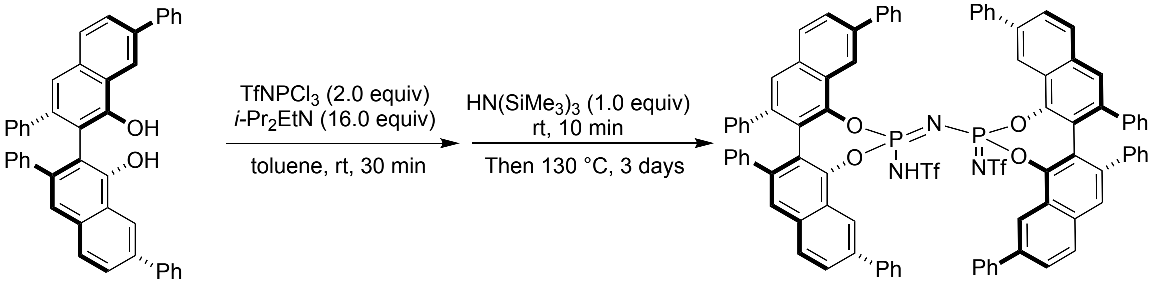
according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*S*)-(3a)$_2$-D** was obtained as an off white solid in 38% isolated yield (0.39 mmol, 0.48 g). mp: 235 °C.

Spectral data for (*S*)-(3a)$_2$-D: ^{1}H NMR (500 MHz,CDCl$_3$) δ 8.30 (d, *J* = 8.4 Hz, 1H), 7.94 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.79 (dd, *J* = 8.3, 6.9 Hz, 1H), 7.68 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.53 (s, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.19 – 7.13 (m, 1H), 7.11 – 7.02 (m, 3H), 6.97 (t, *J* = 7.6 Hz, 2H), 6.92 (dd, *J* = 8.0, 6.8 Hz, 1H), 6.85 (t, *J* = 7.5 Hz, 2H), 6.53 (s, 2H), 6.43 – 6.37 (m, 2H), 6.35 (dd, *J* = 8.5, 1.3 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 144.61, 144.57, 144.53, 143.43, 143.39, 143.35, 139.95, 139.50, 139.46, 139.36, 139.29, 139.15, 134.31, 133.78, 133.23, 129.05, 129.02, 128.95, 128.87, 128.11, 128.02, 127.96, 127.89, 127.77, 127.72, 127.67, 127.54, 127.42, 127.33, 127.28, 127.13, 126.82, 126.76, 126.68, 126.61, 125.16, 125.14, 125.12, 124.98, 124.41, 122.36, 122.01, 121.96, 121.15, 120.86, 118.31, 60.57, 53.48, 21.09, 14.20. ^{31}P NMR (202 MHz, CDCl$_3$) δ -10.44. ^{19}F NMR (470 MHz, CDCl$_3$) δ -77.95. IR (cm^{-1}): 1218, 1053, 841, 683, 592, 565, 520. HRMS (ESI+TOF) *m/z* 1244.1790, [(M+H$^+$); calcd for $C_{66}H_{41}F_6N_3O_8P_2S_2$: 1244. 1792].



Synthesis of imidodiphosphorimidate (*R*)-(3aΔ)$_2$-D: Compound **(*R*)-(3aΔ)$_2$-D** was prepared from compound **(*R*)-3aΔ** (1.0 mmol, 0.70 g), toluene (0.1 M, 10 mL), $TfNPCl_3$ (1.01 mmol, 0.31 g),[72] *i*-Pr_2EtN (8.0 mmol, 1.4 mL) and $HN(SiMe_3)_3$ (0.5 mmol, 105 μL) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*R*)-(3aΔ)$_2$-D** was obtained in 83% isolated yield (0.83 mmol, 1.45 g). mp: 287 °C. [59]

Spectral data for (*R*)-(3aΔ)$_2$-D: ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, *J* = 8.6 Hz, 2H), 8.30 – 8.16 (m, 6H), 7.98 (t, *J* = 9.4 Hz, 4H), 7.95 – 7.88 (m, 6H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.67 (s, 2H), 7.65 – 7.59 (m, 4H), 7.58 – 7.51 (m, 6H), 7.45 (m, 2H), 7.39 (d, *J* = 4.4 Hz, 6H), 7.24 (s, 2H), 7.12 (t, *J* = 7.5 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 2H), 6.98 (s, 2H), 6.86 (dt, *J* = 11.2, 7.6 Hz, 8H), 6.38 (t, *J* = 8.0 Hz, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.66, 143.59, 140.68, 140.52, 139.79, 139.40, 139.23, 139.05, 137.51, 136.36, 134.84, 133.73, 133.72, 133.42, 132.93, 132.93, 132.65, 128.92, 128.81, 128.72, 128.56, 128.52, 128.44, 128.10, 127.92, 127.71, 127.42, 127.00, 126.70, 126.49, 126.29, 126.19, 126.11, 125.95, 125.73, 125.50, 124.85, 124.68, 124.28, 124.27, 123.66, 122.60, 122.41, 122.26, 121.54, 119.28. ^{31}P NMR (202 MHz, CDCl$_3$) δ -10.21. IR: 1140, 1143, 786, 582, 548, 520 cm^{-1}. HRMS (ESI+TOF) *m/z* 1240.1415, [(M+H$^+$); calcd for $C_{106}H_{65}F_6N_3O_8P_2S_2$:1240.1479].



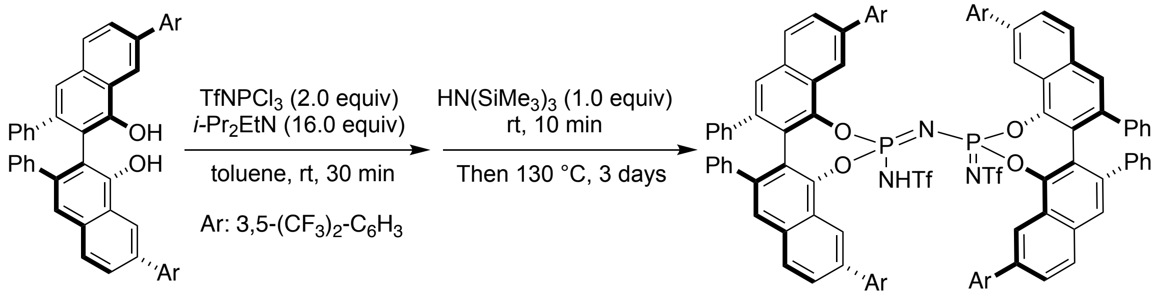
(*R*)-3f

(*R*)- (3f)$_2$-D

Synthesis of imidodiphosphorimidate (*R*)-(3f)$_2$-D: Compound **(*R*)-(3f)$_2$-D** was prepared from compound **(*R*)-3f** (0.46 mmol, 0.26 g), toluene (0.1 M, 4.6 mL), TfNPCl$_3$ (0.46 mmol, 0.13 g),$^{S-2}$ *i*-Pr$_2$EtN (3.7 mmol, 0.63 mL) and HN(SiMe$_3$)$_3$ (0.23 mmol, 48 μL) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*R*)-(3f)$_2$-D** was obtained as a white solid in 49% isolated yield (0.11 mmol, 0.17 g). mp: 320-325 ˚C (decomposed). [59]

Spectral data for (*R*)-(3f)$_2$-D: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.90 (s, 2H), 8.32 – 8.24 (m, 2H), 8.04 (dd, *J* = 17.3, 8.6 Hz, 6H), 7.95 (d, *J* = 8.6 Hz, 2H), 7.69 – 7.58 (m, 8H), 7.56 – 7.48 (m, 2H), 7.45 (s, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.12 – 7.05 (m, 2H), 7.01 (s, 2H), 6.99 – 6.91 (m, 10H), 6.76 (t, *J* = 7.6 Hz, 4H), 6.45 (s, 4H), 6.25 – 6.17 (m, 4H), 5.92 (s, 4H), 5.14 (s, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 144.61, 143.11, 141.03, 140.68, 140.12, 139.93, 139.40, 139.17, 139.02, 138.80, 133.48, 132.54, 129.40, 129.24, 128.89, 128.83, 128.64, 128.23, 127.98, 127.82, 127.74, 127.44, 127.21, 127.10, 126.59, 126.54, 125.67, 124.60, 122.59, 122.24, 119.20, 118.83. ^{31}P NMR (202 MHz, CDCl$_3$) δ -13.06. ^{19}F NMR

(470 MHz, $CDCl_3$) δ -77.71. IR (cm^{-1}): 1198s, 1073s, 757s, 694s, 602s, 579m, 524w. HRMS (ESI+TOF) *m/z* 1548.3085, [(M+H$^+$); calcd for $C_{90}H_{57}F_6N_3O_8P_2S_2$: 1548.3044.

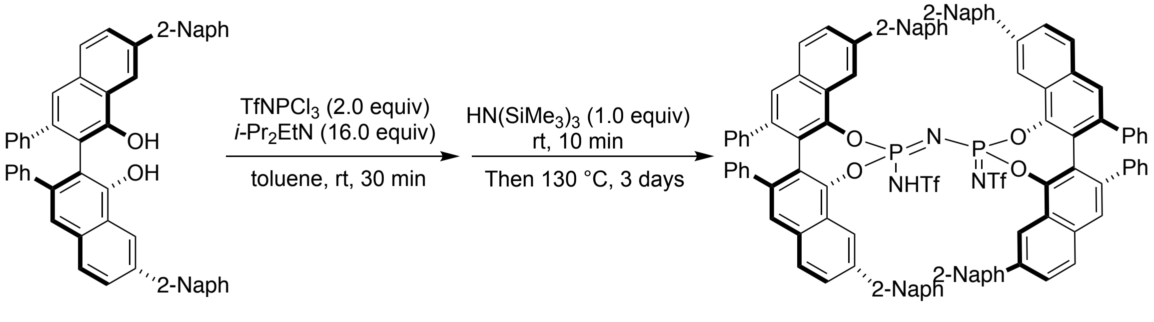


(*R*)- 3g

(*R*)- (3g)$_2$-D

Synthesis of imidodiphosphorimidate (*R*)-(3g)$_2$-D: Compound **(*R*)-(3g)$_2$-D** was prepared from compound **(*R*)-3g** (1.0 mmol, 0.9 g), toluene (0.1 M, 10 mL), $TfNPCl_3$ (1.0 mmol, 0.3 g),$^{S-2}$ *i*-Pr_2EtN (8.00 mmol, 1.40 mL) and $HN(SiMe_3)_3$ (0.50 mmol, 112 μL) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*R*)-(3g)$_2$-D** was obtained as a white solid in 76% isolated yield (0.397 mmol, 0. 831g). mp: 229-230 ˚C. [59]

Spectral data for (*R*)-(3g)$_2$-D: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 2H), 8.39 (s, 4H), 8.28 (d, *J* = 1.9 Hz, 2H), 8.05 – 7.89 (m, 10H), 7.65 (s, 2H), 7.60 – 7.49 (m, 4H), 7.23 – 7.10 (m, 6H), 7.06 – 6.94 (m, 4H), 6.76 (t, *J* = 7.5 Hz, 4H), 6.64 – 6.49 (m, 4H), 6.21 – 6.14 (m, 4H), 6.02 (d, *J* = 7.5 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.87, 143.23, 141.85, 139.81, 135.47, 134.42, 132.77, 132.51, 132.24, 131.98, 129.17, 128.95, 127.73, 127.63, 127.60, 127.57, 127.12, 126.80, 126.62, 124.64, 123.15, 122.47, 122.03, 121.76, 121.20, 121.17, 121.14, 120.29, 113.61. ^{31}P NMR (202 MHz, $CDCl_3$) δ -9.16. ^{19}F NMR (470 MHz, $CDCl_3$) δ -78.23, -63.37, -62.93. IR (cm^{-1}): 1276s, 1172m, 1127s, 1106m, 1064m, 682m. HRMS (ESI+TOF) *m/z* 2092.2063, [(M+H$^+$); calcd for $C_{98}H_{51}F_{30}N_3O_8P_2S_2$: 2092.2036].

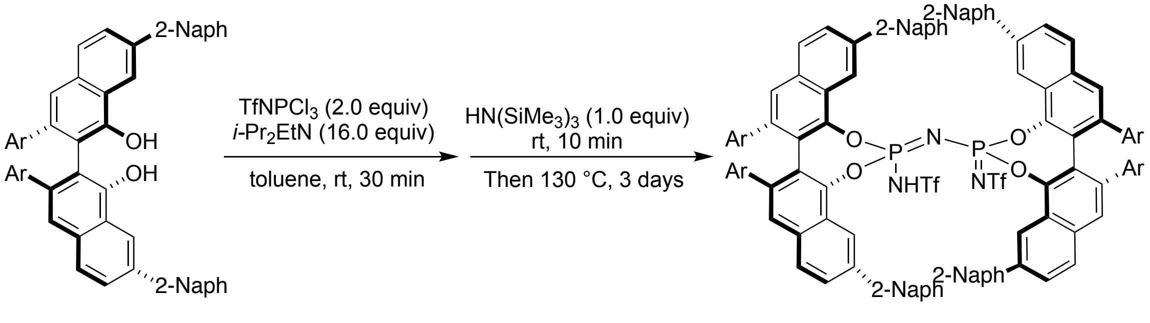


(*R*)-3e

(*R*)- (3e)$_2$-D

Synthesis of imidodiphosphorimidate (R)-(3e)$_2$-D: Compound **(*R*)-(3e)$_2$-D** was prepared from compound **(*R*)-3e** (0.64 mmol, 0.51 g), toluene (0.1 M, 6.4 mL), $TfNPCl_3$ (0.64 mmol, 0.2 g), *i*-Pr_2EtN (5.12 mmol, 0.9 mL) and $HN(SiMe_3)_3$ (0.32 mmol, 67 *μ*L) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*R*)-(3e)$_2$-D** was obtained as a white solid in 65% isolated yield (0.21 mmol, 0.37 g). mp: 253-255 °C. [59]

Spectral data for (*R*)-(3e)$_2$-D: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (s, 2H), 8.60 (s, 2H), 8.47 (d, *J* = 1.8 Hz, 2H), 8.29 (d, *J* = 8.6 Hz, 2H), 8.16 (dd, *J* = 10.5, 8.4, 3.1 Hz, 6H), 8.04 (d, *J* = 1.9 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.80 (dd, *J* = 8.5, 1.9 Hz, 2H), 7.66 – 7.52 (m, 8H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.44 – 7.36 (m, 6H), 7.20 (dd, *J* = 8.0, 6.7 Hz, 2H), 7.16 (dd, *J* = 8.5, 1.8 Hz, 2H), 7.08 (s, 2H), 6.95 (t, *J* = 7.3 Hz, 2H), 6.87 (t, *J* = 7.4 Hz, 2H), 6.75 (t, *J* = 7.8 Hz, 4H), 6.26 (s, 1H), 6.22 – 6.17 (m, 4H), 5.95 (s, 4H), 5.26 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.89, 143.42, 140.71, 139.97, 139.44, 139.22, 138.74, 138.71, 138.02, 137.33, 134.13, 133.62, 133.52, 133.20, 132.67, 132.61, 129.17, 129.09, 129.01, 128.82, 128.70, 128.57, 128.35, 127.99, 127.86, 127.71, 127.58, 127.33, 127.18, 126.90, 126.68, 126.52, 126.49, 126.43, 126.20, 126.12, 125.85, 125.83, 125.79, 125.06, 124.79, 122.73, 122.31, 119.95, 119.31. ^{31}P NMR (202 MHz, $CDCl_3$) δ -11.41. ^{19}F NMR (470 MHz, $CDCl_3$) δ -77.62. IR (cm^{-1}): 1193s, 1072s, 806s, 763m, 694s, 604s, 505m. HRMS (ESI+TOF) *m/z* 1748.3668, [(M+H$^+$); calcd for $C_{106}H_{65}F_6N_3O_8P_2S_2$: 1748.3671].



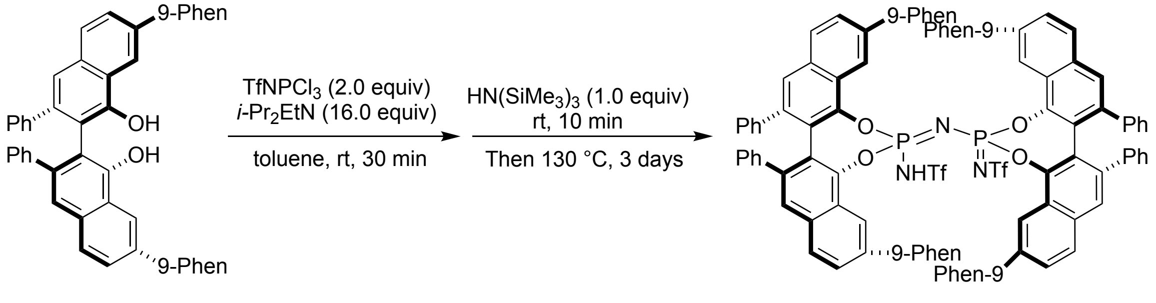
Ar: 4-*t*-Bu-C_6H_4
(*R*)-3eγ

Ar: 4-*t*-Bu-C_6H_4
(*R*)- (3eγ)$_2$-D

Synthesis of imidodiphosphorimidate (*R*)-(3eγ)$_2$-D: Compound **(*R*)-(3eγ)$_2$-D** was prepared from compound (***R*)- 3eγ** (0.45 mmol, 0.36 g), toluene (0.1 M, 4.5 mL), $TfNPCl_3$ (0.45 mmol, 0.13 g), *i*-Pr_2EtN (3.6 mmol, 0.63 mL) and $HN(SiMe_3)_3$ (0.225 mmol, 47 *μ*L) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*R*)- (3eγ)$_2$-D** was obtained as a white solid in 61% isolated yield (0.14 mmol, 0.27 g). mp: 290-291 ˚C. [59]

Spectral data for (*R*)- (3eγ)$_2$-D: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.17 (t, *J* = 1.1 Hz, 2H), 8.59 (d, *J* = 1.8 Hz, 2H), 8.49 – 8.39 (m, 2H), 8.30 (dd, *J* = 8.6, 1.8 Hz, 2H), 8.17 (td, *J* = 6.4, 3.2 Hz, 6H), 8.03 – 7.95 (m, 7H), 7.84 (dd, *J* = 8.6, 1.9 Hz, 2H), 7.65 – 7.59 (m, 4H), 7.59 – 7.52 (m, 4H), 7.48 – 7.43 (m, 4H), 7.41 – 7.36 (m, 4H), 7.24 – 7.17 (m, 4H), 7.08

(s, 2H), 6.76 – 6.67 (m, 4H), 6.25 – 5.94 (m, 7H), 5.67 (s, 4H), 1.19 (s, 18H), 1.15 (s, 18H). NMR (126 MHz, $CDCl_3$) δ 149.22, 149.01, 144.70, 143.23, 140.66, 139.76, 139.17, 138.10, 137.00, 136.59, 135.85, 134.14, 133.72, 133.58, 133.21, 132.75, 132.61, 129.14, 129.05, 128.83, 128.60, 128.41, 128.15, 127.91, 127.85, 127.53, 127.15, 126.97, 126.88, 126.64, 126.43, 126.20, 126.07, 125.86, 125.79, 124.91, 124.80, 124.61, 124.06, 122.85, 122.40, 119.85, 118.94, 34.36, 34.24, 31.34, 31.28. ^{31}P NMR (202 MHz, $CDCl_3$) δ -11.46. ^{19}F NMR (470 MHz, $CDCl_3$) δ -77.62. IR (cm^{-1}): 2985w, 1465m, 1192s, 1069s, 606s, 557s. HRMS (ESI+TOF) *m/z* 1972.6218, [(M+H$^+$); calcd for $C_{122}H_{97}F_6N_3O_8P_2S_2$: 1972.6174].

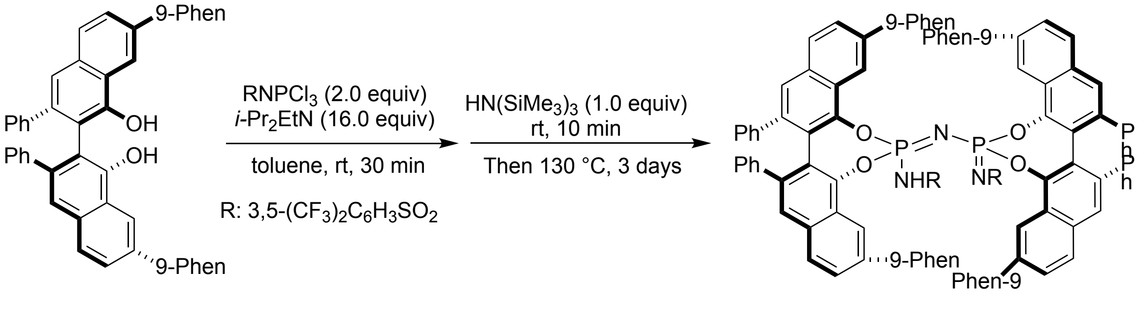


(*S*)-3h **(*S*)- (3h)$_2$-D**

Synthesis of imidodiphosphorimidate (*S*)-(3h)$_2$-D: Compound **(*S*)-(3h)$_2$-D** was prepared from compound **(*S*)-3h** (0.61 mmol, 0.48 g), toluene (0.1 M, 6.1 mL), $TfNPCl_3$ (0.61 mmol, 0.17 g), *i*-Pr_2EtN (4.96 mmol, 0.86 mL) and $HN(SiMe_3)_3$ (0.31 mmol, 65 μL) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*S*)-(3h)$_2$-D** was obtained as a white solid in 37% isolated yield (0.11 mmol, 0.21 g). mp: 318-320 ˚C. [59]

Spectral data for (*S*)-(3h)$_2$-D: ^1H NMR (500 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 20.0, 8.5 Hz, 6H), 8.63 (s, 2H), 8.40 (s, 2H), 8.13 – 7.34 (m, 34H), 7.07 – 6.95 (m, 5H), 6.84 (t, *J* = 7.4

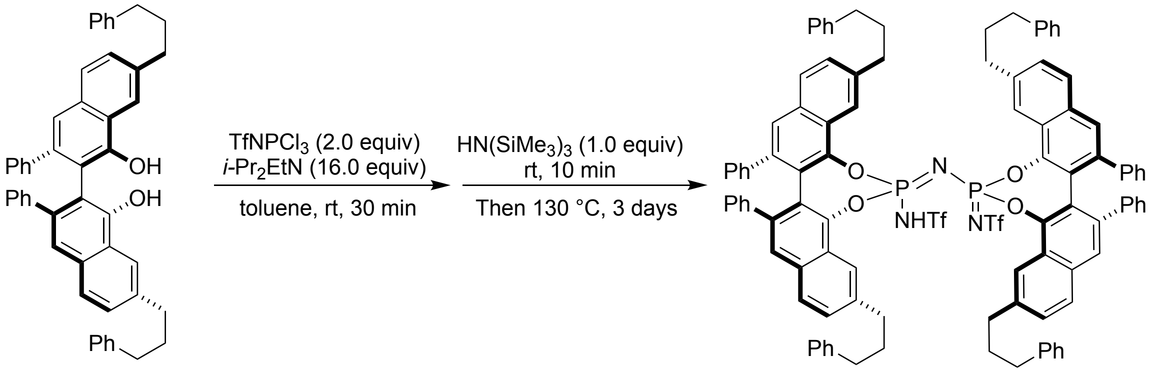
Hz, 5H), 6.75 (s, 2H), 6.62 (t, *J* = 7.3 Hz, 5H), 6.32 (d, *J* = 7.6 Hz, 5H), 6.07 (d, *J* = 7.3 Hz, 4H), 5.05 (s, 4H), (^{1}H-NMR was complicated, most of the proton's peak were broad and overlapped with each other). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.28, 140.38, 140.19, 140.02, 139.82, 139.13, 137.91, 133.06, 131.87, 130.69, 130.21, 129.21, 129.18, 129.06, 128.52, 127.97, 127.73, 127.41, 127.11, 126.86, 126.71, 126.58, 125.31, 122.96, 122.72, 122.52, 121.67, 118.20. ^{31}P NMR (202 MHz, $CDCl_3$) δ -2.90. ^{19}F NMR (470 MHz, $CDCl_3$) δ -77.16. IR (cm^{-1}): 1193s, 746m, 724s, 694m, 597m. HRMS (ESI+TOF) *m/z* 1948.4305, [(M+H$^+$); calcd for $C_{122}H_{73}F_6N_3O_8P_2S_2$: 1948.4298].



(*S*)-3h **(*S*)- (3h)$_2$-E**

Synthesis of imidodiphosphorimidate (*S*)-(3h)$_2$-E: Compound **(*S*)-(3h)$_2$-E** was prepared from compound **(*S*)-3h** (0.9 mmol, 0.7 g), toluene (0.1 M, 9 mL), $RNPCl_3$ [3,5-$(CF_3)_2C_6H_4NPCl_3$] (0.9 mmol, 0.33 g) (this compound was synthesized *in situ* by reacting 3,5-$(CF_3)_2C_6H_4NH_2$ (0.90 mmol, 0.26 g) with PCl_5 (0.9 mmol, 0.19 g) at 110 ˚C under reduced pressure), *i*-Pr_2EtN (7.2 mmol, 1.25 mL) and $HN(SiMe_3)_3$ (0.45 mmol, 94 μL) according to GP VII .The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*S*)-(3h)$_2$-E** was obtained as a white solid in 60% isolated yield (0.27 mmol, 0.60 g). mp: 275-276 ˚C. [59]

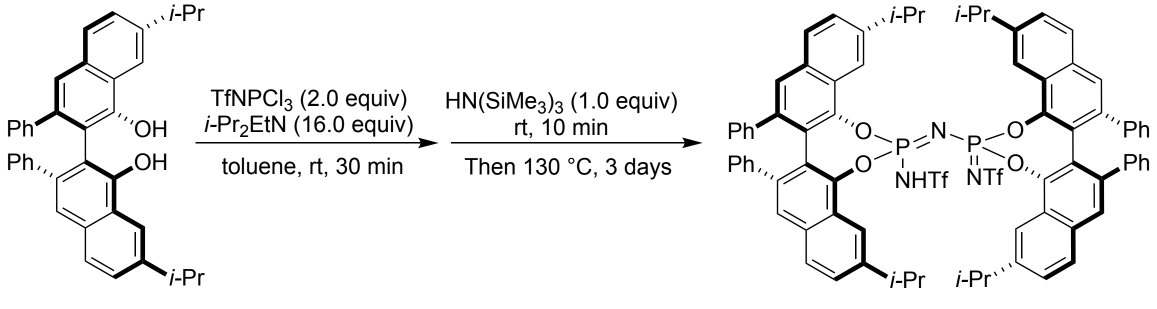
Spectral data for (*S*)-(3h)$_2$-E: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.97 – 8.55 (m, 9H), 8.18 – 7.35 (m, 45H), 7.03 (t, *J* = 7.4 Hz, 6H), 6.84 (t, *J* = 7.4 Hz, 5H), 6.68 (t, *J* = 7.2 Hz, 5H), 6.26 (d, *J* = 7.2 Hz, 6H), 6.09 (s, 4H), 4.00 (s, 4H), (^{1}H-NMR was complicated, most of the proton's peak were broad and overlapped with each other). ^{13}C NMR (126 MHz, CDCl$_3$) δ 145.77, 143.79, 140.41, 139.82, 139.20, 137.62, 133.07, 132.99, 132.16, 131.88, 131.10, 130.65, 130.50, 130.20, 129.18, 128.93, 128.30, 128.01, 127.70, 127.51, 127.24, 127.15, 127.04, 126.81, 126.70, 126.58, 125.48, 123.26, 122.90, 122.49, 121.52, 121.08, 118.91. ^{31}P NMR (202 MHz, CDCl$_3$) δ -5.57, -4.19, -2.99. ^{19}F NMR (470 MHz, CDCl$_3$) δ -63.23, -63.07. IR (cm^{-1}): 1277s, 1135s, 725s, 694s, 590m. HRMS (ESI+TOF) *m/z* 2236.4741, [(M+H$^+$); calcd for $C_{136}H_{80}F_{12}N_3O_8P_2S_2$: 2236.4670].



(*R*)-3i **(*R*)- (3i)$_2$-D**

Synthesis of imidodiphosphorimidate (*R*)-(3i)$_2$-D: Compound **(*R*)-(3j)$_2$-D** was prepared from compound **(*R*)-3i** (0.74 mmol, 0.50 g), toluene (0.1 M, 7.4 mL), TfNPCl$_3$ (0.74 mmol, 0.21 g), *i*-Pr$_2$EtN (5.92 mmol, 1.03 mL) and HN(SiMe$_3$)$_3$ (0.37 mmol, 78 *μ*L) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*R*)-(3j)$_2$-D** was obtained as an off-white solid in 32% isolated yield (0.12 mmol, 0.20 g). mp: 107-108 ˚C. [59]

Spectral data for (*R*)-(3j)$_2$-D: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.35 (s, 2H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.60 – 7.51 (m, 6H), 7.37 – 7.29 (m, 8H), 7.24 – 7.17 (m, 4H), 7.16 – 7.10 (m, 8H), 7.09 – 7.04 (m, 2H), 7.01 (t, *J* = 7.4 Hz, 2H), 6.91 – 6.85 (m, 8H), 6.82 (t, *J* = 7.6 Hz, 4H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.34 (t, *J* = 8.4 Hz, 8H), 3.04 (dd, *J* = 9.2, 6.4 Hz, 4H), 2.92 – 2.80 (m, 4H), 2.40 (dt, *J* = 14.5, 7.5 Hz, 2H), 2.34 – 2.21 (m, 8H), 2.15 (dt, *J* = 14.6, 7.7 Hz, 2H), 1.70 (h, *J* = 7.3 Hz, 4H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 144.24, 143.30, 142.64, 142.48, 142.01, 141.15, 139.72, 139.43, 139.33, 138.31, 133.16, 132.09, 129.78, 129.26, 128.90, 128.82, 128.70, 128.49, 128.36, 128.32, 128.13, 127.98, 127.75, 127.31, 127.26, 126.77, 126.49, 125.88, 125.77, 125.50, 124.60, 122.70, 122.01, 120.60, 119.25, 36.25, 35.90, 35.85, 35.36, 33.19, 32.40. ^{31}P NMR (202 MHz, CDCl$_3$) δ -10.66. ^{19}F NMR (470 MHz, CDCl$_3$) δ -78.04. IR (cm^{-1}): 2930w, 1191m, 1067m, 945m, 695s, 602m. HRMS (ESI+TOF) *m/z* 1716.4926, [(M+H$^+$); calcd for $C_{102}H_{81}F_6N_3O_8P_2S_2$: 1716.4923].

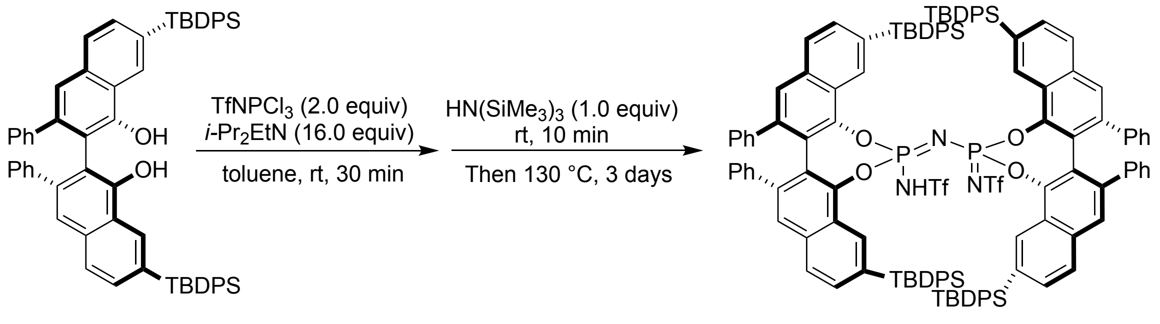


(*R*)- 3j

(*R*)- (3j)$_2$-D

Synthesis of imidodiphosphorimidate (*R*)-(3j)$_2$-D: Compound **(*R*)-(3j)$_2$-D** was prepared from compound **(*R*)-3j** (1.5 mmol, 0.803 g), toluene (0.1 M, 15 mL), TfNPCl$_3$ (1.5 mmol, 0.438 g), *i*-Pr$_2$EtN (12.0 mmol, 2.1 mL) and HN(SiMe$_3$)$_3$ (0.75 mmol, 157 *μ*L) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*R*)-(3j)$_2$-D** was obtained as a white solid in 79% isolated yield (0.59 mmol, 0.84 g). mp: 215-216 ˚C. [59]

Spectral data for (*R*)-(3j)$_2$-D: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.32 (s, 2H), 7.86 – 7.75 (m, 4H), 7.61 (dd, *J* = 8.5, 1.7 Hz, 2H), 7.49 (s, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 2H), 7.08 (s, 2H), 7.02 – 6.92 (m, 8H), 6.81 (t, *J* = 7.6 Hz, 4H), 6.28 (d, *J* = 7.1 Hz, 4H), 6.26 – 6.23 (m, 4H), 3.31 (hept, *J* = 6.9 Hz, 2H), 2.70 (hept, *J* = 6.9 Hz, 2H), 1.54 (dd, *J* = 6.9, 6.0 Hz, 12H), 1.14 (d, *J* = 6.8 Hz, 6H), 0.95 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 148.89, 147.08, 144.20, 143.32, 139.74, 139.23, 139.17, 138.34, 133.16, 132.22, 129.33, 128.78, 128.17, 128.13, 128.06, 127.99, 127.71, 127.54, 127.20, 126.97, 126.69, 126.42, 125.46, 124.61, 122.40, 121.70, 118.16, 117.13, 34.86, 33.51, 23.94, 23.91, 23.89, 23.88, 22.59. ^{31}P NMR (202 MHz, CDCl$_3$) δ -11.97. ^{19}F NMR (470 MHz, CDCl$_3$) δ -77.92. IR (cm^{-1}): 2963w, 1198s, 1081s, 944s, 885m, 767m, 717m, 694s, 635w, 601s, 508w. HRMS (ESI+TOF) *m/z* 1412.3713, [(M+H$^+$); calcd for C$_{78}$H$_{65}$F$_6$N$_3$O$_8$P$_2$S$_2$: 1412.3671].

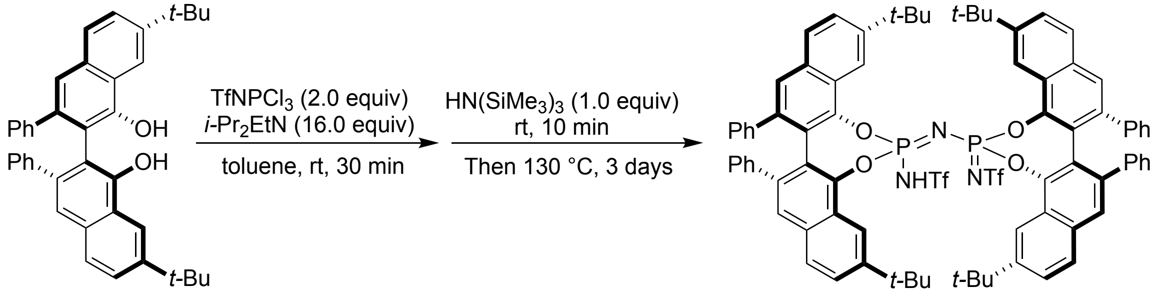


(*R*)- 3k

(*R*)- (3k)$_2$-D

Synthesis of imidodiphosphorimidate (*R*)-(3k)$_2$-D: Compound **(*R*)-(3k)$_2$-D** was prepared from compound **(*R*)-3k** (0.24 mmol, 0.5 g), toluene (0.1 M, 2.4 mL), $TfNPCl_3$ (0.24 mmol, 0.07 g), *i*-Pr_2EtN (1.92 mmol, 0.33 mL) and $HN(SiMe_3)_3$ (0.12 mmol, 25 μL) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*R*)-(3k)$_2$-D** was obtained as a white solid in 79% isolated yield (0.59 mmol, 0.84 g). mp: 275 ˚C. [59]

Spectral data for (*R*)-(3k)$_2$-D^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 2H), 8.70 (s, 2H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.81 (dd, *J* = 8.0, 3.3 Hz, 6H), 7.61 – 7.51 (m, 7H), 7.49 (s, 2H), 7.47 – 7.41 (m, 5H), 7.37 (t, *J* = 7.3 Hz, 3H), 7.34 – 7.30 (m, 5H), 7.30 – 7.27 (m, 5H), 7.24 (d, *J* = 7.5 Hz, 2H), 7.23 – 7.18 (m, 4H), 7.14 (t, *J* = 7.5 Hz, 4H), 6.96 (d\d, *J* = 8.2 Hz, 2H), 6.94 – 6.90 (m, 2H), 6.86 (s, 2H), 6.82 (t, *J* = 7.4 Hz, 3H), 6.72 (t, *J* = 7.6 Hz, 4H), 6.68 (t, *J* = 8.7 Hz, 4H), 6.62 (d, *J* = 8.1 Hz, 2H), 6.17 (s, 1H), 6.01 (d, *J* = 7.6 Hz, 4H), 5.83 (s, 4H), 1.24 (s, 18H), 0.84 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.28, 145.24, 144.01, 140.64, 139.59, 139.45, 137.29, 136.97, 136.79, 136.48, 136.21, 136.00, 135.23, 134.97, 134.69, 134.55, 134.30, 133.72, 133.68, 133.40, 130.29, 129.80, 129.09, 129.06, 129.02, 128.45, 128.36, 128.25, 127.65, 127.58, 127.46, 127.36, 127.20, 126.89, 126.78, 126.56, 126.46, 126.31, 124.68, 123.36, 122.60, 121.36, 118.20, 28.97, 27.50, 19.08, 18.04, 1.03. ^{31}P NMR (202 MHz, $CDCl_3$) δ -16.27. ^{19}F NMR (470 MHz, $CDCl_3$*)* δ -76.16. IR (cm^{-1}): 2880s, 2811m, 1310s, 1051s, 870m, 725s, 618s. HRMS (ESI+TOF) *m/z* 2196.6581, [(M+H$^+$); calcd for $C_{130}H_{113}F_6N_3O_8P_2S_2Si_4$: 2196.6504].

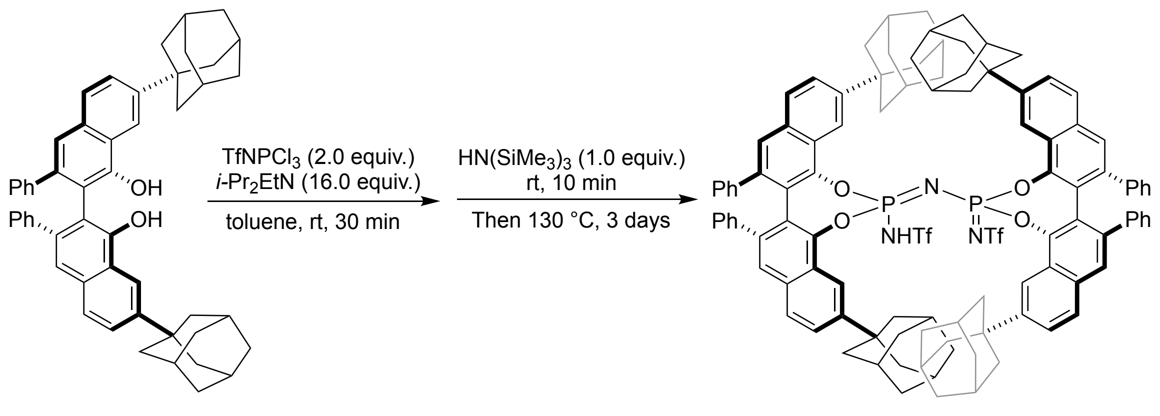


(*R*)- 3d

(*R*)- (3d)$_2$-D

Synthesis of imidodiphosphorimidate (*R*)-(3d)$_2$-D: Compound **(*R*)-(3d)$_2$-D** was prepared from compound **(*S*)-3d** (0.54 mmol, 0.31 g), toluene (0.1 M, 5.4 mL), $TfNPCl_3$ (0.54 mmol, 0.17 g), *i*-Pr_2EtN (4.32 mmol, 0.75 mL) and $HN(SiMe_3)_3$ (0.27 mmol, 57 μL) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*R*)-(3d)$_2$-D** was obtained as an off-white solid in 82% isolated yield (0.225 mmol, 0.331 g). mp: 250-251 ˚C. [59]

Spectral data for (*R*)-(3d)$_2$-D: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 2H), 8.12 (d, *J* = 1.9 Hz, 2H), 7.80 – 7.72 (m, 4H), 7.40 (s, 2H), 7.30 – 7.25 (m, 4H), 7.14 – 7.05 (m, 4H), 6.99 – 6.92 (m, 4H), 6.88 (t, *J* = 7.7 Hz, 4H), 6.76 (t, *J* = 7.5 Hz, 4H), 6.18 (d, *J* = 7.7 Hz, 4H), 6.03 (d, *J* = 7.5 Hz, 4H), 1.59 (s, 18H), 1.25 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.62, 149.25, 144.48, 143.79, 139.83, 139.21, 138.95, 138.61, 132.53, 132.06, 129.60, 128.71, 127.71, 127.64, 127.34, 127.29, 127.15, 127.07, 126.57, 126.35, 126.32, 125.14, 124.55, 122.16, 121.45, 117.13, 116.62, 35.47, 35.13, 31.14, 31.04. ^{31}P NMR (202 MHz, $CDCl_3$) δ -14.01. ^{19}F NMR (470 MHz, $CDCl_3$) δ -77.94. IR (cm^{-1}): 2957w, 1200s, 1108s, 1067m, 942m, 764m, 695s, 633w, 599s, 524m, 507s. HRMS (ESI+TOF) *m/z* 1468.4316, [(M+H$^+$); calcd for $C_{82}H_{74}F_6N_3O_8P_2S_2$: 1468.4297].

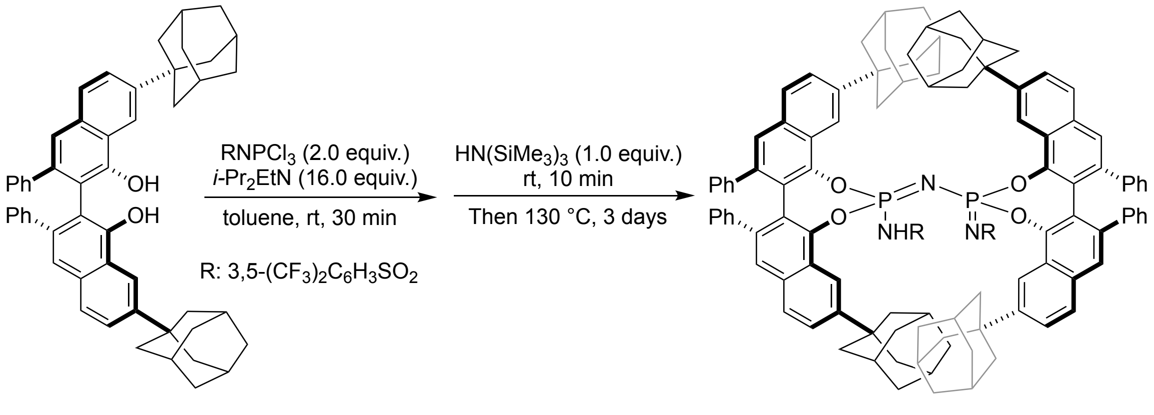


(*S*)- 3l

(*S*)- $(3l)_2$-D

Synthesis of imidodiphosphorimidate (*S*)-$(3l)_2$-D: Compound **(*S*)-$(3l)_2$-D** was prepared from compound **(*S*)-3l** (1.76 mmol, 1.25 g), toluene (0.1 M, 17.6 mL), $RNPCl_3$ (1.77 mmol, 0.503 g), *i*-Pr_2EtN (14.1 mmol, 2.45 mL) and $HN(SiMe_3)_3$ (0.88 mmol, 185 μL) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound **(*S*)-$(3l)_2$-D** was obtained as a white solid in 70% isolated yield (0.612 mmol, 1.09 g). mp: 350-355 ˚C (decomposed). [59]

Spectral data for (*S*)-$(3l)_2$-D: ^1H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 2H), 8.10 (s, 2H), 7.85 – 7.71 (m, 4H), 7.44 (s, 2H), 7.29 (dd, *J* = 8.5, 1.9 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.15 – 7.07 (m, 4H), 7.01 – 6.95 (m, 2H), 6.91 (t, *J* = 7.6 Hz, 4H), 6.80 (t, *J* = 7.5 Hz, 4H), 6.30 – 6.18 (m, 8H), 2.29 – 2.13 (m, 18H), 2.01 – 1.81 (m, 30H), 1.65 (s, 6H), 1.54 – 1.46 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.82, 149.66, 144.36, 139.95, 139.35, 139.22, 138.67, 132.75, 132.28, 129.53, 128.70, 127.88, 127.72, 127.38, 126.91, 126.72, 126.64, 126.54, 126.29, 125.20, 124.86, 122.33, 121.39, 116.82, 66.01, 42.84, 42.68, 37.01, 36.98, 36.76, 36.71, 29.10, 28.81, 15.41. ^{31}P NMR (202 MHz, $CDCl_3$) δ -11.87. ^{19}F NMR (470 MHz, $CDCl_3$) δ -78.06. IR (cm^{-1}): 2899s, 2848m, 1200s, 1071s, 940m, 765s, 694s, 603s, 580m. HRMS (ESI+TOF) *m/z* 1780.6183, [(M+H$^+$); calcd for $C_{106}H_{97}F_6N_3O_8P_2S_2$: 1780.6174].



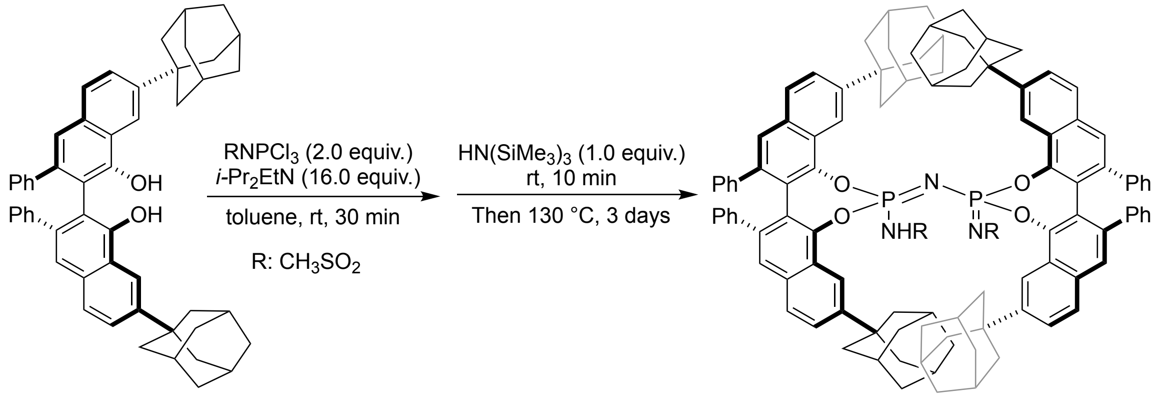
(*R*)- 3l

(*R*)- (3l)$_2$-E

Synthesis of imidodiphosphorimidate *(R)*-(3l)$_2$-E: Compound ***(R)*-(3l)$_2$-E** was prepared from compound **(*R*)-3l** (0.5 mmol, 177 mg), toluene (0.1 M, 5 mL), $ArNPCl_3$ (0.5 mmol), i-Pr_2EtN (4.0 mmol, 0.7 mL) and $HN(SiMe_3)_3$ (0.25 mmol, 52 μL) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound ***(R)*-(3l)$_2$-E** was obtained as a yellow solid in 72% isolated yield (0.25 mmol, 350 mg). mp: 250 ˚C. [59]

Spectral data for *(R)*-(3l)$_2$-E: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (q, *J* = 13.2 Hz, 12H), 1.68 – 2.00 (m, 30H), 2.02 – 2.12 (m, 18H), 6.34 (d, *J* = 7.5 Hz, 5H), 6.43 (d, *J* = 7.7 Hz, 4H), 6.86 (dt, *J* = 16.1, 7.6 Hz, 9H), 7.01 – 7.10 (m, 5H), 7.20 (s, 2H), 7.37 – 7.41 (m, 2H), 7.43 (s, 2H), 7.45 – 7.53 (m, 3H), 7.63 – 7.71 (m, 3H), 7.78 (d, *J* = 8.7 Hz, 3H), 8.32 (s, 2H), 8.47 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.19, 28.60, 28.83, 36.54, 36.55, 36.63, 36.63, 36.76, 42.55, 42.73, 114.71, 115.14, 116.90, 120.02, 120.15, 120.69, 122.09, 123.58, 124.78, 126.08, 127.27, 129.22, 131.04, 132.32, 133.38, 134.60, 136.74, 136.99, 139.08, 139.71, 140.16, 140.46, 141.90, 143.27, 148.79, 151.21, 152.99, 153.45. ^{31}P

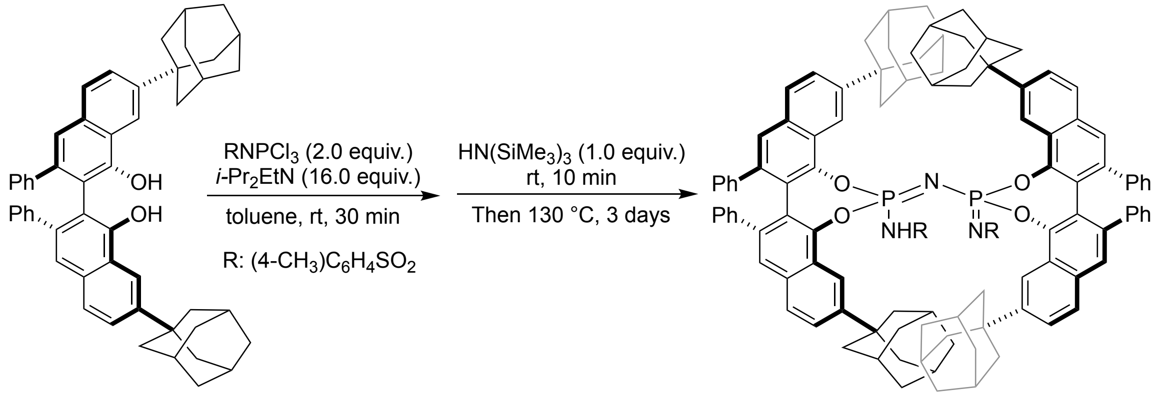
NMR (202 MHz, CDCl$_3$) δ -3.95. ^{19}F NMR (470 MHz, CDCl$_3$) δ -62.94. IR (cm^{-1}): 2850s, 2828m, 1230s, 1051s, 940m, 765s, 694s, 600s, 580m. HRMS (ESI+TOF) *m/z* 2068.6500, [(M+H$^+$); Calc. for $C_{120}H_{103}F_{12}N_3O_8P_2S_2$: 2068.6548].



(***R***)- **3l** (***R***)- **(3l)$_2$-F**

Synthesis of imidodiphosphorimidate *(R)*-(3l)$_2$-F: Compound ***(R)*-(3l)$_2$-F** was prepared from compound **(*R*)-3l** (0.25 mmol, 176.7 mg), toluene (0.1 M, 2.5 mL), RNPCl$_3$ (0.25 mmol, 58 mg), *i*-Pr$_2$EtN (2.0 mmol, 0.35 mL) and HN(SiMe$_3$)$_3$ (0.125 mmol, 26 μL) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound ***(R)*-(3l)$_2$-F** was obtained as a brown solid in 70% isolated yield (0.125 mmol, 146 mg). mp: 338 ˚C. [59]

Spectral data for *(R)*-(3l)$_2$-F: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.43 (d, *J* = 1.8 Hz, 2H), 8.22 (s, 2H), 7.79 (dd, *J* = 8.8, 1.5 Hz, 4H), 7.73 (dd, *J* = 12.6, 8.7 Hz, 4H), 7.49 (s, 4H), 7.09 (q, *J* = 7.3 Hz, 4H), 6.92 (t, *J* = 7.6, 8H), 6.43 (dd, *J* = 10.6, 8.3, 6H), 3.51 (s, 6H), 2.18 (d, *J* = 6.6 Hz, 10H), 2.16 – 2.09 (m, 18H), 1.84 (dt, *J* = 6.4, 2.9 Hz, 20H), 1.34 – 1.21 (m, 12H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 151.43, 140.60, 139.77, 139.44, 139.23, 138.13, 132.78, 132.77, 129.08, 128.94, 128.94, 127.82, 127.75, 127.73, 127.70, 127.56, 127.37, 126.63, 126.63, 126.41, 124.85, 122.95, 116.91, 116.11, 63.74, 53.46, 44.04, 42.89, 42.85, 42.82, 36.79, 36.76, 28.95, 28.94, 28.91. ^{31}P NMR (202 MHz, $CDCl_3$) -1.88. IR (cm^{-1}): 2870s, 2795s, 1330s, 1026s, 980s, 675s, 580m. HRMS (ESI+TOF) *m/z* 1710.7699, [(M+K$^+$); Calc. for $C_{106}H_{97}F_6N_3O_8P_2S_2K$: 1710.7642].



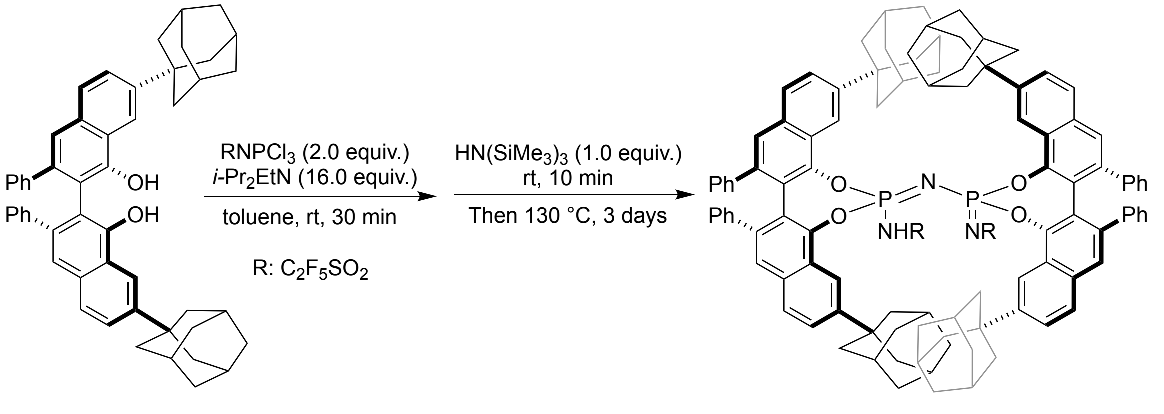
(*R*)- 3l

(*R*)- (3l)$_2$-G

Synthesis of imidodiphosphorimidate (*R*)-(3l)$_2$-G: Compound ***(R)*-(3l)$_2$-G** was prepared from compound **(*R*)-3l** (0.5 mmol, 353 mg), toluene (0.1 M, 5 mL), $RNPCl_3$ (0.5 mmol, 153 mg), *i*-Pr_2EtN (8.0 mmol, 1.4 mL) and $HN(SiMe_3)_3$ (0.25 mmol, 52.4 μL) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound ***(R)*-(3l)$_2$-G** was obtained as a white solid in 61% isolated yield (0.158 mmol, 288 mg). mp: 250 ˚C. [59]

Spectral data for (*R*)-(3l)$_2$-G : ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 2H), 8.07 (s, 2H), 7.97 (d, *J* = 7.9 Hz, 4H), 7.82 – 7.71 (m, 8H), 7.68 (dd, J = 8.7, 1.9 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 4H), 7.27 (d, *J* = 6.7 Hz, 4H), 7.09 (td, *J* = 7.4, 5.9 Hz, 4H), 6.92 (td, *J* = 7.7, 1.8 Hz, 8H), 6.43 (ddt, *J* = 19.9, 7.3, 1.4 Hz, 4H), 2.41 (s, 6H), 2.20 – 2.07 (m, 26H), 2.06 – 2.03 (s, J = 2.9 Hz, 12H), 1.87 – 1.82 (m, 12H), 1.77 – 1.73 (m, 10H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 151.34, 150.41, 145.02, 144.93, 144.37, 144.08, 144.01, 143.69, 140.05, 139.94, 139.40, 139.33, 139.12, 137.99, 132.82, 132.80, 129.81, 129.68, 129.63, 129.05, 129.02, 127.83, 127.72, 127.58, 127.51, 127.27, 127.20, 126.59, 126.57, 126.55, 126.45, 126.34, 125.76, 125.74, 125.31, 125.29, 122.67, 122.65, 122.42, 122.40, 117.43, 117.33, 43.03, 42.91, 37.13, 36.91, 36.87, 36.84, 29.11, 29.04, 21.75. ^{31}P NMR (202 MHz, $CDCl_3$) δ –1.92. IR (cm^{-1}): 2850s, 1380s, 1350s, 1206s, 988s, 675s, 580m. HRMS (ESI+TOF) *m/z* 1843.6692, [($M+NH_4^+$); Calc. for $C_{106}H_{103}N_3O_8P_2S_2$: 1843.6604].



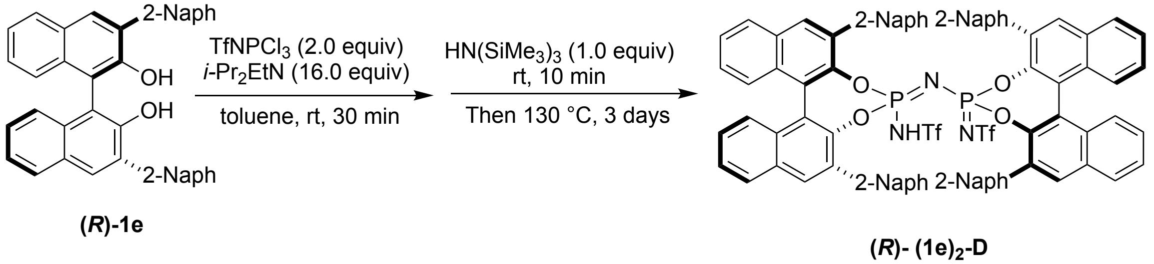
(***R***)**- 3l**

(***R***)**- (3l)$_2$-H**

Synthesis of imidodiphosphorimidate (*R*)-(3l)$_2$-H: Compound ***(R)*-(3l)$_2$-H** was prepared from compound **(*R*)-3l** (0.5 mmol, 353 mg), toluene (0.1 M, 5.0 mL), $RNPCl_3$ (0.5 mmol, 167 mg), *i*-Pr_2EtN (4.0 mmol, 0.7 mL) and $HN(SiMe_3)_3$ (0.25 mmol, 52 μL) according to GP VII. The crude product was purified via column chromatography on silica gel (30 mm X 250 mm, hexane: EtOAc, 3:1, 2:1, 1:1 and 1:2 as the eluent). The desired compound ***(R)*-(3l)$_2$-H** was obtained as a white solid in 67% isolated yield (0.25 mmol, 292 mg). mp: 268 ˚C. [59]

Spectral data for *(R)*-(3l)$_2$-H: ^1H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 2H), 8.25 (s, 2H), 7.82 (dd, *J* = 14.0, 8.6 Hz, 4H), 7.74 (dd, *J* = 8.8, 1.9 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 17.6 Hz, 4H), 7.16 – 7.09 (m, 4H), 6.96 (q, *J* = 7.5 Hz, 8H), 6.55 – 6.45 (m, 8H), 2.14 (s, 18H), 2.11 – 1.89 (m, 30H), 1.81 (d, *J* = 3.0 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.68, 149.48, 147.05, 140.67, 140.53, 132.84, 132.48, 129.13, 129.01, 127.74, 127.66, 127.45, 127.17, 126.35, 126.16, 125.75, 125.60, 118.58, 118.25, 45.88, 43.23, 42.95, 37.03, 37.00, 29.19, 29.09, 8.45.

^{31}P NMR (202 MHz, $CDCl_3$) δ -2.18. ^{19}F NMR (470 MHz, $CDCl_3$) δ -78.66 (s, 6F), -116.41 (d, *J* = 488.6 Hz, 4F). IR (cm^{-1}): 2850s, 2828m, 1230s, 1051s, 940m, 765s, 694s, 600s, 580m. HRMS (ESI+TOF) *m/z* 1918.7011, [(M+K$^+$); Calc. for $C_{108}H_{96}F_{10}N_3O_8P_2S_2K$: 1918.7013].

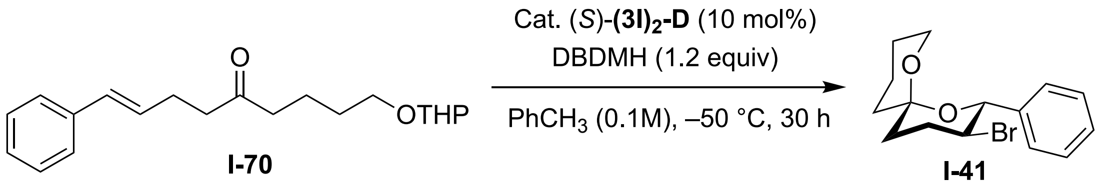


Synthesis of 3,3'-naphthyl$_2$BINOL *i*DPI (*R*)-(1e)$_2$-D: Compound **(*R*)-(1e)$_2$-D** was prepared via GP V and the spectral data were in good agreement with the literature values. [82]

General method for growing the crystal of VANOL and VAPOL-imidodiphosphorimidates

Illustrated for Ad$_4$VIPEtN$_3$ ***(S)*-(3l)$_2$-D***:* In a 4 mL vial was added Ad$_4$VIP-Et$_3$N (20 mg) followed by the addition of CH_2Cl_2 (0.5 mL). Once the catalyst-triethylamine complex was fully dissolved in CH_2Cl_2, hexane (~3 mL) was slowly added (the layer between CH_2Cl_2 and hexane should not be disturbed). The 4 mL vial was placed inside another 20 mL vial, caped loosely. The crystal growth was noticed after 24 hours, and they were collected after 48 hours.

General Procedure for the mono bromospiroketalisation of THP-protected keto-alkenols (GP VIII): [59]

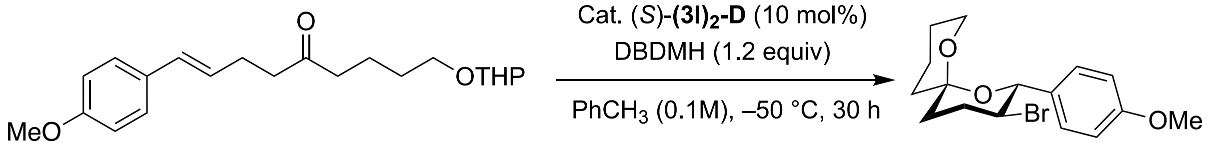


Synthesis of (2*R*,3*S*,6*S*)-3-bromo-2-phenyl-1,7-dioxaspiro[5.5]undecane I-94:

In a clean oven dried sealed tube fitted with a magnetic stir bar was introduced 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) (34.3 mg, 1.20 mmol) and catalyst (*S*)**-(3I)$_2$-D** (17.8 mg, 0.0100 mmol) in dry toluene (0.8 mL) under inert atmosphere. The reaction mixture was stirred for 10 min at rt and then quickly transferred to a pre-cooled bath kept at -50 °C. Substrate **I-70** (31.6 mg, 0.100 mmol, 0.500 M in toluene, 200 μL) was then transferred and the reaction mixture was stirred at this temperature for an additional 30 h. The progress of the reaction was monitored through TLC, whereupon complete consumption of the starting material indicated the completion of the reaction. The reaction was quenched by adding excess ethanol (5 mL) and slowly warmed up to room temperature where sodium sulfite (10% aq. solution, 2 mL) was added and stirred for an additional 10 min. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 X 5mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. Crude ^{1}H-NMR spectra was recorded to determine the diastereomeric ratio of the corresponding substrate. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent).

Compound **I-41** was obtained as a colorless liquid in 92% (28.6 mg, 0.090 mmol) isolated yield with >98:2 diastereomeric ratio. The enantiomeric ratio of compound **I-41 (**94:6) was determined by chiral HPLC [OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min]. R_f: 0.3 (95:5, hexane: ethyl acetate).

Spectral data for compound I-41: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45 – 7.41 (m, 2H), 7.41 – 7.31 (m, 3H), 4.68 (d, *J* = 10.3 Hz, 1H), 4.02 (ddd, *J* = 12.0, 10.3, 4.5 Hz, 1H), 3.73 – 3.64 (m, 2H), 2.52 (qd, *J* = 12.8, 5.0 Hz, 1H), 2.29 (dtd, *J* = 12.9, 4.4, 2.9 Hz, 1H), 1.84 – 1.66 (m, 4H), 1.64 – 1.54 (m, 1H), 1.53 – 1.44 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.81, 128.46, 128.23, 128.12, 96.13, 76.48, 60.93, 52.54, 37.79, 35.02, 31.39, 25.15, 18.49. IR (cm^{-1}): 3065, 2900, 1440, 1263, 1176, 1081. HRMS: TOF MS ES$^+$ ($C_{15}H_{20}BrO_2$): Calc. [M + H]$^+$: 311.0647, Found [M + H]$^+$: 311.0645. $[\alpha]^{20}_D$ (*c* 1.0, CHCl$_3$): –13.33.

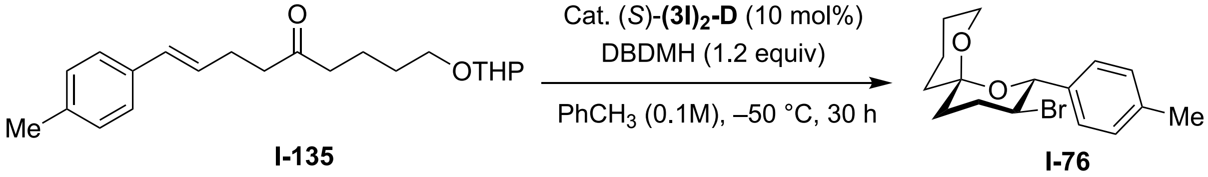


I-140 **I-80**

Synthesis of (2R,3S,6S)-3-bromo-2-(4-methoxyphenyl)-1,7-dioxaspiro[5.5]undecane I-80: Compound **I-80** was synthesized from compound **I-140** (34.6 mg, 0.100 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be >98:2 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-80** was obtained as a colorless liquid in 87% (29.7 mg, 0.0900 mmol) isolated yield. The enantiomeric ratio of compound **I-80** (58:42) was determined by chiral HPLC

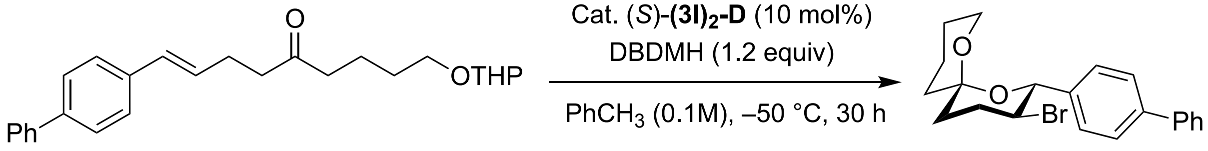
(OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R_f: 0.25 (97:3, hexane: ethyl acetate).

Spectral data for I-80: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.61 (d, J = 10.4 Hz, 1H), 3.99 (ddd, J = 12.0, 10.3, 4.5 Hz, 1H), 3.80 (s, 3H), 3.71 – 3.60 (m, 2H), 2.49 (tdd, J = 12.9, 12.0, 4.9 Hz, 1H), 2.25 (dtd, J = 12.9, 4.4, 2.9 Hz, 1H), 1.80 – 1.62 (m, 4H), 1.66 – 1.63 (m, 1H), 1.62 – 1.58 (m, 1H), 1.55 – 1.50 (m, 1H), 1.50 – 1.44 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.61, 132.15, 129.20, 113.61, 96.16, 75.99, 60.92, 55.36, 52.93, 37.80, 35.03, 31.43, 25.17, 18.50. IR (cm^{-1}): 3035, 2905, 2835, 1465, 1378, 1335, 1276, 1145, 1100, 1080, 987, 787. HRMS: TOF MS ES$^+$ ($C_{16}H_{22}BrO_3$): Calc. [M + H]$^+$: 341.0752, Found [M + H]$^+$: 341.0741. $[\alpha]^{20}_D$ (*c* 1.0, $CHCl_3$): –2.91.



Synthesis of (2*R*,3*S*,6*S*)-3-bromo-2-(p-tolyl)-1,7-dioxaspiro[5.5]undecane I-76*:* Compound **I-76** was synthesized from compound **I-135** (33 mg, 0.10 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be >98:2 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-76** was obtained as a colorless liquid in 78% (26.0 mg, 0.080 mmol) isolated yield. The enantiomeric ratio of compound **I-76** (88:12) was determined by chiral HPLC (OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.5 mL/min. R_f: 0.45 (95:5, hexane: ethyl acetate).

Spectral data for I-76: ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.30 (d, J = 8.0, 2H), 7.16 (d, J = 8.0 Hz, 2H), 4.63 (d, J = 10.3 Hz, 1H), 4.00 (ddd, J = 12.0, 10.3, 4.5 Hz, 1H), 3.72 – 3.59 (m, 2H), 2.56 – 2.43 (m, 1H), 2.35 (s, 3H), 2.26 (dtd, J = 12.9, 4.4, 2.9 Hz, 1H), 1.83 – 1.66 (m, 4H), 1.54 – 1.41 (m, 4H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 138.21, 136.92, 128.99, 128.00, 96.13, 76.27, 52.69, 37.81, 35.03, 31.42, 25.16, 21.44, 18.48. IR (cm^{-1}): 3010, 2939, 2869, 1517, 1440, 1380, 1274, 1175, 1040, 998, 968, 811. HRMS: TOF MS AP$^+$ ($C_{16}H_{22}BrO_2$): Calc. [M + H]$^+$: 325.0803, Found [M + H]$^+$: 325.0803. $[\alpha]^{20}_D$ (*c* 1.0, CHCl$_3$): –4.36.

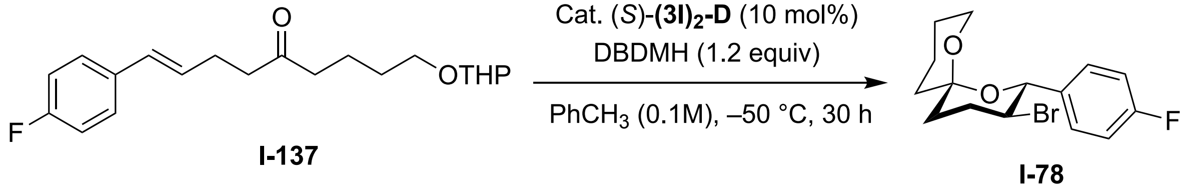


I-138

I-79

Synthesis of (2*R*,3*S*,6*S*)-2-([1,1'-biphenyl]-4-yl)-3-bromo-1,7-dioxaspiro[5.5]undecane I-79: Compound **I-79** was synthesized from compound **I-138** (31.2 mg, 0.100 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be >98:2 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-79** was obtained as a colorless liquid in 80% (31 mg, 0.080 mmol) isolated yield. The enantiomeric ratio of compound **I-79** (92:8) was determined by chiral HPLC (OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R$_f$: 0.25 (97:3, hexane: ethyl acetate).

Spectral data for I-79: ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.62 – 7.57 (m, 4H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.46 – 7.41 (m, 2H), 7.37 – 7.32 (m, 1H), 4.73 (d, *J* = 10.4 Hz, 1H), 4.06 (ddd, *J* = 12.0, 10.3, 4.5 Hz, 1H), 3.78 – 3.59 (m, 2H), 2.60 – 2.48 (m, 1H), 2.30 (dtd, *J* = 12.9, 4.4, 2.9 Hz, 1H), 1.86 – 1.74 (m, 3H), 1.73 – 1.67 (m, 1H), 1.63 – 1.56 (m, 1H), 1.54 – 1.45 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.33, 141.02, 138.83, 128.87, 128.53, 127.42, 127.32, 127.03, 124.96, 96.20, 76.21, 60.99, 52.50, 37.81, 35.03, 31.40, 25.16, 18.52. IR (cm^{-1}): 3030, 2924, 2869, 2853, 1448, 1263, 1176, 1079, 1045, 999, 968, 747. HRMS: TOF MS AP$^+$ (C$_{21}$H$_{24}$BrO$_2$): Calc. [M + H]$^+$:387.0915, Found [M + H]$^+$: 387.0960. $[\alpha]^{20}_D$ (*c* 1.0, CHCl$_3$): –8.33.

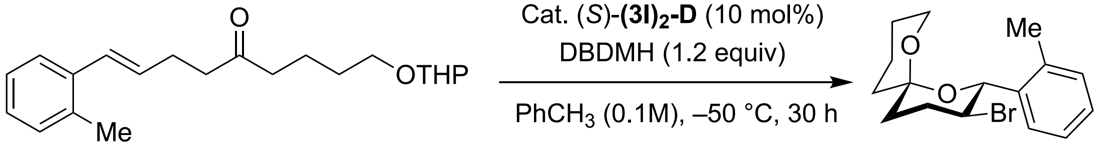


I-137

I-78

Synthesis of (2*R*,3*S*,6*S*)-3-bromo-2-(4-fluorophenyl)-1,7-dioxaspiro[5.5]undecane I-78: Compound **I-78** was synthesized from compound **I-137** (33.4 mg, 0.100 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be >98:2 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-78** was obtained as a colorless liquid in 77% (25.3 mg, 0.0800 mmol) isolated yield. The enantiomeric ratio of compound **I-78** (95:5) was determined by chiral HPLC (OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R$_f$: 0.25 (97:3, hexane: ethyl acetate).

Spectral data for I-78: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H), 7.09 – 6.99 (m, 2H), 4.64 (d, J = 10.3 Hz, 1H), 3.93 (ddd, J = 12.1, 10.3, 4.5 Hz, 1H), 3.68 (ddt, J = 11.0, 5.0, 1.8 Hz, 1H), 3.64 – 3.57 (m, 1H), 2.49 (tdd, J = 13.1, 12.0, 4.8 Hz, 1H), 2.25 (dtd, J = 13.0, 4.4, 2.8 Hz, 1H), 1.85 – 1.58 (m, 5H), 1.54 – 1.43 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.75, 129.69, 115.20, 115.03, 96.21, 75.80, 60.98, 52.70, 37.75, 34.99, 31.74, 31.33, 25.12, 22.81, 18.49, 14.29. ^{19}F NMR (470 MHz, $CDCl_3$) δ -113.92. IR (cm^{-1}): 2941, 2870, 1605, 1510, 1450, 1379, 1271, 1177, 1080, 999, 892. HRMS: TOF MS ES$^+$ ($C_{15}H_{19}BrFO_2$): Calc. [M + H]$^+$: 329.0552, Found [M + H]$^+$: 329.0544. [α]$^{20}_D$ (*c* 1.0, $CHCl_3$): –41.24.

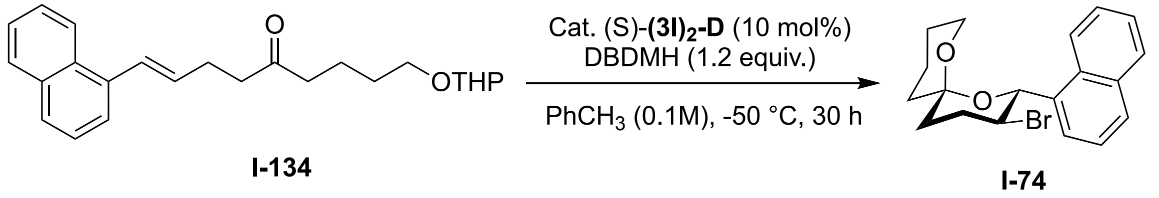


I-136

I-77

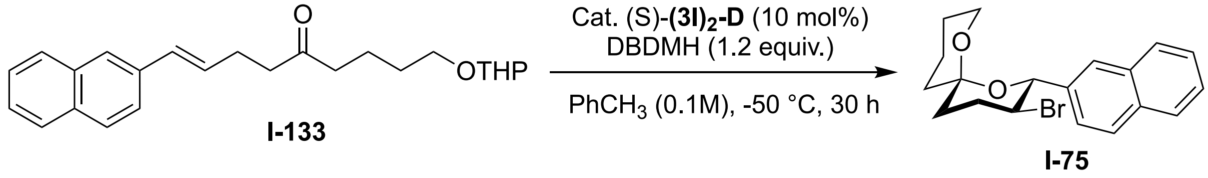
Synthesis of (2*R*,3*S*,6*S*)-3-bromo-2-(o-tolyl)-1,7-dioxaspiro[5.5]undecane I-77: Compound **I-77** was synthesized from compound **I-136** (33.0 mg, 0.10 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be >98:2 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-77** was obtained as a colorless liquid in 90% (29.3 mg, 0.090 mmol) isolated yield. The enantiomeric ratio of compound **I-77** (80:20) was determined by chiral HPLC (OT(+) column, 99:1 hexane/2-propanol at 215 nm, flow-rate: 0.5 mL/min). R_f: 0.25 (97:3, hexane: ethyl acetate).

Spectral data for I-77: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 1H), 7.25 – 7.20 (m, 2H), 7.20 – 7.14 (m, 1H), 5.06 (d, J = 10.4 Hz, 1H), 4.11 (ddd, J = 12.1, 10.4, 4.4 Hz, 1H), 3.76 – 3.63 (m, 2H), 2.59 – 2.52 (m, 1H), 2.51 (s, 3H), 2.29 (dtd, J = 13.0, 4.3, 2.8 Hz, 1H), 1.87 – 1.65 (m, 5H), 1.62 – 1.42 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 138.50, 136.61, 130.28, 128.11, 126.26, 96.10, 60.86, 53.25, 37.89, 35.08, 31.48, 25.16, 20.36, 18.46. IR (cm^{-1}): 3001, 2939, 2869, 1487, 1300, 1274, 1175, 1080, 998, 960. HRMS: TOF MS AP$^+$ ($C_{16}H_{22}BrO_2$): Calc. [M + H]$^+$: 325.0803, Found [M + H]$^+$: 325.0803. $[\alpha]^{20}_D$ (*c* 1.0, CHCl$_3$): –2.16.



Synthesis of (2*R*,3*S*,6*S*)-3-bromo-2-(naphthalen-1-yl)-1,7-dioxaspiro[5.5]undecane I-74: Compound **I-74** was synthesized from compound **I-134** (36.6 mg, 0.100 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be >98:2 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-74** was obtained as a white solid in 95% (34.3 mg, 0.095 mmol) isolated yield. The enantiomeric ratio of compound **I-74** (84:16) was determined by chiral HPLC (OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R$_f$: 0.35 (97:3, hexane: ethyl acetate).

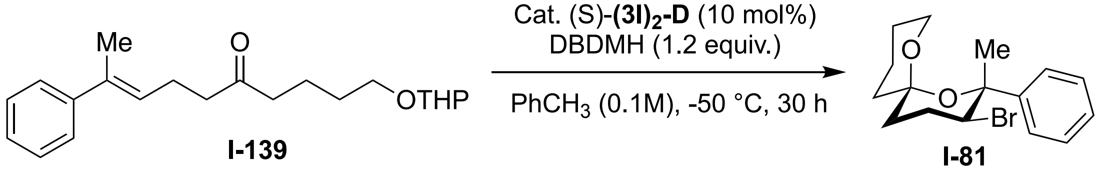
Spectral data for I-74: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.37 (d, *J* = 8.6 Hz, 1H), 7.85 (dd, *J* = 16.0, 8.1 Hz, 2H), 7.67 – 7.56 (m, 1H), 7.49 (dq, *J* = 15.4, 7.4 Hz, 3H), 5.51 (br, 1H), 4.38 (br, 1H), 3.82 – 3.54 (m, 2H), 2.64 (qd, *J* = 12.1, 7.5 Hz, 1H), 2.34 (dq, *J* = 12.6, 4.0 Hz, 1H), 1.92 – 1.83 (m, 2H), 1.75 – 1.65 (m, 2H), 1.65 – 1.57 (m 1H), 1.55 – 1.43 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 129.03, 129.00, 125.99, 125.55, 125.37, 96.33, 61.10, 37.92, 35.16, 31.74, 31.70, 25.13, 18.47, 14.28. IR (cm^{-1}): 3055, 2911, 2850, 1439, 1376, 1267, 1225, 1175, 1132, 970, 705. HRMS: TOF MS AP$^+$ ($C_{19}H_{22}BrO_2$): Calc. [M + H]$^+$:361.0803, Found [M + H]$^+$: 361.0803. $[\alpha]^{20}_D$ (*c* 1.0, CHCl$_3$): –1.90.



Synthesis of (2*R*,3*S*,6*S*)-3-bromo-2-(naphthalen-2-yl)-1,7-dioxaspiro[5.5]undecane I-75: Compound **I-75** was synthesized from compound **I-133** (36.6 mg, 0.100 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be >98:2 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-75** was obtained as an off-white solid in 95% (34.3 mg, 0.095 mmol) isolated yield. The enantiomeric ratio of compound **I-75** (89:11) was determined by chiral HPLC (OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min. R$_f$: 0.35 (97:3, hexane: ethyl acetate).

Spectral data for I-75: ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.89 – 7.81 (m, 4H), 7.56 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.50 – 7.46 (m, 2H), 4.85 (d, *J* = 10.4 Hz, 1H), 4.14 (ddd, *J* = 12.0, 10.3, 4.5 Hz, 1H), 3.75 – 3.69 (m, 2H), 2.64 – 2.50 (m, 1H), 2.32 (dtd, *J* = 12.9, 4.4, 3.1 Hz, 1H), 1.88 – 1.80 (m, 2H), 1.78 – 1.68 (m, 2H), 1.65 – 1.57 (m, 1H), 1.54 – 1.43 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 137.18, 133.55, 133.12, 128.30, 128.04, 127.86, 127.70, 126.19, 125.53, 96.23, 76.70, 61.02, 52.41, 37.84, 35.04, 31.43, 25.16, 18.51. IR (cm^{-1}):

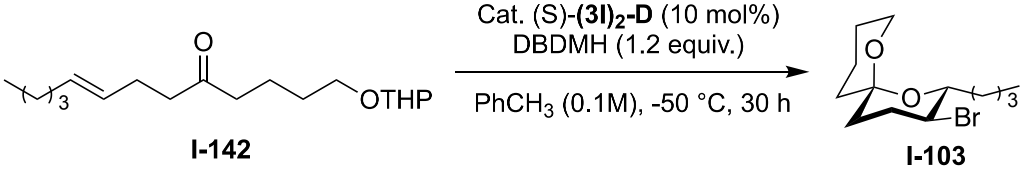
3054, 2939, 2869, 1448, 1375, 1349, 1270, 1080. HRMS: TOF MS AP+ ($C_{19}H_{22}BrO_2$): Calc. [M + H]+: 361.0803, Found [M + H]+: 361.0803. $[\alpha]^{20}_{D}$ (*c* 1.0, $CHCl_3$): –8.13.



Synthesis of (2*R*,3*S*,6*S*)-3-bromo-2-methyl-2-phenyl-1,7-dioxaspiro[5.5]undecane I-81: Compound **I-81** was synthesized from compound **I-139** (33.0 mg, 0.10 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)₂-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be >98:2 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-81** was obtained as a pale yellowish green oil in 80% (26.0 mg, 0.08 mmol) isolated yield. The enantiomeric ratio of compound **I-81** (86:14) was determined by chiral HPLC (OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R_f: 0.25 (98:2, hexane: ethyl acetate).

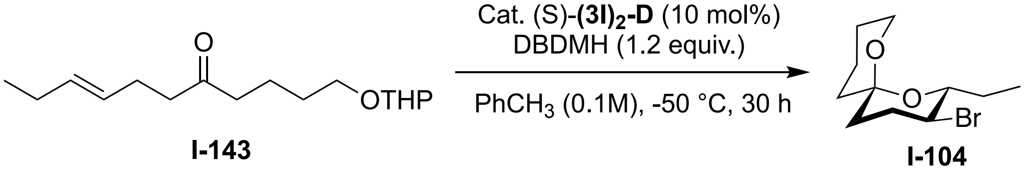
Spectral data for I-81: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 – 7.61 (m, 2H), 7.43 – 7.35 (m, 2H), 7.34 – 7.28 (m, 1H), 4.71 (dd, *J* = 12.8, 3.7 Hz, 1H), 4.19 (t, *J* = 3.1 Hz, 1H), 3.87 (ddd, J = 12.3, 11.2, 3.0 Hz, 1H), 3.69 (ddt, *J* = 11.1, 4.3 Hz, 1H), 3.20 (ddd, J = 14.3, 12.8, 3.1 Hz, 1H), 2.49 (dt, *J* = 14.3, 3.5 Hz, 1H), 2.32 – 2.21 (m, 1H), 2.04 (s, 3H), 1.82 – 1.69 (m, 2H), 1.64 – 1.59 (m, 1H), 1.55 – 1.49 (m, 1H), 1.39 (td, *J* = 13.5, 4.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 127.99, 127.77, 126.38, 97.10, 79.55, 63.05, 57.28, 54.50, 36.91, 36.62, 24.97, 19.72, 19.39. IR (cm^{-1}): 2935, 2865, 1575, 1448, 1378, 1310, 1210,

1145, 1100, 1076, 998, 742. HRMS: TOF MS AP+ ($C_{16}H_{22}BrO_2$): Calc. [M + H]+: 325.0824, Found [M + H]+: 325.0803. $[\alpha]^{20}_{D}$ (*c* 1.0, $CHCl_3$): –31.53.



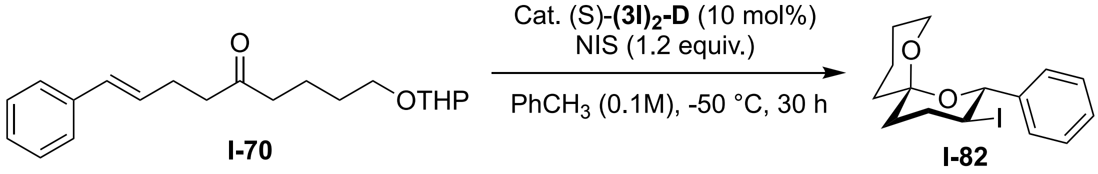
Synthesis of (2*R*,3*S*,6*S*)-3-bromo-2-butyl-1,7-dioxaspiro[5.5]undecane I-103: Compound **I-103** was synthesized from compound **I-142** (29.6 mg, 0.100 mmol) and DBDMH (34.3 mg, 0.12 mmol) using catalyst (*S*)-**(3I)₂-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be 15:1 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-103** was obtained as a pale greenish-yellow liquid in 70% (19.4 mg, 0.0700 mmol) isolated yield. The enantiomeric ratio of compound **I-103** (80:20) was determined by chiral HPLC (OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R_f: 0.3 (95:5, hexane: ethyl acetate).

Spectral data for I-103: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (dd, *J* = 10.2, 4.6 Hz, 1H), 4.49 (dt, *J* = 8.9, 8.0 Hz, 1H), 4.33 – 4.23 (m, 1H), 4.07 – 3.97 (m, 1H), 3.29 (ddd, *J* = 9.8, 7.4, 3.2 Hz, 1H), 2.60 – 2.43 (m, 2H), 2.17 (ddd, *J* = 13.6, 9.9, 4.6 Hz, 1H), 2.05 – 2.03 (m, 1H), 1.96 – 1.81 (m, 3H), 1.55 – 1.49 (m, 1H), 1.45 – 1.29 (m, 5H), 0.98 – 0.88 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 107.02, 71.78, 65.15, 59.45, 47.88, 44.67, 40.71, 40.61, 35.38, 29.85, 27.04, 25.89, 22.22, 14.05. IR (cm^{-1}): 2940, 2800, 1448, 1378, 1310, 1210, 1145, 1100, 1076, 998, 742. HRMS: TOF MS AP$^+$ ($C_{13}H_{24}BrO_2$): Calc. [M + H]$^+$: 291.0961, Found [M + H]$^+$: 291.0903. $[\alpha]^{20}_D$ (*c* 1.0, $CHCl_3$): –3.80.



Synthesis of (2*R*,3*S*,6*S*)-3-bromo-2-ethyl-1,7-dioxaspiro[5.5]undecane I-104: Compound **I-104** was synthesized from compound **I-143** (26.9 mg, 0.100 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be 10:1 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-104** was obtained as a pale-yellow liquid in 90% (23.7 mg, 0.0900 mmol) isolated yield. The enantiomeric ratio of compound **I-104** (85:15) was determined by chiral HPLC (OT (+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R_f: 0.3 (95:5, hexane: ethyl acetate).

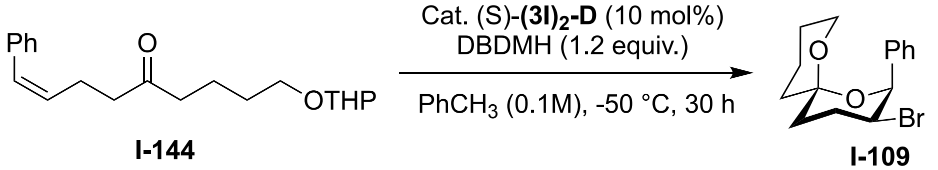
Spectral data for I-104: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 – 4.19 (m, 1H), 3.96 (dt, *J* = 9.6, 4.1 Hz, 1H), 3.85 (td, *J* = 10.8, 4.0 Hz, 1H), 3.59 (ddt, *J* = 10.2, 5.6, 2.0 Hz, 1H), 2.23 – 2.04 (m, 2H), 2.00 – 1.89 (m, 2H), 1.89 – 1.79 (m, 3H), 1.79 – 1.69 (m, 3H), 1.68 – 1.58 (m, 2H), 1.08 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 106.95, 80.52, 62.38, 53.49, 37.92, 33.84, 28.60, 28.25, 26.93, 25.86, 20.85, 13.32. IR (cm^{-1}): 2960, 2801, 1550, 1301, 1270, 1145, 1111, 1076, 998, 742 cm^{-1}. HRMS: TOF MS AP$^+$ ($C_{11}H_{20}BrO_2$): Calc. [M + H]$^+$: 263.0646, Found [M + H]$^+$: 263.0656. $[\alpha]^{20}_D$ (*c* 1.0, $CHCl_3$): –11.79.



Synthesis of (2*R*,3*S*,6*S*)-3-iodo-2-phenyl-1,7-dioxaspiro[5.5]undecane I-82: Compound **I-82** was synthesized from compound **I-70** (31.6 mg, 0.100 mmol) and NIS (27.0 mg, 0.12 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be >98:2 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-82** was obtained as a yellow liquid in 80% (28.6 mg, 0.0800 mmol) isolated yield. The enantiomeric ratio of compound **I-82** (91:9) was determined by chiral HPLC (OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R$_f$: 0.3 (97:3, hexane: ethyl acetate).

Spectral data for I-82: ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.42 – 7.32 (m, 5H), 4.78 (d, *J* = 10.8 Hz, 1H), 4.18 (m, 1H), 3.75 – 3.63 (m, 2H), 2.72 (qd, *J* = 13.1, 4.4 Hz, 1H), 2.52 – 2.31 (m, 1H), 1.81 – 1.71 (m, 3H), 1.69 – 1.61 (m, 3H), 1.49 – 1.45 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 128.54, 128.24, 128.12, 126.11, 96.42, 77.38, 60.92, 38.98, 35.30, 33.75, 32.80, 25.18, 18.39. IR (cm^{-1}): 3004, 2909, 1521, 1439, 1305, 1267, 1250, 1175, 1111, 989, 787. HRMS: TOF MS AP$^+$ ($C_{15}H_{20}IO_2$): Calc. [M + H]$^+$: 359.0508, Found [M + H]$^+$: 359.0501. [α]$^{20}_D$ (*c* 1.0, CHCl$_3$): –2.52.

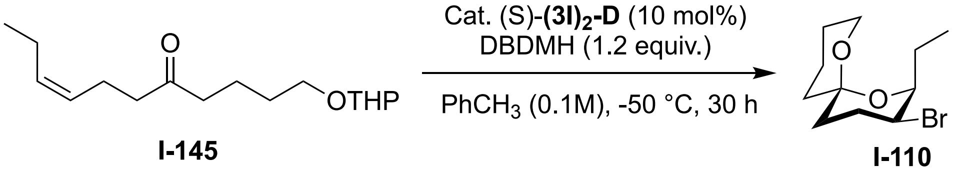
Synthesis of (2*S*,3*S*,6*S*)-3-bromo-2-phenyl-1,7-dioxaspiro[5.5]undecane I-109: Compound **I-109** was synthesized from compound **I-144** (31.6 mg, 0.100 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be



5:1 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-109** was obtained as a white solid in 80% (24.9 mg, 0.0800 mmol) isolated yield. The enantiomeric ratio of compound **I-109** (85:15) was determined by chiral HPLC (OT(+) column, 99:1 hexane/2-propanol at 215 nm, flow-rate: 0.5 mL/min). R_f: 0.25 (98:2, hexane: ethyl acetate).

Spectral data for I-109: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.35 – 7.28 (m, 3H), 4.92 (d, *J* = 6.2 Hz, 1H), 4.60 – 4.44 (m, 1H), 3.91 (dt, *J* = 11.2, 3.5 Hz, 1H), 3.69 – 3.53 (m, 1H), 2.08 – 1.99 (m, 1H), 1.98 – 1.90 (m, 1H), 1.88 – 1.82 (m, 1H), 1.76 – 1.70 (m, 2H), 1.70 – 1.57 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.57, 128.59, 128.27, 128.00, 97.75, 80.05, 62.01, 52.05, 37.90, 32.57, 28.19, 25.33, 18.09.

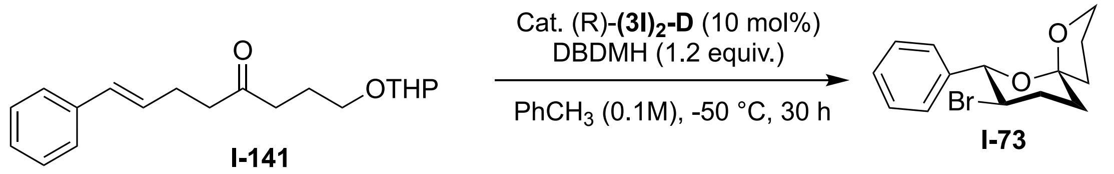
IR (cm^{-1}): 3065, 2900, 1440, 1263, 1176, 1081 cm^{-1}. HRMS: TOF MS ES$^+$ ($C_{15}H_{20}BrO_2$): Calc. $[M + H]^+$: 311.0647, Found $[M + H]^+$: 311.0641. $[\alpha]^{20}_D$ (*c* 1.0, $CHCl_3$): –6.28.



Synthesis of (2*S*,3*S*,6*S*)-3-bromo-2-ethyl-1,7-dioxaspiro[5.5]undecane I-110: Compound **I-110** was synthesized from compound **I-145** (26.8 mg, 0.100 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be 2:1 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-110** was obtained in 40%

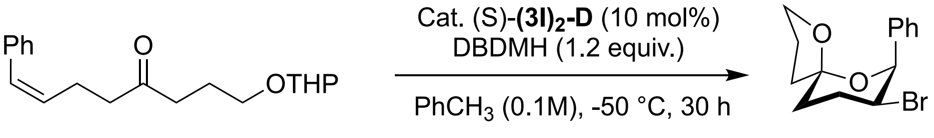
(10.5 mg, 0.040 mmol) isolated yield. The enantiomeric ratio of compound **I-110** (69:31) was determined by chiral HPLC (OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R_f: 0.25 (98:2, hexane: ethyl acetate).

Spectral data for I-110: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (ddd, *J* = 6.0, 5.2, 3.9 Hz, 1H), 4.00 (dt, *J* = 6.6, 4.0 Hz, 1H), 3.89 (td, *J* = 11.4, 3.0 Hz, 1H), 3.63 (dt, *J* = 11.2, 4.3 Hz, 1H), 2.25 – 2.17 (m, 1H), 2.02 – 1.93 (m, 2H), 1.92 – 1.90 (m, 1H), 1.90 – 1.85 (m, 1H), 1.85 – 1.80 (m, 2H), 1.80 – 1.74 (m, 2H), 1.73 – 1.61 (m, 2H), 1.58 – 1.52 (m, 1H), 1.12 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 103.17, 80.03, 62.13, 61.90, 37.43, 33.35, 28.11, 27.76, 25.38, 20.36, 12.74. IR (cm^{-1}): 2960, 2801, 1550, 1301, 1270, 1145, 1111, 1076, 998, 742. HRMS: TOF MS AP$^+$ ($C_{11}H_{20}BrO_2$): Calc. [M + H]$^+$: 263.0646, Found [M + H]$^+$: 263.0656. $[\alpha]^{20}_D$ (*c* 1.0, $CHCl_3$): –9.87.



Synthesis of (5*R*,7*S*,8*R*)-8-bromo-7-phenyl-1,6-dioxaspiro[4.5]decane I-73: Compound **I-73** was synthesized from compound **I-141** (30.2 mg, 0.100 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*R*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be >98:2 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-73** was obtained as a white solid in 77% (22.9 mg, 0.0800 mmol) isolated yield. The enantiomeric ratio of compound **I-73** (88:12) was determined by chiral HPLC (OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R_f: 0.25 (95:5, hexane: ethyl acetate).

Spectral data for I-73: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 4.83 (d, *J* = 10.4 Hz, 1H), 4.03 (ddd, J = 12.0, 10.3, 4.6 Hz, 1H), 3.99 – 3.84 (m, 2H), 2.51 (tdd, *J* = 13.4, 12.0, 4.3 Hz, 1H), 2.40 (dtd, *J* = 13.0, 4.6, 2.8 Hz, 1H), 2.09 (td, *J* = 13.6, 4.5 Hz, 1H), 2.04 – 1.92 (m, 2H), 1.90 – 1.79 (m, 2H), 1.77 – 1.67 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.88, 128.47, 128.29, 128.08, 106.31, 77.65, 67.52, 52.21, 37.34, 35.36, 32.87, 23.79. IR (cm^{-1}): 3030, 2889, 1468, 1203, 1166, 1079, 968, 740. TOF MS ES$^+$ ($C_{14}H_{18}BrO_2$): Calc. [M + H]$^+$: 297.0490, Found [M + H]$^+$: 297.0482. $[\alpha]^{20}_D$ (*c* 1.0, $CHCl_3$): 19.90.

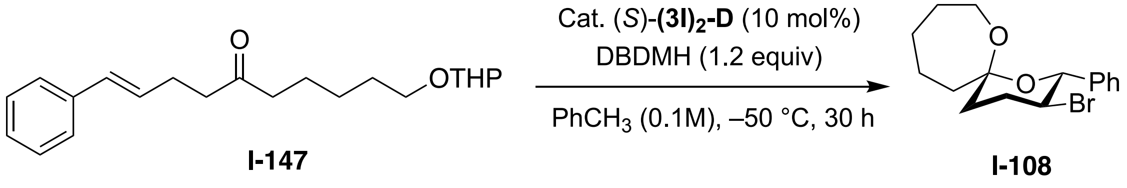


I-146 **I-107**

Synthesis of (5*S*,7*S*,8*S*)-8-bromo-7-phenyl-1,6-dioxaspiro[4.5]decane I-107: Compound **I-107** was synthesized from compound **I-146** (30.2 mg, 0.100 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**$(3I)_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be 5:1 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-107** was obtained as a pale green liquid in 80% (23.8 mg, 0.0800 mmol) isolated yield. The enantiomeric ratio of compound **I-107** (75:25) was determined by chiral HPLC (OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R_f: 0.2 (97:3, hexane: ethyl acetate).

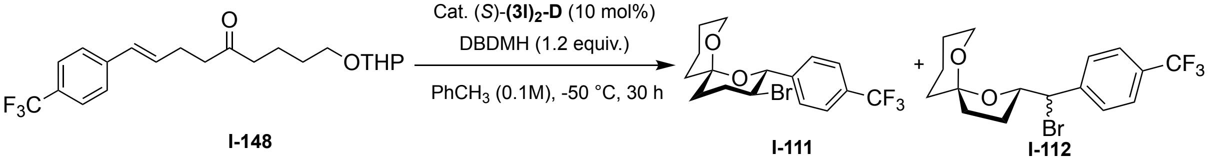
Spectral data for I-107: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 2H), 7.36 – 7.28 (m, 3H), 4.89 (d, *J* = 6.5 Hz, 1H), 4.72 – 4.65 (dt, J = 10.4, 6.2 Hz, 1H), 4.15 – 4.08 (m, 1H), 3.67– 3.71 (m, 1H), 2.04 – 2.00 (m, 1H), 1.96 – 1.91 (m, 1H), 1.75 (dt, *J* = 10.4, 3.7

Hz, 1H), 1.74 – 1.67 (m, 3H), 1.63 – 1.59 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.68, 128.62, 128.57, 127.61, 106.64, 81.05, 62.03, 57.80, 37.50, 33.57, 28.43, 25.34, 20.37. IR (cm^{-1}): 3030, 2924, 2869, 2853, 1448, 1263, 1176, 1079, 1045, 999, 968, 747. TOF MS ES$^+$ ($C_{14}H_{18}BrO_2$): Calc. [M + H]$^+$: 297.0490, Found [M + H]$^+$: 297.0491. $[\alpha]^{20}_D$ (*c* 1.0, CHCl$_3$): –16.70.



Synthesis of (2*R*,3*S*,6*S*)-3-bromo-2-phenyl-1,7-dioxaspiro[5.6]dodecane I-108: Compound **I-108** was synthesized from compound **I-147** (33.0 mg, 0.10 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be >98:2 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-108** was obtained as a yellow oil in 80% (26.0 mg, 0.080 mmol) isolated yield. The enantiomeric ratio of compound **I-108** (88:12) was determined by chiral HPLC (OT(+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R$_f$: 0.25 (97:3, hexane: ethyl acetate).

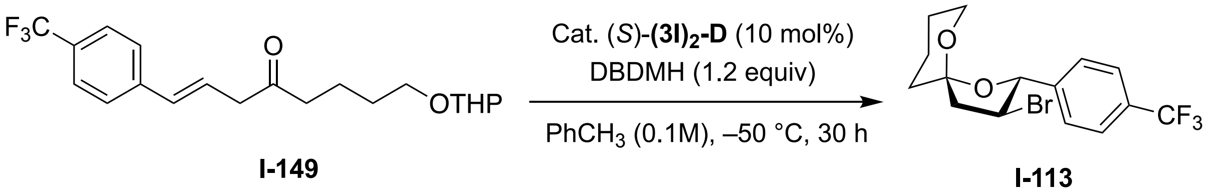
Spectral data for I-108: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.44 – 7.40 (m, 2H), 7.40 – 7.31 (m, 3H), 4.78 (d, *J* = 10.4 Hz, 1H), 4.04 (ddd, *J* = 12.0, 10.4, 4.6 Hz, 1H), 3.81 – 3.68 (m, 2H), 2.49 (tdd, *J* = 13.4, 12.0, 4.1 Hz, 1H), 2.29 (dtd, *J* = 12.7, 4.4, 3.1 Hz, 1H), 2.09 – 2.03 (m, 1H), 1.96 – 1.89 (m, 1H), 1.85 – 1.76 (m, 2H), 1.74 – 1.61 (m, 4H), 1.45 – 1.32 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.92, 128.51, 128.35, 128.11, 101.18, 77.39, 62.05, 52.79, 40.84, 37.59, 31.73, 30.65, 29.86, 22.77. IR (cm^{-1}): 3030, 2924, 1558, 1363, 1276, 1079, 991, 955, 723 cm^{-1}. HRMS: TOF MS AP^{+} ($C_{16}H_{23}BrO_2$): Calc. [M + H]$^{+}$: 325. 0803, Found [M + H]$^{+}$: 325.0799. [α]$^{20}_{D}$ (*c* 1.0, $CHCl_3$): –39.74.



Synthesis of (2R,3S,6S)-3-bromo-2-(4-(trifluoromethyl)phenyl)-1,7-dioxaspiro[5.5]undecane I-111 and (2R,5R)-2-((S)-bromo(4-(trifluoromethyl)phenyl)methyl)-1,6-dioxaspiro[4.5]decane I-112: Compound **I-111** and **I-112** were synthesized from compound **I-148** (38.0 mg, 0.10 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. Compound **I-111** and **I-112** were obtained in a 1:1 ratio. The diastereomeric ratios of the crude mixture were determined to be >98:2 for **I-111** and 10:1 for **I-112** by ^{1}H-NMR. The crude products were purified and separated via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compounds **I-111** and **I-112** were obtained in 45% (17.1 mg, 0.045 mmol) and 40% (15.2 mg, 0.040 mmol) isolated yields, respectively. The enantiomeric ratio of compound **I-111** (90:10) and the enantiomeric ratio of compound **I-112** (80:20) was determined by chiral HPLC (OT(+) column, 99:1 hexane/2-propanol at 215 nm, flow-rate: 0.5 mL/min).

Spectral data for I-111: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.61 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 4.74 (d, *J* = 10.3 Hz, 1H), 3.95 (ddd, *J* = 11.9, 10.3, 4.4 Hz, 1H), 3.72 (ddd, *J* = 10.9, 4.5, 2.1 Hz, 1H), 3.62 (ddd, *J* = 12.0,11.1, 2.5 Hz, 1H), 2.53 (tdd, *J* = 12.9, 12.0, 4.8 Hz, 1H), 2.30 (dtd, *J* = 12.9, 4.4, 2.8 Hz, 1H), 1.86 – 1.79 (m, 2H), 1.78 – 1.67 (m, 3H), 1.54 – 1.46 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.65, 128.52, 125.20, 125.17, 96.25, 75.94, 61.05, 52.03, 37.71, 34.96, 31.26, 25.07, 18.46. ^{19}F NMR (470 MHz, CDCl$_3$) δ -62.52. IR (cm^{-1}): 3010, 2964, 1570, 1276, 1172, 1127, 1106, 1064, 682 cm^{-1}. HRMS: TOF MS AP$^+$ ($C_{16}H_{19}F_3BrO_2$): Calc. [M + H]$^+$: 379.0520, Found [M + H]$^+$: 379.0525. $[\alpha]^{20}_D$ (*c* 1.0, CHCl$_3$): –9.07.

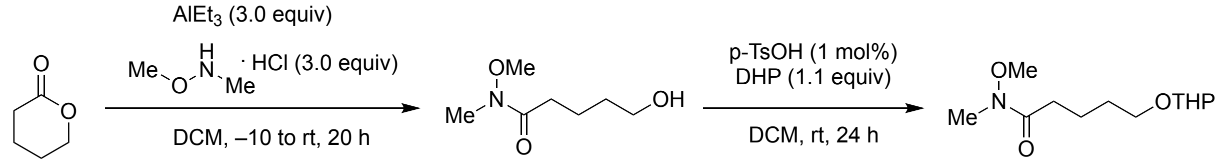
Spectral data for I-112: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.66 – 7.59 (m, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 4.90 (d, *J* = 10.4 Hz, 1H), 4.01 – 3.94 (m, 2H), 3.94 – 3.88 (m, 1H), 2.58 – 2.47 (m, 1H), 2.45 – 2.38 (m, 1H), 2.10 (td, *J* = 13.7, 4.5 Hz, 1H), 2.00 (ddt, *J* = 14.8, 8.1, 4.4 Hz, 2H), 1.92 – 1.83 (m, 2H), 1.81 – 1.72 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 143.42, 128.66, 125.91, 125.88, 106.57, 83.42, 62.39, 58.13, 39.12, 33.65, 28.72, 25.41, 20.33. ^{19}F NMR (470 MHz, CDCl$_3$) δ -62.75. IR (cm^{-1}): 3075, 2960, 1570, 1316, 1272, 1127, 1064, 682. HRMS: TOF MS AP$^+$ ($C_{16}H_{19}F_3BrO_2$): Calc. [M + H]$^+$: 379.0520, Found [M + H]$^+$: 379.0529. $[\alpha]^{20}_D$ (*c* 1.0, CHCl$_3$): –7.77.



Synthesis of (5*S*,7*R*,8*S*)-8-bromo-7-phenyl-1,6-dioxaspiro[4.5]decane I-113: Compound **I-113** was synthesized from compound **I-149** (30.2 mg, 0.100 mmol) and DBDMH (34.3 mg, 0.120 mmol) using catalyst (*S*)-**(3I)$_2$-D** (17.8 mg, 0.0100 mmol) according to GP VIII. The diastereomeric ratio of the crude mixture was determined to be >98:2 by ^{1}H-NMR. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **I-113** was obtained in 90% (22.9 mg, 0.0900 mmol) isolated yield. The enantiomeric ratio of compound **I-113** (88:12) was determined by chiral HPLC (OT (+) column, 99.4:0.6 hexane/2-propanol at 215 nm, flow-rate: 0.3 mL/min). R_f: 0.25 (95:5, hexane: ethyl acetate).

Spectral data for I-113: ^{1}H NMR (500 MHz, $CDCl_3$^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.8 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 4.89 (d, *J* = 10.4 Hz, 1H), 4.00 – 3.93 (m, 2H), 3.93 – 3.86 (m, 1H), 2.51 (tdd, *J* = 13.4, 12.0, 4.2 Hz, 1H), 2.41 (dtd, *J* = 12.9, 4.5, 2.8 Hz, 1H), 2.09 (td, *J* = 13.7, 4.5 Hz, 1H), 2.04 – 1.93 (m, 2H), 1.92 – 1.82 (m, 2H), 1.80 – 1.71 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.39, 128.49, 125.24, 125.07, 106.41, 77.08, 67.70, 51.69, 37.35, 35.27, 32.71, 23.76. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.55. IR (cm^{-1}): 3010, 1450, 1272, 1260, 764, 682. HRMS: TOF MS AP$^+$ ($C_{15}H_{17}F_3BrO_2$): Calc. [M + H]$^+$: 365.0364, Found [M + H]$^+$: 365.0367. $[\alpha]^{20}_D$ (*c* 1.0, $CHCl_3$): –22.79.

Procedure for the synthesis of THP-protected Weinreb amide:



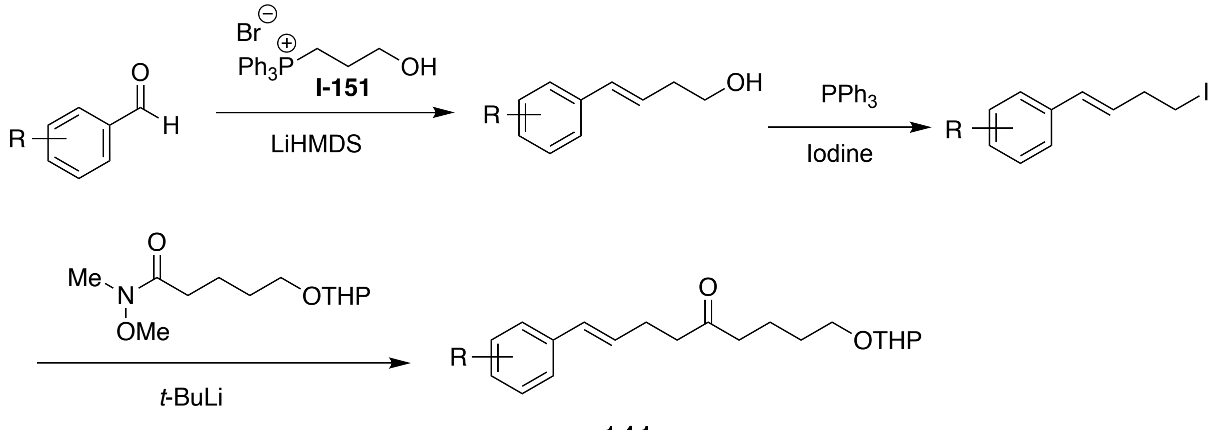
I-150

A flame dried round bottom flask was charged with N,O-dimethyl hydroxyl amine hydrochloride (6.00 g, 61.5 mmol) in dry DCM (60 mL). To this suspension, triethyl aluminum (1.0 M in heptane, 60.0 mL, 60.0 mmol) was added dropwise at –10 °C. The resulting mixture was stirred at rt for 30 min and then subsequently cooled down to –10 °C followed by the addition of a solution of δ-valerolactone (2.00 g, 20.0 mmol) in dry DCM (10 mL). The reaction mixture was gradually warmed up to rt and stirred for an additional 20 h before being quenched by a slow dropwise addition of sodium bicarbonate (1 M, 100 mL) at 0 °C. The aqueous layer was extracted with DCM (5 X 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude alcohol was used in the next step without further purification.

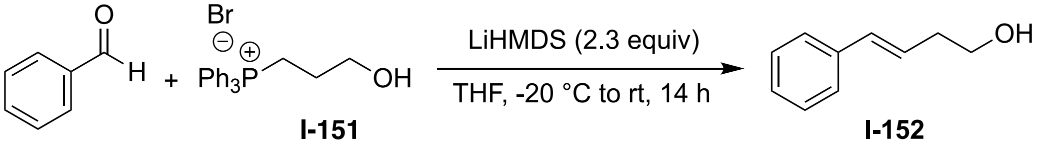
In a clean dry 250 mL rb flask was added the crude alcohol along with *p*-toluenesulfonic acid (p-TsOH, 100 mg, 3 mol%) and 3,4-dihydropyran (DHP, 2.00 mL, 22.0 mmol) in dry DCM (100 mL) at 0 °C under inert atmosphere. The reaction mixture was then warmed up to rt and stirred for 36 h. The crude reaction mixture was concentrated under reduced pressure and purified using column chromatography [50 mm X 300 mm silica gel, ethyl acetate: hexanes (3:7)] to furnish the THP-protected Weinreb amide **I-150** as a colorless oil (2.6 g, 53% yield).

Spectral data for I-150: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (dd, *J* = 4.4, 2.8 Hz, 1H), 3.87 – 3.79 (m, 1H), 3.74 (dt, *J* = 9.6, 6.5 Hz, 1H), 3.65 (s, 3H), 3.51 – 3.42 (m, 1H), 3.38 (dt, *J* = 9.7, 6.3 Hz, 1H), 3.15 (s, 3H), 2.43 (t, *J* = 7.5 Hz, 2H), 1.90 – 1.74 (m, 2H), 1.73 – 1.58 (m, 4H), 1.57 – 1.44 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.8, 69.4, 67.2, 62.2, 61.2, 30.7, 29.4, 25.5, 22.3, 21.4, 19.6, 19.1. TOF MS ES$^+$ ($C_{12}H_{23}NNaO_4$): Calc. [M + Na]$^+$: 268.1525, found [M + Na]$^+$: 268.1548. These spectral data are in agreement with the literature values. [53, 59]

General Scheme for the synthesis of Substrates (Scheme A):

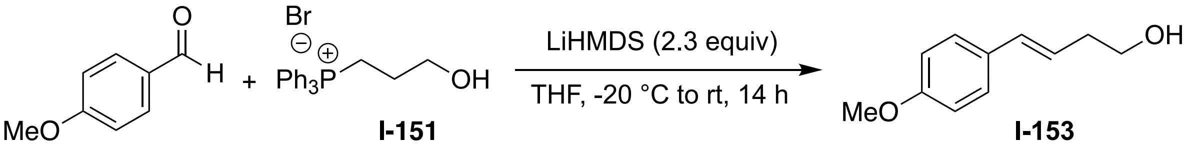


General Procedure for the synthesis of but-3-en-1-ol derivatives (GP IX):

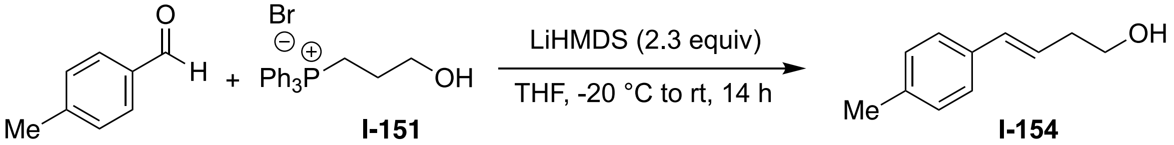


Synthesis of (E)-4-phenylbut-3-en-1-ol (I-152): A flame-dried round bottom flask was charged with (3-propan-1-ol)triphenylphosphonium bromide **I-151** (7.23 g, 18.0 mmol, 1.20 equiv) in dry THF (70.0 mL). The resulting suspension was cooled down to –20 °C, followed by the dropwise addition of LiHMDS (1.0 M in THF, 35.0 mL, 35.0 mmol). To this solution at –20 °C, benzaldehyde (15.0 mmol, 1.00 equiv) was added and stirred at –20 °C for 2 h and at rt for an additional 12 h. The reaction mixture was quenched by adding saturated ammonium chloride solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 X 30 mL). The organic layers were combined and dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The resulting crude product was purified via column chromatography silica gel (50 mm X 300 mm, hexanes: ethyl acetate 9:1 to 4:1 as the eluent) to afford the corresponding alcohol **I-152** in 48% isolated yield (1.07 g, 7.20 mmol).

Spectral data for I-152: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.31 – 7.26 (m, 2H), 7.23 – 7.16 (m, 1H), 6.49 (d, J = 15.9, 1H), 6.19 (dt, J = 15.8, 7.1 Hz, 1H), 3.74 (t, J = 6.3 Hz, 2H), 2.48 (dt, J = 7.6, 6.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 137.1, 132.7, 128.5, 127.2, 126.1, 126.0, 62.0, 36.3. These spectral data are in agreement with the literature values. [53, 59]



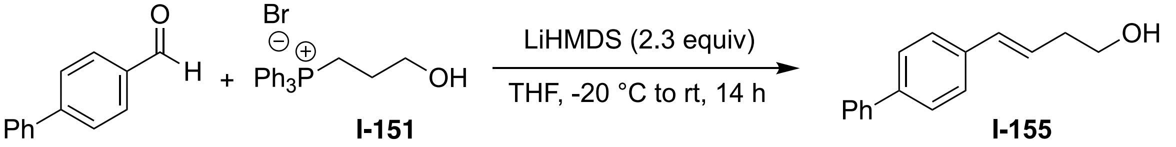
Synthesis of (E)-4-(4-methoxyphenyl)but-3-en-1-ol (I-153): Compound **I-153** was synthesized from compound 4-methoxybenzaldehyde (2.04 g, 15.0 mmol), LiHMDS (1.0 M in THF, 35.0 mL, 35.0 mmol) and (3-propan-1-ol)triphenylphosphonium bromide **I-151** (7.23 g, 18.0 mmol) according to GP IX. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 9:1 to 2:1 as the eluent). The desired compound **I-153** was obtained as a white solid in 60% isolated yield (9.20 mmol, 1.64 g). mp = 73–75°.



Spectral data for I-153: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.27 (d, *J* = 6.5 Hz, 2H), 6.82 (d, *J* = 6.5 Hz, 2H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.04 (dt, *J* = 16.0, 7.2 Hz, 1H), 3.79 (s, 3H), 3.72 (t, *J* = 6.5 Hz, 2H), 2.45 (td, *J* = 7.2, 6.5 Hz, 2H), 1.44 (s, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.9, 132.3, 130.0, 127.2, 124.0, 113.9, 62.1, 55.3, 36.4. These spectral data are in agreement with the literature values. [53, 59]

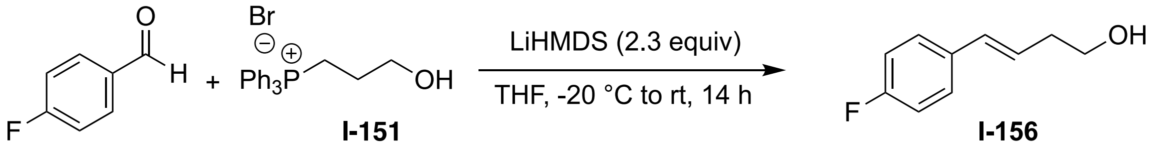
Synthesis of (E)-4-(p-tolyl)but-3-en-1-ol (I-154): Compound **I-154** was synthesized from compound 4-methylbenzaldehyde (1.8 g, 15 mmol, 1.0 equiv), LiHMDS (1.0 M in THF, 35.0 mL, 35.0 mmol) and (3-propan-1-ol)triphenyl phosphonium bromide **I-151** (7.23 g, 18.0 mmol, 1.2 equiv) according to the GP IX. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 9:1 to 4:1 as the eluent). The desired compound **I-154** was obtained as a white solid in 72% isolated yield (10.80 mmol, 1.75 g).

Spectral data for I-154: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.31 – 7.26 (m, 2H), 7.23 – 7.16 (m, 1H), 6.49 (d, J = 15.9 Hz, 1H), 6.19 (dt, J = 15.8, 7.1 Hz, 1H), 3.74 (t, J = 6.3 Hz, 2H), 2.48 (dt, J = 7.6, 6.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 137.1, 132.7, 128.5, 127.2, 126.1, 126.0, 62.0, 36.3. These spectral data are in agreement with the literature values. [53, 59]



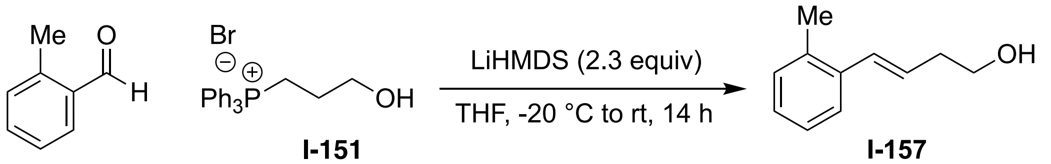
Synthesis of (E)-4-([1,1'-biphenyl]-4-yl) but-3-en-1-ol (I-155): Compound **I-155** was synthesized from compound biphenyl-4-carboxaldehyde (3.36 g, 15.0 mmol), LiHMDS (1.0 M in THF, 35.0 mL, 35.0 mmol) and (3-propan-1-ol)triphenylphosphonium bromide (7.23 g, 18.0 mmol) according to GP IX. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 9:1 to 2:1 as the eluent). The desired compound **I-155** was obtained as a white solid in 49% isolated yield (7.40 mmol, 1.66 g). mp = 132–133°.

Spectral data for I-155: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.56 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.43 – 7.40 (m, 4H), 7.34 – 7.30 (m, 1H), 6.53 (d, J = 15.9 Hz, 1H), 6.28 – 6.20 (dt, J = 15.9, 7.5 Hz, 1H), 3.76 (q, J = 6.0 Hz, 2H), 2.53 – 2.48 (m, 2H), 1.43 (t, J = 5.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7, 140.0, 136.2, 132.4, 128.8, 127.2, 127.2, 126.9, 126.5, 62.0, 36.5. These spectral data are in agreement with the literature values. [53, 59]



Synthesis of (E)-4-(2-fluorophenyl)but-3-en-1-ol (I-156): Compound **I-156** was synthesized from compound 4-fluorobenzaldehyde (1.86 g, 15.0 mmol), LiHMDS (1.0 M in THF, 35.0 mL, 35.0 mmol) and (3-propan-1-ol)triphenylphosphonium bromide **I-151** (7.23 g, 18.0 mmol) according to GP IX. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 9:1 to 2:1 as the eluent). The desired compound **I-156** was obtained in 62% isolated yield (9.33 mmol, 1.55 g).

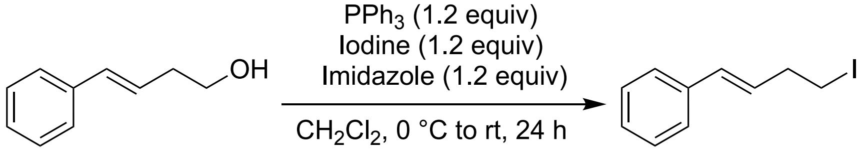
Spectral data for I-156: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.33 – 7.25 (m, 2H), 7.01 – 6.92 (m, 2H), 6.44 (d, J = 15.7 Hz, 1H), 6.10 (dt, J = 15.8, 7.2 Hz, 1H), 3.74 (t, J = 6.3 Hz, 2H), 2.49 – 2.39 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 162.1 (d, $J_{C\text{-}F}$ = 246.1 Hz), 133.4 (d, $J_{C\text{-}F}$ = 3.3 Hz), 131.6, 127.5 (d, $J_{C\text{-}F}$ = 8.0 Hz), 126.1 (d, $J_{C\text{-}F}$ = 2.3 Hz), 62.0, 36.3. These spectral data are in agreement with the literature values. [53, 59]



Synthesis of (E)-4-(o-tolyl)but-3-en-1-ol (I-157): Compound **I-157** was synthesized from compound *o*-tolualdehyde (1.80 g, 15.0 mmol), LiHMDS (1.0 M in THF, 35.0 mL, 35.0 mmol) and (3-propan-1-ol)triphenylphosphonium bromide **I-151** (7.23 g, 18.0 mmol) according to GP IX. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 9:1 to 2:1 as the eluent). The desired compound **I-157** was obtained as a white solid in 78% isolated yield (11.7 mmol, 1.90 g).

Spectral data for I-157: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 – 7.32 (m, 2H), 7.31 – 7.26 (m, 2H), 7.23 – 7.16 (m, 1H), 6.49 (d, J = 15.9 Hz, 1H), 6.19 (dt, J = 15.8, 7.1 Hz, 1H), 3.74 (t, J = 6.3 Hz, 2H), 2.48 (dt, J = 7.6, 6.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 137.1, 132.7, 128.5, 127.2, 126.1, 126.0, 62.0, 36.3. These spectral data are in agreement with the literature values. [53, 59]

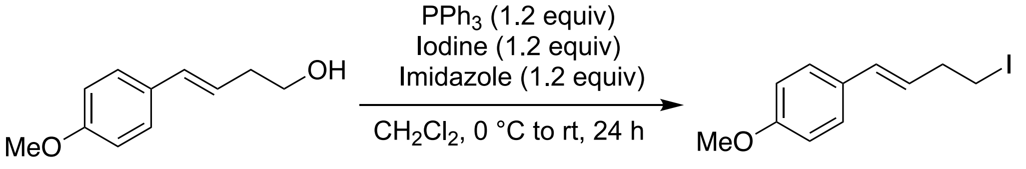
General Procedure for the synthesis of homoallylic iodine (GP X):



I-152 **I-158**

Synthesis of (E)-(4-iodobut-1-en-1-yl)benzene (I-158): Triphenylphosphine (1.57 g, 6.0 mmol), iodine (1.52 g, 6.0 mmol) and imidazole (408 mg, 6.0 mmol) were added to the solution of homoallylic alcohol **I-152** (0.74 g, 4.99 mmol) in dry DCM (30 mL) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 10 h. The reaction was quenched by adding water (15 mL), organic layer was separated, and the aqueous layer was extracted with DCM (3 X 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 19:1 as the eluent). The desired compound **I-158** was obtained in 80% isolated yield as a pale-yellow oil (3.99 mmol, 1.03 g).

Spectral data for I-158: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.29 (dd, J = 8.5, 6.8 Hz, 2H), 7.24 – 7.19 (m, 1H), 6.45 (d, J = 15.8 Hz, 1H), 6.13 (dt, J = 15.8, 7.0 Hz, 1H), 3.23 (t, J = 7.3 Hz, 2H), 2.77 (q, J = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.0, 132.3, 130.9, 128.6, 127.0, 126.2, 37.0, 5.1. These spectral data are in agreement with the literature values. [53, 59]

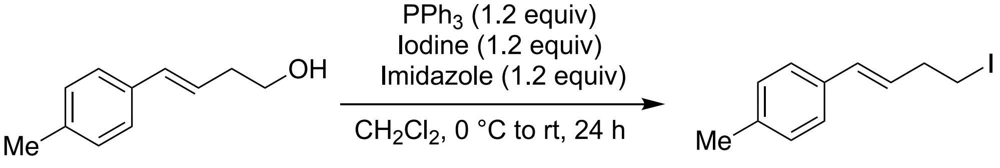


I-153

I-159

Synthesis of (E)-1-(4-iodobut-1-en-1-yl)-4-methoxybenzene (I-159): Compound **I-159** was synthesized from compound **I-153** (0.89 g, 5.0 mmol), triphenylphosphine (1.57 g, 6.00 mmol), iodine (1.52 g, 6.00 mmol) and imidazole (0.41 g, 6.00 mmol) according to GP X. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 19:1 as the eluent). The desired compound **I-159** was obtained as a pale-yellow oil in 92% isolated yield (4.62 mmol, 1.33 g).

Spectral data for I-159: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.89 – 6.78 (m, 2H), 6.39 (d, *J* = 15.8 Hz, 1H), 5.99 (dt, *J* = 15.7, 7.0 Hz, 1H), 3.79 (s, 3H), 3.21 (t, *J* = 7.3 Hz, 2H), 2.74 (q, *J* = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 131.6, 129.8, 127.3, 126.3, 114.0, 55.3, 37.1, 5.5. These spectral data are in agreement with the literature values. [53, 59]

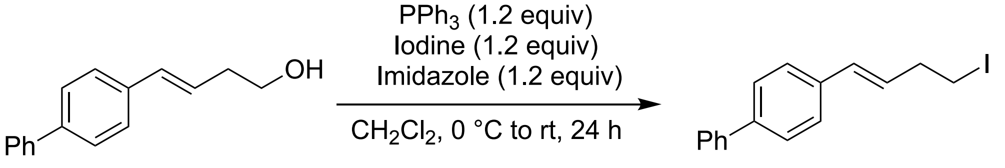


I-154

I-160

Synthesis of (E)-1-(4-iodobut-1-en-1-yl)-4-methylbenzene (I-160): Compound **I-160** was synthesized from compound **I-154** (0.81 g, 5.0 mmol), triphenyl phosphine (1.57 g, 6.00 mmol), iodine (1.52 g, 6.00 mmol) and imidazole (0.41 g, 6.0 mmol) according to GP X. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 19:1 as the eluent). The desired compound **I-160** was obtained as a colorless oil in 90% isolated yield (4.48 mmol, 1.22 g).

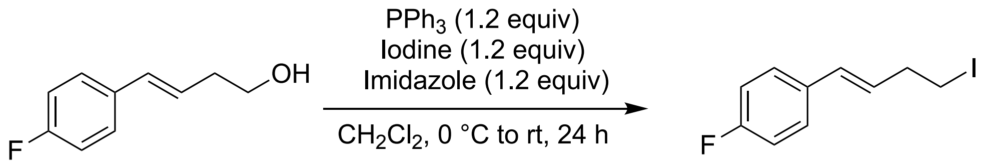
Spectral data for I-160: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.42 (d, *J* = 15.8, 1.5 Hz, 1H), 6.08 (dt, *J* = 15.8, 7.0 Hz, 1H), 3.22 (t, *J* = 7.3 Hz, 2H), 2.78 – 2.73 (dt, *J* = 7.3, 7.0 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 137.2, 134.2, 132.1, 129.3, 127.4, 126.0, 37.0, 21.2, 5.2. These spectral data are in agreement with the literature values. [53, 59]



I-155 **I-161**

Synthesis of (E)-4-(4-iodobut-1-en-1-yl)-1,1'-biphenyl (I-161): Compound **I-161** was synthesized from compound **I-155** (1.12 g, 5.00 mmol), triphenylphosphine (1.57 g, 6.00 mmol), iodine (1.52 g, 6.00 mmol) and imidazole (0.41 g, 6.0 mmol) according to GP X. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 19:1 as the eluent). The desired compound **I-161** was obtained as a colorless oil in 92% isolated yield (4.60 mmol, 1.54 g).

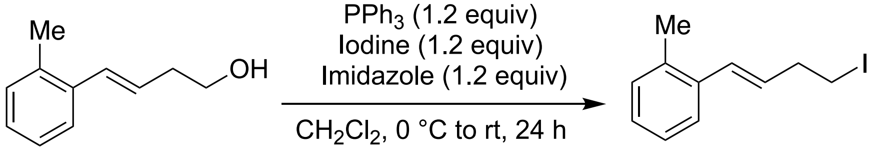
Spectral data for I-161: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.59 – 7.52 (m, 4H), 7.43 – 7.40 (m, 4H), 7.35 – 7.29 (m, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.18 (dt, *J* = 15.8, 7.0 Hz, 1H), 3.24 (t, *J* = 7.2 Hz, 2H), 2.79 (dt, *J* = 7.2, 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 140.7, 140.2, 136.1, 131.8, 128.8, 128.6, 127.3, 126.9, 126.6, 37.0, 5.1. These spectral data are in agreement with the literature values. [53, 59]



I-156 **I-162**

Synthesis of (E)-1-fluoro-4-(4-iodobut-1-en-1-yl)benzene (I-162): Compound **I-162** was synthesized from compound **I-156** (0.83 g, 5.0 mmol), triphenylphosphine (1.57 g, 6.00 mmol), iodine (1.52 g, 6.00 mmol) and imidazole (0.41 g, 6.0 mmol) according to GP X. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 19:1 as the eluent). The desired compound **I-162** was obtained as a colorless oil in 89% isolated yield (4.46 mmol, 1.23 g).

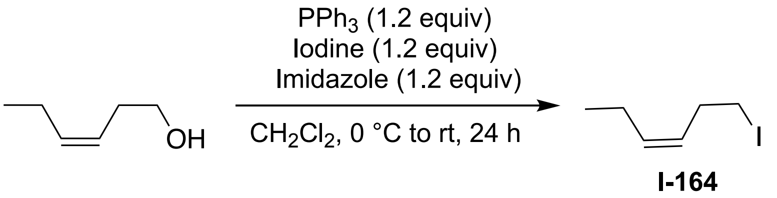
Spectral data for I-162: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.04 – 6.95 (m, 2H), 6.41 (d, *J* = 15.8 Hz, 1H), 6.04 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.22 (t, *J* = 7.2 Hz, 2H), 2.75 (q, *J* = 7.1 Hz, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2 (d, $J_{C\text{-}F}$ = 246.5 Hz), 133.2 (d, $J_{C\text{-}F}$ = 3.3 Hz), 131.1, 128.2 (d, $J_{C\text{-}F}$ = 2.3 Hz), 127.7 (d, $J_{C\text{-}F}$ = 8.1 Hz), 115.5 (d, $J_{C\text{-}F}$ = 21.7 Hz), 36.9, 5.1. These spectral data are in agreement with the literature values.[53, 59]



I-157 **I-163**

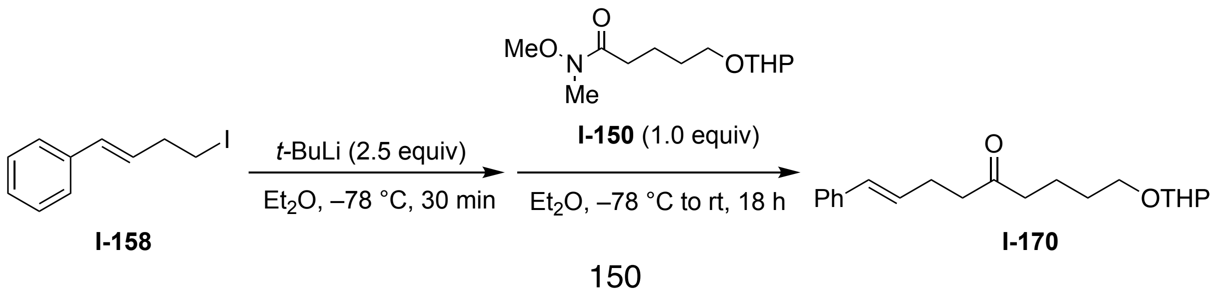
Synthesis of ((E)-1-(4-iodobut-1-en-1-yl)-2-methylbenzene (I-163): Compound **I-163** was synthesized from compound **I-157** (0.81 g, 5.0 mmol), triphenylphosphine (1.57 g, 6.00 mmol), iodine (1.52 g, 6.00 mmol) and imidazole (0.41 g, 6.0 mmol) according to GP X. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 19:1 as the eluent). The desired compound **I-163** was obtained as an oily liquid in 88% isolated yield (4.40 mmol, 1.19 g).

Spectral data for I-163: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.42 – 7.39 (m, 1H), 7.14 (m, 3H), 6.66 (d, *J* = 15.6 Hz, 1H), 5.99 (dt, *J* = 15.6, 7.0 Hz, 1H), 3.25 (t, *J* = 7.2 Hz, 2H), 2.78 (dt, *J* = 7.2, 7.0 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 136.3, 135.2, 130.3, 130.2, 129.8, 127.4, 126.1, 125.6, 37.2, 19.9, 5.4. These spectral data are in agreement with the literature values. [53, 59]



Synthesis of (Z)-6-iodohex-3-ene (I-164): Compound **I-164** was synthesized from compound *cis*-3-hexen-1-ol (1.20 mL, 10.0 mmol), triphenylphosphine (3.13 g, 12.0 mmol), iodine (3.03 g, 12.0 mmol) and imidazole (0.80 g, 12.0 mmol) according to GP X. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 19:1 as the eluent). The desired compound **I-164** was obtained in 74% isolated yield (1.56 g, 7.43 mmol) as a clear oil. Note: The final product is volatile, so it must be carefully dried under reduced pressure.

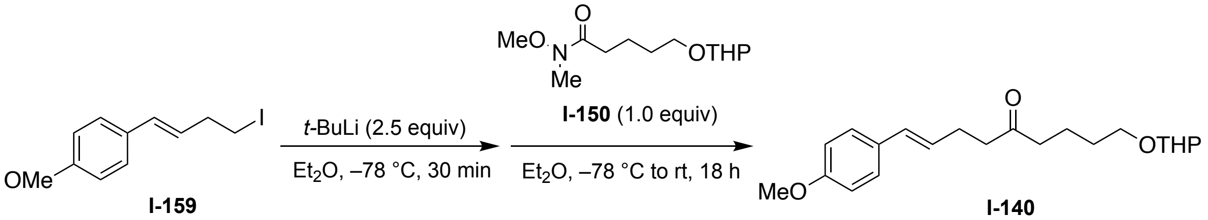
Spectral data for I-164: ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.54 (dt, *J* = 10.4, 7.3 Hz, 1H), 5.34 – 5.25 (m, 1H), 3.14 (t, *J* = 7.3 Hz, 2H), 2.69 – 2.58 (m, 2H), 2.10 – 2.00 (m, 2H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 134.29, 127.15, 31.42, 20.76, 14.18, 5.65. These spectral data are in agreement with the literature values. [118]



General Procedure for the synthesis of substrates (GP XI): [53, 59]

Synthesis of (*E*)-1-phenyl-9-((tetrahydro-2H-pyran-2-yl)oxy)non-1-en-5-one (I-70): In a 250 mL flame-dried round bottom flask **I-158** (1.29 g, 5.00 mmol) was dissolved in dry Et_2O (30 mL). The resulting solution was cooled down to –78 °C followed by dropwise addition of *t*-BuLi (1.7 M solution in pentane, 7.35 mL, 12.5 mmol) with subsequent stirring for 30 min at the same temperature. A solution of the Weinreb amide **I-150** (1.23 g, 5.00 mmol) in dry Et_2O (10 mL) was added over a period of 15 min. The reaction mixture was stirred at -78 °C for 30 min followed by gradual warm up to rt over a period of 2 h whereupon it was stirred for an additional 16 h. The reaction mixture was then transferred to an ice-bath where it was quenched by adding satd. NH_4Cl solution (15 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 4:1 as the eluent). The desired compound **I-70** was obtained as colorless oil in 75% isolated yield (3.76 mmol, 1.19 g).

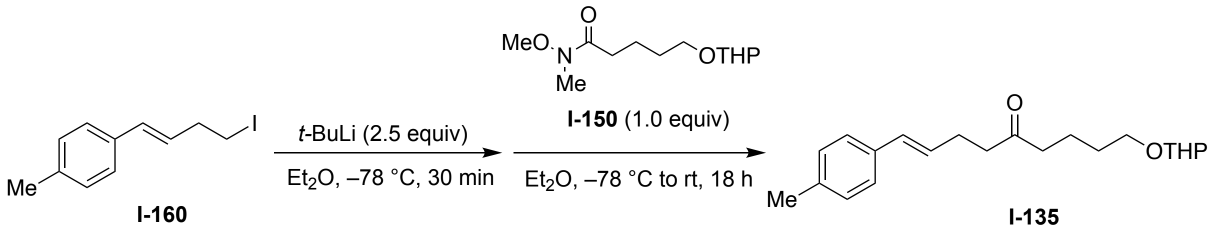
Spectral data for I-70: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.31 (m, 2H), 7.31-7.27 (m, 2H), 7.22 – 7.17 (m, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.19 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.56 (dd, *J* = 4.4, 2.7 Hz, 1H), 3.85 (m, 1H), 3.74 (dt, *J* = 9.7, 6.5 Hz, 1H), 3.54 – 3.44 (m, 1H), 3.38 (dt, *J* = 9.7, 6.3 Hz, 1H), 2.66 – 2.53 (m, 2H), 2.48 (dt, *J* = 9.4, 6.7 Hz, 4H), 1.85 – 1.77 (m, 1H), 1.75 – 1.65 (m, 4H), 1.64 – 1.47 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.08, 137.40, 130.68, 128.97, 128.49, 127.07, 125.99, 98.87, 67.15, 62.35, 42.64, 42.23, 30.73, 29.23, 27.12, 25.46, 20.64, 19.65. IR (cm^{-1}): 3100, 3011, 2900, 1707, 1545, 1525, 1440, 1263, 1176, 1081, 981, 749. TOF MS ES+ ($C_{20}H_{28}NaO_3$): Calc. [M + Na]+: 339.1936, Found [M + Na]+: 339.1923. These spectral data are in agreement with the literature values. [53, 59]



Synthesis of (*E*)-1-(4-methoxyphenyl)-9-((tetrahydro-2H-pyran-2-yl)oxy)non-1-en-5-one (I-140): Compound **I-140** was synthesized from compound **I-159** (1.44 g, 5.00 mmol), t-BuLi (1.7 M solution in pentane, 7.35 mL, 12.5 mmol), Weinreb amide **I-150** (1.23 g, 5.00 mmol) according to GP XI. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 4:1 as the eluent). The desired compound **I-140** was obtained as a colorless oil in 80% isolated yield (4.01 mmol, 1.39 g).

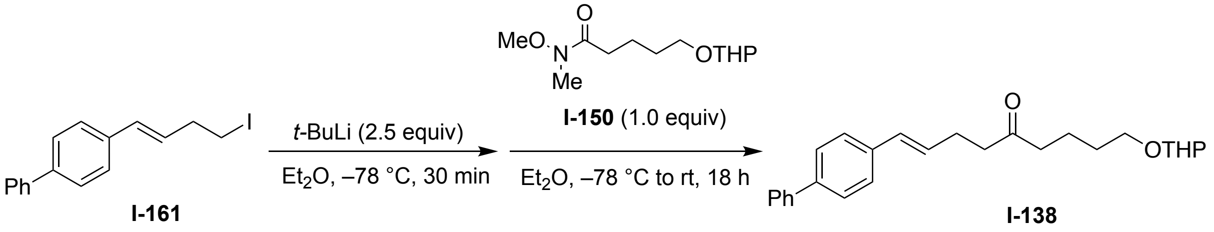
Spectral data for I-140: ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.32 (d, *J* = 15.9 Hz, 1H), 6.02 (dt, *J* = 15.7, 6.8 Hz, 1H), 4.54 (dd, *J* = 4.5, 2.7 Hz, 1H), 3.83 (ddd, *J* = 10.9, 7.7, 3.2 Hz, 1H), 3.77 (s, 3H), 3.72 (dt, *J* = 9.4, 6.4 Hz, 1H), 3.53 – 3.43 (m, 1H), 3.36 (dt, *J* = 9.5, 6.2 Hz, 1H), 2.55 (t, *J* = 7.3 Hz, 2H), 2.43 (qd, *J* = 7.2, 2.2 Hz, 4H), 1.79 (td, *J* = 8.4, 7.5, 3.9 Hz, 1H), 1.73 – 1.62 (m, 3H), 1.61 – 1.46 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.26, 158.85, 130.28, 130.08, 127.13, 126.79, 113.94, 98.90, 67.20, 62.38, 55.30, 42.67, 42.44, 30.78, 29.27, 27.19, 25.51, 20.68, 19.69.

IR (cm^{-1}): 3245, 3111, 3015, 2940, 2815, 1725, 1605, 1555, 1495, 1420, 1381, 1365, 1263, 1176, 979, 719. TOF MS ES$^+$ ($C_{21}H_{30}NaO_4$): Calc. [M + Na]$^+$: 369.2042, Found [M + Na]$^+$: 369.2060. These spectral data were in agreement with the literature values. [53, 59]



Synthesis of (*E*)-1-phenyl-9-((tetrahydro-2H-pyran-2-yl)oxy)non-1-en-5-one (I-135): Compound **I-135** was synthesized from compound **I-160** (1.36 g, 5.00 mmol), *t*-BuLi (1.7 M solution in pentane, 7.35 mL, 12.5 mmol), Weinreb amide **I-150** (1.23 g, 5.00 mmol) according to GP XI. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 4:1 as the eluent). The desired compound **I-135** was obtained as a colorless oil in 67% isolated yield (3.36 mmol, 1.11 g).

Spectral data for I-135: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.23 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.14 (dt, *J* = 15.6, 6.8 Hz, 1H), 4.57 (dd, *J* = 3.7, 2.2 Hz, 1H), 3.86 (td, *J* = 8.0, 7.6 Hz, 1H), 3.75 (dt, *J* = 9.5, 6.4 Hz, 1H), 3.52-3.48 (m, 1H), 3.39 (dt, *J* = 9.6, 6.3 Hz, 1H), 2.59 (t, *J* = 7.4 Hz, 2H), 2.47 (q, *J* = 6.7 Hz, 4H), 2.33 (s, 3H), 1.88 – 1.78 (m, 1H), 1.75 – 1.65 (m, 3H), 1.64 – 1.48 (m, 6H).^{13}C NMR (126 MHz, CDCl$_3$) δ 210.35, 136.81, 134.63, 130.52, 129.20, 127.90, 125.89, 98.88, 67.17, 62.36, 42.66, 42.34, 30.73, 29.24, 27.16, 25.47, 21.16, 20.64, 19.65. IR (cm^{-1}): 3011, 2910, 1695,

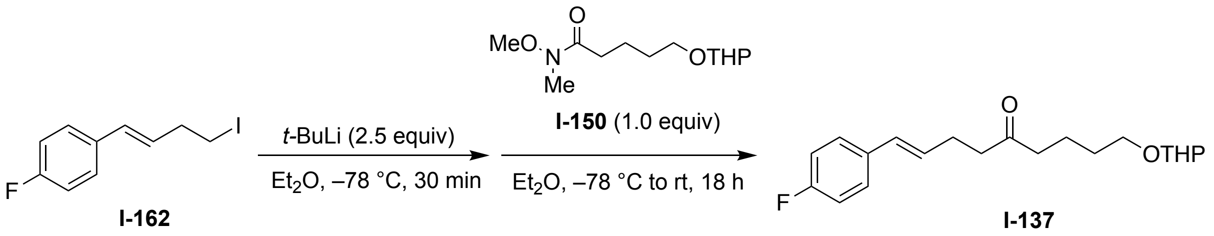


1505, 1425, 1203, 1100, 1030, 981, 885, 725. TOF MS ES$^+$ ($C_{21}H_{30}NaO_3$): Calc. [M + Na]$^+$: 353.2093, Found [M + Na]$^+$: 353.2107. These spectral data are in agreement with the literature values. [53, 59]

Synthesis of (*E*)-1-([1,1'-biphenyl]-4-yl)-9-((tetrahydro-2H-pyran-2-yl)oxy)non-1-en-5-one (I-138): Compound **I-138** was synthesized from compound **I-161** (1.67 g, 5.00 mmol), *t*-BuLi (1.7 M solution in pentane, 7.35 mL, 12.5 mmol), Weinreb amide (1.23 g, 5.00 mmol) according to GP XI. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 4:1 as the eluent). The desired compound **I-138** was obtained as an off-white solid in 66% isolated yield (3.31 mmol, 1.30 g). mp = 46 °C.

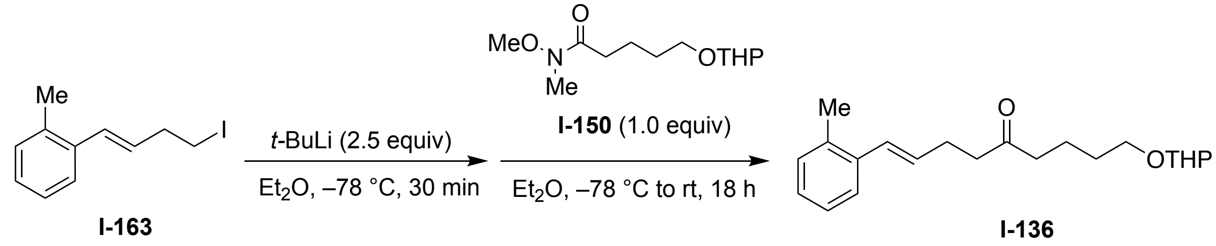
Spectral data for I-138: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.9, 7.0 Hz, 2H), 7.29 – 7.25 (m, 2H), 7.25 – 7.20 (m, 1H), 6.44 (d, *J* = 11.5 Hz, 1H), 5.59 (dt, *J* = 11.6, 7.1 Hz, 1H), 4.56 (dd, *J* = 4.5, 2.8 Hz, 1H), 3.85 (ddd, *J* = 11.0, 7.7, 2.9 Hz, 1H), 3.73 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.52 – 3.46 (m, 1H), 3.37 (dt, *J* = 9.7, 6.2 Hz, 1H), 2.61 (dtt, *J* = 8.1, 6.6, 1.6 Hz, 2H), 2.54 (ddd, *J* = 8.4, 6.7, 1.6 Hz, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 1.86 – 1.77 (m, 1H), 1.74 – 1.62 (m, 4H), 1.61 – 1.57 (m, 2H), 1.55 – 1.48 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.25, 137.35, 130.95, 129.98, 128.84, 128.35, 126.85, 99.01, 67.29, 62.49, 42.80, 42.64, 30.86, 29.34, 25.59, 23.00, 20.77, 19.78. IR (cm^{-1}): 3117, 3087, 3011, 2901, 1705, 1425, 1213, 1159, 885, 625. TOF MS ES$^+$ ($C_{26}H_{32}NaO_3$): Calc. [M + Na]$^+$: 415.2249, Found [M + Na]$^+$: 415.2264.

Synthesis of (*E*)-1-(4-fluorophenyl)-9-((tetrahydro-2H-pyran-2-yl)oxy)non-1-en-5-one (I-137): Compound **I-137** was synthesized from compound **I-162** (1.38 g, 5.00 mmol),



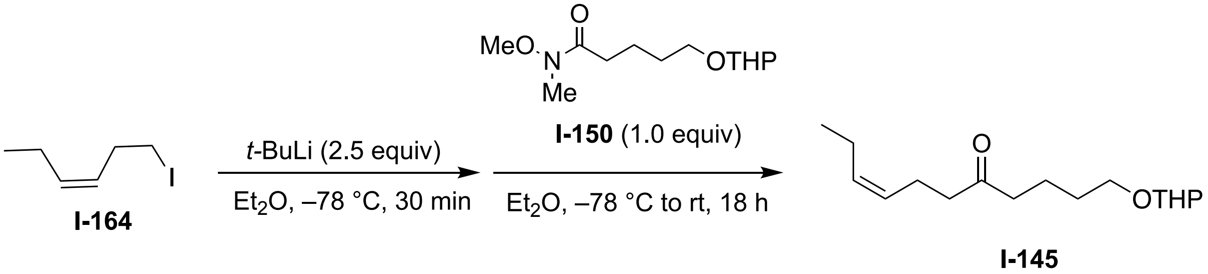
t-BuLi (1.7 M solution in pentane, 7.35 mL, 12.5 mmol), Weinreb amide (1.23 g, 5.00 mmol) according to GP XI. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 4:1 as the eluent). The desired compound **I-137** was obtained as a colorless oil in 68% isolated yield (3.41 mmol, 1.14 g).

Spectral data for I-137: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 6.99 – 6.93 (m, 2H), 6.35 (d, *J* = 15.8 Hz, 1H), 6.09 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.55 (dd, *J* = 4.5, 2.7 Hz, 1H), 3.84 (ddd, *J* = 11.0, 7.7, 3.2 Hz, 1H), 3.73 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.53 – 3.44 (m, 1H), 3.37 (dt, *J* = 9.6, 6.3 Hz, 1H), 2.57 (t, *J* = 7.3 Hz, 2H), 2.46 (t, *J* = 7.3 Hz, 4H), 1.84 – 1.77 (m, 1H), 1.73 – 1.64 (m, 3H), 1.62 – 1.46 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.13, 162.10 (d, $J_{C\text{-}F}$ = 246.0 Hz), 133.69 (d, $J_{C\text{-}F}$ = 3.3 Hz), 129.63, 128.83 (d, $J_{C\text{-}F}$ = 2.2 Hz), 127.55 (d, $J_{C\text{-}F}$ = 7.7 Hz), 115.53, 115.52, 115.36, 115.35, 99.00, 67.26, 62.48, 42.74, 42.28, 30.84, 29.33, 27.14, 25.56, 20.74, 19.76. IR (cm^{-1}): 3005, 2950, 1690, 1571, 1105, 930, 845. TOF MS ES$^+$ ($C_{20}H_{27}FNaO_3$): Calc. [M + Na]$^+$: 357.1842, Found [M + Na]$^+$: 357.1869.



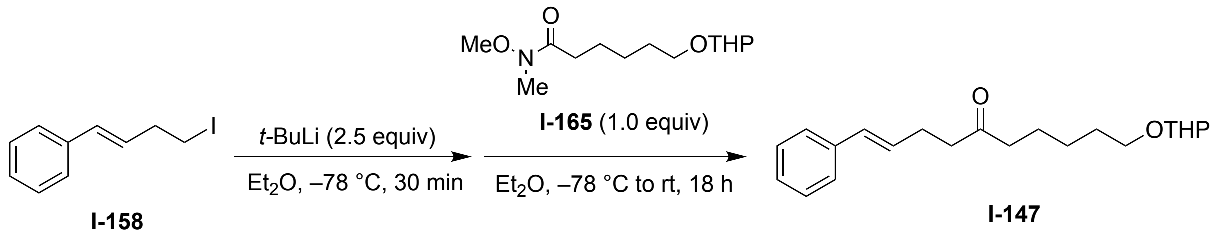
Synthesis of (*E*)-9-((tetrahydro-2H-pyran-2-yl)oxy)-1-(o-tolyl)non-1-en-5-one (I-136): Compound **I-136** was synthesized from compound **I-163** (1.36 g, 5.00 mmol), *t*-BuLi (1.7 M solution in pentane, 7.35 mL, 12.5 mmol), Weinreb amide **I-150** (1.23 g, 5.00 mmol) according to GP XI. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 4:1 as the eluent). The desired compound **I-136** was obtained as a colorless oil in 81% isolated yield (4.02 mmol, 1.33 g).

Spectral data for I-136: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.40 – 7.37 (m, 1H), 7.21 – 7.07 (m, 3H), 6.61 (dt, *J* = 15.8, 1.5 Hz, 1H), 6.06 (dt, *J* = 15.6, 6.8 Hz, 1H), 4.57 (dd, *J* = 4.5, 2.8 Hz, 1H), 3.86 (ddd, *J* = 11.0, 7.7, 3.2 Hz, 1H), 3.76 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.55 – 3.46 (m, 1H), 3.39 (dt, *J* = 9.6, 6.2 Hz, 1H), 2.61 (dd, *J* = 8.2, 6.9 Hz, 2H), 2.56 – 2.46 (m, 4H), 2.33 (s, 3H), 1.90 – 1.79 (m, 1H), 1.77 – 1.66 (m, 3H), 1.66 – 1.49 (m, 6H), . ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.2, 136.8, 134.6, 130.5, 129.2, 127.9, 125.9, 98.8, 67.1, 62.3, 42.6, 42.3, 30.7, 29.2, 27.1, 25.4, 21.1, 20.6, 19.6. IR (cm^{-1}): 3201, 3100, 2950, 2905, 1700, 1525, 1501, 1475, 1175, 930, 881, 858. TOF MS ES^{+} ($C_{21}H_{30}NaO_3$): Calc. [M + Na]$^{+}$: 353.2093, Found [M + Na]$^{+}$: 353.2099.



Synthesis of (*Z*)-1-((tetrahydro-2H-pyran-2-yl)oxy)undec-8-en-5-one (I-145): Compound **I-145** was synthesized from compound **I-164** (0.855 g, 4.07 mmol), *t*-BuLi (1.7 M solution in pentane, 6.00 mL, 10.2 mmol) and Weinreb amide **I-150** (1.00 g, 4.07 mmol) according to GP XI. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 4:1 as the eluent). The desired compound **I-145** was obtained in 73% yield (800 mg, 3.81 mmol) as a colorless oil.

Spectral data for I-145: ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.37 (dtd, *J* = 10.7, 7.2, 1.7 Hz, 1H), 5.25 (dtd, *J* = 10.7, 7.2, 1.7 Hz, 1H), 4.60 – 4.50 (m, 1H), 3.84 (tt, *J* = 8.3, 2.0 Hz, 1H), 3.73 (dtd, *J* = 9.6, 6.4, 1.6 Hz, 1H), 3.52 – 3.45 (m, 1H), 3.37 (dtd, *J* = 9.7, 6.2, 1.6 Hz, 1H), 2.43 (td, *J* = 7.5, 3.7 Hz, 4H), 2.29 (q, *J* = 7.4 Hz, 2H), 2.09 – 1.97 (m, 2H), 1.84 – 1.78 (m, 1H), 1.77 – 1.65 (m, 2H), 1.65 – 1.57 (m, 1H), 1.54 – 1.47 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.67, 132.91, 127.32, 98.98, 67.28, 62.46, 42.79, 42.72, 36.30, 30.84, 29.40, 29.34, 26.53, 25.58, 21.70, 20.86, 20.73, 20.59, 19.76, 19.73, 14.40. IR (cm^{-1}): 2885, 2835, 1693, 1435, 1065, 1007, 908. TOF MS ES$^+$ ($C_{16}H_{29}O_3$): Calc. [M + H]$^+$: 269.2118, Found [M + H]$^+$: 269.2178.

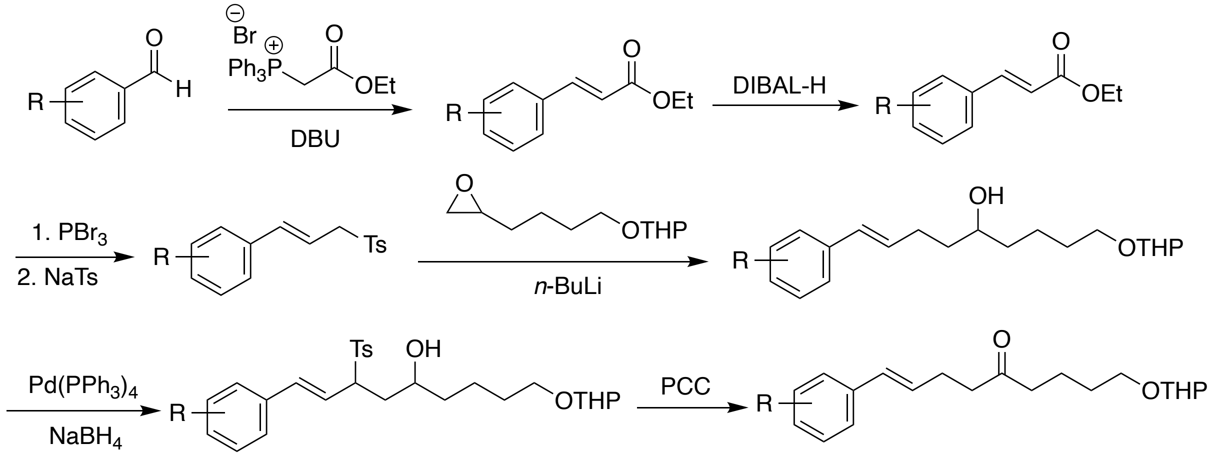


Synthesis of (*E*)-1-phenyl-10-((tetrahydro-2H-pyran-2-yl)oxy)dec-1-en-5-one (I-147): Compound **I-147** was synthesized from compound **I-158** (645 mg, 2.50 mmol), *t*-BuLi (1.7 M solution in pentane, 3.68 mL, 6.25 mmol) and amide **I-165** (648 mg, 2.50 mmol) according to GP XI. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 4:1 as the eluent). The desired compound **I-147** was obtained in 50% yield (416 mg, 1.26 mmol) as pale yellowish oil.

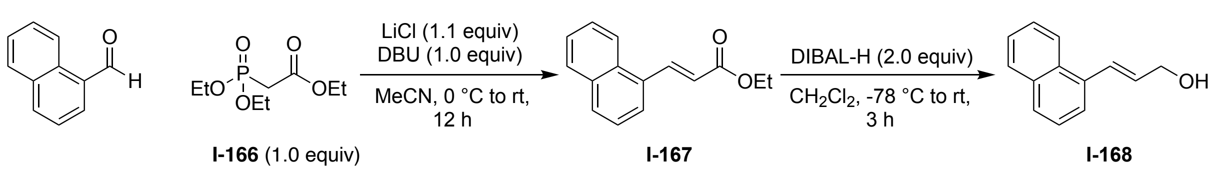
Spectral data for I-147: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 – 7.27 (m, 4H), 7.22 – 7.17 (m, 1H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.21 (ddt, *J* = 20.0, 15.8, 6.8 Hz, 1H), 4.57 (ddd, *J* =

12.5, 4.6, 2.8 Hz, 1H), 3.87 (dddd, *J* = 11.1, 9.3, 7.2, 3.2 Hz, 1H), 3.78 – 3.69 (m, 1H), 3.53 – 3.46 (m, 1H), 3.43 – 3.34 (m, 1H), 2.60 – 2.56 (m, 1H), 2.51 – 2.46 (m, 1H), 2.44 (t, *J* = 7.5 Hz, 1H), 2.34 – 2.22 (m, 1H), 1.82 (dqd, *J* = 11.1, 7.8, 7.4, 5.0 Hz, 1H), 1.75 – 1.68 (m, 2H), 1.66 – 1.61 (m, 2H), 1.61 – 1.58 (m, 2H), 1.55 – 1.49 (m, 4H), 1.44 – 1.30 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.26, 130.68, 128.98, 128.50, 127.07, 126.87, 125.99, 125.90, 98.92, 67.37, 62.43, 42.88, 30.76, 27.14, 25.92, 25.85, 25.47, 23.62, 19.72. IR (cm^{-1}): 3148, 3001, 2910, 1690, 1600, 1545, 1440, 1285, 1100, 1085, 901.TOF MS ES$^+$ ($C_{21}H_{31}O_3$): Calc. [M + H]$^+$: 331.2275, Found [M + H]$^+$: 331.2289.

General Scheme for the synthesis of Substrates (Scheme B):



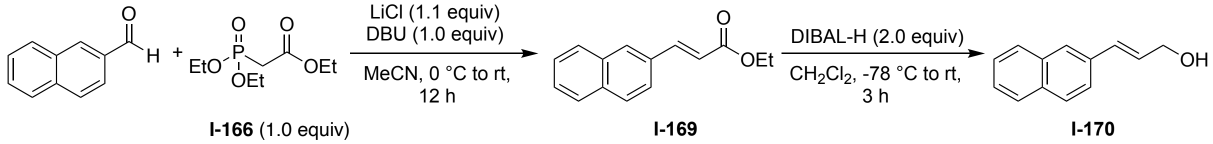
General Procedure for the synthesis of allyl alcohol (GP XII):



Synthesis of (E)-3-(naphthalen-1-yl)prop-2-en-1-ol (I-168): 1-Napthaldehyde (1.56 g, 10.0 mmol) and triethylphosphonoacetate **I-166** (2.24 g, 10.0 mmol) were added to a solution of lithium chloride (dried under vacuum, 0.466 g, 11.0 mmol) in dry acetonitrile at 0 °C followed by the addition of DBU (1.49 mL, 10.0 mmol) after 5 min. The reaction was brought up to room temperature and stirred for 12 h. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 9:1 as the eluent) giving an off-white solid **I-167** in quantitative yield (2.26 g, 10.0 mmol).

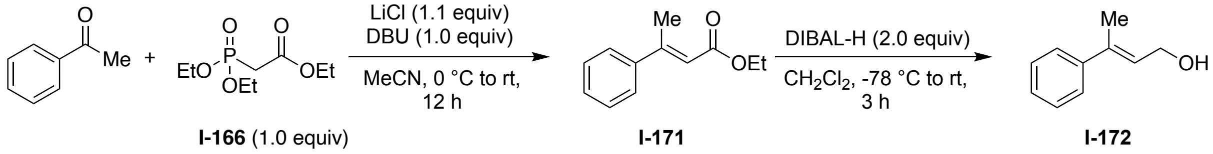
The resulting ester **I-167** was dissolved in dry DCM (20 mL) and cooled down to –78 ˚C followed by the addition of DIBAL-H (1.0 M in hexane, 20.0 mL, 20.0 mmol). The reaction mixture was warmed up to rt over a period of 2 h, where it was stirred for an additional hour. The reaction mixture was then transferred to an ice-bath where it was quenched by adding methanol (10.0 mL). Saturated potassium sodium tartrate solution (20.0 mL) was added to the solution and the mixture was stirred at room temperature for 2 h. The aqueous layer was extracted with DCM (3 X 30 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Crude reaction mixture was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 3:1 as the eluent) giving **I-168** as pale yellowish green oil in quantitative yield (1.8 g, 10 mmol).

Spectral data for I-168[53, 59] : ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.84 (dd, *J* = 7.5, 2 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.51-7.46 (m, 2H), 7.43 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.37 (d, *J* = 15.5 Hz, 1H), 6.38 (m, 1H), 4.42 (d, *J* = 5 Hz, 2H), 1.66 (br, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.4, 133.5, 131.7, 131.1, 128.5, 128.1, 127.9, 126.0, 125.7, 125.5, 123.8, 123.6, 63.9 ppm.



Synthesis of (E)-3-(naphthalen-2-yl)prop-2-en-1-ol (I-170): According to GP XII, compound **I-170** was synthesized from compound 2-naphthaldehyde (1.56 g, 10.0 mmol), lithium chloride (dried under vacuum, 0.466 g, 11.0 mmol), triethylphosphonoacetate **I-166** (2.24 g, 10.0 mmol) and DBU (1.49 mL, 10.0 mmol) to give a white solid in quantitative yield, which was then reduced with DIBAL-H (1.0 M in hexane, 20.0 mL, 20.0 mmol). Crude reaction mixture was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 3:1 as the eluent) that yielded a yellow oil **I-170** in quantitative yield (1.80 g, 10.0 mmol).

Spectral data for I-170: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80 (td, *J* = 5.6, 2.9 Hz, 3H), 7.74 (s, *J* = 1.2 Hz, 1H), 7.61 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.49 – 7.42 (m, 2H), 6.79 (d, *J* = 15.9, 1H), 6.51 (dt, *J* = 15.9, 5.7 Hz, 1H), 4.39 (d, *J* = 5.8, 2H), 1.52 (s, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 134.09, 133.56, 133.03, 131.27, 128.84, 128.25, 127.98, 127.67, 126.48, 126.29, 125.93, 123.53, 63.85. [53, 59]

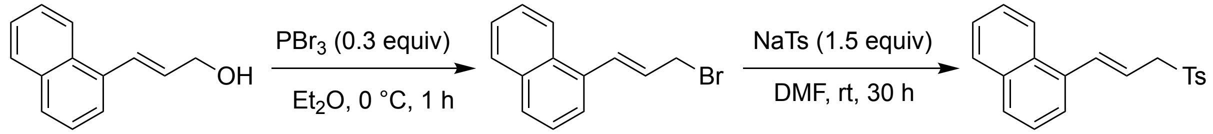


Synthesis of (E)-3-phenylbut-2-en-1-ol (I-172): Compound **I-172** was synthesized from acetophenone (1.20 g, 10.00 mmol), lithium chloride (dried under vacuum, 0.47 mg, 11 mmol), triethylphosphonoacetate (2.25 g, 10.0 mmol), DBU (1.49 mL, 10.0 mmol) and DIBAL-H (1.0 M in hexane, 20.0 mL, 20.0 mmol) according to GP XII. Crude reaction mixture was purified via column chromatography on silica gel (50 mm X 300 mm, hexane:

ethyl acetate, 3:1 as the eluent) yielding the allylic alcohol in 68% yield (1.01 g, 6.81 mmol) over 2 steps.

Spectral data for I-172: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 2H), 7.34 – 7.29 (m, 2H), 7.27 – 7.23 (m, 1H), 5.98 – 5.94 (m, 1H), 4.3 (d, J = 6.5 Hz, 2H), 2.08 – 2.06 (m, 3H), 1.73 (br, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.79, 137.73, 128.08, 127.21, 126.45, 125.71, 59.86, 15.95.

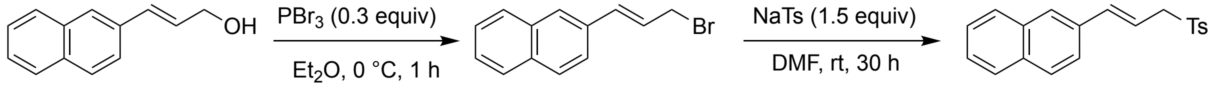
General Procedure for the synthesis of allyl sulfonyl (GP XIII):



I-168 **I-173** **I-174**

Synthesis of (E)-1-(3-tosylprop-1-en-1-yl)naphthalene (I-174): I-168 (3.00 g, 16.2 mmol) was dissolved in dry Et_2O (10 mL) followed by the dropwise addition of phosphorous tribromide (5.4 mmol, 0.51 mL) at 0 °C. The reaction mixture was stirred for 1 h and quenched by slow addition of satd. $NaHCO_3$ solution (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 X 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure (protected from light). The resulting crude allyl bromide **I-173** was quickly reacted with sodium *p*-toluenesulfinate (4.33 g, 24.3 mmol) in DMF (10 mL) at rt where it was stirred for 30 h before being quenched by adding satd. NH_4Cl solution (20 mL). The aqueous layer was extracted with ethyl acetate (3 X 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Crude allyl sulfonyl product **I-174** was purified by crystallization from ethyl acetate: hexane (1:1) at –20 °C to give an orangish white solid in overall yield of 79% (4.11 g, 12.7 mmol).

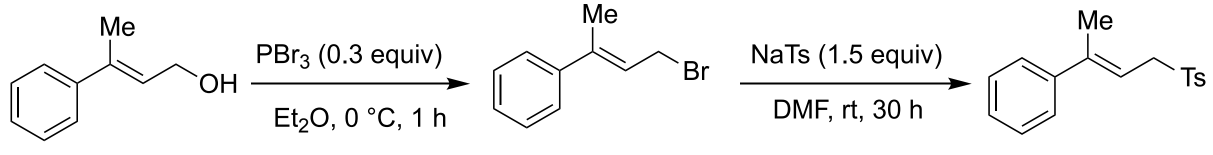
Spectral data for I-174: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 3H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.48-7.40 (m, 4H), 7.31 (d, *J* = 8.0, 2H), 7.05 (d, *J* = 15.0 Hz, 1H), 6.11 (m, 1H), 4.03 (d, *J* = 7.5 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 136.7, 135.2, 133.5, 133.4, 130.7, 129.7, 128.7, 128.6, 128.5, 126.1, 125.9, 125.5, 124.2, 123.4, 118.7, 60.7, 21.6 ppm.



I-170 **I-175**

Synthesis of (E)-2-(3-tosylprop-1-en-1-yl)naphthalene (I-175): Compound **I-175** was synthesized from compound **I-170** (2.95 g, 16.0 mmol), phosphorous tribromide (0.50 mL, 5.3 mmol) and sodium *p*-toluenesulfinate (4.28 g, 24.0 mmol) according to GP XIII giving the final recrystallized product in 59% yield (3.1 g, 9.6 mmol).

Spectral data for I-175: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75-7.79 (m, 5H), 7.63 (s, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.42-7.47 (m, 2H), 7.30 (d, *J* = 7.5 Hz, 2H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.21 (m, 1H), 3.97 (d, J = 7.5 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 139.0, 135.4, 133.3, 133.28, 133.21, 129.7, 128.5, 128.3, 128.0, 127.6, 127.0, 126.4, 126.3, 123.2, 115.5, 60.6, 21.6 ppm.

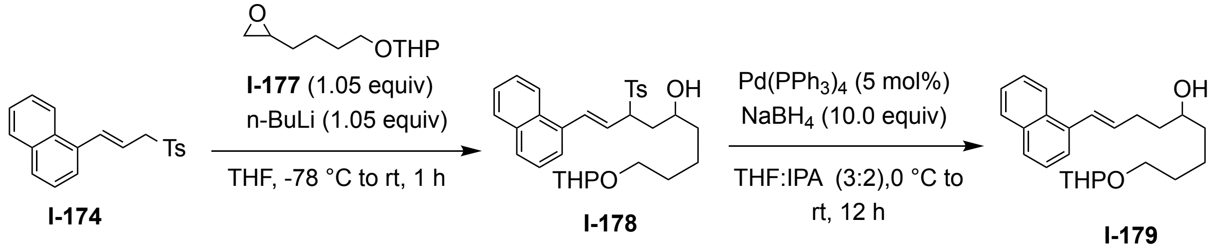


I-172 **I-176**

Synthesis of (E)-1-methyl-4-((3-phenylbut-2-en-1-yl)sulfonyl)benzene (I-176): Compound **I-176** was synthesized from compound **I-172** (2.37 g, 16.00 mmol), phosphorous tribromide (0.5 mL, 5.3 mmol) and sodium *p*-toluenesulfinate (4.28 g, 24.0 mmol) according to GP XIII giving the final recrystallized product in 66% yield (3.02 g, 10.5 mmol). [53, 59]

Spectral data for I-176: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.76 – 7.74 (m, 2H), 7.31 – 7.24 (m, 7H), 5.71 – 5.69 (t, *J* = 8.0 Hz, 1H), 3.97 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 144.65, 144.34, 142.24, 135.69, 129.67, 128.51, 128.33, 127.83, 125.81, 113.40, 56.72, 21.63, 15.98.

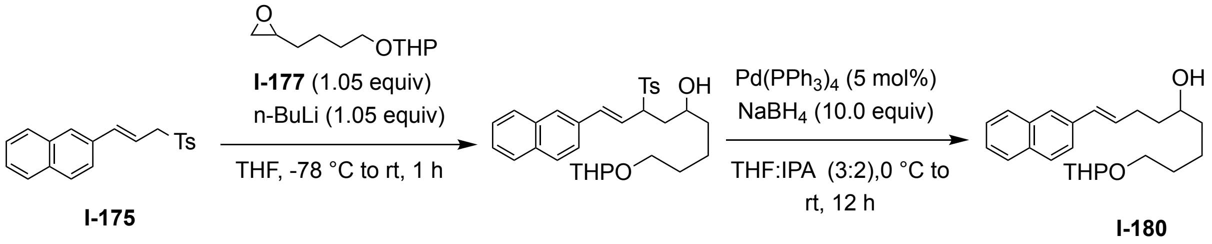
General Procedure for the synthesis of alcohol S-40a-c (GP XIV):



Synthesis of (E)-1-(naphthalen-1-yl)-9-((tetrahydro-2H-pyran-2-yl)oxy)non-1-en-I-179: A flame-dried round bottom flask was charged with allyl sulfonyl substrate **I-174** (0.64 g, 2.0 mmol) in dry THF (3 mL). The resulting solution was cooled down to –78 °C followed by the dropwise addition of *n*-BuLi (1.8 M in hexane, 1.2 mL, 2.1 mmol) and stirred for 15 min. A solution of the THP-protected epoxyalcohol **I-177** (421 mg, 2.10 mmol) in dry THF (1.0 mL) was added via a syringe over 5 minutes. Once the addition was complete, the reaction mixture was warmed up to rt and stirred for an hour. After completion of the reaction, it was quenched by adding satd. NH$_4$Cl solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified via column chromatography yielding **I-178** ~1:1 diastereomeric mixture in 82% yield (860 mg, 1.64 mmol), which was taken to the next step without further.

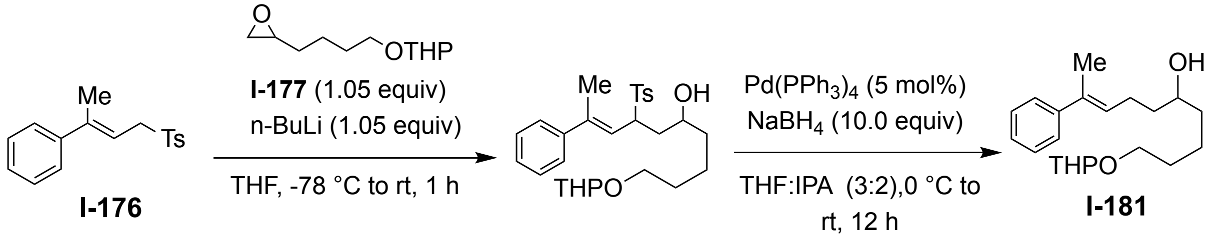
Sulfonyl alcohol **I-178** (0.78 g, 1.5 mmol) was dissolved in a mixture of THF:IPA (3:2, 20 mL) under an argon atmosphere and was treated with tetrakis(triphenylphosphine)palladium (86.7 mg, 0.075 mmol) at rt. The resulting solution was cooled down to 0 ºC and sodium borohydride (0.57 g, 15 mmol) was added in 4 portions. The reaction was stirred at room temperature for 12 h and quenched by careful addition of water (10 mL) at 0 °C. The aqueous layer was extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Crude reaction mixture was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 2:1 as the eluent) yielding alcohol **I-179** in 48% yield (265 mg, 0.720 mmol). [53, 59]

Spectral data for I-179: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 8.07 (m, 1H), 7.83 – 7.79 (m, 1H), 7.75 – 7.70 (m, 1H), 7.53 (d, J = 7.1 Hz, 1H), 7.50 – 7.38 (m, 3H), 7.21 – 7.10 (m, 1H), 6.23 (dt, *J* = 15.5, 6.9 Hz, 1H), 4.58 – 4.51 (m, 1H), 3.89 – 3.82 (m, 1H), 3.79 – 3.65 (m, 2H), 3.52 – 3.44 (m, 1H), 3.38 (m, 1H), 2.55 – 2.32 (m, 2H), 1.81 (d, *J* = 8.7 Hz, 1H), 1.75 – 1.39 (m, 14H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.52, 133.83, 128.49, 127.37, 127.32, 125.86, 125.68, 123.92, 123.56, 98.99, 67.58, 67.55, 62.46, 37.36, 37.34, 37.01, 36.29, 30.79, 29.77, 25.49, 22.41, 19.72.



Synthesis of (E)-1-(naphthalen-2-yl)-9-((tetrahydro-2H-pyran-2-yl)oxy)non-1-en-5-ol (I-180): Compound **I-180** was synthesized from compound **I-175** (0.64 g, 2.00 mmol), *n*-BuLi (1.8 M in hexane, 1.2 mL, 2.1 mmol), **I-177** (421 mg, 2.10 mmol), tetrakis(triphenylphosphine)palladium (116 mg, 0.100 mmol) and sodium borohydride (0.76 g, 20 mmol) according to GP XIV. Crude reaction mixture was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 2:1 as the eluent) yielding generating the final alcohol in 61% isolate yield (450 mg, 1.22 mmol) over 2 steps. 53, 59

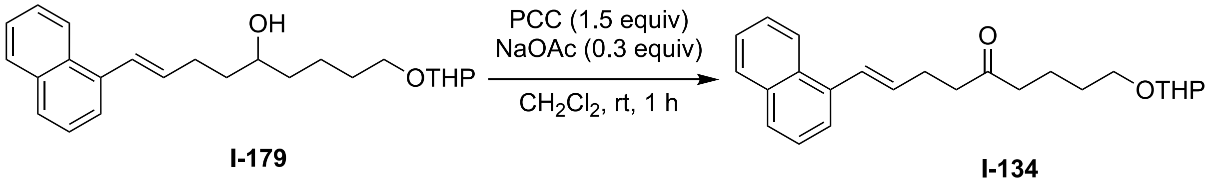
Spectral data for I-180: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.73 (m, 3H), 7.65 (s, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.44 – 7.37 (m, 2H), 6.60 – 6.53 (m, 1H), 6.35 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.55 (dd, *J* = 4.6, 2.8 Hz, 1H), 3.89 – 3.81 (m, 1H), 3.77 – 3.66 (m, 2H), 3.54 – 3.43 (m, 2H), 3.39 (dt, *J* = 9.7, 6.4 Hz, 1H), 2.38 (m, 2H), 1.88 – 1.75 (m, 2H), 1.73 – 1.37 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.13, 133.69, 132.69, 130.94, 128.09, 127.84, 127.63, 126.16, 125.52, 123.52, 98.99, 67.55, 62.46, 37.33, 36.98, 30.78, 29.70, 29.47, 25.48, 22.43, 19.74.



Synthesis of (E)-9-phenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)dec-8-en-5-ol (I-181): Compound **I-181** was synthesized from compound **I-176** (0.57 g, 2.00 mmol), *n*-BuLi (1.8 M in hexane, 1.2 mL, 2.1 mmol), **I-177** (421 mg, 2.10 mmol), tetrakis(triphenylphosphine)palladium (116 mg, 0.100 mmol) and sodium borohydride (0.76 g, 20 mmol) according to GP XIV. Crude reaction mixture was purified via column chromatography on silica gel (50 mm X 300 mm, hexane: ethyl acetate, 2:1 as the eluent) giving the final product in 35% yield (233 mg, 0.701 mmol). [53, 59]

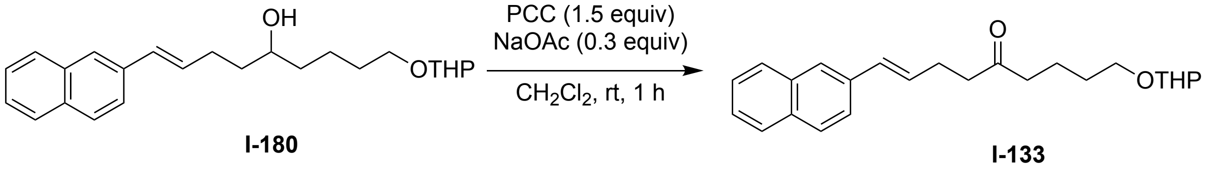
Spectral data for I-181: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.34 (m, 2H), 7.29 – 7.26 (m, 2H), 7.20 – 7.18 (m, 1H), 5.78(t, *J* = 7.5 Hz, 1H), 4.56 (m, 1H), 3.86 – 3.83 (m, 1H), 3.77 – 3.72 (m, 1H), 3.66 (m, 1H), 3.50 – 3.47 (m, 1H), 3.41 – 3.37 (m, 1H), 2.34 – 2.27 (m, 2H), 2.04 (s, 3H), 1.81 – 1.78 (m, 1H), 1.71 – 1.66 (m, 1H), 1.63 – 1.43 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.81, 135.15, 128.12, 127.88, 126.52, 125.56, 98.92, 71.46, 67.48, 62.37, 37.31, 37.14, 30.75, 29.66, 25.46, 25.06, 22.40, 19.66, 15.78.

General Procedure for the synthesis of olefinic ketones (GP XV):



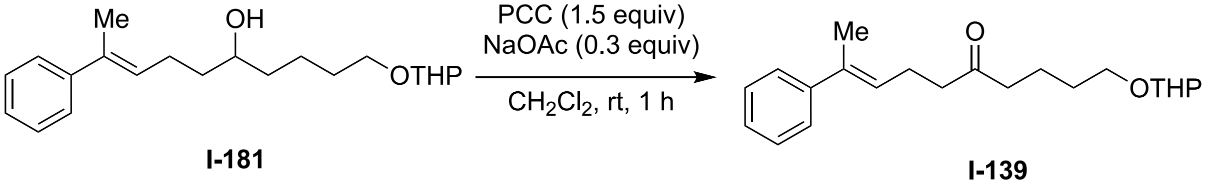
Synthesis of (E)-1-(naphthalen-1-yl)-9-((tetrahydro-2H-pyran-2-yl)oxy)non-1-en-5-one (I-134): In a 20 mL screw-top vial alcohol **I-179** (0.37 g, 1.0 mmol) was dissolved in DCM (5 mL) to which pyridinium chlorochromate (0.32 mg, 1.5 mmol) and sodium acetate (25 mg, 0.30 mmol) were added at rt and stirred for an hour. The crude mixture was diluted with DCM (10 mL) and the precipitates were removed by passing the mixture through a celite pad. Volatiles were removed and the resulting crude ketone was purified via column chromatography on silica gel (50 mm X 300 mm, ethyl acetate : hexanes = 1:4) in 82% yield (301 mg, 0.821 mmol). [53, 59]

Spectral data for I-134: ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.13 – 8.07 (m, 1H), 7.85 – 7.81 (m, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.54 – 7.51 (m, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.44 – 7.40 (m, 1H), 7.15 (d, *J* = 15.5 Hz, 1H), 6.20 (dt, *J* = 15.5, 6.6 Hz, 1H), 4.55 (dt, *J* = 5.7, 2.7 Hz, 1H), 3.84 (td, *J* = 8.3, 3.9 Hz, 1H), 3.75 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.54 – 3.45 (m, 1H), 3.38 (dt, *J* = 9.8, 6.4 Hz, 1H), 2.71 – 2.64 (m, 2H), 2.65 – 2.58 (m, 2H), 2.51 (t, *J* = 7.3 Hz, 2H), 1.85 – 1.77 (m, 1H), 1.74 – 1.66 (m, 3H), 1.66 – 1.44 (m, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.10, 132.27, 128.47, 127.98, 127.50, 125.89, 125.69, 125.63, 123.84, 123.60, 98.89, 67.17, 62.36, 42.72, 42.29, 30.74, 29.25, 27.57, 25.46, 20.68, 19.66. TOF MS ES$^+$ ($C_{24}H_{30}NaO_3$): Calc. [M + Na]$^+$: 389.2193, Found [M + Na]$^+$: 389.2119.



Synthesis of (E)-1-(naphthalen-2-yl)-9-((tetrahydro-2H-pyran-2-yl)oxy)non-1-en-5-one (I-133): Compound **I-133** was synthesized from compound **I-180** (0.37 g, 1.0 mmol), pyridinium chlorochromate (0.32 mg, 1.5 mmol) and sodium acetate (25 mg, 0.30 mmol) according to GP XV. Volatiles were removed and the resulting crude ketone was purified via column chromatography on silica gel (50 mm X 300 mm, ethyl acetate : hexanes = 1:4) in 80% isolated yield (293 mg, 0.799 mmol). [53, 59]

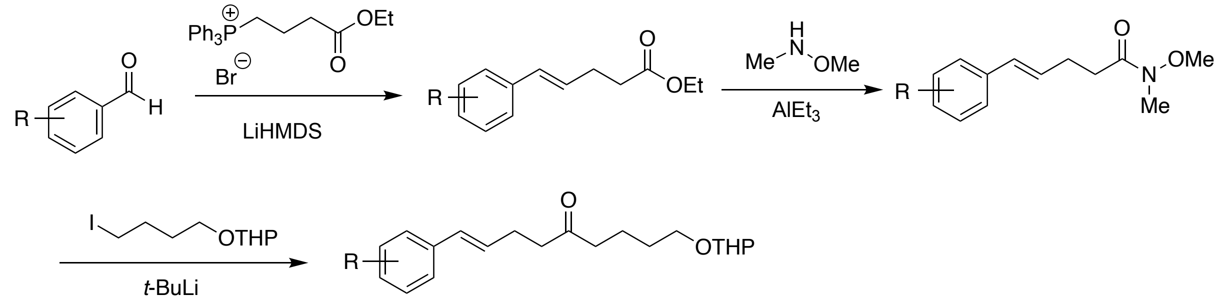
Spectral data for I-133: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.81 – 7.74 (m, 3H), 7.67 (s, 1H), 7.55 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.47 – 7.37 (m, 2H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.33 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.56 (t, *J* = 3.6 Hz, 1H), 3.89 – 3.82 (m, 1H), 3.75 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.48 (dd, *J* = 11.1, 5.2 Hz, 1H), 3.38 (dt, *J* = 9.6, 6.3 Hz, 1H), 2.63 (t, *J* = 7.4 Hz, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.49 (t, *J* = 7.3 Hz, 2H), 1.85 – 1.77 (m, 1H), 1.74 – 1.65 (m, 3H), 1.65 – 1.57 (m, 3H), 1.55 – 1.46 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.28, 135.01, 133.77, 132.88, 130.96, 129.58, 128.23, 127.99, 127.76, 126.31, 125.72, 123.60, 99.03, 67.31, 62.51, 53.58, 42.82, 42.40, 30.87, 29.38, 27.39, 25.59, 20.80, 19.79, 14.28. TOF MS ES$^+$ ($C_{24}H_{30}NaO_3$): Calc. [M + Na]$^+$: 389.2193, Found [M + Na]$^+$: 389.2209.



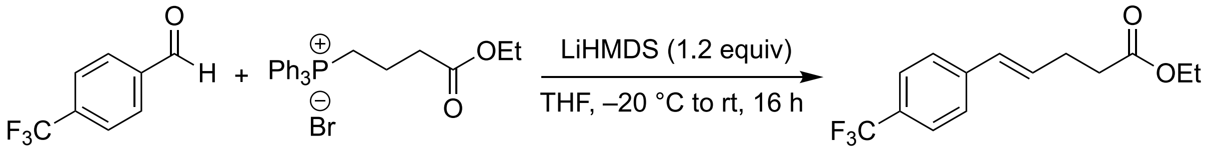
Synthesis of (E)-9-phenyl-1-((tetrahydro-2*H*-pyran-2-yl)oxy)dec-8-en-5-one (I-139): Compound **I-139** was synthesized from compound **I-181** (0.33 g, 1.0 mmol), pyridinium chlorochromate (0.32 mg, 1.5 mmol) and sodium acetate (25 mg, 0.30 mmol) according to GP XV. Volatiles were removed and the resulting crude ketone was purified via column chromatography on silica gel (50 mm X 300 mm, ethyl acetate : hexanes = 1:4) in 68% isolated yield (225 mg, 0.681 mmol). [53, 59]

Spectral data for I-139: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 – 7.32 (m, 2H), 7.29 – 7.24 (m, 2H), 7.20 – 7.18 (m, 1H), 5.67 (t, *J* = 6.5 Hz, 1H), 4.54 (m, 1H), 3.84 – 3.80 (m, 1H), 3.74 – 3.70 (m, 1H), 3.49 – 3.46 (m, 1H), 3.38 – 3.33 (m, 1H), 2.53 (t, *J* = 6.5 Hz, 2H), 2.46 – 2.43 (m, 4H), 2.02 (s, 3H), 1.80 – 1.76 (m, 1H), 1.70 – 1.63 (m, 3H), 1.60 – 1.51 (m, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.36, 143.61, 135.80, 128.14, 126.65, 126.46, 125.59, 98.85, 67.13, 62.32, 42.61, 42.35, 30.71, 29.22, 25.44, 23.12, 20.64, 19.62, 15.79. TOF MS ES$^+$ ($C_{21}H_{31}O_3$): Calc. [M + H]$^+$: 331.2275, Found [M + H]$^+$: 331.2209.

General Scheme for the synthesis of Substrates (Scheme B):



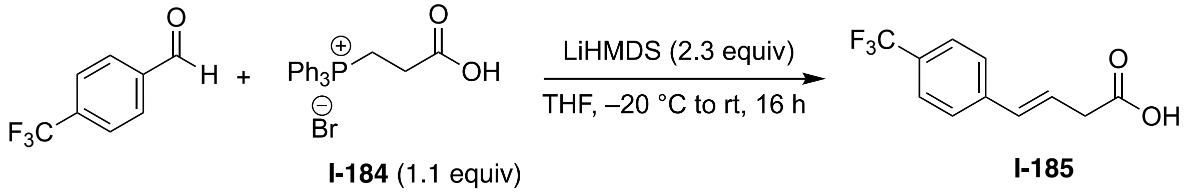
General Procedure for the synthesis of esters (GP XVI):



I-182 (1.0 equiv) **I-183**

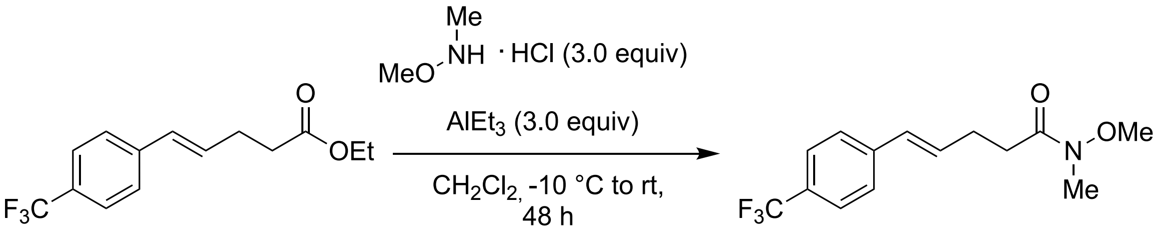
Synthesis of ethyl (E)-5-(4-(trifluoromethyl)phenyl)pent-4-enoate (I-183): A flame-dried 100 mL round bottom flask was charged with (4-ethoxy-4-oxobutyl)triphenylphosphonium bromide **I-182** (549 mg, 1.20 mmol) and dry THF (10.0 mL). The resulting suspension was cooled down to –20 °C, followed by the dropwise addition of LiHMDS (1.0 M in THF, 1.2 mL, 1.2 mmol) and stirred for 2h. To this solution at –20 °C, 4-(trifluromethyl)benzaldehyde (0.14 mL, 1.0 mmol) dissolved in dry THF (2 mL) was added and stirred at –20 °C for 2 h and then at room temperature for 12 h. The reaction mixture was quenched by adding satd. NH_4Cl solution (5 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 X 30 mL). The organic layers were combined and dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The resulting crude product was purified via column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 9:1 to 4:1 as the eluent) on silica gel to afford the corresponding ester **I-183** in 62% isolated yield (170 mg, 0.624 mmol) as colourless oil. [119]

Spectral data for I-183: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 6.49 (d, *J* = 11.7 Hz, 1H), 5.75 (dt, *J* = 11.6, 7.3 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.65 (q, *J* = 7.4 Hz, 2H), 2.45 (t, *J* = 7.4 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) ^{13}C NMR (126 MHz, CDCl$_3$) δ 172.64, 138.77, 134.65, 133.30, 129.18, 127.96, 123.43, 121.64, 60.58, 34.04, 23.93, 14.22. ^{19}F NMR (470 MHz, CDCl$_3$) δ -61.84.



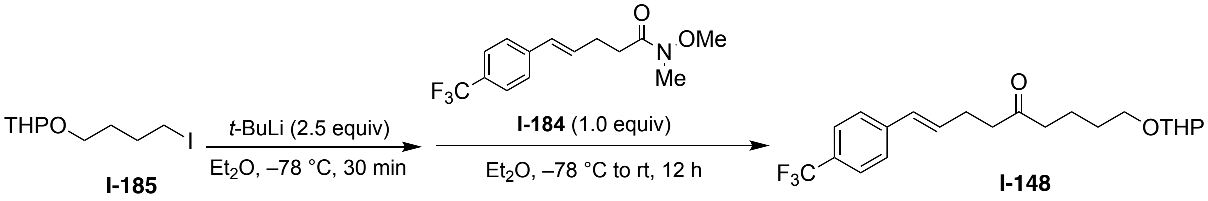
Synthesis of (E)-(4-(trifluoromethyl)phenyl)pent-4-enoic acid (I-185): Compound **I-185** was synthesized from 4-(trifluromethyl)benzaldehyde (0.14 mL, 1.0 mmol), (2-carboxyethyl)triphenylphosphonium bromide **I-184** (456 mg, 1.1 mmol) and LiHMDS (1.0 M in THF, 2.3 mL, 2.3 mmol) according to GP XVI. The resulting crude product was purified via column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 1:1 as the eluent) on silica gel providing the final product in 74% isolated yield (170 mg, 0.738 mmol) as a pale green oily liquid. [119]

Spectral data for I-185: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.57 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.39 (dt, *J* = 15.9, 7.0 Hz, 1H), 3.34 (dd, *J* = 7.1, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.74, 132.31, 132.23, 128.77, 128.67, 126.59, 125.66, 125.63, 124.47, 38.03. ^{19}F NMR (470 MHz, CDCl$_3$) δ -62.50.

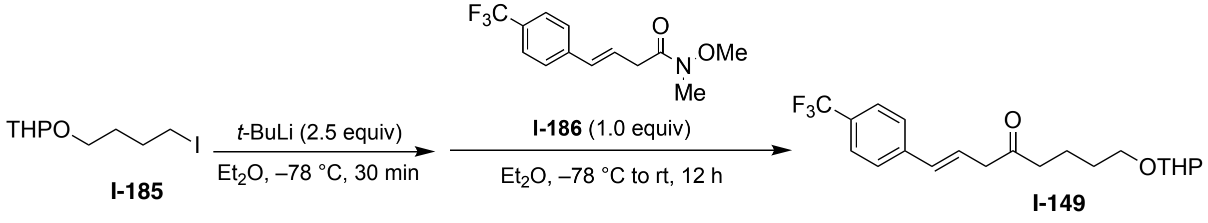


Synthesis of (E)-N-methoxy-N-methyl-5-(4-(trifluoromethyl)phenyl)pent-4-enamide (I-184): Compound **I-184** was synthesized from compound **I-183** (110 mg, 0.404 mmol), triethylaluminum (1.0 M in heptane, 1.2 mL) and N,O-dimethylhydroxylamine hydrochloride (117 mg, 1.20 mmol) according to GP VIII. The resulting crude product was purified via column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 1: 2 as the eluent) on silica gel providing the final product in 40% isolated yield (46 mg, 0.16 mmol) as a colourless oil. [120]

Spectral data for I-184: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 6.46 (d, *J* = 11.7 Hz, 1H), 5.78 (dt, *J* = 11.6, 7.2 Hz, 1H), 3.65 (s, 3H), 3.17 (s, 3H), 2.64 (qd, *J* = 6.9, 3.6 Hz, 2H), 2.56 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.46, 140.90, 133.35, 128.94, 128.55, 125.31, 125.13, 123.15, 61.20, 32.13, 31.79, 23.66. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.47.



Synthesis of (*E*)-9-((tetrahydro-2H-pyran-2-yl)oxy)-1-(4-(trifluoromethyl)phenyl)non-1-en-5-one (I-148): Compound **I-148** was synthesized from compound **I-185** (148 mg, 0.521 mmol), *t*-BuLi (1.7 M solution in pentane, 0.77 mL, 1.3 mmol) and Weinreb amide **I-184** (150 mg, 0.522 mmol) according to GP XI. The crude

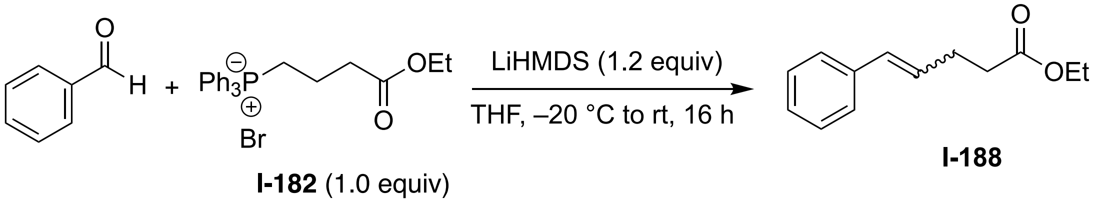


reaction mixture was purified via column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 4:1 as the eluent) on silica gel in 70% isolated yield (140 mg, 0.364 mmol).

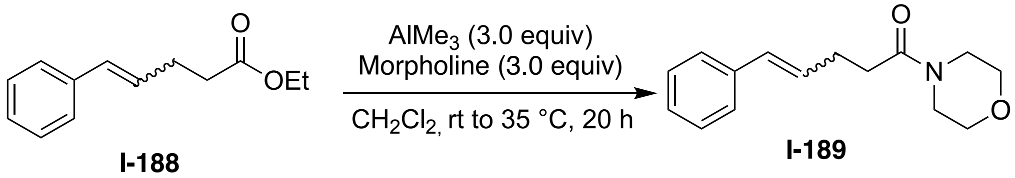
Spectral data for I-148: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.45 (d, *J* = 11.3 Hz, 1H), 5.69 (dt, *J* = 11.7, 6.9 Hz, 1H), 4.55 (dd, *J* = 4.6, 2.7 Hz, 1H), 3.84 (ddd, *J* = 11.0, 7.6, 3.0 Hz, 1H), 3.73 (dt, *J* = 9.5, 6.4 Hz, 1H), 3.52 – 3.45 (m, 1H), 3.37 (dt, *J* = 9.5, 6.2 Hz, 1H), 2.61 – 2.52 (m, 4H), 2.44 (t, *J* = 7.3 Hz, 2H), 1.85 – 1.76 (m, 1H), 1.73 – 1.57 (m, 5H), 1.56 – 1.46 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 209.86, 140.90, 133.16, 129.02, 128.70, 125.27, 99.01, 67.24, 62.50, 42.66, 42.42, 30.83, 29.30, 25.55, 22.88, 20.74, 19.77. ^{19}F NMR (470 MHz, CDCl$_3$) δ -62.47.

Synthesis of(E)-1-((tetrahydro-2H-pyran-2-yl)oxy)-8-(4-(trifluoromethyl)phenyl)oct-7-en-4-one (I-149): Compound **I-149** was synthesized from compound **I-185** (148 mg, 0.521 mmol), *t*-BuLi (1.7 M solution in pentane, 0.77 mL, 1.3 mmol) and Weinreb amide **I-186** (142 mg, 0.520 mmol) according to GP XI. The crude reaction mixture was purified via column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 4:1 as the eluent) on silica gel in 80% isolated yield (154 mg, 0.416 mmol) as a colourless oil. [59]

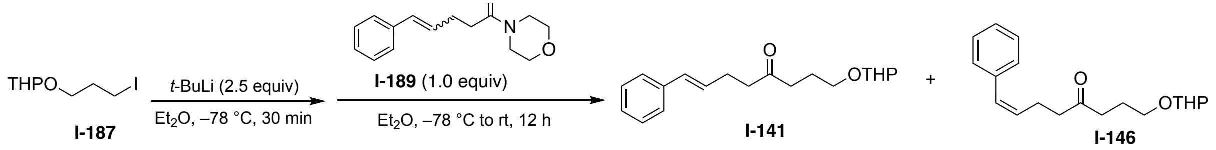
Spectral data for I-149: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.58 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 6.45 (d, *J* = 11.6 Hz, 1H), 5.70 (ddd, *J* = 11.6, 7.0, 4.7 Hz, 1H), 4.53 (t, *J* = 3.8 Hz, 1H), 3.82 (ddd, *J* = 10.9, 7.4, 3.4 Hz, 1H), 3.72 (dt, *J* = 9.6, 6.3 Hz, 1H), 3.48 (ddt, *J* = 10.6, 4.8, 2.5 Hz, 1H), 3.39 (dt, *J* = 9.7, 6.1 Hz, 1H), 2.62 – 2.55 (m, 2H), 2.51 (td, *J* = 7.2, 4.4 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.79 (tdt, *J* = 11.5, 7.9, 2.9 Hz, 1H), 1.72 – 1.64 (m, 1H), 1.55 – 1.45 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 209.64, 140.93, 133.21, 129.05, 128.73, 125.27, 99.10, 66.69, 62.67, 42.49, 39.82, 30.82, 25.54, 24.08, 22.92, 19.85. ^{19}F NMR (470 MHz, CDCl$_3$) δ -62.46.



Synthesis of ethyl 5-phenylpent-4-enoate (I-188): Compound **I-188** was obtained by reacting benzaldehyde (1.53 mL, 15.0 mmol), LiHMDS (1.0 M in THF, 18.0 mL, 1.2 mmol) and (4-ethoxy-4-oxobutyl)triphenylphosphonium bromide (8.23 g, 18.0 mmol) according to GP IX as a (1:1) mixture of *cis* and *trans* isomers with a combined yield of 78% (2.390 g, 11.7 mmol). The *cis*- and *trans*-isomers were used in the next step without further purification.



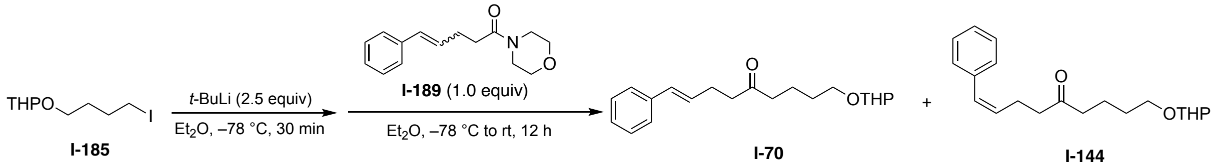
Synthesis of 1-morpholino-5-phenylpent-4-en-1-one (I-189): Compound **I-189** was obtained by reacting **I-188** (2.04 g, 10.0 mmol), trimethylaluminum (2.0 M in heptane, 15 mL, 15 mmol) and morpholine (2.6 mL, 30 mmol) according to GP VIII providing the final product as a mixture of *cis* and *trans* isomer in 73% yield (1.8 g, 7.34 mmol). The mixture of *cis*- and *trans*-isomers were used in the next step without further purification.



Synthesis of (Z)-8-phenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)oct-7-en-4-one (I-146): Compound **I-146** was synthesized from the mix **I-189** (1.28 g, 5.20 mmol), *t*-BuLi (1.7 M solution in pentane, 7.7 mL, 13 mmol) and **I-187** (1.40 g, 5.18 mmol) according to GP XI.

The crude reaction mixture was purified via column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 9:1 to 3:1 as the eluent) on silica gel. The desired product **I-146** was obtained in 35% isolated yield (550 mg, 1.82 mmol) as pure *cis*- isomer separated from the *trans* isomer **I-141** (30% isolated yield, 465 mg, 1.54 mmol). The *trans*- isomer's characterization has already been provided. [59]

Spectral data for I-146: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.28 (d, *J* = 1.6 Hz, 2H), 7.22 (td, *J* = 7.1, 1.4 Hz, 1H), 6.44 (d, *J* = 10.6 Hz, 1H), 5.60 (dt, *J* = 10.6, 6.9 Hz, 1H), 4.53 (dd, *J* = 4.7, 2.8 Hz, 1H), 3.83 (ddd, *J* = 11.0, 7.6, 2.8 Hz, 1H), 3.72 (dt, *J* = 9.6, 6.3 Hz, 1H), 3.52 – 3.45 (m, 1H), 3.39 (dt, *J* = 9.6, 6.1 Hz, 1H), 2.65 – 2.59 (m, 2H), 2.58 – 2.55 (m, 2H), 2.51 (td, *J* = 7.3, 5.2 Hz, 2H), 1.91 – 1.84 (m, 2H), 1.83 – 1.75 (m, 1H), 1.68 (tt, *J* = 9.9, 3.9 Hz, 1H), 1.57 – 1.48 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.99, 137.37, 130.99, 129.97, 128.85, 128.35, 126.85, 99.04, 66.70, 62.61, 42.83, 39.75, 30.81, 25.56, 24.07, 23.01, 19.82.

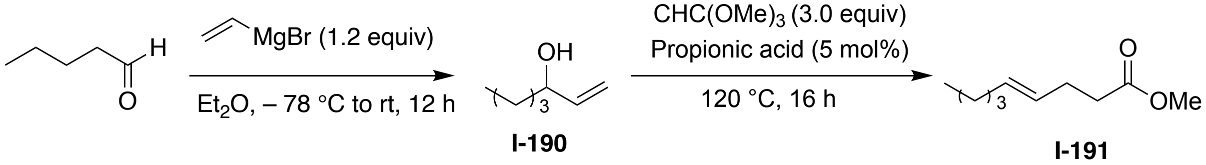


(Z)-8-phenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)oct-7-en-4-one (I-144): Compound **I-144** was synthesized from the mix **I-189** (1.28 g, 5.20 mmol), *t*-BuLi (1.7 M solution in pentane, 7.7 mL, 13 mmol) and compound **I-185** (1.48 g, 5.20 mmol) according to GP XI. Compound **I-70** and **I-144** were produced in 1:1 mixture. *cis* and *trans* isomers were separated via column chromatography and compound **I-144** was obtained in 30% isolated yield (494 mg, 1.56 mmol). The *trans*- isomer's characterization has already been provided. [59]

Spectral data for I-144: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 – 7.31 (m, 2H), 7.29 – 7.25 (m, 2H), 7.23 (t, *J* = 7.1 Hz, 1H), 6.44 (d, *J* = 11.5 Hz, 1H), 5.59 (dt, *J* = 11.6, 7.1 Hz, 1H), 4.56 (dd, *J* = 4.5, 2.8 Hz, 1H), 3.85 (dd, *J* = 11.0, 7.6 Hz, 1H), 3.73 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.55 – 3.46 (m, 1H), 3.37 (dt, *J* = 9.7, 6.3 Hz, 1H), 2.60 (dd, *J* = 8.1, 6.8 Hz, 2H), 2.54 (dd, *J* = 8.4, 6.6 Hz, 2H), 2.44 (t, *J* = 7.3 Hz, 2H), 1.87 – 1.77 (m, 1H), 1.75 – 1.62 (m, 4H), 1.61 – 1.56 (m, 3H), 1.55 – 1.47 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.12, 137.22, 130.82, 129.84, 128.71, 128.22, 126.71, 98.87, 67.15, 62.36, 42.66, 42.50, 30.72, 29.21, 25.46, 22.87, 20.63, 19.65.

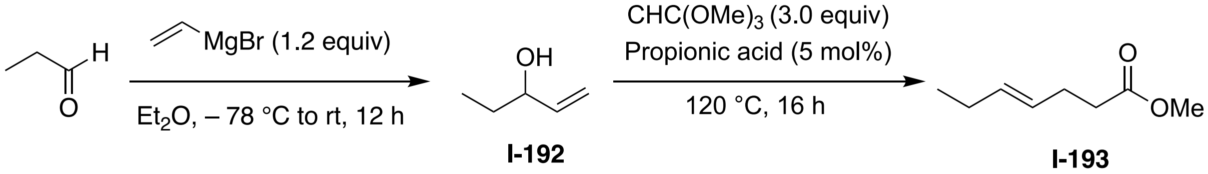
General Procedure for the synthesis alkyl substrates (GP XVII):

Synthesis of methyl (E)-non-4-enoate (I-191): In a clean dry sealed tube fitted with a stir bar were added the allyl alcohol **I-190** (2.00 g, 17.5 mmol, 1.0 equiv.), trimethyl orthoformate (5.74 mL, 52.5 mmol, 3.00 equiv.) and propanoic acid (66 *μ*L, 0.88 mmol, 5.0 mol%). The reaction mixture was heated in an oil bath at 120 °C for 16 h. This was then allowed to cool to rt whereupon it was unsealed and again was reheated back at 120 °C for another 2 h in open air. Finally, the reaction mixture was cooled to rt and diluted with DCM (20 mL) and stirred with 1M HCl (10 mL) for another hour before the layers were separated. The aqueous layer was extracted with DCM (3 X 10 mL) and the combined aq. layers were washed with satd. NaHCO$_3$ (15 mL) solution dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified through



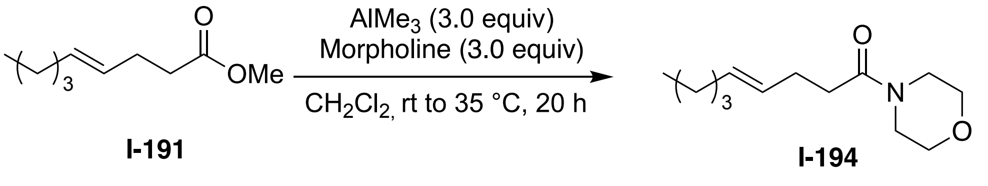
column chromatography (hexane: ethyl acetate = 19:1) which yield the desired product in 58% yield (1.73 g, 10.2 mmol). [121]

Spectral data for I-191: ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.51 – 5.42 (m, 1H), 5.42 – 5.34 (m, 1H), 3.66 (s, 3H), 2.37 (dd, *J* = 7.8, 6.7 Hz, 2H), 2.34 – 2.26 (m, 2H), 2.01 – 1.92 (m, 2H), 1.33 – 1.24 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 173.73, 131.88, 127.82, 51.47, 34.19, 32.16, 31.59, 27.91, 22.13, 13.93.



Synthesis of methyl (E)-hept-4-enoate (I-193): Compound **I-193** was synthesized from compound **I-192** (1.50 g, 17.4 mmol, 1.00 equiv), trimethylorthoformate (5.74 mL, 52.5 mmol, 3.00 equiv) and propanoic acid (66 μL, 0.88 mmol, 5.0 mol%) according to GP XVII. The crude reaction mixture was purified via column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 19:1 as the eluent) on silica gel in 72% yield (1.78 g, 12.5 mmol) as a colourless oil. [121]

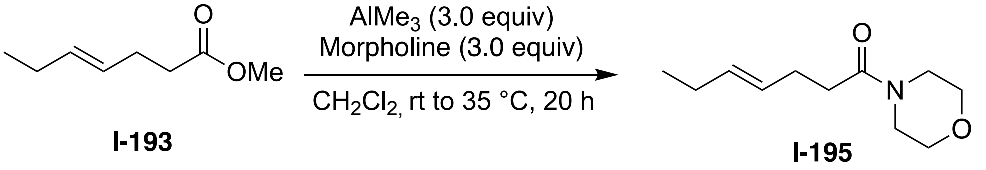
Spectral data for I-193: ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.51 (dt, *J* = 15.2, 6.2 Hz 1H), 5.40 (dt, *J* = 15.2, 7.9 Hz, 1H), 3.67 (s, 3H), 2.38 (dd, *J* = 7.8, 6.7, Hz, 2H), 2.31 (dt, *J* = 8.2, 6.8 Hz, 2H), 2.00 (t, *J* = 7.5 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 173.76, 133.40, 126.88, 51.49, 34.18, 27.87, 25.52, 13.79.



General Procedure for the synthesis of morpholine amide (GP XVIII):

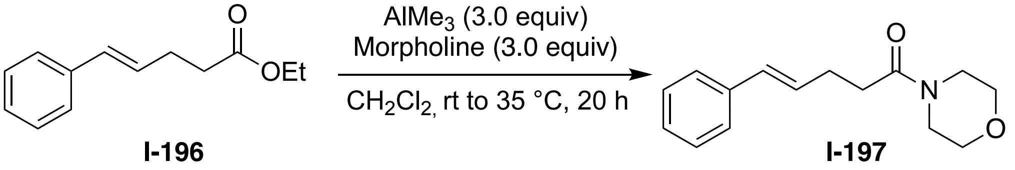
Synthesis of (E)-1-morpholino-non-4-en-1-one (I-194): To a solution of morpholine (1.03 ml, 12.0 mmol) in dry DCM (10 mL) was slowly added trimethylaluminium (2.0 M in hexane, 6.0 mL, 12 mmol) at rt. The resulting mixture was stirred at rt for 30 min and ester **I-191** (0.68 g, 4.0 mmol) dissolved in DCM (5 mL) was added dropwise. The resultant reaction mixture was heated overnight at 35 °C. After cooling to rt, the reaction mixture was quenched with 1 M HCl (10 mL) and then extracted with DCM (3 X 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. This reaction mixture was further purified by column chromatography (hexane: ethyl acetate = 1:2) to yield a colorless oil in 47% yield (0.42 g, 1.9 mmol). [121]

Spectral data for I-194: ^1H NMR (500 MHz, $CDCl_3$) δ 5.49 – 5.38 (m, 2H), 3.65 (dd, *J* = 5.8, 4.0 Hz, 4H), 3.60 (dd, *J* = 5.9, 3.9 Hz, 2H), 3.49 – 3.39 (m, 2H), 2.40 – 2.26 (m, 4H), 2.01 – 1.91 (m, 2H), 1.29 (td, *J* = 10.5, 6.8 Hz, 4H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.24, 131.70, 128.38, 66.94, 66.66, 46.01, 41.86, 33.13, 32.20, 31.61, 28.25, 22.18, 13.94.



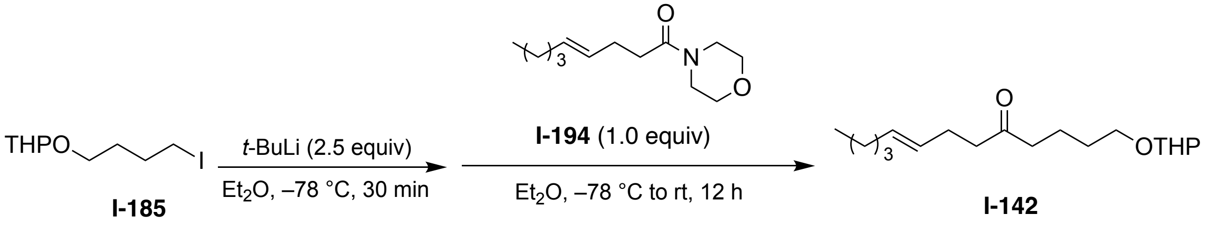
Synthesis of (E)-1-morpholinohept-4-en-1-one I-195: Compound **I-195** was synthesized from compound **I-193** (0.57 g, 4.0 mmol), trimethylaluminium (2.0 M in hexane, 6.0 mL, 12 mmol) and morpholine (1.03 ml, 12.0 mmol) according to GP XVIII. The final product was isolated in 53% yield (0.42 g, 2.1 mmol) after column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 1:2 as the eluent) on silica gel. [121]

Spectral data for I-195: ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.56 – 5.46 (m, 1H), 5.45 – 5.36 (m, 1H), 3.65 (dd, *J* = 5.8, 4.0 Hz, 4H), 3.60 (dd, *J* = 5.7, 3.7 Hz, 2H), 3.47 – 3.43 (m, 2H), 2.41 – 2.26 (m, 4H), 2.05 – 1.92 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.24, 133.20, 127.44, 127.43, 66.94, 66.66, 46.00, 41.86, 33.12, 28.20, 25.52, 13.78.



Synthesis of (E)-1-morpholino-5-phenylpent-4-en-1-one (I-197): Compound **I-197** was synthesized from compound **I-196** (4.08 g, 20.0 mmol), trimethylaluminum (2.0 M in heptane, 30.0 mL, 60.0 mmol) and morpholine (5.2 mL, 60.0 mmol) according to GP XVIII. The final product was isolated in 65% yield (3.19 g, 13.0 mmol) after column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 1:2 as the eluent) on silica gel. [122]

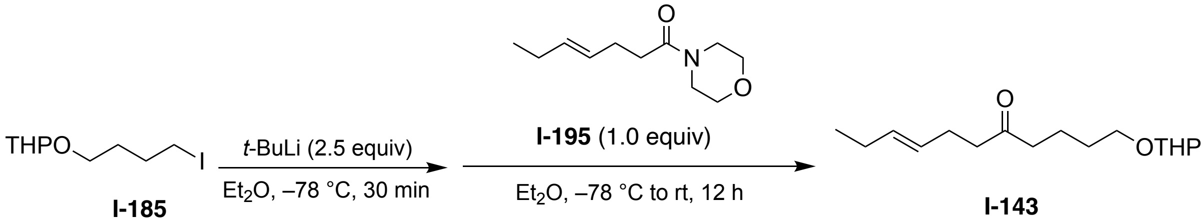
Spectral data for I-197: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.25 (d, *J* = 7.4 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 7.3 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 6.17 (d, *J* = 15.8 Hz, 1H), 3.54 (dq, *J* = 8.0, 4.3 Hz, 6H), 3.36 (t, *J* = 4.8 Hz, 2H), 2.52 – 2.41 (m, 2H), 2.38 (dd, *J* = 8.3, 5.8 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 170.81, 137.30, 130.86, 130.73,



129.87, 129.84, 129.05, 128.65, 128.51, 128.46, 128.18, 127.05, 127.01, 126.69, 125.94, 66.79, 66.76, 66.52, 45.86, 41.87, 32.64, 28.49.

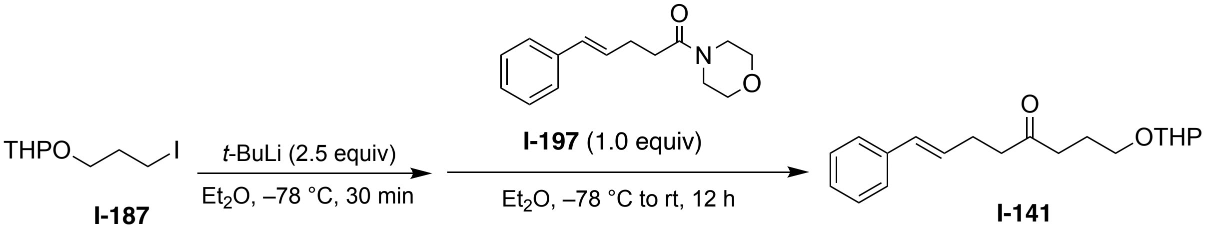
Synthesis of (E)-1-((tetrahydro-2H-pyran-2-yl)oxy)tridec-8-en-5-one (I-142): Compound **I-142** was synthesized from **I-185** (1.16 g, 4.07 mmol), *t*-BuLi (1.7 M solution in pentane, 6 mL, 10.2 mmol) and amide **I-194** (0.92 g, 4.07 mmol) according to GP XI. The reaction mixture was purified via column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 4:1 as the eluent) on silica gel returning the final product in 62% yield (748 mg, 2.52 mmol) as a colorless oil.[59]

Spectral data for I-142 : ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.43 – 5.35 (m, 1H), 5.35 – 5.28 (m, 1H), 4.52 (dd, *J* = 4.4, 2.8 Hz, 1H), 3.81 (ddd, *J* = 11.0, 7.7, 3.2 Hz, 1H), 3.70 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.49 – 3.42 (m, 1H), 3.34 (dt, *J* = 9.6, 6.2 Hz, 1H), 2.44 – 2.37 (m, 4H), 2.24 – 2.17 (m, 2H), 1.92 (q, *J* = 6.2 Hz, 2H), 1.81 – 1.74 (m, 1H), 1.67 (dt, *J* = 12.9, 3.4 Hz, 1H), 1.62 (dd, *J* = 8.4, 7.2 Hz, 1H), 1.57 – 1.43 (m, 4H), 1.29 – 1.21 (m, 4H), 0.83 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.57, 131.54, 128.35, 98.89, 67.21, 62.35, 42.70, 42.61, 32.22, 31.67, 30.77, 29.28, 26.91, 26.90, 25.52, 22.20, 20.65, 19.68, 13.98.



Synthesis of (E)-1-((tetrahydro-2H-pyran-2-yl)oxy)undec-8-en-5-one (I-143): Compound **I-143** was synthesized from **I-185** (1.16 g, 4.07 mmol), *t*-BuLi (1.7 M solution in pentane, 6.0 mL, 10.2 mmol) and amide **I-195** (803 mg, 4.07 mmol) according to GP XI. The crude mixture was purified via column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 4:1 as the eluent) on silica gel returning the final product in 70% yield (764 mg, 2.85 mmol) as a colorless oil. [59]

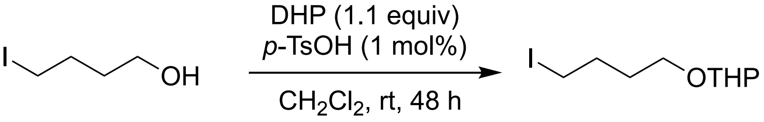
Spectral data for I-143: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (dtt, *J* = 15.0, 6.1, 1.3 Hz, 1H), 5.33 (dtt, *J* = 15.3, 6.5, 1.4 Hz, 1H), 4.53 (dd, *J* = 4.5, 2.8 Hz, 1H), 3.81 (ddd, *J* = 11.0, 7.7, 3.2 Hz, 1H), 3.70 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.50 – 3.42 (m, 1H), 3.34 (dt, *J* = 9.6, 6.3 Hz, 1H), 2.41 (dt, *J* = 9.7, 7.4 Hz, 4H), 2.26 – 2.18 (m, 2H), 1.98 – 1.89 (m, 2H), 1.82 – 1.74 (m, 1H), 1.67 (dt, *J* = 13.0, 3.4 Hz, 1H), 1.65 – 1.57 (m, 3H), 1.56 – 1.52 (m, 2H), 1.52 – 1.44 (m, 3H), 0.91 (t, *J* = 7.5 Hz, 3H) ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.62, 133.07, 127.40, 98.90, 67.22, 62.37, 42.69, 42.68, 42.62, 30.78, 30.77, 29.29, 26.86, 25.57, 25.53, 20.66, 19.69, 13.86.



Synthesis of (E)-8-phenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)oct-7-en-4-one (I-141): Compound **I-141** was synthesized from compound **I-187** (675 mg, 2.50 mmol), *t*-BuLi (1.7 M solution in pentane, 3.68 mL, 6.25 mmol) and amide **I-197** (613 mg, 2.50 mmol) according to GP XI. The crude reaction mixture was further purified via column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 19:1 as the eluent) on silica gel to obtain the final product in 72% isolated yield (544 mg, 1.79 mmol). [59]

Spectral data for I-141 : ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.31 (m, 2H), 7.31 – 7.27 (m, 2H), 7.22 – 7.17 (m, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 6.20 (dt, *J* = 15.7, 6.8 Hz, 1H), 4.54 (dd, *J* = 4.7, 2.8 Hz, 1H), 3.83 (ddd, *J* = 11.1, 7.5, 2.9 Hz, 1H), 3.74 (dt, *J* = 9.7, 6.3

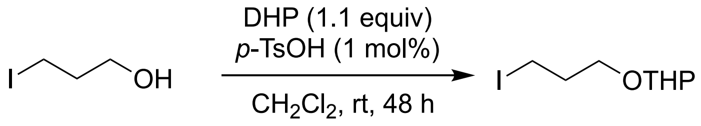
Hz, 1H), 3.48 (ddd, *J* = 11.1, 5.3, 4.0 Hz, 1H), 3.41 (dt, *J* = 9.7, 6.2 Hz, 1H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.54 (td, *J* = 7.3, 5.6 Hz, 2H), 2.52 – 2.45 (m, 2H), 1.93 – 1.86 (m, 2H), 1.83 – 1.75 (m, 1H), 1.73 – 1.65 (m, 1H), 1.57 – 1.46 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.99, 137.55, 130.81, 129.14, 128.64, 127.21, 126.13, 99.06, 66.72, 62.63, 42.40, 39.88, 30.83, 27.27, 25.56, 24.07, 19.84.



I-185

Synthesis of 2-(4-iodobutoxy)tetrahydro-2H-pyran (I-185): 4-Iodobutanol (4.0 g, 20 mmol) was dissolved in DCM (100 mL) and reacted with *p*-toluenesulfonic acid (*p*-TsOH, 34 mg, 0.01 mmol) and 3,4-dihydro-2H-pyran (DHP, 2.0 mL, 22 mmol) at rt. The reaction mixture was stirred for 48 h. The reaction mixture was concentrated under reduced pressure and purified via column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 19:1 as the eluent) on silica gel. Compound **I-185** was obtained as a yellow oil in 81% yield (4.60 g, 16. 2 mmol). [123]

Spectral data for I-185: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56 (dd, *J* = 4.5, 2.8 Hz, 1H), 3.83 (ddd, *J* = 11.1, 7.8, 3.3 Hz, 1H), 3.75 (dt, *J* = 9.8, 6.5 Hz, 1H), 3.53 – 3.45 (m, 1H), 3.40 (dt, *J* = 9.7, 6.2 Hz, 1H), 3.22 (t, *J* = 7.0 Hz, 2H), 1.98 – 1.88 (m, 2H), 1.86 – 1.75 (m, 1H), 1.74 – 1.63 (m, 3H), 1.61 – 1.47 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.83, 66.25, 62.34, 30.69, 30.63, 30.52, 25.44, 19.61, 6.87.



I-187

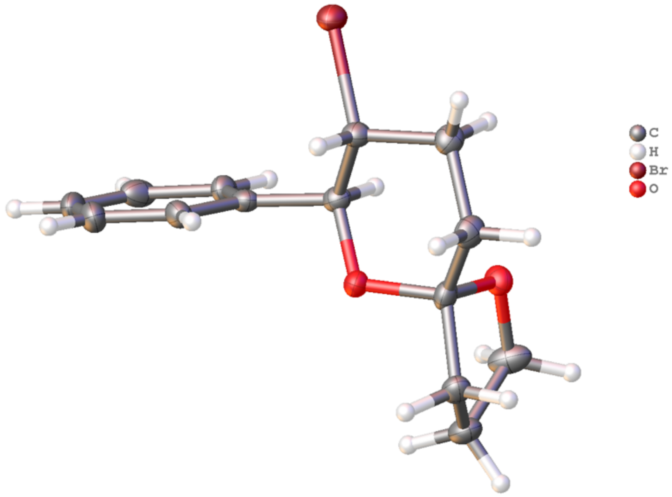
Synthesis of 2-(3-iodopropoxy)tetrahydro-2H-pyran (I-187): 3-Iodopropanol (3.7 g, 20 mmol) was dissolved in DCM (100 mL) and reacted with *p*-toluenesulfonic acid (*p*-TsOH, 34 mg, 0.01 mmol) and 3,4-dihydro-2H-pyran (DHP, 2.0 mL, 22.0 mmol) at rt. The reaction mixture was concentrated under reduced pressure and purified via column chromatography (50 mm X 300 mm, hexanes: ethyl acetate 19:1 as the eluent) on silica gel. Compound **I-187** was obtained as an orange oil in 86% yield (4.65 g, 17.2 mmol). [124] **Spectral data for I-187**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (dd, *J* = 4.3, 2.8 Hz, 1H), 3.87 (dd, *J* = 11.1, 8.1 Hz, 1H), 3.81 (dt, *J* = 10.0, 5.8 Hz, 1H), 3.56 – 3.49 (m, 1H), 3.44 (dt, *J* = 10.0, 5.9 Hz, 1H), 3.30 (t, *J* = 6.8 Hz, 2H), 2.14 – 2.05 (m, 2H), 1.85 – 1.78 (m, 1H), 1.76 – 1.68 (m, 1H), 1.63 – 1.56 (m, 2H), 1.55-1.50 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.90, 66.83, 62.30, 33.54, 30.59, 25.41, 19.48, 3.51.

Crystal Structure:

Crystal Structure of Compound **I-106**:

Chirality was determined of this crystal.

Crystal Data and Experimental



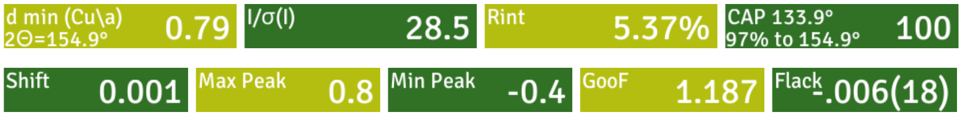
Experimental. Single colourless needle-shaped crystals of **I-106** used as received. A suitable crystal with dimensions 0.14 × 0.05 × 0.02 mm^3 was selected and mounted on a nylon loop with paratone oil on a XtaLAB Synergy, Dualflex, HyPix diffractometer. The crystal was kept at a steady T = 99.9(2) K during data collection. The structure was solved with the **ShelXS** (Sheldrick, 2008) solution program using direct methods and by using **Olex2** 1.5-alpha (Dolomanov et al., 2009) as the graphical interface. The model was refined with **ShelXL** 2018/3 (Sheldrick, 2015) using full matrix least squares minimisation on F^2. [125,126,127]

Crystal Data. $C_{14}H_{17}BrO_2$, M_r = 297.18, orthorhombic, $P2_12_12_1$ (No. 19), a = 5.66337(11) Å, b = 9.23167(19) Å, c = 24.8166(4) Å, $\alpha = \beta = \gamma = 90^\circ$, V = 1297.47(4) Å^3, T = 99.9(2) K, Z = 4,

Z' = 1, μ(Cu K$_\alpha$) = 4.217, 14121 reflections measured, 2632 unique (R$_{int}$ = 0.0537) which were used in all calculations. The final wR_2 was 0.1012 (all data) and R_1 was 0.0425 (I≥2 σ(I)).

Compound	**I-102**
Formula	$C_{14}H_{17}BrO_2$
CCDC	2086375
Dcalc	1.521
μ/mm^{-1}	4.217
Formula Weight	297.18
Colour	colourless
Shape	needle-shaped
Size/mm^3	0.14×0.05×0.02
T/K	99.9(2)
Crystal System	orthorhombic
Flack Parameter	-0.006(18)
Hooft Parameter	0.013(14)
Space Group	$P2_12_12_1$
a/Å	5.66337(11)
b/Å	9.23167(19)
c/Å	24.8166(4)
α/°	90
β/°	90
γ/°	90
V/Å^3	1297.47(4)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K$_\alpha$
Θ_{min}/°	3.562
Θ_{max}/°	77.470
Measured Refl's.	14121
Indep't Refl's	2632
Refl's I≥2 σ(I)	2496
R_{int}	0.0537
Parameters	154
Restraints	0
Largest Peak	0.769
Deepest Hole	-0.424
GooF	1.187
wR_2 (all data)	0.1012
wR_2	0.1006
R_1 (all data)	0.0442
R_1	0.0425

Structure Quality Indicators



Reflections:	d min (Cu\a) 2Θ=154.9° 0.79	I/σ(I) 28.5	Rint 5.37%	CAP 133.9° 97% to 154.9° 100	
Refinement:	Shift 0.001	Max Peak 0.8	Min Peak -0.4	GooF 1.187	Flack -.006(18)

A colourless needle-shaped-shaped crystal with dimensions 0.14×0.05×0.02 mm^3 was mounted on a nylon loop with paratone oil. Data were collected using a XtaLAB Synergy, Dualflex, HyPix diffractometer equipped with an Oxford Cryosystems low-temperature device, operating at T = 99.9(2) K.

MSU Data were measured using *w* scans using Cu K_a radiation (micro-focus sealed X-ray tube, 50 kV, 1 mA). The total number of runs and images was based on the strategy calculation from the program CrysAlisPro 1.171.41.110a (Rigaku OD, 2021). The actually achieved resolution was Q = 77.470.

Cell parameters were retrieved using the CrysAlisPro 1.171.41.110a (Rigaku OD, 2021) software and refined using CrysAlisPro 1.171.41.110a (Rigaku OD, 2021) on 9252 reflections, 66 % of the observed reflections. Data reduction was performed using the CrysAlisPro 1.171.41.110a (Rigaku OD, 2021) software which corrects for Lorentz polarization. The final completeness is 100.00 out to 77.470 in Q CrysAlisPro 1.171.41.110a (Rigaku Oxford Diffraction, 2021)Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

The structure was solved in the space group $P2_12_12_1$ (# 19) by using direct methods using the ShelXS (Sheldrick, 2008) structure solution program. The structure was refined by Least Squares ShelXL incorporated in Olex2 software program. All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model, except for the hydrogen atom on the non-carbon atom(s) which were found by difference Fourier methods and refined isotropically when data permits.

CCDC 2086375 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

The Flack parameter was refined to -0.006(18). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in 0.013(14). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

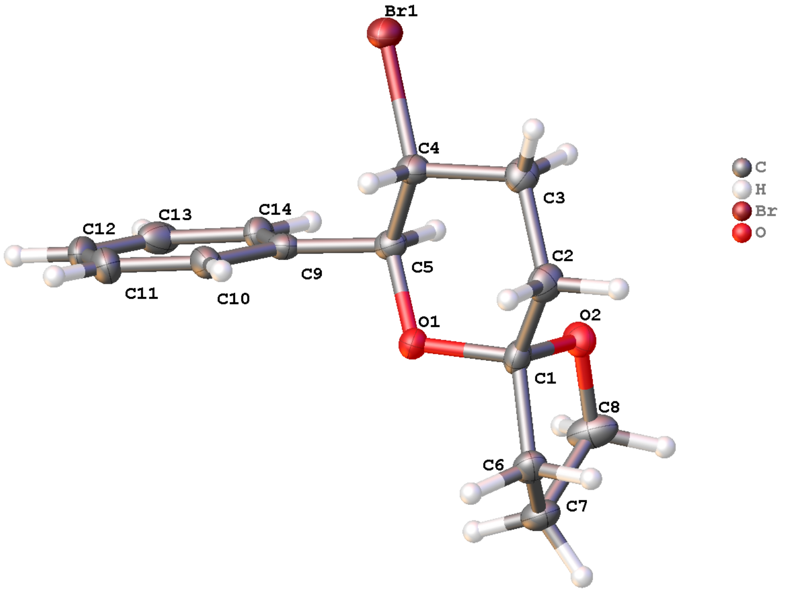


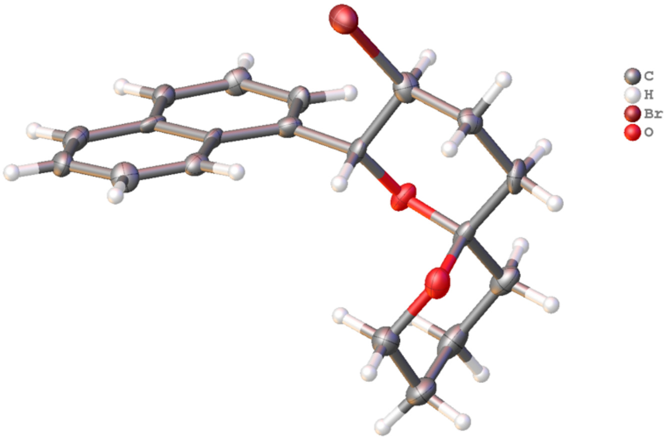
Figure I-41: Model has Chirality at C1 (Sohnke SpGr) R; Model has Chirality at C4 (Sohnke SpGr) R: Model has Chirality at C5 (Sohnke SpGr) S.

Solvent molecules were found to reside in the lattice void, which is presumably octane resulting from crystallization. Attempts to model these solvents and or redefine as CH2Cl2 failed to generate a chemically sensible model. The SQUEEZE (P.v.d. Sluis & Spek, 1990) function of PLATON (Spex, 2003) was used to eliminate the contribution of the electron density in the void from the intensity data. The total solvent area volume was found to be 1377 Ã…3, with electron count of about 237 electrons. This corresponds to approximately three molecules of octane residing in the cell. Although the electron count is slightly higher than calculated, the large volume suggests that this void is mostly consumed by octane and not the other potential solvent, dichloromethane. The calculate F(000) and density was calculated for the cell containing three molecules of octane per cell or 1.5 per molecule of interest. The refinement was carried out on the new reflection file generated by PLATON.

Crystal Structure of **I-100**

Crystal structure shows the chirality of the crystal by X-ray diffraction.

Crystal Data and Experimental

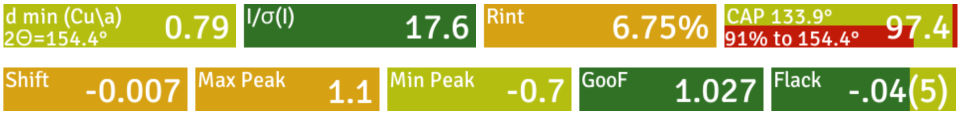


Experimental. Single colourless block-shaped crystals of **I-100** used as received. A suitable crystal with dimensions 0.15 × 0.11 × 0.03 mm^3 was selected and mounted on a nylon loop with paratone oil on a XtaLAB Synergy, Dualflex, HyPix diffractometer. The crystal was kept at a steady T = 99.97(11) K during data collection. The structure was solved with the **ShelXT** (Sheldrick, 2015) solution program using dual methods and by using **Olex2** 1.5-alpha (Dolomanov et al., 2009) as the graphical interface. The model was refined with **ShelXL** 2018/3 (Sheldrick, 2015) using full matrix least squares minimisation on F^2.

Crystal Data. $C_{19}H_{21}BrO_2$, M_r = 361.27, orthorhombic, $Pna2_1$ (No. 33), a = 9.0441(4) Å, b= 16.6452(9) Å, c = 10.8143(5) Å, $\alpha = \beta = \gamma = 90^\circ$, V = 1627.99(14) Å^3, T = 99.97(11) K, Z = 4, Z' = 1, m(Cu K_a) = 3.472, 6941 reflections measured, 2528 unique (R_{int} = 0.0675) which were used in all calculations. The final wR_2 was 0.1511 (all data) and R_1 was 0.0602 ($I \geq 2\ s(I)$). [125,126,127]

Compound	**I-100**
Formula	$C_{19}H_{21}BrO_2$
CCDC	2086599
Dcalc	1.474
m/mm^{-1}	3.472
Formula Weight	361.27
Colour	colourless
Shape	block-shaped
Size/mm^3	0.15×0.11×0.03
T/K	99.97(11)
Crystal System	orthorhombic
Flack Parameter	-0.04(5)
Hooft Parameter	-0.01(2)
Space Group	$Pna2_1$
a/Å	9.0441(4)
b/Å	16.6452(9)
c/Å	10.8143(5)
α/°	90
β/°	90
γ/°	90
V/Å^3	1627.99(14)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K$_a$
Q_{min}/°	4.877
Q_{max}/°	77.218
Measured Refl's.	6941
Indep't Refl's	2528
Refl's I≥2 s(I)	2253
R_{int}	0.0675
Parameters	199
Restraints	1
Largest Peak	1.136
Deepest Hole	-0.731
GooF	1.027
wR_2 (all data)	0.1511
wR_2	0.1483
R_1 (all data)	0.0658
R_1	0.0602

Structure Quality Indicators



Reflections:	d min (Cu\a) 2Θ=154.4° 0.79	I/σ(I) 17.6	Rint 6.75%	CAP 133.9° 91% to 154.4° 97.4
Refinement:	Shift -0.007	Max Peak 1.1	Min Peak -0.7	GooF 1.027
	Flack -.04(5)			

A colourless block-shaped-shaped crystal with dimensions 0.15×0.11×0.03 mm^3 was mounted on a nylon loop with paratone oil. Data were collected using a XtaLAB Synergy, Dualflex, HyPix diffractometer equipped with an Oxford Cryosystems low-temperature device, operating at T = 99.97(11) K.

MSU Data were measured using *w* scans using Cu K$_a$ radiation (micro-focus sealed X-ray tube, 50 kV, 1 mA). The total number of runs and images was based on the strategy calculation from the program CrysAlisPro 1.171.41.110a (Rigaku OD, 2021). The actually achieved resolution was Q = 77.218.

Cell parameters were retrieved using the CrysAlisPro 1.171.41.110a (Rigaku OD, 2021) software and refined using CrysAlisPro 1.171.41.110a (Rigaku OD, 2021) on 5294 reflections, 76 % of the observed reflections. Data reduction was performed using the CrysAlisPro 1.171.41.110a (Rigaku OD, 2021) software which corrects for Lorentz polarization. The final completeness is 97.30 out to 77.218 in Q CrysAlisPro 1.171.41.110a (Rigaku Oxford Diffraction, 2021) Numerical absorption correction based on gaussian integration over a multifaceted crystal model Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

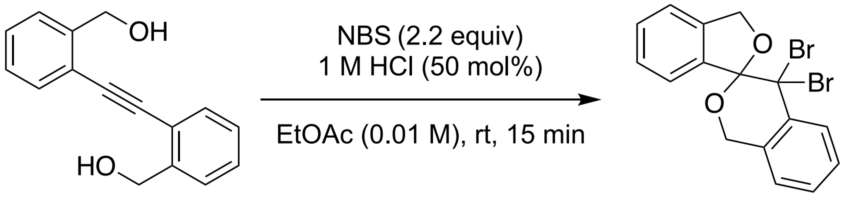
The structure was solved in the space group *Pna*2$_1$ (# 33) by using dual methods using the ShelXT (Sheldrick, 2015) structure solution program. The structure was refined by Least Squares ShelXL incorporated in Olex2 software program. All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model, except for the hydrogen atom on the non-carbon atom(s) which were found by difference Fourier methods and refined isotropically when data permits.

CCDC 2086599 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

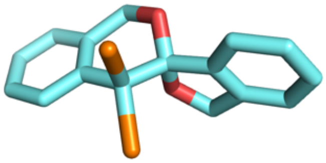
There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

Solvent molecules were found to reside in the lattice void, which is presumably octane resulting from crystallization. Attempts to model these solvents and or redefine as CH2Cl2 failed to generate a chemically sensible model. The SQUEEZE (P.v.d. Sluis & Spek, 1990) function of PLATON (Spex, 2003) was used to eliminate the contribution of the electron density in the void from the intensity data. The total solvent area volume was found to be 1377 Ã…3, with electron count of about 237 electrons. This corresponds to approximately three molecules of octane residing in the cell. Although the electron count is slightly higher than calculated, the large volume suggests that this void is mostly consumed by octane and not the other potential solvent, dichloromethane. The calculate F(000) and density was calculated for the cell containing three molecules of octane per cell or 1.5 per molecule of interest. The refinement was carried out on the new reflection file generated by PLATON.

I.III.3. Desymmetrization of alkyne-diol:



I-45 **I-48**

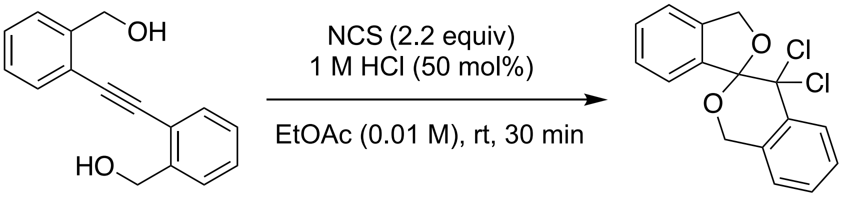


X-ray structure of **I-48**

In a clean dry 25 mL rb was added NBS (1.645 g, 9.24 mmol) in EtOAc (42 mL). To this was added 1M HCl (2.1 mL, 2.1 mmol) and the reaction mixture was stirred at rt for 10 min. Alkyne-diol substrate **I-45** (1.0 g, 4.2 mmol) was then transferred to this at once. The rb was covered up with aluminium foil and stirred at rt for 15 min. When TLC showed complete conversion of the starting alkyne-diol **I-45** substrate, the reaction was quenched immediately by adding saturated Na_2SO_3 (15 mL). The solution turned colourless and layers were separated. The organic layer was extracted with EtOAc (3 X 15 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give a white solid. The crude reaction mixture was then further purified by column chromatography (5% EtOAc-Hexane) to give a white crystalline solid **I-48** as the pure product in 96% yield (1.6 g, 4.03 mmol).

Analytical data for I-48: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.49 (td, *J* = 7.5, 1.1 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.36 – 7.29 (m, 2H), 7.01 (dd, *J* = 7.6, 1.3 Hz, 1H), 5.34 (d, *J* = 15.5 Hz, 1H), 5.28 (s, 2H), 5.02 (d, *J* = 15.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.26, 138.88, 136.64, 131.04, 130.28, 130.14, 129.47, 127.82, 127.70, 125.73, 123.28, 120.92, 110.47, 74.54, 66.21, 64.54.

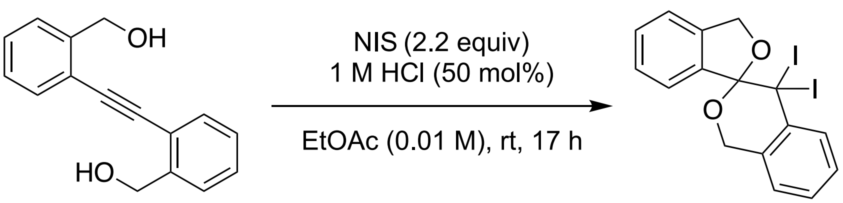
Synthesis of I-130: In a clean dry 25 mL rb was added NCS (40.1 mg, 0.3 mmol) in EtOAc (5 mL). To this was added 1M HCl (0.05 mL, 0.05 mmol) and the reaction mixture was stirred at rt for 10 min. Alkyne-diol substrate **I-45** (23.8 mg, 0.1 mmol) was



I-45 **I-130**

then transferred to this at once. The rb was covered up with aluminium foil and stirred at rt for 15 min. When TLC showed complete conversion of the starting alkyne-diol **I-45** substrate, the reaction was quenched immediately by adding saturated Na_2SO_3 (5 mL). The solution turned colourless and layers were separated. The organic layer was extracted with EtOAc (3 X 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give a white solid. The crude reaction mixture was then further purified by column chromatography (5% EtOAc-Hexane) to give a white solid **I-130** as the pure product in 87% yield (26.7 mg, 0.087 mmol).

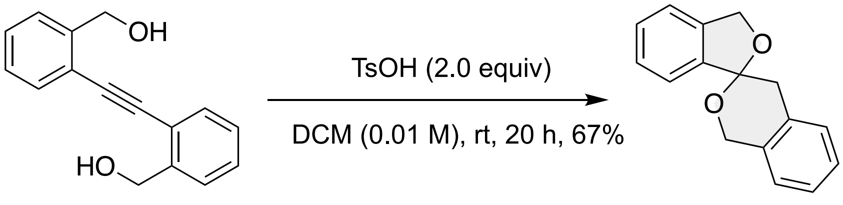
Analytical data for I-130: ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.95 (m, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.50 (td, *J* = 7.5, 1.1 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.41 – 7.37 (m, 2H), 7.31 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.08 (ddt, *J* = 7.2, 2.0, 0.9 Hz, 1H), 5.34 – 5.29 (m, 1H), 5.28 – 5.25 (m, 2H), 5.03 (dd, *J* = 15.5, 0.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.26, 136.78, 135.89, 131.71, 130.34, 129.53, 127.87, 127.81, 127.66, 125.80, 123.50, 120.83, 110.62, 86.60, 74.56, 64.37.



I-45 **I-131**

In a clean dry 25 mL rb was added NIS (49.5 mg, 0.22 mmol) in EtOAc (5 mL). To this was added 1M HCl (0.05 mL, 0.05 mmol) and the reaction mixture was stirred at rt for 10 min. Alkyne-diol substrate **I-45** (23.8 mg, 0.1 mmol) was then transferred to this at once. The rb was covered up with aluminium foil and stirred at rt for 15 min. When TLC showed complete conversion of the starting alkyne-diol **I-45** substrate, the reaction was quenched immediately by adding saturated $Na_2S_2O_3$ (5 mL). The solution turned colourless and layers were separated. The organic layer was extracted with EtOAc (3 X 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give a white solid. The crude reaction mixture was then further purified by column chromatography (5% EtOAc-Hexane) to give **I-131** as the pure product in 56% yield (27.4 mg, 0.056 mmol).

Analytical data for I-131: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.97 (m, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.50 (td, *J* = 7.5, 1.1 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.40 – 7.37 (m, 2H), 7.33 – 7.30 (m, 1H), 7.09 – 7.07 (m, 1H), 5.33 – 5.29 (m, 1H), 5.26 (s, 2H), 5.03 (d, *J* = 15.5, 0.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.25, 136.78, 135.89, 131.71, 130.34, 129.52, 127.87, 127.81, 127.65, 125.80, 123.50, 120.83, 110.62, 86.60, 74.56, 64.36.



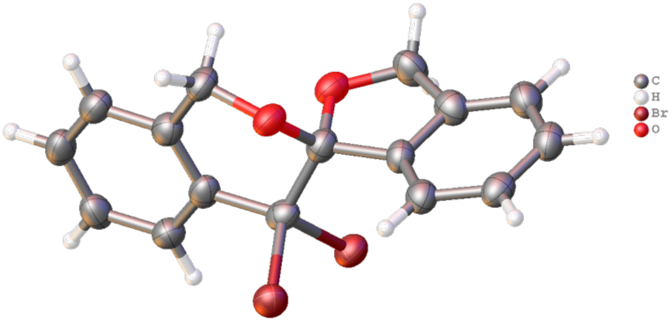
I-45 **I-132**

In a clean dry 25 mL rb was added alkyne-diol substrate **I-45** (23.8 mg, 0.1 mmol) in EtOAc (5 mL). To this was added TsOH (35 mg, 0.2 mmol) at once and the reaction mixture was stirred at rt for 20 h. When TLC showed complete conversion of the starting alkyne-diol substrate, the reaction was quenched by adding 1(M) NaOH (1 mL) and brine solution (3 mL). Layers were separated and the organic layer was extracted with DCM (3×5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give a white solid. This was then further purified by column chromatography (10% EtOAc-Hexane) to give **I-132** in 67% isolated yield (16 mg, 0.067 mmol).

Analytical data for I-132: ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.2, 1.5 Hz, 1H), 7.36 (td, *J* = 7.3, 1.1 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.25 – 7.21 (m, 2H), 7.21 – 7.16 (m, 1H), 7.10 (dd, *J* = 5.3, 3.6 Hz, 1H), 5.26 (d, *J* = 12.7 Hz, 1H), 5.17 (d, *J* = 14.8 Hz, 1H), 5.08 (d, *J* = 12.6 Hz, 1H), 4.88 (d, *J* = 14.8 Hz, 1H), 3.62 – 3.55 (m, 1H), 3.09 (d, *J* = 16.3, 1.1 Hz, 1H).. ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.67, 140.18, 133.86, 131.61, 129.35, 129.02, 127.90, 126.87, 126.45, 124.13, 122.07, 121.41, 107.62, 71.75, 64.54, 36.99.

Crystal Structure for I-48:

Crystal structure from crystal chosen.

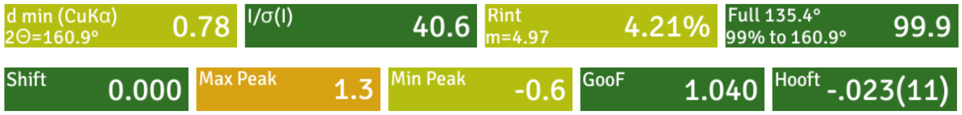


Experimental. Single colourless block-shaped crystals of **I-48** used as received. A suitable crystal with dimensions 0.47 × 0.41 × 0.08 mm^3 was selected and mounted on a nylon loop with paratone oil on a XtaLAB Synergy, Dualflex, HyPix diffractometer. The crystal was kept at a steady T = 100.00(10) K during data collection. The structure was solved with the ShelXT (Sheldrick, 2015) solution program using dual methods and by using Olex2 1.5 (Dolomanov et al., 2009) as the graphical interface. The model was refined with ShelXL 2018/3 (Sheldrick, 2015) using full matrix least squares minimisation on $\boldsymbol{F}^2$.

Crystal Data. $C_{16}H_{12}Br_2O_2$, M_r = 396.08, orthorhombic, $P2_12_12_1$ (No. 19), a = 7.26750(10) Å, b = 8.70150(10) Å, c = 21.9198(4) Å, $\alpha = \beta = \gamma = 90^\circ$, V = 1386.17(4) Å^3, T = 100.00(10) K, Z = 4, Z' = 1, m(Cu K_a) = 7.403, 14730 reflections measured, 2977 unique (R_{int} = 0.0421) which were used in all calculations. The final wR_2 was 0.1225 (all data) and R_1 was 0.0437 (I≥2 s(I)).

Compound	**I-48**
Formula	$C_{16}H_{12}Br_{2}O_{2}$
CCDC	2291840
$D_{calc.}$/ g cm^{-3}	1.898
m/mm^{-1}	7.403
Formula Weight	396.08
Colour	colourless
Shape	block-shaped
Size/mm^{3}	0.47×0.41×0.08
T/K	100.00(10)
Crystal System	orthorhombic
Flack Parameter	-0.039(17)
Hooft Parameter	-0.023(11)
Space Group	$P2_{1}2_{1}2_{1}$
a/Å	7.26750(10)
b/Å	8.70150(10)
c/Å	21.9198(4)
α/°	90
β/°	90
γ/°	90
V/Å^{3}	1386.17(4)
Z	4
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K$_{a}$
Q_{min}/°	4.034
Q_{max}/°	80.431
Measured Refl's.	14730
Indep't Refl's	2977
Refl's I≥2 s(I)	2923
R_{int}	0.0421
Parameters	181
Restraints	0
Largest Peak	1.262
Deepest Hole	-0.632
GooF	1.040
wR_{2} (all data)	0.1225
wR_{2}	0.1221
R_{1} (all data)	0.0442
R_{1}	0.0437

Structure Quality Indicators



Reflections:	d min (CuKα) 2Θ=160.9° 0.78	I/σ(I) 40.6	Rint m=4.97 4.21%	Full 135.4° 99% to 160.9° 99.9	
Refinement:	Shift 0.000	Max Peak 1.3	Min Peak -0.6	GooF 1.040	Hooft -.023(11)

A colourless block-shaped-shaped crystal with dimensions 0.47×0.41×0.08 mm^3 was mounted on a nylon loop with paratone oil. Data were collected using a XtaLAB Synergy, Dualflex, HyPix diffractometer equipped with an Oxford Cryosystems low-temperature device, operating at T = 100.00(10) K.

MSU Data were measured using w scans using Cu K_a radiation (micro-focus sealed X-ray tube, 50 kV, 1 mA). The total number of runs and images was based on the strategy calculation from the program CrysAlisPro 1.171.42.99a (Rigaku OD, 2023). The achieved resolution was Q = 80.431.

Cell parameters were retrieved using the CrysAlisPro 1.171.42.99a (Rigaku OD, 2023) software and refined using CrysAlisPro 1.171.42.99a (Rigaku OD, 2023) on 11110 reflections, 75 % of the observed reflections. Data reduction was performed using the CrysAlisPro 1.171.42.99a (Rigaku OD, 2023) software which corrects for Lorentz polarization. The final completeness is 99.90 out to 80.431 in Q CrysAlisPro 1.171.42.99a (Rigaku Oxford Diffraction, 2023) Spherical absorption correction using equivalent radius and absorption coefficient. Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

The structure was solved in the space group $P2_12_12_1$ (# 19) by using dual methods using the ShelXT (Sheldrick, 2015) structure solution program. The structure was refined by Least Squares ShelXL incorporated in Olex2 software program. All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model, except for the hydrogen atom on the non-carbon atom(s) which were found by difference Fourier methods and refined isotropically when data permits.

CCDC 2291840 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

There is a single formula unit in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1. The moiety formula is C16 H12 Br2 O2. The Flack parameter was refined to -0.039(17). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in -0.023(11). The chiral atoms in this structure are: C1(S). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

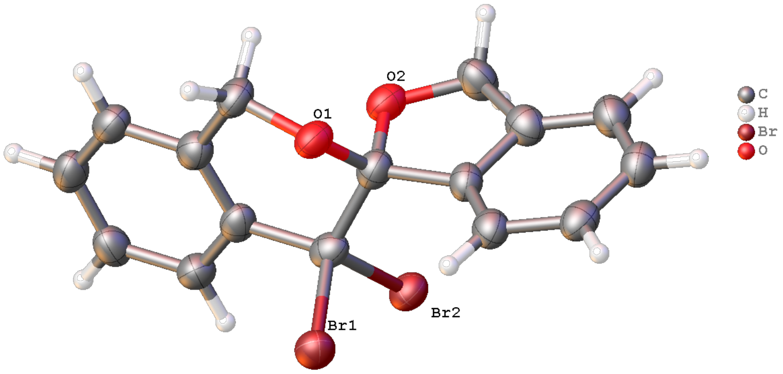


Figure I-42: Drawing at 50% ellipsoids with the hetero atoms labelled.

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CHAPTER II: TOWARDS THE TOTAL SYNTHESIS OF OBTUSIN APPLYING THE CONCEPT OF DIBROMOSPIROKETALIZATION

INTRODUCTION

Obtusin is a 15-carbon non-terpenoid natural product isolated by Clardy *et. al*. from the Mediteranean red alga *Laurencia obtusa* in 1979.[1-3] Obtusin contains a uniquely fused bicyclic-spiroketal system and a propargylic bromide unit which provides a unique pharmacological feature such as cytotoxic activities against various cancer cell lines and/or showed antiviral, antibacterial, antimalarial, antifouling, antifungal, antioxidant, and other activities.[4-7] These molecules have a unique [5-5-5] fused ring system, among which two rings are spirocylic. Having eight contiguous stereocenters with three bromine atoms as core functional group incorporated in their structure, they possess synthetic challenges to make them attractive target molecules. Interestingly, there has been no reports thus far for the total synthesis of Obtusin. Our strategy towards Obtusin takes advantage of the crucial rule of protecting groups to access the desirable selectivity in forging the skeleton of this molecule. We envisioned the synthesis of Obtusin using the already developed diastereoselective bromospiroketalisation approach. As illustrated in Figure II-1, we envisioned this to be assembled from a linear analogue **II-1**[8] through two-bromo functionalization pathway: firstly, a diastereoselective bromo-etherification followed by a consecutive dibromospiroketalisation (discussed in detail in the subsequent sections).

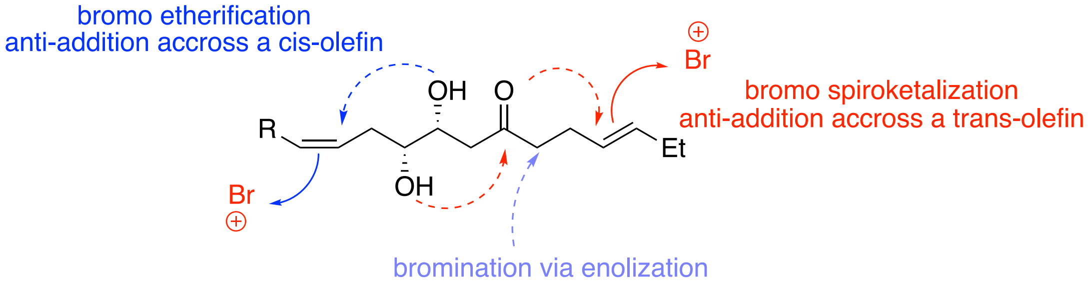


Figure II-1: Conceptual design towards the synthesis of Obtusin from the linear analogue **II-1.**

Initial result and Development of the Dibromospiroketalization

During the development of the mono-bromospiroketalization reaction an interesting observation was noted. When the reaction was carried out in the absence of ethanol, a second bromine atom was incorporated at the α-position of initial carbonyl centre. In order to rationalize the above observation, the stereoelectronics associated with the 6-membered oxocarbenium were exploited towards a dual functionalization of the keto-alkenols **II-2**. As depicted in Figure **II-2**, when ethanol was excluded from the reaction mixture, the oxacarbenium intermediate putatively undergoes α-deprotonation to generate vinyl ether **B**. This vinyl ether **B** would then capture an additional bromonium ion under the reaction conditions to finally furnish its dibromo-congener **II-3**. This process is known as **dibromospiroketalization**.[9] The second bromenium is captured in a pseudo

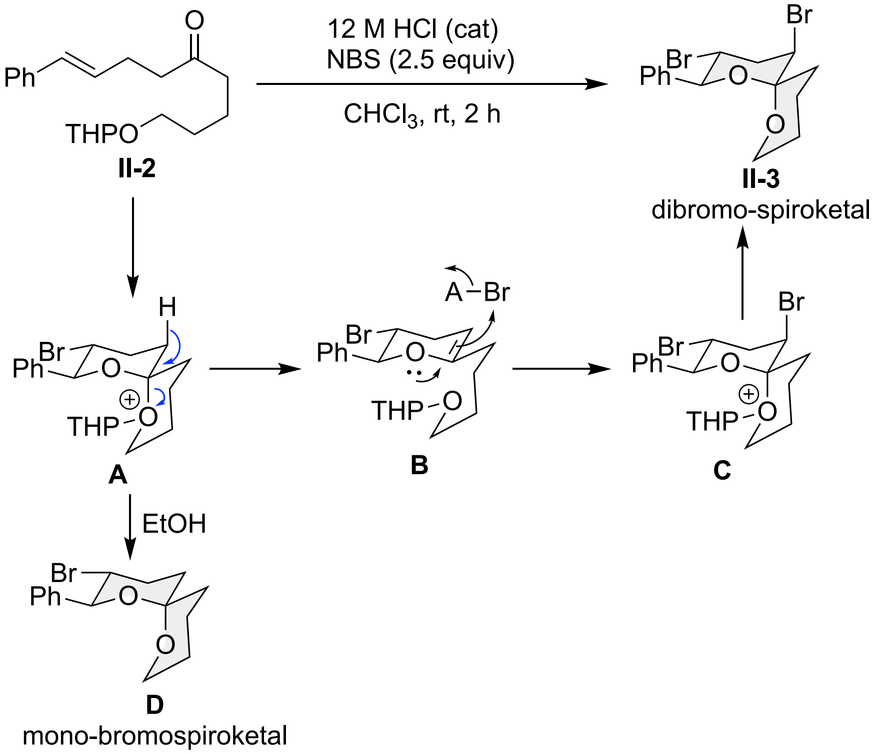
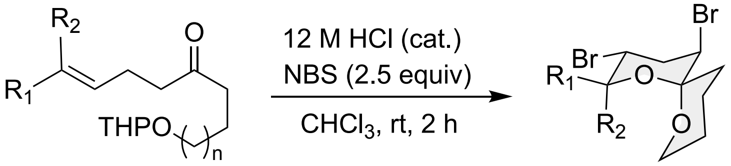


Figure II-2: Probable mechanistic pathway for dibromospiroketalization.

axial approach (compound **C**) that leads to the high diastereoselectivity of the product. This highly diastereoselective dibromo-spiroketalization would readily lead to the construction of the spirocyclic motif in Obtusin in one step and thus reduce the number of steps and ease the synthetic strategy.

Table II-1: Substrate scope for dibromospiroketalization.



Entry[a]	R_1	R_2	n	Yield (%)[b]	*dr*[c]
1	Ph (**II-3**)	H	2	87	>98 : 2
2	Ph (**II-4**)	H	1	73	>98 : 2
3	α-naphthyl (**II-5**)	H	2	88	>98 : 2
4	β-naphthyl (**II-6**)	H	2	61	>98 : 2
5	*p-Me*-Ph (**II-7**)	H	2	74	>98 : 2
6	*p-F*-Ph (**II-8**)	H	2	65	>98 : 2
7	H (**II-9**)	*n*-Bu	1	88	2 : 1

[a] Reactions were performed on 0.1 mmol scale. [b] Isolated yield. [c] *dr* were obtained from ^{1}H NMR.

After the successful development of this methodology, in order to showcase the generality a brief substrate scope was investigated. **Table II-1** summarizes the results for a handful of keto-alkenols that were subjected to the optimized conditions for di-bromospiroketalization. Most of these substrates were well tolerated and generated the desired product in good yield and excellent diastereoselection. Catalytic amount of acid was instrumental in facilitating the above transformation. The role of acid was crucial, as it served two purposes. Firstly, it helped in the generation of a stronger brominating agent through protonation of NBS and thus decreasing its *HalA* values [*HalA*$_{\text{(NBS)}}$ = 197 kcal/mol, *HalA*$_{(NBS+HCl)}$ = 166.6 kcal/mol].[9-11] Secondly, the conjugate base was also helpful in deprotonation at the α-position and generation of the vinyl ether **B**. Sterics and electronics of the substituted olefins did not have a significant effect on the overall outcome. *Trans*-disubstituted substrates with different *p*-substituted arenes were well tolerated, providing products **II-3** – **II-8** in good yields (>60%), excellent *dr* (>98:2). Even when the chain length was shortened the [6,5]-dibromospiroketal **II-4** was formed in high yield (73%) and excellent *dr* (>98:2).

A significant outcome of this substrate scope was the fact that when the carbon chain length was shortened it generated the [5,5]-di-bromospiroketal **II-9** albeit in less selective fashion (*dr* : 1: 1.6). This is presumably due to the fact that these 5-membered rings are devoid of the anomeric stabilization because of the skewed stereoelectronics of the oxocarbenium embedded in a 5- membered ring. Unlike the [6,6]-spiroketals, the stereoelectronics involved in the skewed framework of [5,5]-spiroketals does not benefit fully from the anomeric effect.[12] The diastereomeric transition states corresponding to the assembly of [5,5]-spiroketals do not have a significant energetic bias hence, the observed moderate diastereoselectivity.[13] But this result was inspiring to pursue the total synthesis of Obtusin.

Retro-Synthesis of Obtusin

Our retrosynthetic approach to Obtusin was inspired by the proposed biosynthetic pathway.[1] Our initial research plan was construed based on the stereochemistry around C_3, C_4, C_{12}, C_{13} involving an *anti*-addition across both *trans* C_{12}-C_{13} and C_3-C_4 *cis*-double bonds. Obtusin can be obtained from its congener compound **II-14** through functional group modifications. Compound **II-14** can be synthesized from keto-alkenol **II-13** through our dibromospiroketalization protocol. Compound **II-13** is an ether consisting of a highly functionalized THF ring. Cyclisation of the protected keto-en-ol **II-12** involving a bromo-etherification reaction can lead to the formation of **II-13**. This linear polyketide **II-12** can be perceived through the installation of alkyl chains across the chiral R,R-dioxirane **II-11** which can be easily synthesized from (D)-tartaric acid following known synthetic procedures.[14, 15]

Towards the total synthesis of Obtusin

Initial Research Plan

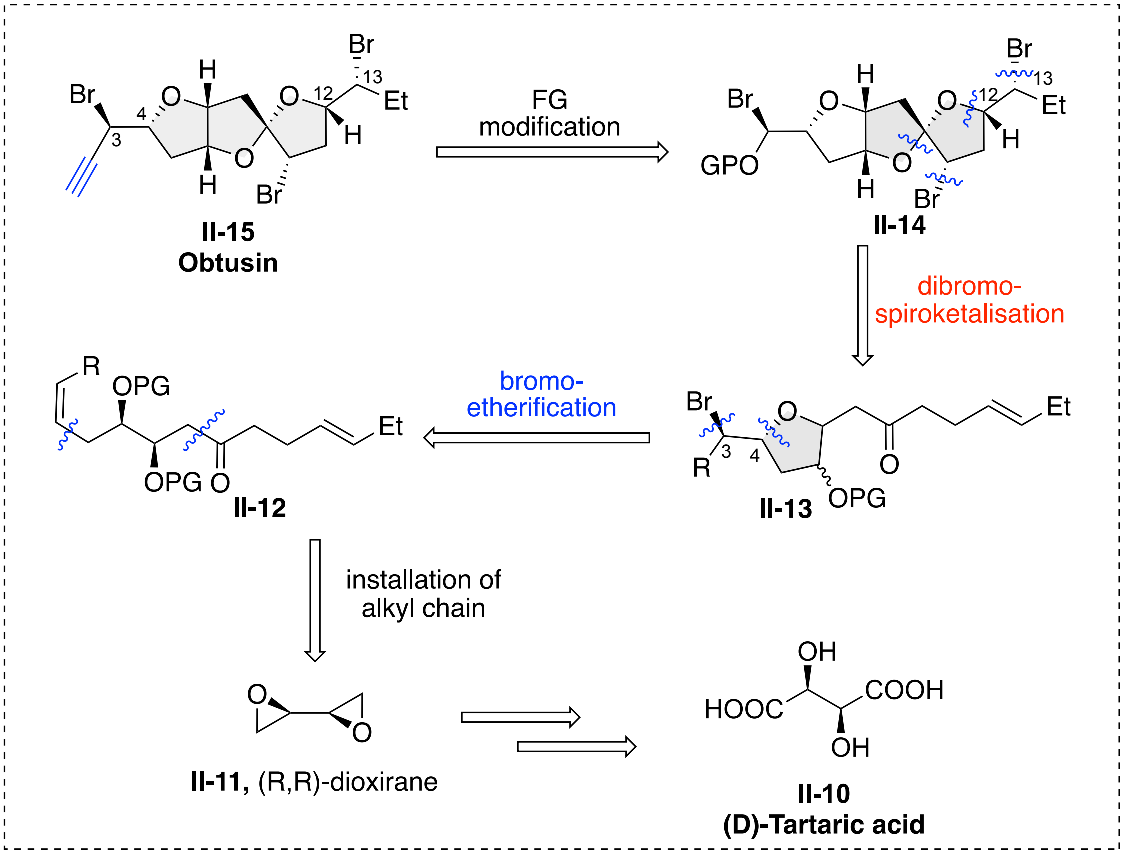


Figure II-3: Retrosynthetic approach towards obtusin.

Our total synthesis of Obtusin began with the synthesis of the enantiopure R,R-dioxirane **II-11**, which was the lynchpin for setting up the stereochemistry for the rest of the carbon chain for the natural product. As depicted in Figure II-4, the R,R-dioxirane **II-11** was synthesized from (D)-tartaric acid **II-10** following a sequence of 6 steps in decent yields.[14, 15]

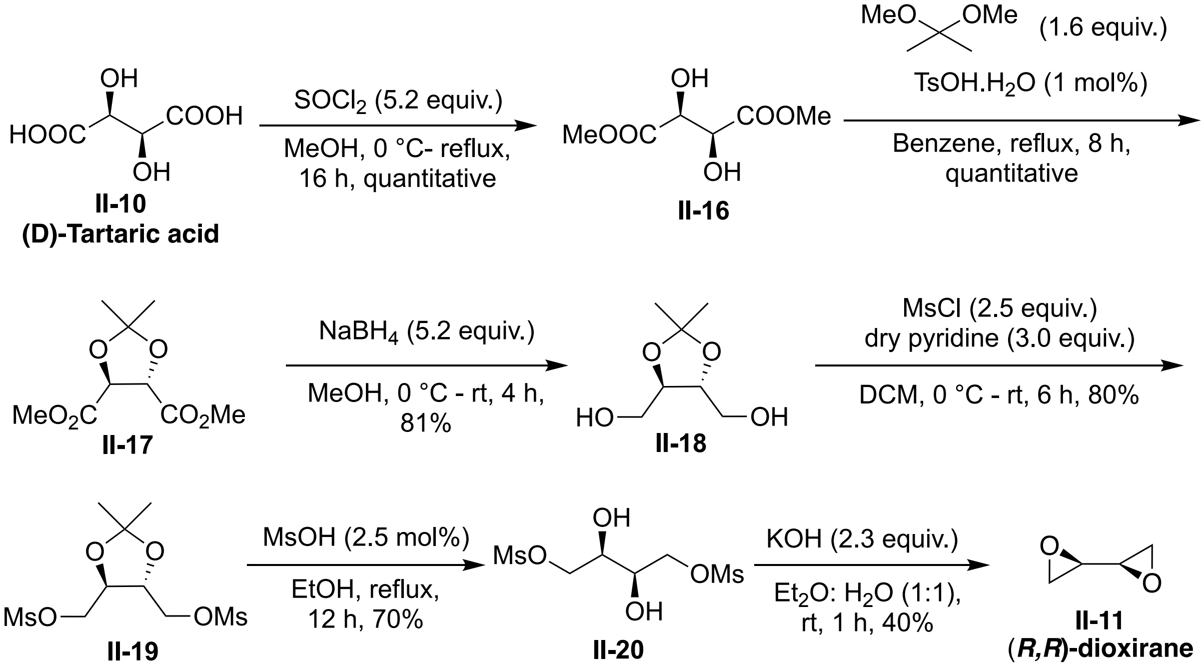


Figure II-4: Synthesis of (*R,R*) **II-11** from tartaric acid.

The synthetic strategy involves the differential addition of alkyl chains across the two epoxide rings to generate molecule **II-12**. The synthesis began with the ring opening of one epoxide ring of the R,R-dioxirane to generate the epoxy-alcohol (**II-22**) with the

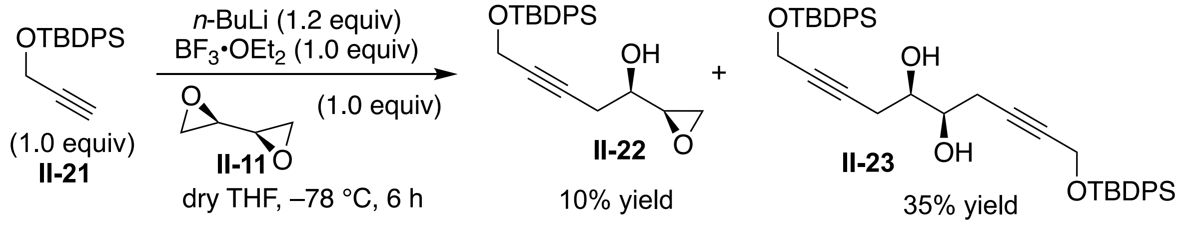
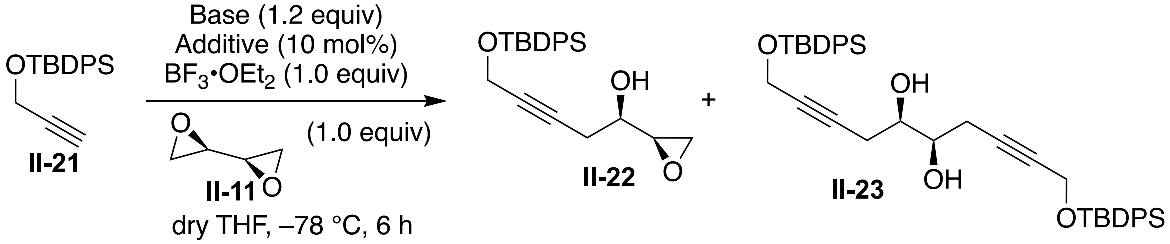


Figure II-5: Reaction of the alkynyl anion with (*R,R)*-**II-11**.

alkynyl anion formed from the treatment of **II-21** with *n*-BuLi.[16] The side product of this reaction was the formation of the diol involving a double addition of the alkynyl anion across both epoxides. Unfortunately, the mono-epoxy alcohol **II-22** and the diol product **II-23** appear at the same R_f, rendering their separation difficult. Thus, a second reaction was performed on the crude reaction mixture involving the protection of the corresponding diol **II-23** to an acetal which would correspondingly change the diol to a non-polar product and ease the separation on the mono-ol **II-22** and the diol **II-23**. As a result, the overall yield of this step was low (5% -10%). A series of reaction conditions were tried to improve

Table II-2: Optimization of reaction parametersfor the formation of epoxyalkynol **II-22.**



Entry[a]	Base	Additive	Yield (%)	
			II-22	**II-23**
1	*n*-BuLi	none	10	35
2[b]	*n*-BuLi	none	25	30
3[c]	*n*-BuLi	none	12	30
4	*t*-BuLi	none	12	22
5	NEt_3	CuBr	10	12
6	*i*-Pr_2NEt	CuBr	10	12
7	*n*-BuLi	CuBr	35	30
8[d]	*n*-BuLi	CuBr	33	22
9	*n*-BuLi	CuI	30	25
10	*n*-BuLi	$AlMe_3$	-	-

[a] Reactions were performed on 0.1 mmol scale. [b] Inverse addition. [c] 2.0 equiv of *n*-BuLi was used. [d] 20 mol% CuBr was used.

the overall yield of this step but none gave a significant improvement. The highest yield achieved was 35% when the alkynyl anion was reacted with (*R,R*)- **II-11** in the presence of *n*-BuLi (1.2 equiv) and $BF_3.Et_2O$ (1.0 equiv) with CuBr (10 mol%) (Table II-2, entry 7).

With the optimised condition in hand, subsequent reduction of the epoxyalkynol **II-22** was performed to generate the corresponding *cis*-alkene **II-24** (Figure II-6). The reduction was monitored through ^{1}H NMR as over reduction led to formation of inseparable mixtures. The reduction was completed in 15 min resulting in the formation of the *cis*-olefin **II-24** in quantitative yields. Allowing longer reaction time leads to the formation of the over reduced product, rendering the separation of the mixtures difficult, so was the case when incomplete reduction occurred since the R_f of the alkyne and the alkene were close. The installation of the second alkyl chain was pursued with multiple groups being used as surrogate for the alkyl chain.

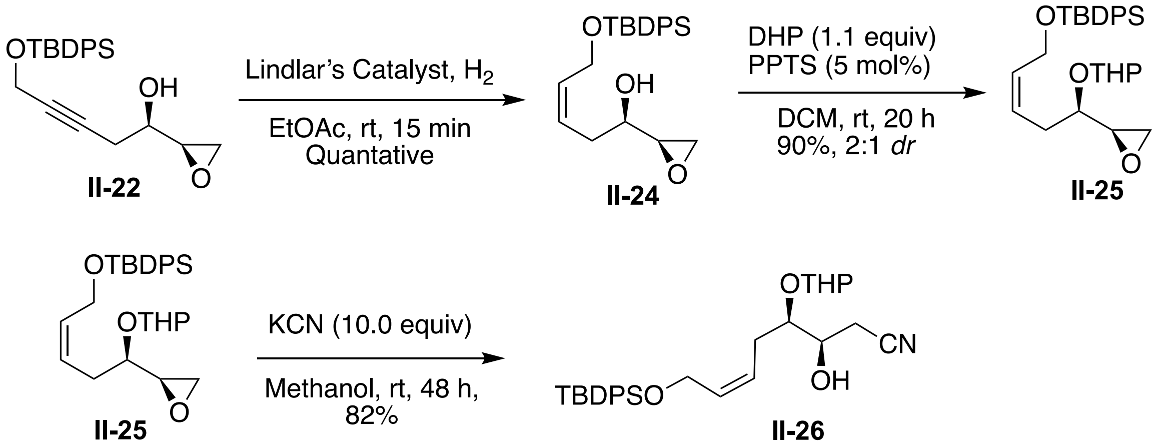


Figure II-6: Installation of the alkyl fragments to synthesize **II-26.**

The addition of the dithianyl anion **II-43** was pursued under multiple different conditions only to yield the starting material back from the reaction mixture. Another effort involved the displacement of a leaving good leaving group with the carbanion **II-43,** but such attempts were also unsuccessful under multiple different reaction conditions (Figure II-7). It was realized that the nitrile can serve as the best surrogate for this purpose (Figure II-6). Hence the epoxide was treated with potassium cyanide in methanol to give the alcohol **II-26** in good yield.[17]

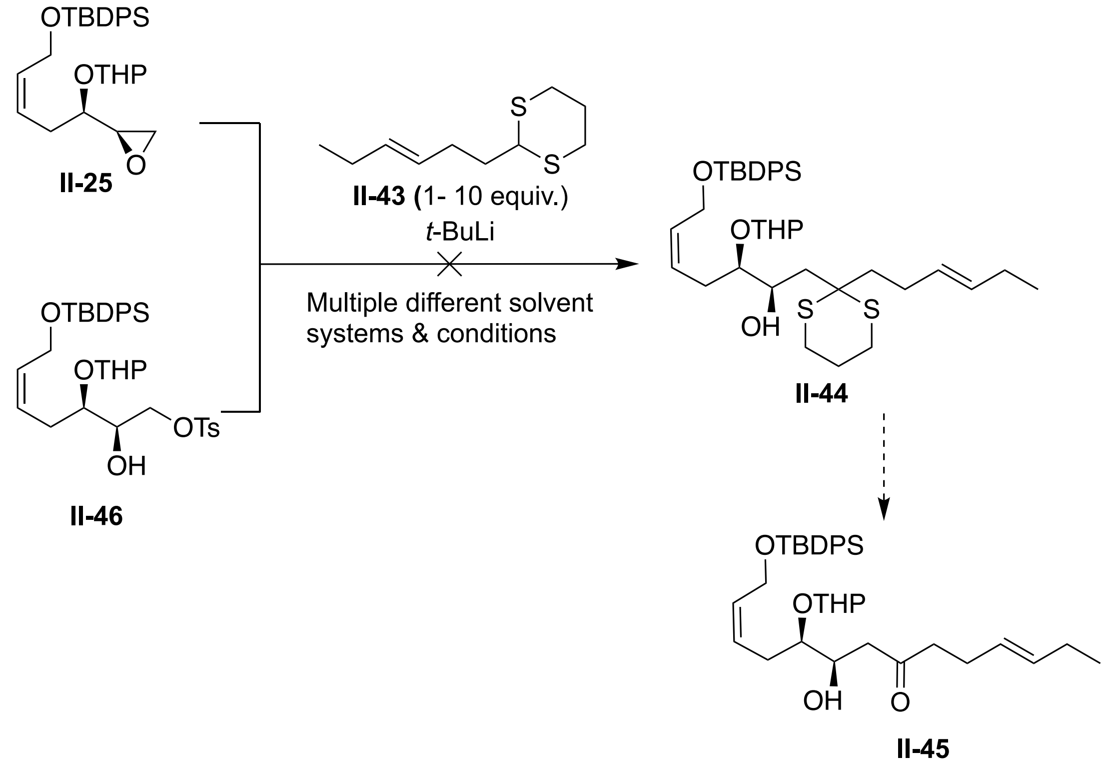
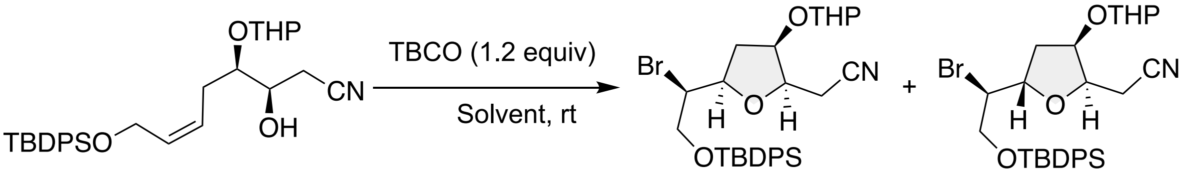


Figure II-7: Efforts towards the installation of the second alkyl fragments.

With **II-26** in hand, bromo-etherification of the *cis* olefin was attempted. Bromo etherification of **II-26** resulted in the formation of two diastereomeric tetrahydrofuran rings **II-27** (minor, desired) and **II-28** (major, undesired) in ratio of 1: 20. This result stems from the opposing face selectivity of the *cis* olefin in the bromo etherification step (*Re* face attack leading to **II-27** while *Si* face attack yields **II-28**).

Table II-3: Initial screening result for the bromo-etherification reaction.



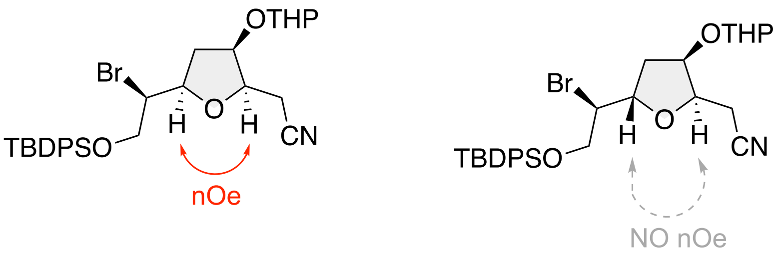
II-27 Desired diastereomer

II-28 Undesired diastereomer

Entry[a]	Solvent	% Conversion[b]	*dr* (**II-27** : **II-28**)[c]
1	DCM	>99	1 : 20
2	Toluene	>99	1 : 16
3	DMF	>99	1 : 1.6
4	Methanol	>99	1 : 1.5
5	ACN	>99	1 : 1.6
6	ACN : TFE (1:1)	>99	1 : 1.7
7[d]	THF : HMPA (50:1)	>99	1 : 1
8[e]	THF : HMPA (50:1)	>99	1 : 1
9[f]	THF : HMPA (50:1)	30	1 : 1
10[g]	THF : HMPA (50:1)	>99	1 : 1

[a] Reactions were performed on 0.1 mmol scale. [b] Conversions were obtained from ^{1}H NMR using MTBE as an internal standard. [c] *dr* were obtained from ^{1}H NMR. [d] Isolated yields of **II-27** was 46% and **II-28** was 49%. [e] Reaction was done at 0 °C. [f] Reaction was done at –78 °C. [g] NBS was used instead of TBCO.

TBCO has been used in the literature as a mild brominating agent for bromo-etherifications, delivering products in high yields and diastereoselectivity.[18, 19] Using TBCO (2,4,4,6-tetrabromo-2,5-cyclohexadienone) as the bromine source in DCM led to the formation of undesired diastereomer **II-28** as the major diastereomer (>20: 1 *dr*), (entry 1, Table II-3). The use of more polar solvents favored the formation of the desired diastereomer **II-27**. When HMPA was added to THF as co-solvent in a ratio of (50 : 1) the formation of the desired diastereomer was enhanced to a ~1:1 ratio. Other brominating agents like NBS also gave poor diastereoselectivity of the desired product (Table II-3, entry 10). Reactions performed at different temperatures also did not lead to any improvement in the selectivity of the desired product (entries 8 and 9, Table II-3).



Desired diastereomer

Undesired diastereomer

Figure II-8: Assignment of relative stereochemistry for the desired **II-27** and the undesired diastereomer **II-28.**

The relative stereochemistries of diastereomers **II-27** and **II-28** were established using 2D NMR analysis. As illustrated in Figure II-8, for the desired diastereomer **II-27**, nOe correlations between hydrogen atoms on both ethereal carbon atoms confirm their *syn* geometry. However, for the undesired diastereomer **II-28**, nOe between these two hydrogen atoms was not observed, while a series of the other nOe correlations confirmed the illustrated relative stereochemistry.

Since the optimization studies were not successful in generating the desired diastereomeric product as the major product in the bromo-etherification reaction; we sought to understand the reasons behind the origin of the observed selectivity in this reaction. We were interested in investigating the assembly of the nucleophile, olefin and the bromenium ion at the transition state that putatively generated the two diastereomers in the bromo etherification reaction. Hence the approach of the nucleophilic oxygen and the electrophilic bromenium ion across the *cis* double bond were carefully examined (Figure II-9).

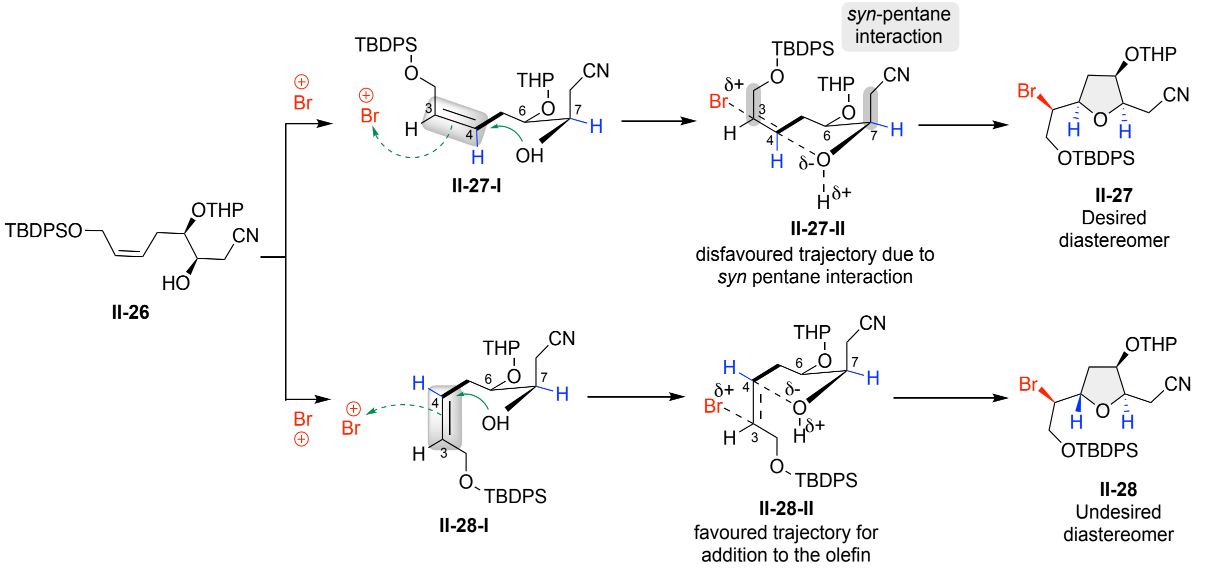


Figure II-9: Relative approaches towards product formation: desired diastereomer **II-27** and the undesired diastereomer **II-28.**

Since halo-etherification is an *anti*-addition process across the double bond, the facial selectivity of the olefin dictated by the presence of the stereocenters in the molecule will result in the generation of the two diastereomers **II-27** & **II-28** as discussed above. As illustrated in Figure II-9, the pre-organized structure **II-27-I** would lead to the desired diastereomer **II-27**, and **II-28-I** would lead to the undesired diastereomer **II-28**. In this putative arrangement, the allylic groups on the *cis* double bond would have a pseudo *syn*-pentane interaction with the group on C-7 that is bearing the nucleophilic oxygen atom. This steric repulsion would disfavor **II-27-II**, and as a result the desired diastereomer will form as the minor product. On the other hand, in **II-28-II**, which leads to the undesired diastereomer, the bulky allylic group on C-3 points to the opposite side of the groups on C-7 and C-6, thus a facile bromo etherification ensues, leading to **II-28** as the major product (Figure II-9). In order to reverse the intrinsic selectivity, the protecting group on of C-6 oxygen was removed. The hypothesis was that with a smaller group on C-6, the carbon chain may adopt a different conformation as compared to **II-26**, thus giving access to the desired diastereomer as the major product. To this end, **II-29** in which the THP group was removed, was subjected to the bromination conditions (Figure II-10). The reaction resulted in a 3:1 diastereomeric ratio in favor of the undesired diastereomer **II-31**.

Since the previous approach towards the bromo-etherification reaction didnot yield the desired result, we sought to look into this problem from a slightly different perspective. From Figure II-9, we can observe that the formation of the undesired diastereomeric product occurres as a result of the less steric interaction in **II-28-II** as compared to **II-27-II**. In order to reverse this effect, we hypothesized the presence of added sterics on the C-7 hydroxyl (since the hydroxyl group is directly involved during the bromo etherification) might lead to the desired product (Figure II-11). The group that would be introduced should have two basic characteristics: First, be large enough to induce steric repulsion as well as, easily removable so that it could participate in the bromo-etherification and thus reverse the intrinsic selectivity. The hypothetical group on the nucleophilic oxygen would suffer from a *syn*-pentane interaction with the groups on the allylic position of the *cis*

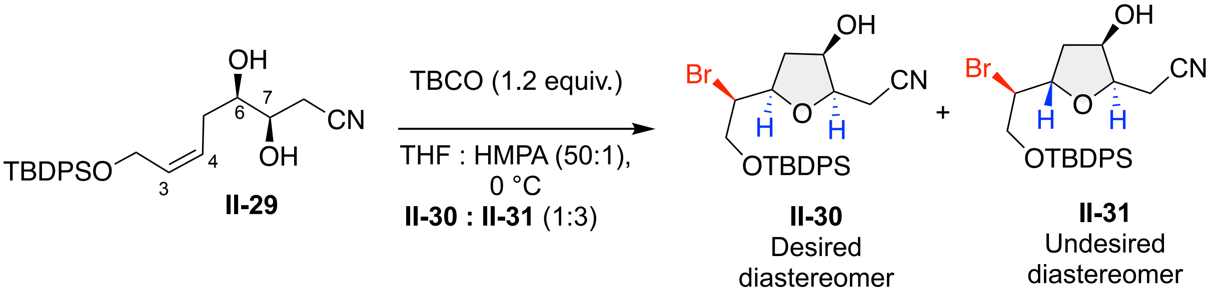


Figure II-10: Results following the C-6 deprotection.

olefin, thus the approach highlighted in **II-28-II** would suffer, hence a reversal in the diastereoselectivity (Figure II-11).

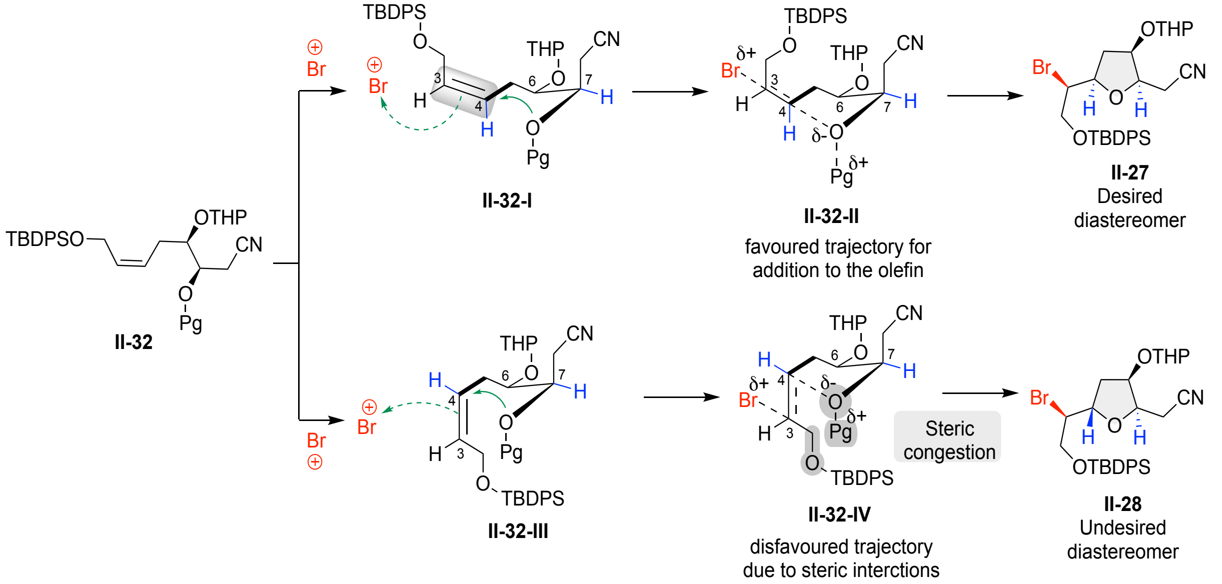
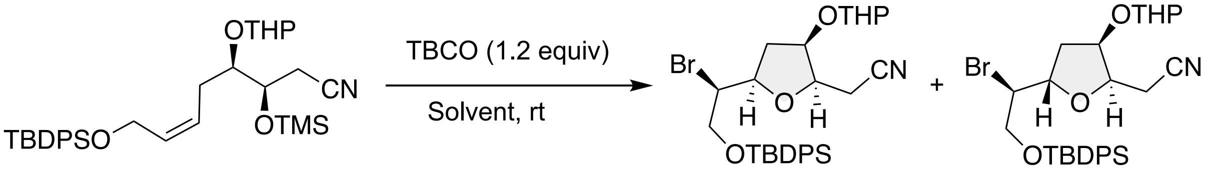


Figure II-11: Relative approaches towards product formation after the introduction of the protecting group: desired diastereomer **II-27** and the undesired diastereomer **II-28.**

To test this hypothesis, trimethylsilylchloride (TMS as the protecting group) was chosen because it satisfies both criteria (Figure II-11). Alcohol **II-26** was reacted with TMSCl to provide the protected alcohol **II-32** in nearly quantitative yield. With **II-32** in hand, when the previously obtained condition of bromo etherification was implemented (Table II-3, entry 7) the desired diastereomer **II-27** formed as a major product with >10:1 selectivity (Table II-4, entry 1). As illustrated in Table II-4, further optimization of the reaction parameters led to DCM as the solvent of choice, with methanol (10.0 equiv.), as the scavenger of TMS group (Table II-4, entry 9) leading to the formation of the desired product **II-27** in >85% yield along with small amount of the undesired diastereomer **II-28** (<5%). The reaction produced similar result even when performed on gram scale.

Table II-4: Final screening result for the bromo-etherification reaction with the protecting group.



II-27
Desired diastereomer

II-28
Undesired diastereomer

Entry[a]	Solvent	% Conversion[b]	*dr* (**II-27** : **II-28**)[c]
1[d]	THF : HMPA (50:1)	>99	>10 : 1
2	DCM	25	>10 : 1
3	THF	90	2 : 1
4	DCM : Water (9:1)	40	>10 : 1
5	DCM : MeOH (9:1)	>99	14 : 1
6	$CHCl_3$: MeOH (9:1)	>99	>15 : 1
7[e]	DCM : MeOH (9:1)	>99	15 : 1
8	DCM : EtOH (9:1)	>99	>10 : 1
9[f]	DCM	>99	>15 : 1
10[f,g]	DCM	>99	>15 : 1

[a] Reactions were performed on 0.1 mmol scale. [b] Conversions were obtained from ^{1}H NMR using MTBE as an internal standard. [c] *dr* were obtained from ^{1}H NMR [d] Isolated yields of **II-27** was 75% and **II-28** was 8%. [e] Reaction was done at 0 °C. [f] MeOH (10.0 equiv) was used as an additive. [g] Reaction was done at 1.0 mmol scale, isolated yield of **II-27** was 85% and **II-28** was 4%.

With **II-27** in hand the we focuused on the introduction of the next alkyl chain fragment. When **II-27** was reacted with *in situ* generated (*E*)-3-hexen-yl lithium **II-33**, compound **II-34** was expected but was obtained in trace amount, returning the nitrile starting material as the major isolated compound. Reaction at higher temperatures or longer reaction times, resulted in complex mixture of products. Products originating from decomposition or degradation of the ring were the major side products of the reaction. Presence of the labile bromide on **II-27** could be the major issue that hampers the ketone formation. Future plan involves the optimization of this step to enhance the yield and subsequent application of the conditions previously developed for dibromospiroketalization to get to the natural product (Figure II-12). This would focus on the use of milder reagents involving alkyl magnesium (Grignard reagents),[20-25] alkyl zinc (Barbier coupling)[23-26] and alkyl chromium reagents (NHK coupling).[27]

Major Drawbacks and Alternate Approach Towards Obtusin:

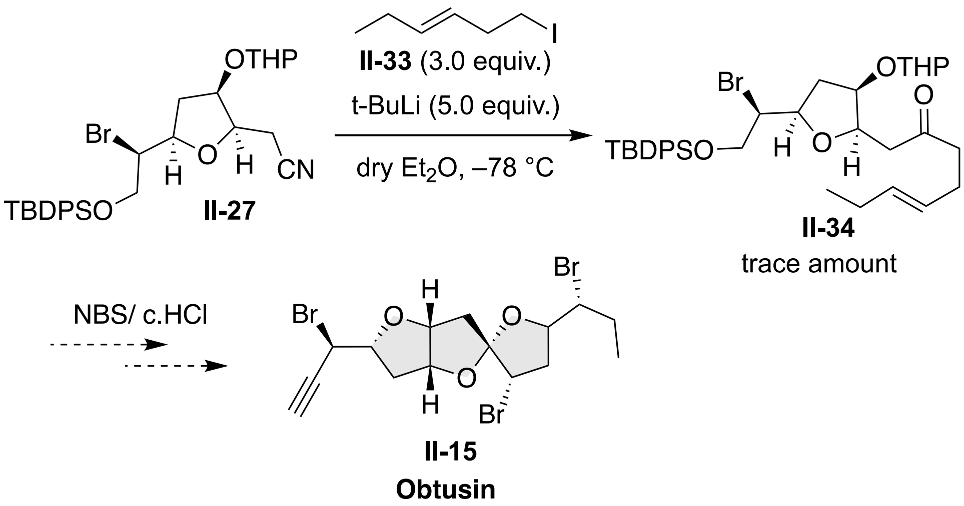


Figure II-12: Conversion of nitrile to the ketone **II-34**.

There were certain drawbacks in our previously devised synthetic route that led to cumbersome isolation procedures and reduction of yield. Firstly, the final step to synthesize the chiral R,R was low yielding (30% - 45%). This was majorly because the final product chiral *R,R-dioxirane* (**II-11**) was volatile and during the purification stage a large part of it would be lost. A reduced yield meant only a small amount of material would actually be used for the total synthesis. Secondly, the first step in the total synthesis involving the opening of one epoxide ring leading to the formation of the epoxy-alcohol **II-22** was tricky and challengeing. Even with our best efforts, only 35% yield of the desired product of the epoxy alcohol **II-22** could be obtained. These two major steps slowed the progress of the total synthesis as large efforts were directed towards the synthesis of the starting materials.

Current Approach:

As illustrated in Figure II-13, our plan of circumventing these challenging issues revolved around the fact that since the major steps were working fine; the two low yielding steps could be bypassed and merged into the actual synthesis route that had been previously developed.

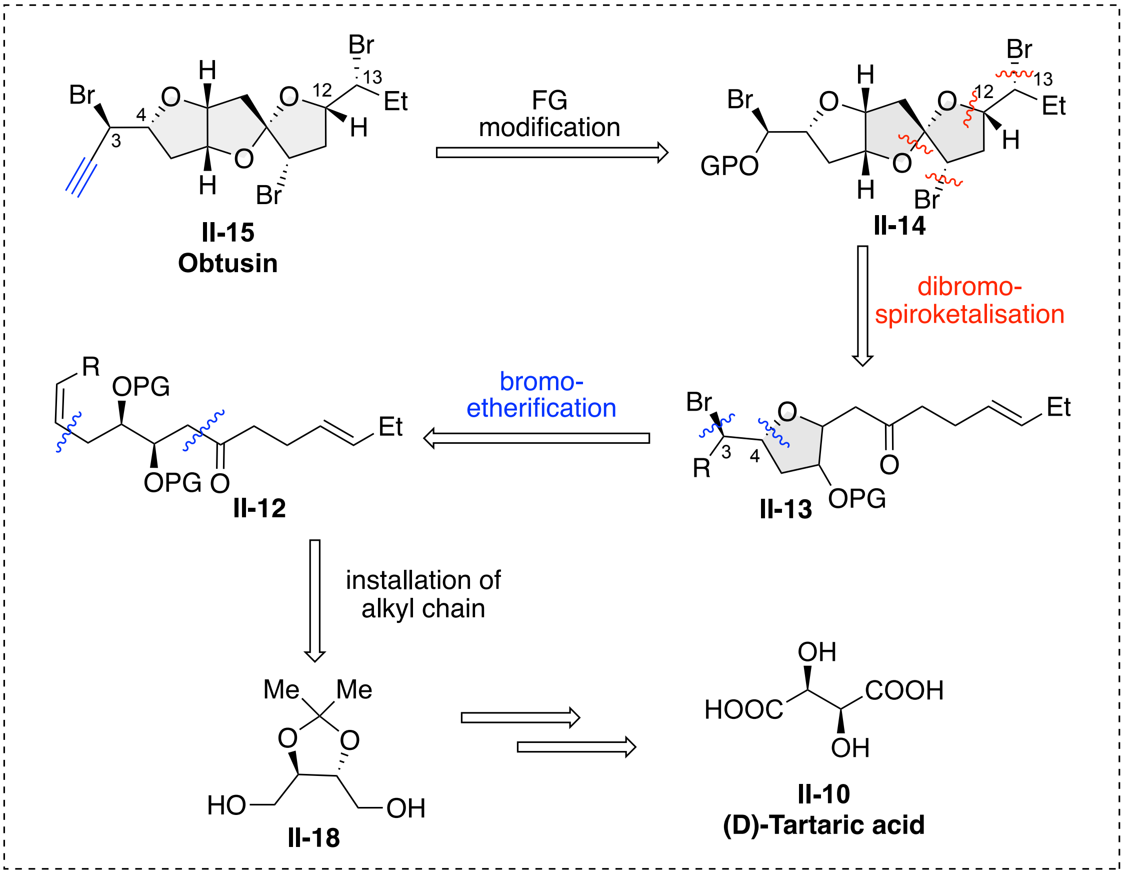


Figure II-13: New retrosynthetic approach towards obtusin.

In this approach, (D)-taratric acid is converted to its diester **II-16**, reacting it first with thionyl chloride, and subsequently refluxing it in methanol. The diols are protected as acetals to generate **II-17**, which is then reduced in the presence of $NaBH_4$ in methanol to generate the desired protected diol **II-18** in 81% yield over 3 steps (Figure II-4).

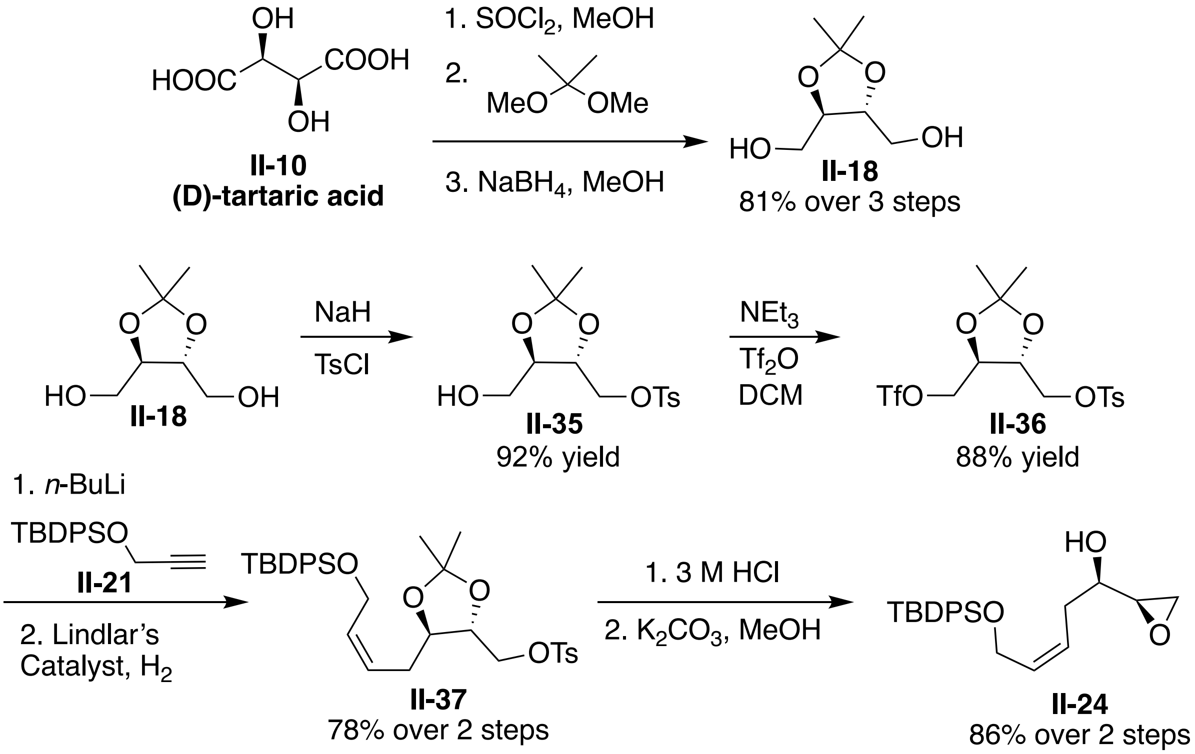


Figure II-14: Current approach towards the total synthesis of obtusin.

The protected diol **II-18** is then differentially protected so as to assemble two different alkyl chains *in lieu* of the alcohols. As shown in Figure II-14, diol **II-18** is mono protected as tosylate **II-35** in the presence of TsCl and NaH.[28] For this transformation equiv of TsCl and base, as well as the reaction time and temperature were important, otherwise the ditosylated product was isolated as the major product. **II-35** was then converted to **II-36** under mild reaction condition in good yield.[29, 30] **II-36** was reacted with alkynyl anion generated from the treatment of **II-21** in the presence of *n*-BuLi to give the alkyne addition product in good yield.[30-33] This acetal protected alkyne was reduced in the presence of Lindlar's catalyst to generate the *cis* oelfin **II-37** in quantitative yield with an overall yield of 78% for 2 steps. With **II-37** in hand, the acetal was cleaved by treatment in mild HCl (3M), and mild basic conditions led to the isolation of **II-24** in 86% yield over two steps (Figure II-14). Care must be taken during this last transformation as prolonged reaction time leads to the rearranged Payne reaction products.[34] This leads us to the same compound as our previous route. Although following this route we were able to generate compound **II-24** in lesser number of steps and better yields (43.7 % in this route vs 6.4 % in the previous route).

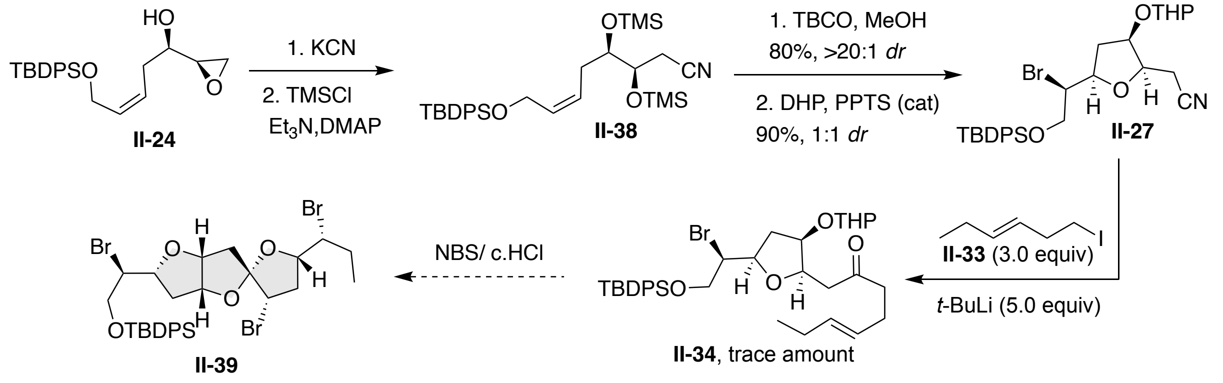


Figure II-15: Current approach towards the total synthesis of tricyclic core **II-39**.

With **II-24** in hand, we approached the total synthesis following two different paths. First, the tri-cycle would be formed in the same step (both bromo etherification and dibromospiroketalization) from the linear polyketide **II-40** & **II-41**. Second, we will persue the path where we will first generate **II-27** and then introduce the alkyl chain to perform the dibromospiroketalization reaction (Figure II-15).

Epoxyalkenol (**II-24**) was reacted with KCN in methanol to generate the cyano-diol **II-29** in 88% yield (Figure II-16).[17] The diols were then protected with TMSCl to generate the diOTMS compound **II-38**. When **II-38** was subjected to the bromo-etherification reaction it generated the correponding desired diastereomer **II-30** with >20:1 selectivity. The free alcohol was protected with DHP to generate compound **II-27** in 90% yield (1:1 *dr*). This would not interfer with the reaction sequence since the THP protection is lost during the dibromospiroketalization. The introduction of the next alkenyl fragment was met with little success, returning the nitrile starting material as the major isolated compound. Reaction at higher temperatures or longer reaction times, resulted in complex mixture of products. Products originating from decomposition or degradation of the ring were the major side products of the reaction. Current efforts are underway to increase the yield of this transformation.

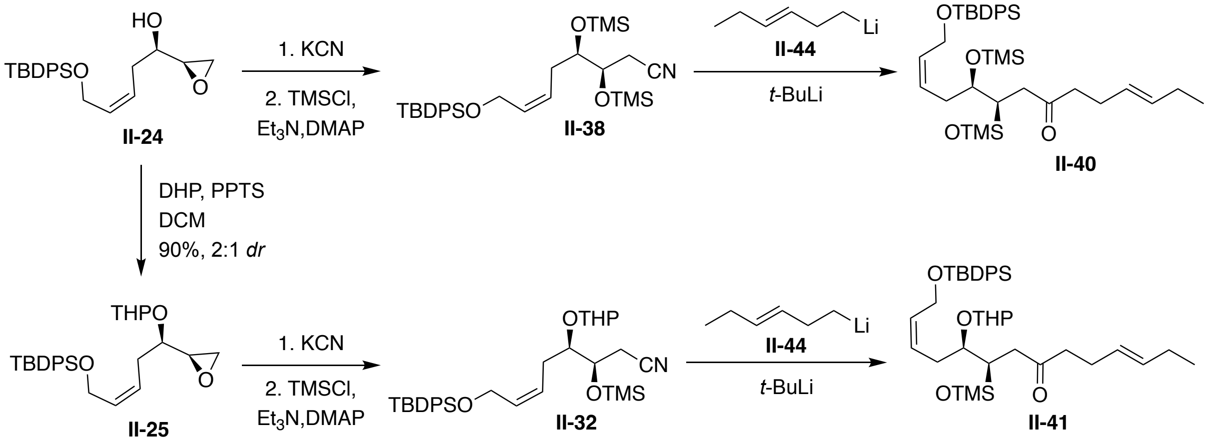


Figure II-16: Synthesis of the linear keto-diene **II-40** & **II-41** for tricyclization.

Since the introduction of the second alkenyl fragment was challenging onto **II-27**, motif we thought to introduce the alkenyl fragment by treating compounds **II-38** and **II-32** with the alkenyl lithium **II-44**. The alkenyl lithium was generated *in situ* from the iodide **II-33** by lithium halogen exchange on treatment with *t*-BuLi. The desired diene **II-40** and **II-41** were formed in good yields. With polyketide **II-40** in hand, we started investigating the possibility of triple bromination condition to generate **II-39**. Unfortunately, we were only able to generate compound **II-42** containing two bromine atoms (Figure II-17). This result is probably because of the deprotection of the acid labile TMS group prior to the entry of third bromine atom. Thus, we envisioned that THP protection would enable us to overcome this challenge and result in the formation of the tricyclic ring.

With the linear keto-dien in hand, current efforts are undergoing for the modification of this protocol and the synthesis of **II-39**. The final cyclisation step is currently being investigated.

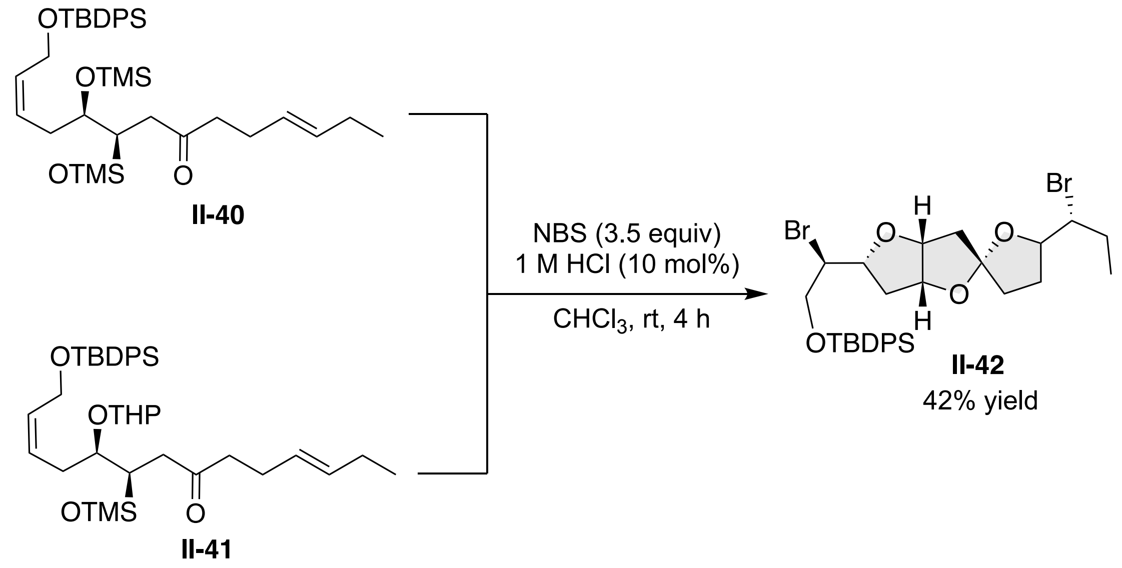


Figure II-17: Current efforts for the cyclization of the linear protected keto-en-ol.

General Remarks:

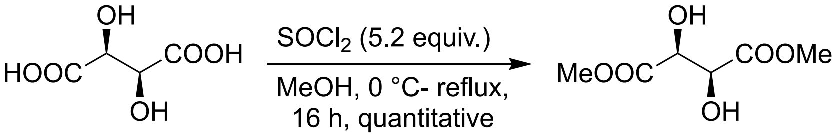
Halofunctionalization reactions were performed in the absence of light. N-chlorosuccinimide (NCS), N-bromosuccinimide (NBS), N-iodosuccinimide (NIS), 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) were re-crystallized prior to use. All other commercially available reagents and solvents were used as received unless otherwise mentioned.

Molecular sieves (4Å) were dried at 160 °C under 0.25 mtorr vacuum prior to use. Unless otherwise mentioned, solvents were purified as follows. $CHCl_3$ (amylene stabilized) was purchased from Sigma Aldrich and incubated over 4Å MS for 48 h prior to use.

Melting points were recorded on a Thomas Hoover capillary melting point apparatus. Agilent Technologies 500/54 Premium Shielded 500 MHz spectrometer was used to record the ^1H NMR and ^{13}C NMR spectra using $CDCl_3$ as solvent. The residual peak of $CDCl_3$ or TMS was used as the internal standard for both ^1H NMR ($\delta = 7.26$ ppm for $CDCl_3$ or $\delta = 0$ ppm for TMS) and ^{13}C NMR ($\delta = 77.16$ ppm). Chemical shifts were reported in parts per million (ppm). Analytical thin-layer chromatography (TLC) was performed on Silicycle silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, or by staining with phosphomolybdic acid in ethanol. Column chromatography was performed with silica gel 60 (230 – 450 mesh). Infrared spectra were recorded on a JASCO FT/IR-6600. Samples were prepared as KBr pellets. High Resolution Mass Spectrometry was performed in the Department of Chemistry at Michigan State University Mass Spec Facility.

Experimental Section

Experimental data towards the synthesis of Obtusin

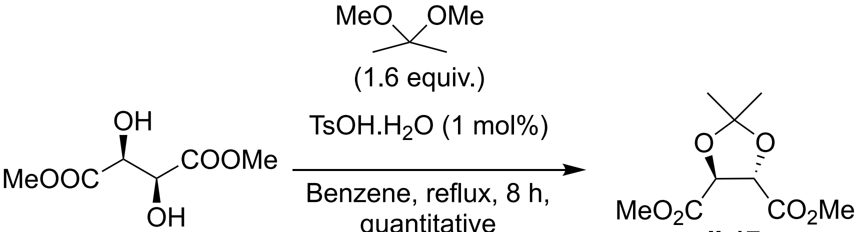


II-10
(D)-Tartaric acid

II-16

Synthesis of *D(-)*-dimethyltartrate (II-16): To a solution of the D(-)-tartaric acid (15.0 g, 100 mmol) in anhydrous methanol (200 ml) was slowly added thionyl chloride (38 ml, 52.4 mmol) at 0 °C. After an hour, the reaction mixture was heated to reflux for 15h to give a pale-yellow solution. Gaseous HCl and methanol were removed under reduced pressure. After extraction of the aqueous layer with ethyl acetate combined ethyl acetate solutions were dried over Na_2SO_4, filtered and concentrated to give the dimethylester **II-16** as pale-yellow jelly oil in quantitative yield (17.8 g, 100.0 mmol). This data is in accordance with the literature reports.[14, 15]

Spectral Data for II-16: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.57 (s, 1H), 3.88 (s, 3H), 2.79 (b, 1H). ^{13}C NMR (125 MHZ, $CDCl_3$): δ 170.01, 76.90, 52.75. IR (cm $^{-1}$): 1690, 1310.

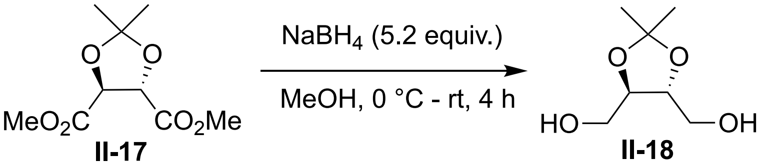


II-16

II-17

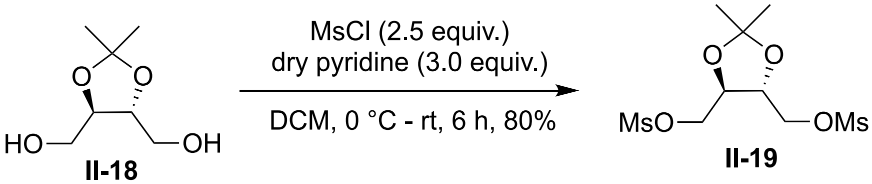
Synthesis of *(-)*-dimethyl 2,3-O-isopropylidene-D-tartrate (II-17): In a round-bottom flask equipped with a magnetic stir bar, Dean-Stark trap and a condenser was added Ddimethyltartrate (29.0 g, 163 mmol), 2,2-dimethoxypropane (31.2 mL, 255 mmol) and benzene (200 mL). TsOH.H_2O (335 mg, 1.76 mmol) was then added at room temperature. The reaction mixture was refluxed and stirred overnight. After stirring for overnight, the reaction mixture was cooled down to room temperature and neutralized with K_2CO_3 till the solution turned pale orangish. The resulting mixture was extracted with ethyl acetate, washed with saturated $NaHCO_3$ solution dried over Na_2SO_4 and concentrated in vacuo to give the crude product. The crude oil was purified by column chromatography (30% ethyl acetate: hexane) to give **II-17** as an orange-yellow oil in quantitative yield (35.6 g, 163 mmol). This data is in accordance with the literature reports.[14, 15]

Spectral data for II-17: ^1H NMR (500 MHz, $CDCl_3$): δ 4.75 (s, 1H), 3.76 (s, 3H), 1.43 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.01, 113.77, 76.90, 52.75. IR (cm^{-1}): 1678, 1370, 1170.



Synthesis of *2,3*-Di-O-isopropylidene-D-theritol (II-18): To a solution of **II-17** (19.6 g, 89.8 mmol) in methanol (300 ml) was added portion-wise $NaBH_4$ (17.8 g, 471 mmol) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 4h at the same temperature. After stirring for 4h the resulting solution was concentrated in *vacuo*. The residue was dissolved in EtOAc and water was added to this solution. The two-phase solution was extracted with EtOAc, dried over Na_2SO_4, and concentrated in *vacuo* to give the to generate **II-18** in 81% yield (11.8 g, 72.7 mmol) as colourless (or sometimes pale yellow) viscous oily liquid. This data is in accordance with the literature reports.[14, 15]

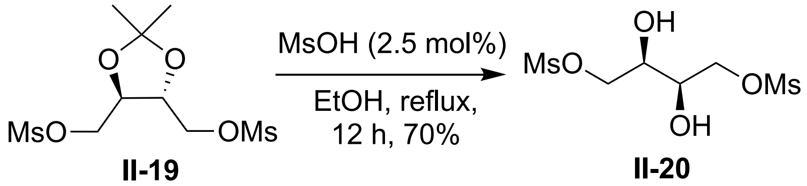
Spectral Data for II-18: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.05 – 4.00 (m, 1H), 3.82 (ddd, *J* = 11.8, 2.5, 1.3 Hz, 1H), 3.71 (ddd, *J* = 11.8, 2.4, 1.3 Hz, 1H), 1.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 109.41, 77.98, 62.04, 27.18. IR (cm $^{-1}$): 3140, 1350, 1100.



Synthesis of *2,3-O*-isopropylidene-D-theritol 1,4-bismethanesulfonate (II-19): A clean dry round-bottom flask equipped with a magnetic stir bar was taken to which *2,3-Di-O-isopropylidene-D-theritol* **II-18** (25.0 g, 0.154 mol) was added. The rb was kept under high vacuum for 10 min and then refilled with Ar atmosphere. Dry DCM (300 mL) and pyridine (37.4 mL, 0.462 mol) were subsequently transferred, and the stirred solution was cooled to 0 ^{o}C. Methanesulfonyl chloride (29.8 ml, 0.385 mol) was added slowly dropwise through a syringe over a period of 30 min. After an additional 30 min, the ice bath was removed, and the solution was allowed to warm to room temperature. After an additional 6h, formation of a precipitate was observed which was dissolved by adding $NaHCO_3$ (50 mL) dropwise. The solution was stirred for an additional 30 min and then transferred to a separatory funnel. The organic layer was extracted with EtOAc (3 X 50 mL), dried over Na_2SO_4, and concentrated under vacuum. The solids were then recrystallized from chloroform-diethyl ether (1:1) to give the product as crystalline white solid **II-19** in 80%

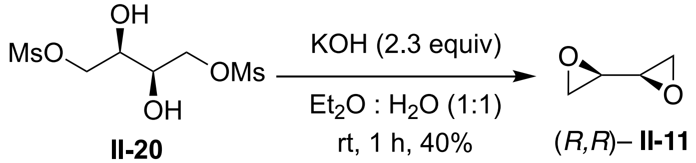
overall yield (39.2 g, 123.2 mmol). This data is in accordance with the literature reports.[14, 15]

Spectral data for II-19: ^{1}H NMR (500 MHz, $CDCl_3$+DMSO-*d6*): δ 4.39 – 4.31 (m, 2H), 4.07 – 3.99 (m, 1H), 3.09 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-*d6*): δ 110.5, 75.8, 68.4, 40.1, 25.8.



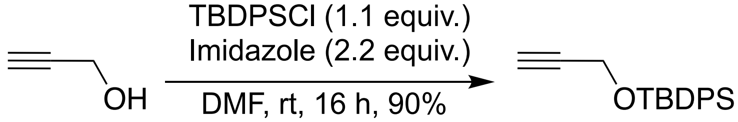
Synthesis of *D*-theritol 1,4-bismethanesulfonate (II-20): In a 1L round-bottom flask *2,3-O-isopropylidene-D-theritol* 1,4-bismethanesulfonate **II-19** (40 g, 0.126 mol) was taken to which ethanol (250 mL) was added and stirred for 10 min. Methanesulfonic acid (0.204 mL, 3.14 mmol) was added to the solution and the reaction mixture was heated to reflux for 12 h. The reaction mixture was then cooled in an ice-bath for 30 min; upon which nice crystal formation was observed. The crystals were collected by suction filtration, washed with cold ethanol (2 X 50 mL) and diethyl ether (2 X 50 mL) and dried in vacuum to give **II-20** in 70% yield (24.5 g, 88.2 mmol) as off white solid. This data is in accordance with the literature reports.[14, 15]

Spectral data for II-20: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.39 – 4.31 (m, 2H), 4.07 – 3.99 (m, 1H), 3.09 (s, 3H), 1.69 (s, 1H). δ 79.8, 65.4, 38.1.



Synthesis of *(R,R)*-1,2,3,4-Diepoxybutane (II-11): In a clean dry 2-neck 500 ml round-bottom flask fitted with a magnetic stir bar and 125 mL pressure-equalizing addition funnel was added *D-theritol* 1,4-bismethanesulfonate **II-20** (25.0 g, 89.8 mmol) and diethyl ether (200 mL). The reaction mixture was stirred vigorously for 15 min and then a solution of potassium hydroxide (11.6 g, 0.207 mol) in water (35 mL) was added slowly dropwise through the addition funnel over a period of 30 min. The suspension immediately turned into a clear solution upon the addition of potassium hydroxide and this clear solution was stirred for an additional hour. The reaction mixture was extracted with Et$_2$O (3 X 50 mL), the organic layer was combined, dried over Na$_2$SO$_4$ and then concentrated to approximately around 100 mL by rotavap. The concentrate was then further fractionally distilled through a 13-cm Vigreux column at atmospheric pressure to give **II-11** as a pale yellow-oil in 40% yield (3.09 g, 35.9 mmol). This data is in accordance with the literature reports.[14, 15]

Spectral data for II-11: ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.92 – 2.86 (m, 2H), 2.83 (ddd, *J* = 4.0, 3.4, 1.2 Hz, 2H), 2.76 – 2.70 (m, 2H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 52.3, 41.7.

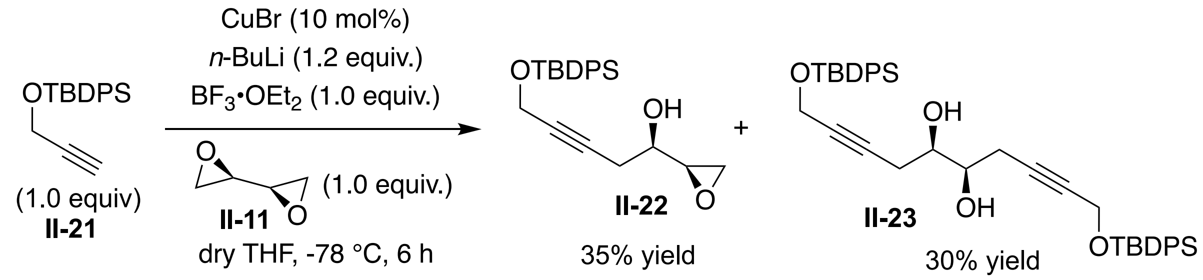


Propargyl alcohol

II-21

Synthesis of tert-butyldiphenyl(prop-2-yn-1-yloxy)silane (II-21): In a 500 mL round bottom flask propargyl alcohol (6 mL, 100 mmol) and imidazole (15 g, 220 mmol) were dissolved in DMF (200 mL) and then transferred to an ice-bath. TBDPSCl (28 mL, 110 mmol) was added slowly to a stirring reaction mixture of the above. The solution was brought to rt and stirred for 16 h at rt. Subsequently, satd. aq. NH$_4$Cl (20 mL) was added to the mixture which was then extracted with EtOAc (3 X 50 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum to give the crude product, which was then further purified by column chromatography (2% EtOAc-hexane) to give the final product as a white crystalline solid in 90% yield (26.5 g, 90 mmol). This data is in accordance with the literature reports.[35]

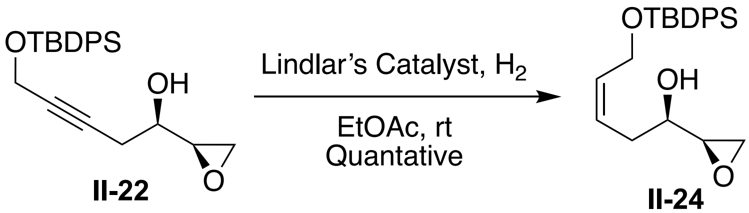
Spectral Data for II-21: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.64 (m, 4H), 7.52 – 7.31 (m, 6H), 4.32 (d, *J* = 2.5 Hz, 2H), 2.40 (t, *J* = 2.4 Hz, 1H), 1.08 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.73, 135.72, 133.06, 129.99, 127.89, 82.15, 73.18, 52.61, 26.80, 26.78, 19.29.



Synthesis of epoxyalkynol II-22: To a clean dry 3-neck round bottom flask flushed with Ar was added tert-butyldiphenyl(prop-2-yn-1-yloxy)silane **II-21** (294.5 mg, 1 mmol), copper bromide (14.3 mg, 0.1 mmol) and dry THF (5 ml) and cooled to -78 ^{o}C. *n*-BuLi (2.0 M in hexane) (0.6 mL, 1.2 mmol) was added dropwise, and the reaction was stirred at this temperature for 30 min. $BF_3.Et_2O$ (0.13 mL, 1.0 mmol) was added dropwise to the reaction mixture followed by a rapid addition of **II-11** (86 mg, 1.0 mmol) in dry THF (2 mL) also at -78 ^{o}C. The reaction mixture was for an additional 5 h before it was quenched by the addition of satd. NH_4Cl (3 mL). The organic layers were extracted with EtOAc (3 X 3 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product as colorless oil.

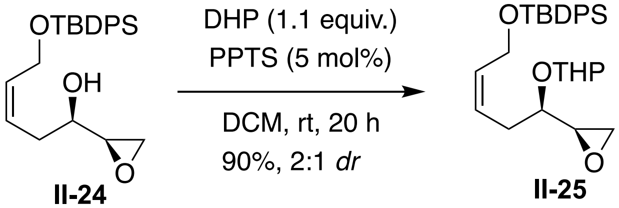
To this reaction mixture was added 2,2-dimethoxypropane (1.0 equiv), *p*-tolunesulphonic acid (5 mol%) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was extracted with EtOAc (3 X 3 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was then purified with column chromatography (30% EtOAc-hexane) to give the epoxyalkynol **II-22** in 35% yield (134 mg, 0.35 mmol) as clear oil. This data is in agreement with the literature report.[16]

Spectral Data for II-22: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.67 (m, 4H), 7.47 – 7.35 (m, 6H), 4.33 (t, *J* = 2.1 Hz, 2H), 3.58 (qd, *J* = 6.3, 4.2 Hz, 1H), 3.08 (td, *J* = 4.2, 2.7 Hz, 1H), 2.79 (dd, *J* = 4.9, 4.1 Hz, 1H), 2.73 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.56 – 2.43 (m, 2H), 2.06 (s, 1H), 1.05 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.73, 133.30, 129.94, 127.82, 81.33, 80.66, 69.60, 54.14, 52.93, 45.02, 26.81, 25.16, 19.28. TOF MS ES$^+$ ($C_{23}H_{29}O_3Si$): Calc. $[M + H]^+$: 381.1886, Found $[M + H]^+$: 381.1875.



Synthesis of epoxyalkenol II-24: In a 100 mL rb fitted with a 2-neck valve, epoxy-alcohol **II-22** (1.9 g, 5.0 mmol), Lindlar's catalyst (200 mg) and EtOAc (25 mL) were taken and stirred at room temperature for 5 min under hydrogen atmosphere. The reaction mixture then subjected to vacuum thrice which was continuously being refilled by hydrogen. The reaction was then stirred for an additional 30 min. When ^{1}H NMR showed complete conversion towards the alkene, the reaction was stopped by removing the valve containing the H_2 balloon. The reaction mixture was passed over a silica bed (5 cm) and was continuously washed with EtOAc (50 mL) to give the *cis* olefin **II-24** (1.91 g, 5.0 mmol) as a pure product in quantitative amount (1.9 g, 5.0 mmol).

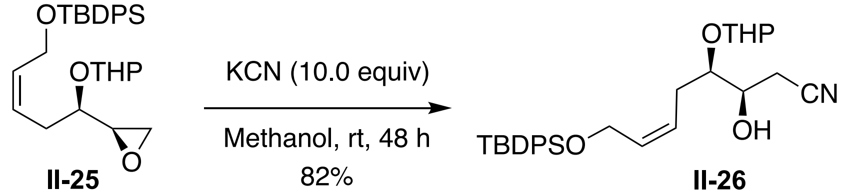
Spectral Data for II-24: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.70 – 7.64 (m, 4H), 7.44 – 7.38 (m, 6H), 5.81 (dtt, J = 11.0, 6.3, 1.5 Hz, 1H), 5.55 (dtt, J = 10.9, 7.7, 1.6 Hz, 1H), 4.30 – 4.17 (m, 2H), 3.45 (qd, J = 6.3, 4.5 Hz, 1H), 2.93 (td, J = 4.3, 2.7 Hz, 1H), 2.75 (dd, J = 5.0, 4.1 Hz, 1H), 2.68 (dd, J = 5.0, 2.7 Hz, 1H), 2.30 – 2.23 (m, 2H), 1.98 (d, J = 6.1 Hz, 1H), 1.05 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 135.59, 135.56, 133.56, 133.54, 132.30, 129.67, 129.55, 127.69, 127.68, 127.66, 127.65, 127.61, 125.66, 70.54, 59.97, 54.69, 44.79, 32.78, 26.77, 19.13. TOF MS ES$^+$ ($C_{23}H_{31}O_3Si$): Calc. [M + H]$^+$: 383.2042, Found [M + H]$^+$: 383.2039.



Synthesis of THP-protected epoxyalkenol II-25: The *cis* olefin **II-24** (1.9 g, 5.0 mmol), pyridinium *p*-toluenesulphonate (63 mg, 0.25 mmol) were taken in a 100 mL rb and was dissolved in dry DCM (40 mL) and stirred at 0 °C for 10 min. DHP (0.47 mL, 5.5 mmol) was then added slowly dropwise and the reaction mixture was gradually brought to room temperature. The reaction mixture was stirred for an additional 20 h upon which TLC showed complete consumption of starting materials. Crude ^{1}H NMR showed the formation of two diastereomers in a ratio of 2:1. The solvent was removed completely to get the crude product which was further purified by column chromatography (5% EtOAc-hexane) to generate a clear liquid **II-25** as the mixture of two diastereomer (2.1 g, 4.5 mmol).

Spectral Data for II-25: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.71 – 7.58 (m, 4H), 7.46 – 7.32 (m, 6H), 5.77 – 5.66 (m, 1H), 5.46 (dtt, *J* = 11.0, 7.6, 1.7 Hz, 1H), 4.82 (dd, *J* = 5.1, 2.9

Hz, 1H), 4.63 (t, *J* = 3.6 Hz, 1H), 4.26 (dt, *J* = 6.1, 1.8 Hz, 2H), 4.03 (ddd, *J* = 11.1, 6.6, 3.9 Hz, 1H), 3.93 (ddd, *J* = 11.5, 8.2, 3.3 Hz, 1H), 3.64 – 3.51 (m, 1H), 3.51 – 3.43 (m, 1H), 2.99 (ddd, *J* = 6.3, 4.1, 2.8 Hz, 1H), 2.57 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.30 – 2.10 (m, 2H), 1.56 – 1.45 (m, 5H), 1.04 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.71, 135.69, 135.63, 133.80, 132.04, 129.78, 127.80, 127.79, 127.74, 125.44, 97.52, 76.67, 63.54, 62.51, 60.34, 54.13, 44.68, 31.09, 30.77, 29.84, 26.98, 26.91, 25.46, 19.96, 19.59, 19.27.

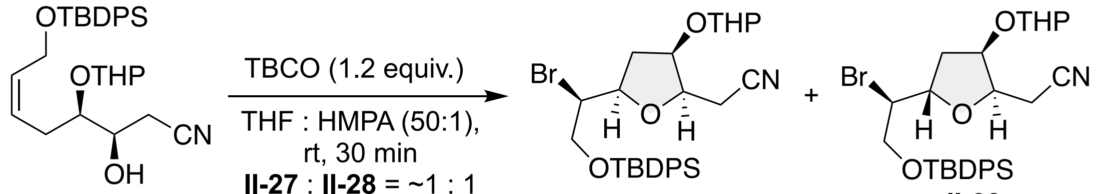


Synthesis of THP-protected-cyano-alkenol II-25: In a clean dry 100 mL rb, epoxide **II-24** (467 mg, 1.0 mmol), freshly dried KCN (10.0 mmol) was added to MeOH (30 mL) at room temperature and the reaction mixture was stirred at the same temperature for 48h upon which TLC showed complete consumption of the starting material. The reaction was quenched by adding $NaHCO_3$ (10 mL) followed by the addition of satd. aq. NH_4Cl (10 mL); whereupon the aqueous layer was extracted by using EtOAc (3 X 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude reaction mixture. The crude product was further purified by the column chromatography (25% EtOAc-hexane) to give the nitrile **II-25** as clear oil in 82% yield (405 mg, 0.82 mmol).

Spectral Data for II-25: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 4H), 7.45 – 7.35 (m, 6H), 5.83 – 5.64 (m, 1H), 5.43 (dtt, J = 10.8, 7.6, 1.6 Hz, 1H), 4.38 (dd, J = 7.3, 2.5 Hz, 1H), 4.27 – 4.21 (m, 1H), 4.23 – 4.14 (m, 1H), 3.99 (d, J = 4.2 Hz, 1H), 3.92 (dtd, J = 11.5, 3.7, 1.4 Hz, 1H), 3.70 (tdd, J = 6.0, 4.9, 4.2 Hz, 1H), 3.54 (dt, J = 7.5, 5.5 Hz, 1H), 3.46 (dddd, J = 11.5, 8.3, 5.7, 3.1 Hz, 1H), 2.56 (dd, J = 16.8, 4.9 Hz, 1H), 2.40 (ddd, J =

16.7, 6.1, 0.8 Hz, 1H), 2.18 – 2.05 (m, 2H), 1.82 – 1.73 (m, 1H), 1.73 – 1.65 (m, 1H), 1.52 – 1.37 (m, 5H), 1.03 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 135.59, 135.57, 135.55, 135.48, 133.51, 133.50, 132.17, 129.71, 127.73, 127.71, 127.70, 127.67, 127.62, 125.33, 117.48, 100.88, 80.76, 68.71, 65.35, 60.02, 31.11, 29.42, 26.78, 24.92, 22.45, 21.23, 19.13.

General Procedure for Bromo-etherification

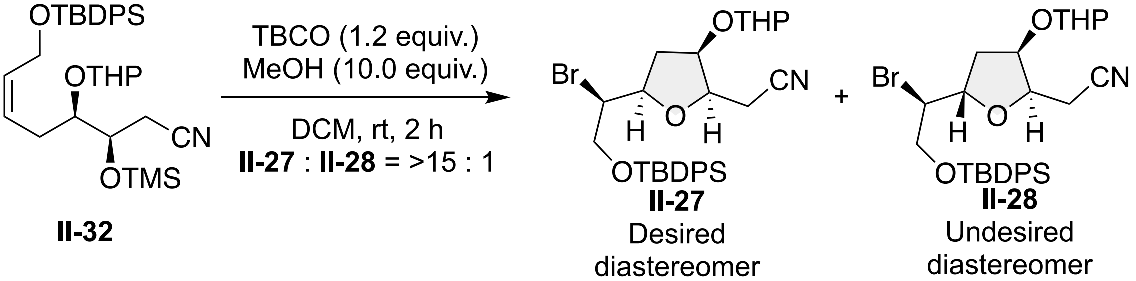


II-26

II-27
Desired
diastereomer

II-28
Undesired
diastereomer

Bromo etherification without the second protecting group: Alcohol **II-26** (50 mg. 0.1 mmol) was dissolved in dry THF (2.5 mL) and dry HMPA (50 µL) in a 20 mL vial and was stirred at rt for 5 min. The vial was wrapped with aluminium foil and then TBCO (49.2 mg, 0.12 mmol) was added to the reaction mixture. It was stirred for an additional 30 min, where TLC showed complete consumption of the starting alcohol. Aqueous sodium sulfite (10%, 2 mL) was added to quench the reaction mixture. The aqueous layer was extracted with EtOAc (3 x 2 mL). The combined organic extracts were washed with brine (2 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. ^{1}H NMR analysis showed the formation of diastereomers in ~1:1 ratio. The crude residue was further purified via column chromatography (15% EtOAc-hexane) to give both diastereomers (26 mg, 45% **II-27** and 27 mg, 47% **II-28** were isolated; 92% combined yield). [Note: **II-27** (bottom spot): 26 mg and **II-28** (top spot): 27 mg on the TLC paper (20% EtOAc-hexane)].



II-32

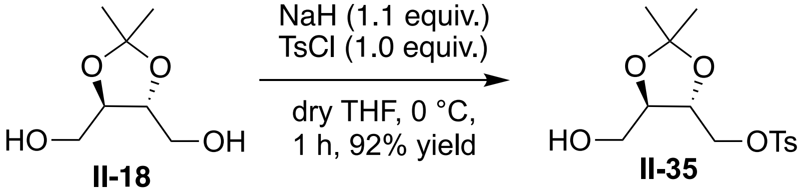
II-27 Desired diastereomer

II-28 Undesired diastereomer

Bromo etherification with TMS protecting group: In a 20 ml vial fitted with a stir bar was added TMS-protected alcohol **II-32** (57 mg, 0.1 mmol) in dry DCM (5 mL). The vial was wrapped with an aluminium foil. TBCO (49.2 mg, 0.12 mmol) and methanol (40 µL, 1.0 mmol) were added. The reaction mixture was then stirred at rt for 2 h and monitored through TLC. After 2 h, TLC showed complete consumption of **II-32**. Solvent was removed under reduced pressure and ^{1}H NMR of the crude reaction mixture showed the formation of diastereomers in ratio of >15:1. The crude residue was further purified via column chromatography (15% EtOAc-hexane) to give two diastereomers in 88% overall yield (52 mg, 0.09 mmol) [**II-27** (84% isolated yield): 48 mg, 0.084 mmol; **II-28** (4% isolated yield): 2.5 mg]. This result is consistent when this reaction was performed in 1 g scale (yield of the major diastereomer varies from 80%-88%).

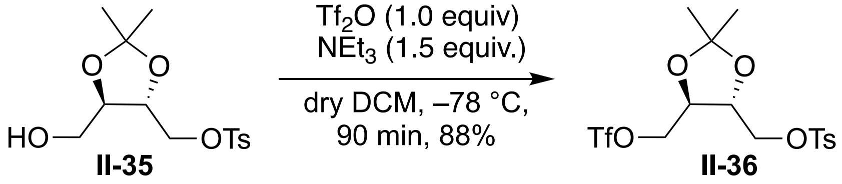
Spectral Data for II-27: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.66 (dd, *J* = 8.3, 1.7 Hz, 4H), 7.41 (ddd, *J* = 18.0, 9.1, 6.8 Hz, 6H), 4.65 – 4.54 (m, 1H), 4.51 (ddd, J = 8.0, 6.1, 2.2 Hz, 1H), 4.21 (qd, *J* = 6.1, 3.1 Hz, 2H), 4.00 (ddd, *J* = 11.0, 8.8, 6.4 Hz, 2H), 3.87 – 3.76 (m, 2H), 3.50 (dd, *J* = 10.7, 5.4 Hz, 2H), 2.77 (dd, *J* = 16.6, 6.2 Hz, 1H), 2.36 (dt, *J* = 13.2, 6.8 Hz, 1H), 2.18 – 2.07 (m, 1H), 1.82 – 1.58 (m, 2H), 1.51 – 1.39 (m, 4H), 1.06 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.36, 135.77, 135.70, 133.18, 130.04, 130.02, 127.95, 127.94, 127.91, 96.85, 78.03, 74.24, 65.43, 62.97, 56.83, 34.57, 30.54, 26.93, 25.36, 19.66, 19.44. IR (cm^{-1}): 3030, 2954, 2210, 1300,1170, 870.TOF MS ES$^+$ ($C_{29}H_{38}BrNO_4SiNa$): Calc. [M + Na]$^+$: 594.1651, Found [M + Na]$^+$: 594.1654.

Spectral Data for II-28: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 4H), 7.46 – 7.32 (m, 6H), 4.71 – 4.65 (m, 1H), 4.54 (ddd, J = 8.8, 6.5, 2.2 Hz, 1H), 4.49 (td, J = 4.7, 2.1 Hz, 1H), 4.35 (ddd, J = 6.9, 6.1, 4.2 Hz, 1H), 4.02 – 3.92 (m, 3H), 3.90 – 3.83 (m, 1H), 3.57 – 3.48 (m, 1H), 2.78 (dd, J = 16.5, 7.0 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.18 (ddd, J = 13.5, 6.5, 2.1 Hz, 1H), 2.08 (ddd, J = 13.7, 9.0, 5.0 Hz, 1H), 1.81 (tdd, J = 9.2, 7.5, 6.3, 4.0 Hz, 1H), 1.77 – 1.68 (m, 1H), 1.55 (pd, J = 9.3, 7.5, 5.6 Hz, 4H), 1.04 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.59, 135.53, 135.52, 133.09, 132.86, 129.85, 127.78, 127.77, 127.74, 96.00, 78.18, 76.24, 74.63, 65.36, 62.70, 58.10, 35.34, 30.64, 26.77, 25.23,19.28, 18.67. IR (cm^{-1}): 3070, 2954, 2260, 1330,1270, 870. TOF MS ES$^+$ ($C_{29}H_{38}BrNO_4SiNa$): Calc. [M + Na]$^+$: 594.1651, Found [M + Na]$^+$: 594.1659.



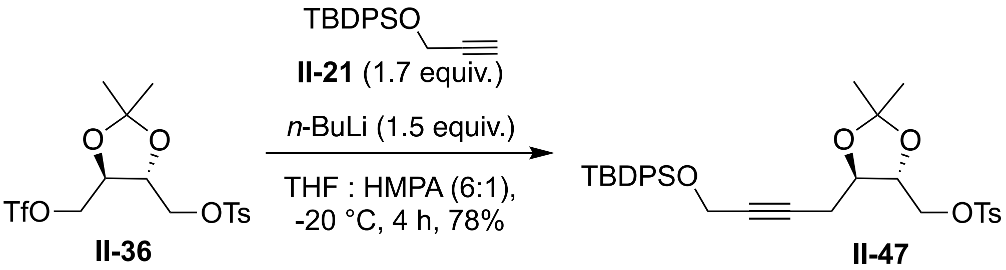
Synthesis of acetal-protected-mono-OTs II-35: In a clean dry 500 mL rb under inert atm was added NaH (1.23 g, 34 mmol) and dry THF (70 mL). The heterogeneous mixture was stirred at rt for 10 min before being transferred to an ice bath. In two separate 100 mL rb, one containing TsCl (5.88 g, 30.83 mmol) dissolved in dry THF (50 mL) and another containing **II-18** (5.0 g, 30.83 mmol) dissolved in dry THF (50 mL) were prepared. To the 500 mL rb kept at 0 °C was transferred all the contents of the rb containing substrate **II-18** slowly added dropwise through a syringe needle. The reaction mixture was stirred at this temperature for an additional 30 min, after which the other rb containing the dissolved TsCl was added rapidly to this reaction mixture. The reaction mixture was stirred for an additional 30 min at 0 °C. The reaction was quenched by adding satd aq NH_4Cl solution (15 mL) slowly. The organic layers were extracted with EtOAc (3 X 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to generate the crude product. The crude mixture was purified through column chromatography (45% EtOAc-hexane) to give pure **II-35** in 92% yield (8.96 g, 28.4 mmol) as colourless liquid. This was in accordance with the literature report.[28]

Spectral Data for II-35: ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 4.14 (dd, *J* = 4.6, 1.6 Hz, 2H), 4.13 – 4.07 (m, 1H), 3.97 (dt, *J* = 7.8, 3.8 Hz, 1H), 3.80 (dd, *J* = 12.1, 3.6 Hz, 1H), 3.62 (dd, *J* = 12.1, 4.0 Hz, 1H), 2.45 (s, 3H), 1.89 (s, 1H), 1.39 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.29, 132.67, 130.06, 128.14, 110.17, 78.13, 74.46, 68.89, 27.12, 26.87, 21.82.



Synthesis of acetal-protected-mono-OTs,OTf II-36: In a clean dry 100 ml rb was added mono-OTs **II-35** (1.0 g, 3.16 mmol) in dry DCM (30 mL) under inert atmosphere. The reaction mixture was transferred to a dry ice bath. To this was added dry NEt_3 (0.67 mL, 4.74 mmol) and Tf_2O (0.54 mL, 3.16 mmol) at –78 °C. The reaction mixture was stirred for 90 min at the same temperature, after which it was quenched by adding satd. aq. NH_4Cl (5 mL) followed by satd. aq. $NaHCO_3$ (5 mL). The layers were separated, the organics were extracted by using DCM (3 X 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to generate the crude product. The crude mixture was purified through column chromatography (30% EtOAc-hexane) to give pure **II-36** in 88% yield as a colourless oil (1.13 g, 2.53 mmol). This was in accordance with the literature report.[29]

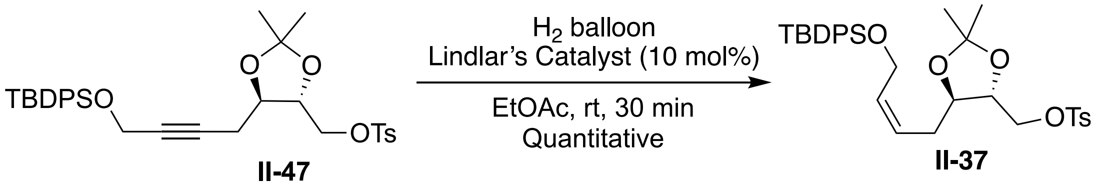
Spectral Data for II-36: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.79 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 7.8 Hz, 2H), 4.65 (dd, J = 11.2, 3.1 Hz, 1H), 4.49 (dd, J = 11.2, 4.3 Hz, 1H), 4.20 (dd, J = 10.3, 4.0 Hz, 1H), 4.18 – 4.06 (m, 3H), 2.46 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 145.66, 132.32, 130.22, 128.11, 111.49, 75.71, 73.96, 73.82, 68.22, 26.90, 26.73, 21.82. ^{19}F NMR (470 MHz, CDCl$_3$) δ -74.41.



Synthesis of acetal-protected-alkynyl-OTs II-47: In a clean dry 100 mL rb was added **II-21** (501 mg, 1.7 mmol) under inert atmosphere. The solids were dissolved by adding dry THF (15 mL). The rb was quickly transferred to a chiller pre-cooled at –20 °C and kept stirring at the same temperature for 15 min. *n*-BuLi (2.5 M, 0.6 mL, 1.5 mmol) was added dropwise to this solution and the reaction mixture was stirred for 30 min at the same temperature.

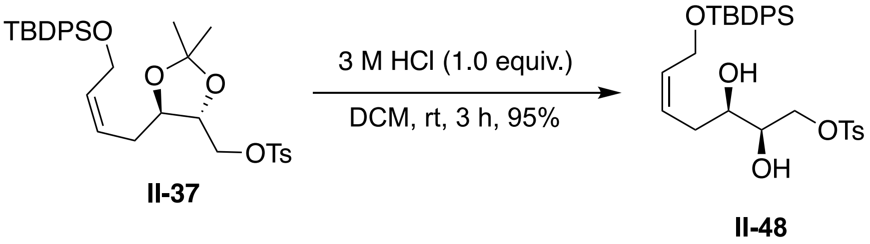
In a separate 50 mL rb **II-36** (448 mg, 1.0 mmol) was taken and was dissolved in dry THF (15 mL). To this was added dry HMPA (5 mL) and the reaction mixture was then transferred to the previous rb kept at –20 °C. The contents of this mixture were stirred for 3.5 h at –20 °C. The reaction mixture was quenched by adding satd. aq. NH$_4$Cl (5 mL) and warming up the reaction mixture to rt. The organic layer was extracted with EtOAc (3 X 10 mL), layers were combined, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to generate the crude product. The pure product **II-47** was isolated by column chromatography (15% EtOAc-hexane) as orangish yellow liquid in 78% yield (462.4 mg, 0.78 mmol).

Spectral Data for II-47: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.76 – 7.68 (m, 4H), 7.49 – 7.37 (m, 6H), 7.32 – 7.26 (m, 2H), 4.29 (t, *J* = 2.1 Hz, 2H), 4.20 (dd, *J* = 10.7, 3.6 Hz, 1H), 4.08 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.95 (ddd, *J* = 8.4, 4.9, 3.6 Hz, 1H), 3.88 (ddd, *J* = 7.8, 6.7, 4.8 Hz, 1H), 2.55 (ddt, *J* = 16.8, 4.6, 2.2 Hz, 1H), 2.46 (ddt, *J* = 16.9, 6.9, 2.1 Hz, 1H), 2.40 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.01, 135.67, 135.66, 133.18, 133.16, 132.79, 129.90, 128.07, 127.79, 109.96, 81.37, 79.99, 77.84, 74.96, 69.19, 52.74, 27.13, 26.86, 26.76, 23.14, 21.68, 19.20.



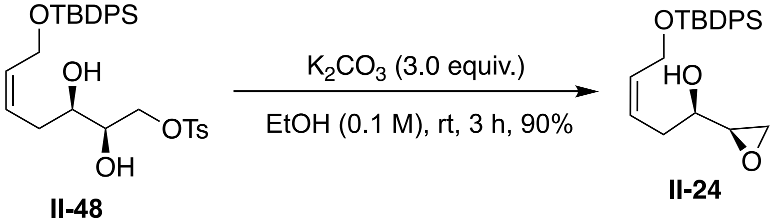
Synthesis of acetal-protected-cis-alkeynyl-OTs II-37: In a 100 mL rb fitted with a 2-neck valve, epoxy-alcohol **II-22** (592 mg, 1.0 mmol), Lindlar's catalyst (59.2 mg) and EtOAc (10 mL) were taken and stirred at room temperature for 5 min under hydrogen atmosphere. The reaction mixture then subjected to vacuum thrice which was continuously being refilled by hydrogen. The reaction was then stirred for an additional 60 min. When ^{1}H NMR showed complete conversion to the alkene, the reaction was stopped by removing the valve containing the H_2 balloon. The reaction mixture was passed over a silica bed (5 cm) and was continuously washed with EtOAc (50 mL) to give the *cis* olefin **II-37** as a pure product (clear viscous liquid) in quantitative amount (590 mg, 1.0 mmol).

Spectral Data: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.75 – 7.66 (m, 4H), 7.42 (tt, *J* = 8.7, 4.6 Hz, 6H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.79 – 5.70 (m, 1H), 5.45 – 5.35 (m, 1H), 4.30 – 4.22 (m, 2H), 4.07 (dd, *J* = 10.7, 3.9 Hz, 1H), 3.99 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.80 (dt, *J* = 8.1, 6.0 Hz, 1H), 3.71 (dq, *J* = 8.6, 4.3 Hz, 1H), 2.42 (s, 3H), 2.19 (q, *J* = 6.6 Hz, 2H), 1.32 (s, 3H), 1.29 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 144.95, 135.54, 135.53, 133.56, 132.67, 132.33, 129.86, 129.84, 129.71, 129.70, 127.97, 127.72, 127.70, 127.63, 124.57, 109.30, 77.74, 76.50, 68.90, 60.19, 30.77, 27.09, 26.78, 26.61, 21.59, 19.11.



Synthesis of *cis*-alkeynyl-diol-OTs II-48: To a solution of **II-37** (1.78 g, 3.0 mmol) in DCM (30 mL) was added 3M HCl (1 mL, 3.0 mmol), and stirred at rt for 3 h. The solvent was removed, and the crude reaction mixture was extracted with DCM (3 X 5 mL). The organic layers were combined, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to generate the crude product. The pure product **II-48** was isolated by column chromatography (40% EtOAc-hexane) as a colorless liquid in 95% yield (1.58 g, 2.85 mmol). [Note: Longer reaction time and stronger concentration of acid is detrimental as it leads to the formation of the triol product].

Spectral Data for II-48: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.71 – 7.63 (m, 4H), 7.45 – 7.35 (m, 6H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.81 – 5.68 (m, 1H), 5.52 – 5.43 (m, 1H), 4.25 – 4.15 (m, 2H), 4.03 (qd, *J* = 10.2, 5.8 Hz, 2H), 3.68 (qd, *J* = 6.3, 2.7 Hz, 1H), 3.54 (qd, *J* = 6.6, 2.6 Hz, 1H), 2.90 (d, *J* = 6.2 Hz, 1H), 2.49 (d, *J* = 6.2 Hz, 1H), 2.42 (s, 3H), 2.24 – 2.16 (m, 2H), 1.02 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 145.09, 135.63, 133.40, 132.65, 131.85, 129.99, 129.86, 128.05, 128.04, 127.82, 127.15, 71.20, 70.49, 69.89, 60.50, 31.87, 26.81, 21.71, 21.12, 19.14.



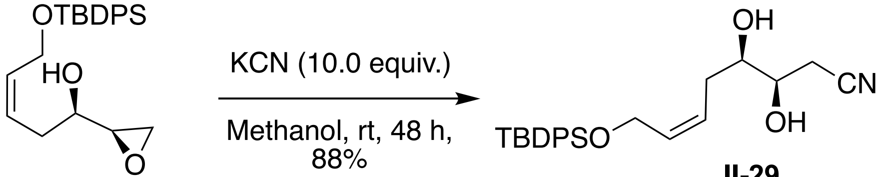
II-48

II-24

Synthesis of epoxyalkenol II-24: To a solution of **II-48** (1.66 g, 3.0 mmol) in EtOH (30 mL) was added K$_2$CO$_3$ (1.24 g, 9.0 mmol) at rt and the reaction mixture was stirred for 3 h. Solvent was removed to half, and the crude reaction mixture was extracted with EtOAc (3 X 15 mL). The organic layers were combined, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to generate the crude product. The pure product **II-48** was isolated by column chromatography (30% EtOAc-hexane) as a colorless liquid in 90% yield (1.03 g, 2.7 mmol). [Note: Product **II-24** is volatile so care must be taken during removal of solvents in high vacuum].

Spectral Data for II-24: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.69 (dd, *J* = 6.1, 1.8 Hz, 4H), 7.46 – 7.33 (m, 6H), 5.84 – 5.75 (m, 1H), 5.57 – 5.48 (m, 1H), 4.25 (ddd, *J* = 6.6, 3.5, 1.4 Hz, 2H), 3.44 (q, *J* = 6.1 Hz, 1H), 2.92 (td, *J* = 4.3, 2.8 Hz, 1H), 2.74 (dd, *J* = 5.0, 4.1 Hz, 1H), 2.66 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.24 (t, *J* = 7.1 Hz, 2H), 1.96 (s, 1H), 1.04 (s, 9H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 135.73, 135.70, 133.70, 133.68, 132.44, 129.82, 127.84, 127.83, 125.81, 70.67, 60.10, 54.82, 44.93, 32.91, 26.90, 19.26, 14.34.

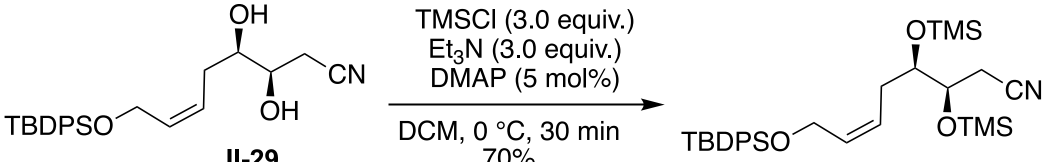


II-24

II-29

Synthesis of cyano-alken-diol II-29: In a clean dry 100 mL rb, epoxide **II-24** (1.15 g, 3.0 mmol), freshly dried KCN (1.95 g, 30.0 mmol) was added to MeOH (30 mL) at room temperature and the reaction mixture was stirred at the same temperature for 48 h upon which TLC showed complete consumption of the starting material. The reaction was quenched by adding $NaHCO_3$ (10 mL) followed by the addition of satd. aq. NH_4Cl (10 mL); whereupon the aqueous layer was extracted by using EtOAc (3 X 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude reaction mixture. The crude product was further purified by the column chromatography (40% EtOAc-hexane) to give the nitrile **II-25** as clear oil in 88% isolated yield (1.08 g, 2.64 mmol).

Spectral Data for II-25: ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.65 (m, 4H), 7.48 – 7.38 (m, 6H), 5.84 – 5.75 (m, 1H), 5.61 – 5.51 (m, 1H), 4.22 (qdd, *J* = 12.6, 6.9, 1.2 Hz, 2H), 3.81 (qd, *J* = 6.7, 2.8 Hz, 1H), 3.56 (qd, *J* = 6.5, 2.8 Hz, 1H), 3.23 (d, *J* = 6.8 Hz, 1H), 2.68 (d, *J* = 6.1 Hz, 1H), 2.57 (dd, *J* = 8.4, 6.5 Hz, 2H), 2.28 (td, *J* = 7.3, 6.7, 1.4 Hz, 2H), 1.06 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.67, 135.66, 133.24, 133.22, 131.89, 130.00, 129.98, 127.90, 127.52, 117.93, 71.66, 69.10, 59.57, 32.00, 26.85, 22.77, 19.18, 14.27.

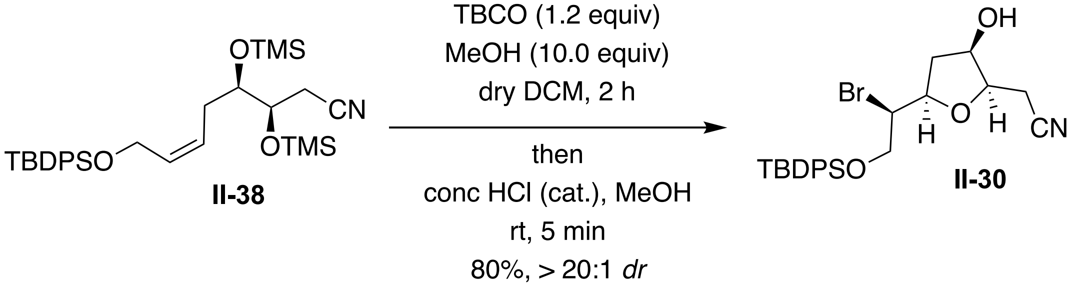


II-29

II-38

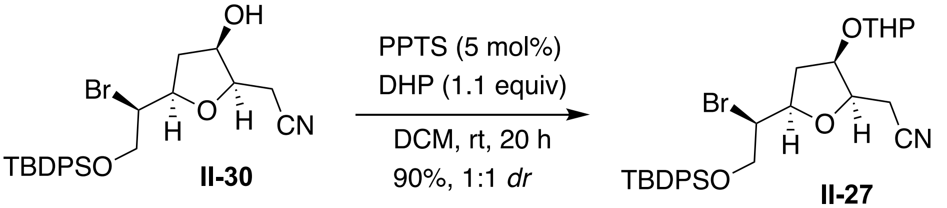
Synthesis of the diOTMS-cyano-alkene II-38: The diol **II-29** (1.22 g, 3.0 mmol) was reacted with TMSCl (1.14 mL, 9.0 mmol) and triethyl amine (1.25 mL, 9.0 mmol) in the presence of DMAP (18.3 mg, 0.15 mmol) in DCM (30 mL) at 0 °C. After completion of the reaction (30 min), the crude product was purified with column chromatography (silica basified with Et_3N, 5% EtOAc-hexane). The pure product was obtained as a clear oil in 70% yield (1.16 g, 2.1 mmol).

Spectral Data for II-38: ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.65 (m, 4H), 7.49 – 7.34 (m, 6H), 5.73 (dt, *J* = 11.7, 6.2 Hz, 1H), 5.43 (q, *J* = 7.9 Hz, 1H), 4.25 (d, *J* = 6.1 Hz, 2H), 3.82 (dt, *J* = 8.3, 3.8 Hz, 1H), 3.53 (dt, *J* = 8.2, 3.9 Hz, 1H), 2.56 (dd, *J* = 16.6, 3.4 Hz, 1H), 2.26 (dd, *J* = 16.6, 8.8 Hz, 1H), 2.17 (ddd, *J* = 15.0, 7.3, 3.3 Hz, 1H), 1.85 (dt, *J* = 15.5, 8.3 Hz, 1H), 1.06 (s, 9H), 0.14 (s, 9H), 0.08 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.70, 135.66, 133.84, 133.83, 131.73, 129.75, 127.80, 127.79, 127.73, 126.85, 119.00, 74.15, 71.73, 60.39, 28.87, 26.98, 26.96, 26.92, 20.83, 19.27, 0.41, 0.27.



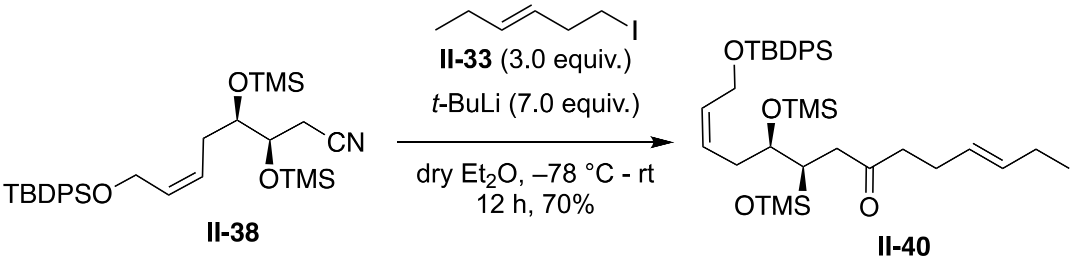
Bromo etherification with diOTMS protecting group II-30: In a 100 mL rb fitted with a stir bar was added TMS-protected alcohol **II-38** (554 mg, 1.0 mmol) in dry DCM (50 mL). The rb was wrapped with an aluminium foil. TBCO (492 mg, 1.2 mmol) and methanol (0.40 mL, 10.0 mmol) were added. The reaction mixture was then stirred at rt for 2 h and monitored through TLC. After 2 h, TLC showed complete consumption of **II-38**. Solvent was removed under reduced pressure and ^{1}H NMR of the crude reaction mixture showed the formation of diastereomers in ratio of >20:1. The crude residue was further purified via column chromatography (20% EtOAc-hexane) to obtain **II-30** in 80% overall yield (488 mg, 0.80 mmol).

Spectral Data for II-30: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (td, *J* = 7.8, 1.5 Hz, 4H), 7.47 – 7.37 (m, 6H), 4.37 (ddd, *J* = 8.8, 5.9, 2.8 Hz, 1H), 4.34 – 4.27 (m, 1H), 4.09 (ddd, *J* = 7.3, 6.0, 2.8 Hz, 1H), 4.05 – 3.97 (m, 2H), 3.94 (td, *J* = 6.6, 3.5 Hz, 1H), 2.78 – 2.66 (m, 2H), 2.48 (ddd, *J* = 14.4, 9.1, 6.5 Hz, 1H), 2.41 (d, *J* = 9.8 Hz, 1H), 1.99 (ddd, *J* = 14.5, 5.9, 1.9 Hz, 1H), 1.07 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.74, 135.66, 133.03, 132.82, 130.10, 127.99, 127.98, 117.74, 78.63, 76.20, 71.93, 65.18, 57.90, 38.84, 26.94, 26.93, 19.42, 18.18.



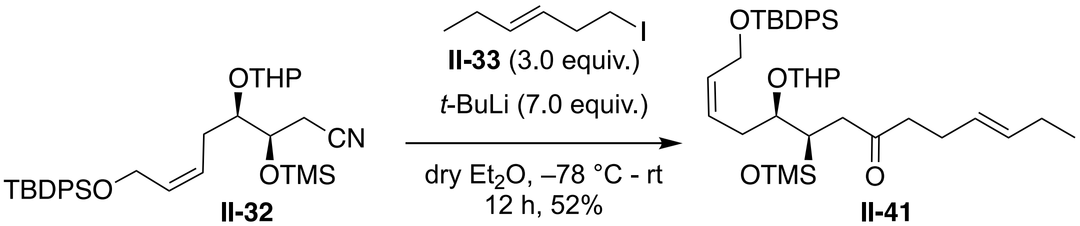
Synthesis of THP-protected-bromo-THF II-27: **II-30** (489 mg, 1.0 mmol), pyridinium *p*-toluenesulphonate (12.6 mg, 0.05 mmol) were taken in a 100 mL rb and was dissolved in dry DCM (20 mL) and stirred at 0 °C for 10 min. DHP (0.1 mL, 1.1 mmol) was then added slowly dropwise and the reaction mixture was gradually brought to room temperature. The reaction mixture was stirred for an additional 20 h upon which TLC showed complete consumption of starting materials. Crude ^{1}H NMR showed the formation of two diastereomers in a ratio of 1:1. The solvent was removed completely to get the crude product which was further purified by column chromatography (5% EtOAc-hexane) to generate a clear liquid **II-27** as the mixture of two diastereomer in 90% overall yield (515.4 mg, 0.9 mmol).

Spectral Data for II-27: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (tt, *J* = 8.3, 1.7 Hz, 8H), 7.41 (ddd, *J* = 18.0, 9.1, 6.8 Hz, 12H), 4.69 – 4.65 (m, 1H), 4.59 (d, *J* = 4.3 Hz, 1H), 4.51 (q, *J* = 6.1 Hz, 1H), 4.43 (q, *J* = 6.5 Hz, 1H), 4.21 (qd, *J* = 6.1, 3.1 Hz, 4H), 4.07 (p, *J* = 5.0 Hz, 2H), 4.00 (ddd, *J* = 11.0, 8.8, 6.4 Hz, 2H), 3.92 (ddd, *J* = 19.1, 11.0, 5.4 Hz, 2H), 3.87 – 3.76 (m, 2H), 3.50 (dd, *J* = 10.7, 5.4 Hz, 2H), 2.77 (dd, *J* = 16.6, 6.2 Hz, 1H), 2.71 – 2.51 (m, 3H), 2.36 (dt, *J* = 13.2, 6.8 Hz, 1H), 2.24 (dt, *J* = 13.3, 6.7 Hz, 1H), 2.18 – 2.07 (m, 1H), 1.98 (ddd, *J* = 13.7, 8.6, 5.8 Hz, 1H), 1.82 – 1.58 (m, 7H), 1.54 – 1.39 (m, 5H), 1.06 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.77, 135.70, 133.18, 130.04, 127.95, 127.94, 127.91, 100.73, 96.85, 78.03, 76.12, 74.24, 65.43, 62.97, 56.83, 56.56, 36.81, 34.57, 30.54, 26.93, 25.41, 25.36, 19.66, 19.51.



Synthesis of bis-alkenyl polyketide II-40: In a clean dry 50 mL rb under inert atmosphere dry Et_2O (8 mL) was taken. The rb was transferred to a dry ice bath, t-BuLi (1.7 M, 1.12 mL, 1.89 mmol) was then added slowly dropwise. In a separate 10 mL rb under inert atmosphere **II-33** (171 mg, 0.81 mmol) was dissolved in dry Et_2O (4 mL). The contents of this rb were completely transferred to the 50 mL rb and stirred at –78 °C for 30 min. In a third rb, **II-38** (150 mg, 0.27 mmol) was dissolved in dry ether (4 mL) under inert atmosphere and stirred at rt till it becomes completely soluble. This was also transferred to the 50 mL rb and the reaction mixture was stirred for an additional 3.5 h at the same temperature. Then the rb was slowly warmed up to rt and stirred for 8 h. The reaction mixture was quenched by dropwise addition of satd aq NH_4Cl (5 mL) solution. The aqueous layer was extracted by using EtOAc (3 X 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude reaction mixture. The crude product was further purified by the column chromatography (3% EtOAc-hexane) to give the product **II-40** as clear oil in 70% yield (121 mg, 0.19 mmol).

Spectral Data for II-40: ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.62 (m, 4H), 7.46 – 7.32 (m, 6H), 5.68 (dd, *J* = 6.3, 4.8 Hz, 1H), 5.53 – 5.26 (m, 3H), 4.26 (d, *J* = 6.6 Hz, 1H), 4.19 – 4.08 (m, 1H), 3.66 (t, *J* = 5.8 Hz, 1H), 3.60 – 3.43 (m, 1H), 2.63 – 2.47 (m, 2H), 2.47 – 2.36 (m, 2H), 2.28 – 2.18 (m, 2H), 1.98 (dddt, *J* = 7.5, 6.2, 2.5, 1.2 Hz, 2H), 1.85 (dt, *J* = 15.5, 8.4 Hz, 1H), 1.04 (s, 9H), 0.99 – 0.88 (m, 3H), 0.04 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 219.51, 135.73, 129.69, 127.78, 127.73, 127.53, 71.28, 64.59, 60.60, 44.46, 27.00, 26.95, 26.59, 25.66, 13.94, 0.47, 0.38.



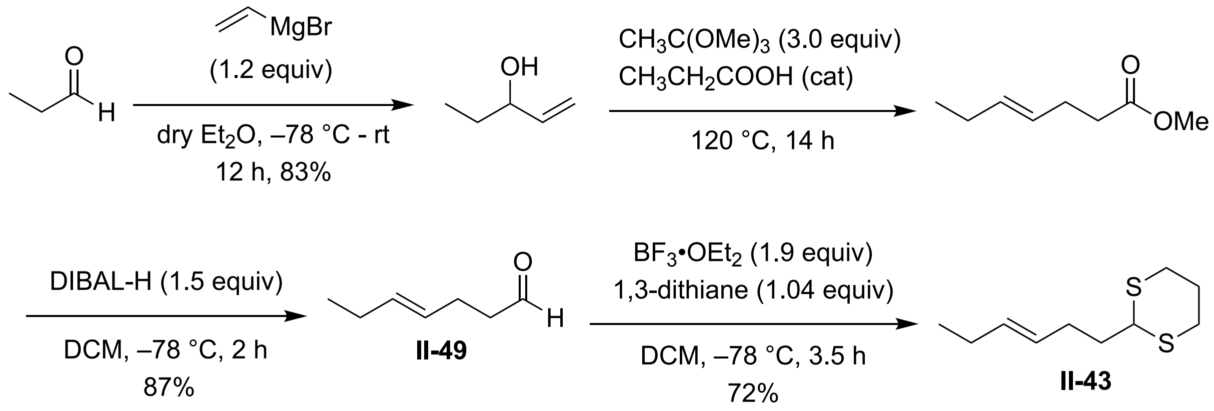
Synthesis of bis-alkenyl polyketide II-41: In a clean dry 50 mL rb under inert atmosphere dry Et_2O (8 mL) was taken. The rb was transferred to a dry ice bath, t-BuLi (1.7 M, 1.12 mL, 1.89 mmol) was then added slowly dropwise. In a separate 10 mL rb under inert atmosphere **II-33** (171 mg, 0.81 mmol) was dissolved in dry Et_2O (4 mL). The contents of this rb were completely transferred to the 50 mL rb and stirred at –78 °C for 30 min. In a third rb, **II-32** (153 mg, 0.27 mmol) was dissolved in dry ether (4 mL) under inert atmosphere and stirred at rt till it becomes completely soluble. This was also transferred to the 50 mL rb and the reaction mixture was stirred for an additional 3.5 h at the same temperature. Then the rb was slowly warmed up to rt and stirred for 8 h. The reaction mixture was quenched by dropwise addition of satd aq NH_4Cl (5 mL) solution. The aqueous layer was extracted by using EtOAc (3 X 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude reaction mixture. The crude product was further purified by the column chromatography (3% EtOAc-hexane) to give the product **II-41** as clear oil in 52% yield (90 mg, 0.14 mmol).

Spectral Data for II-41: ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.60 (m, 4H), 7.44 – 7.32 (m, 6H), 5.73 – 5.62 (m, 1H), 5.56 (dtt, J = 10.6, 7.2, 1.6 Hz, 1H), 5.44 (dtt, J = 15.1, 6.1, 1.3 Hz, 1H), 5.30 – 5.38 (m, 1H), 4.63 – 4.59 (m, 1H), 4.28 (dd, J = 6.7, 5.2 Hz, 2H), 3.83 (ddd, J = 11.1, 8.2, 2.9 Hz, 1H), 3.55 (ddd, J = 8.4, 4.5, 3.4 Hz, 1H), 3.41 – 3.34 (m, 1H), 2.44 – 2.38 (m, 4H), 2.30 – 2.14 (m, 3H), 2.02 – 1.89 (m, 3H), 1.68 (dq, J = 8.5, 5.4, 4.9 Hz, 1H), 1.60 (td, J = 9.3, 3.1 Hz, 1H), 1.51 – 1.40 (m, 4H), 1.03 (s, 9H), 0.01 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.27, 135.58, 133.87, 133.86, 132.95, 130.68, 129.54, 129.53, 127.82, 127.62, 127.31, 97.25, 77.75, 68.19, 62.42, 60.57, 44.49, 44.35, 30.83, 27.44, 26.80, 26.41, 25.52, 25.36, 19.43, 19.17, 13.79, 0.15.

Synthetic Route Towards the Preparation of the dithianyl fragment II-43

Following the reported literature **II-49** was prepared from propanal as illustrated in the Figure in good yields.[36, 37]

Synthesis of II-43: In a clean dry 25 mL rb **II-49** (112.2 mg, 1.0 mmol) was taken, to which was added 1,3 dithaine (125 mg, 1.04 mmol). The reaction mixture was kept under



II-49

II-43

high vacuum and then refilled with Ar. DCM (5 mL) was added and the rb was transferred to a dry-ice bath. $BF_3.Et_2O$ (0.13 mL, 1.0 mmol) was added dropwise to this solution and the reaction mixture was stirred at this temperature for 3.5 h. Then the rb was slowly warmed up to rt and quenched by dropwise addition of satd aq NH_4Cl (5 mL) solution. The aqueous layer was extracted by using DCM (3 X 3 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude reaction mixture. The crude product was further purified by the column chromatography (1% EtOAc-hexane) to give the product **II-43** as clear oil in 72% yield (145.7 mg, 0.72 mmol). The spectral data of **II-43** is in good agreement with the reported values.[38] [Note: The final dithianyl species **II-43** is volatile and has an extremely bad smell].

Spectral data of II-43: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (dtt, *J* = 15.3, 6.2, 1.3 Hz, 1H), 5.36 (dtt, *J* = 15.0, 6.7, 1.5 Hz, 1H), 4.02 (t, *J* = 7.0 Hz, 1H), 2.91 – 2.84 (m, 1H), 2.86 – 2.78 (m, 3H), 2.19 (dt, *J* = 9.0, 6.5 Hz, 2H), 2.16 – 2.06 (m, 1H), 2.00 (dtd, *J* = 8.8, 7.5, 6.3 Hz, 2H), 1.87 (dd, *J* = 14.6, 6.8 Hz, 1H), 1.84 – 1.76 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.59, 127.40, 46.92, 35.40, 30.48, 29.48, 26.20, 25.73, 14.00.

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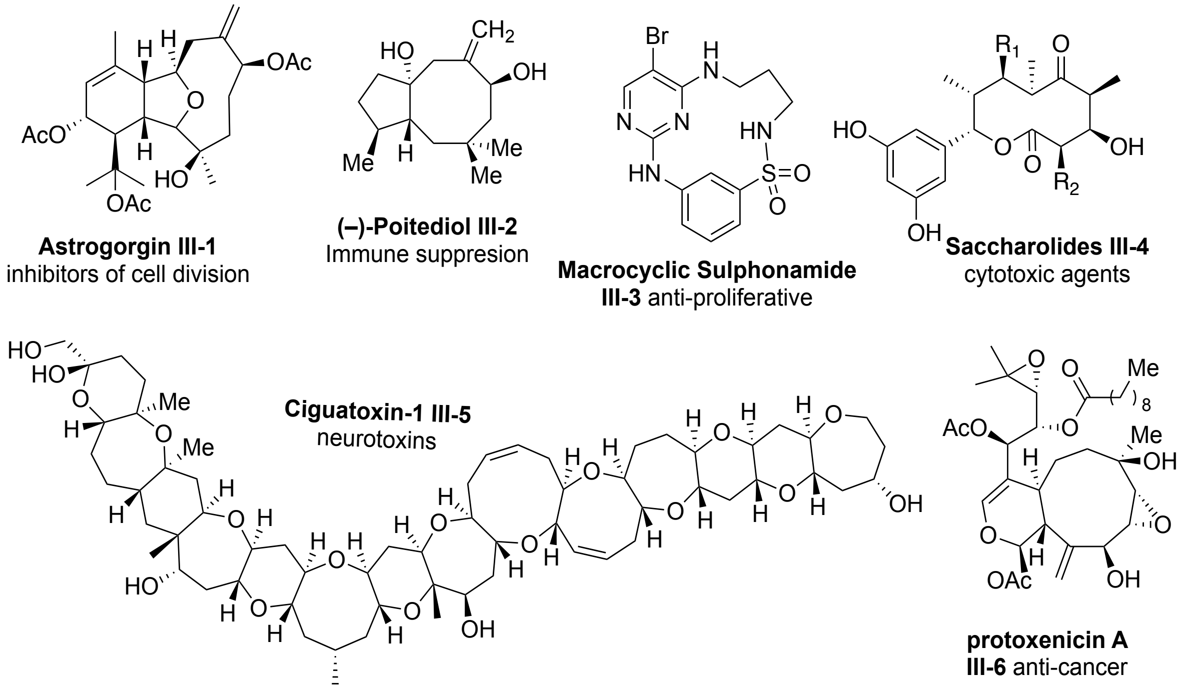
CHAPTER III: A DELICATE KINETIC SWITCH TO ACCESS MACROCYCLIC ETHERS OR SPIROKETALS: A DIVERGENT SCAFFOLD REMODELLING APPROACH

INTRODUCTION

Medium-ring and macrocyclic ketones are found widely as fundamental structures in a large number of biologically active natural products and clinical drugs.[1-3] In these biologically active chemical entities, the medium-ring and macrocyclic ketone structural cores are often indispensable for their pharmaceutical properties.[4-6]

Natural products containing oxygen heterocycles remain in abundance and continue to be reported. Medium-sized carbocyclic compounds, in particular, oxygenated eight- ten membered rings, are important frameworks that can be found in a wide variety of naturally occurring bioactive molecules and pharmaceutical drugs (Figure III-1).[7-10] Medium-sized ethers tend to be the lynchpin in natural products where they are present. Furthermore, the introduction of medium-sized conformationally flexible rings enhances


Astrogorgin III-1
inhibitors of cell division

(–)-Poitediol III-2
Immune suppresion

Macrocyclic Sulphonamide III-3 anti-proliferative

Saccharolides III-4
cytotoxic agents

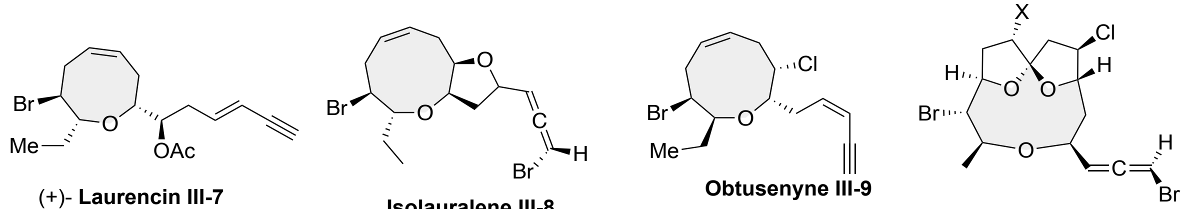
Ciguatoxin-1 III-5
neurotoxins

protoxenicin A III-6 anti-cancer

Figure III-1: Examples of macrocyclic natural product core containing [8-13]-membered rings.

the secondary binding of an inhibitor without adding to the structure's stereochemical complexity. These salient features have witnessed an upsurge in both the synthesis and applications of these privileged motifs in medicinal chemistry discovery programs within academia and the pharmaceutical industry.[7-10] Over the past decades, chemists have devoted significant effort toward the construction of these macrocyclic natural products.

Natural products containing halogens are exceedingly common, including medium-sized ethers (Figure III-2).[11-13] Successful approaches to these scaffolds hinge on various conformational restraints for ring closing metathesis. Indeed, this mirrors a trend seen across other compound classes, where larger ring systems are often underexplored due the additional challenges associated with their synthesis. For example, most often the efficiency of macrocyclization reactions relies on the appropriate conformational preorganization of a linear precursor, ensuring that reactive ends are in spatial proximity prior to ring closure.[14] Added to this are the unfavorable enthalpy and entropic factors and as well as transannular interactions that make medium-sized ring synthesis challenging and most often substrate dependent. As a result, varying the ring size usually requires a different substrate design, which is both time-consuming and expensive.



(+)- **Laurencin III-7**

Isolauralene III-8

Obtusenyne III-9

X = Br **Obtusallene V; III-10**
X = H **Obtusallene VI; III-11**

Figure III-2: Examples of halogenated macrocyclic natural product core.

Our Approach: Our group has been intensely engaged with catalytic asymmetric halofunctionalization of alkenes.[15, 16] We have already developed elegant strategies towards asymmetric halo-etherification.[17] But most of our strategies for intramolecular halofunctionalization have concentrated on the development of 5/6-membered ring.[18-21] Using our developed concept of *HalA*[22] and *NAAA*[23] we envisioned the formation of 10-membered ring through a ring expansion technique. Further exploration revealed that the same methodology could be broadened to access 9 and 11-membered rings as well. This would grant a unified strategy for the synthesis of macrocyclic ethers. Furthermore, we have uncovered that a slight modification of reaction conditions can provide access to both the double anomeric mono bromo-spiroketal as well as the synthesis of single

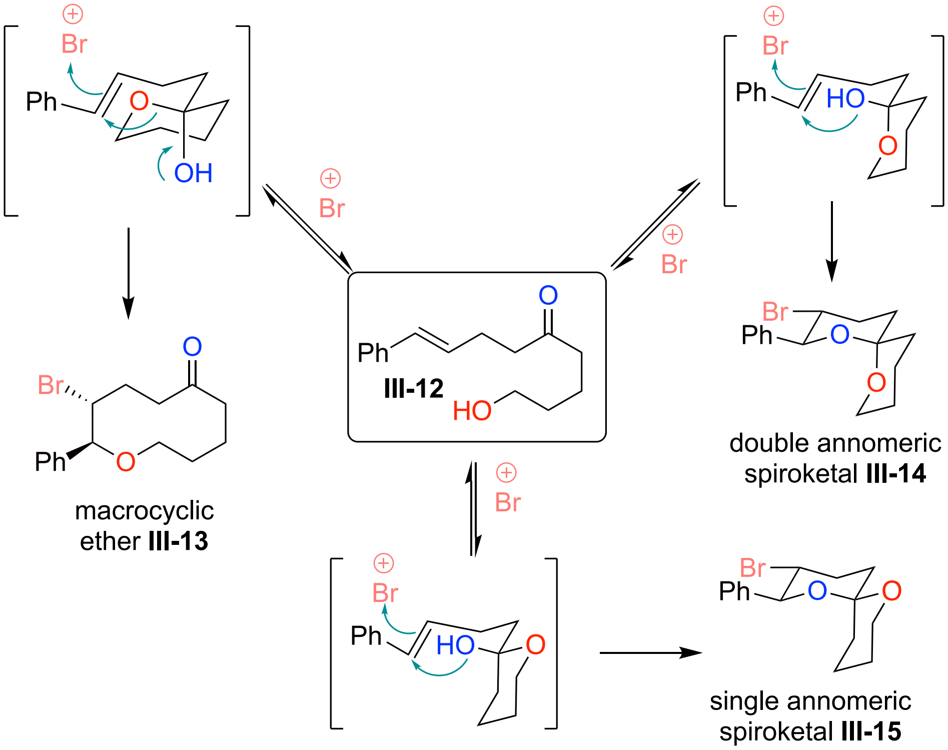


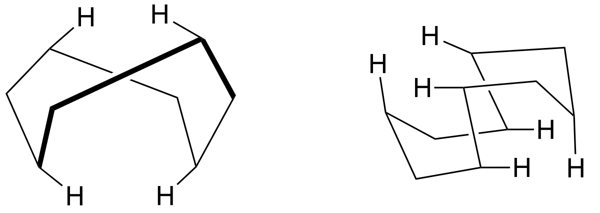
Figure III-3: Our approach on tuning the equilibrium to access both the macrocycle & the spiroketals.

anomeric spiroketals. Small alteration of the reaction conditions helps to dictate the equilibrium of the putative intermediate and direct the formation of different products (Figure III-3).

The literature is rich with reports mostly dedicated towards the formation of 5/6/7 membered rings. The major reason for the scarcity of reports towards the macrocyclic rings can be attributed broadly due to the following reasons:

Trans-annular Strain:

Cyclic compounds comprising of eight- to eleven-membered rings are considered as medium sized ring compounds. These rings exist in a large number of conformations because of the low energy barriers associated with their interconversion and hence these molecules often show transannular interactions.[24-27] Hence for these compounds, bond angles, torsional strains, and non-bonded interactions become important.[27-29] In general, due to conformational flexibility of saturated rings, non-bonded hydrogen-hydrogen atom repulsions are present (Figure III-4). When hydrogen atoms are replaced with functional groups, these non-bonded repulsions lead to transannular interactions. Due to the presence of non-bonded repulsions between atoms in medium-sized rings a considerable



Cyclooctane **III-16**
Boat–Boat conformation

Cyclodecane **III-17**
Boat–Chair–Boat conformation

Figure III-4: Non-bonded interaction present in cyclooctane and cyclodecane.

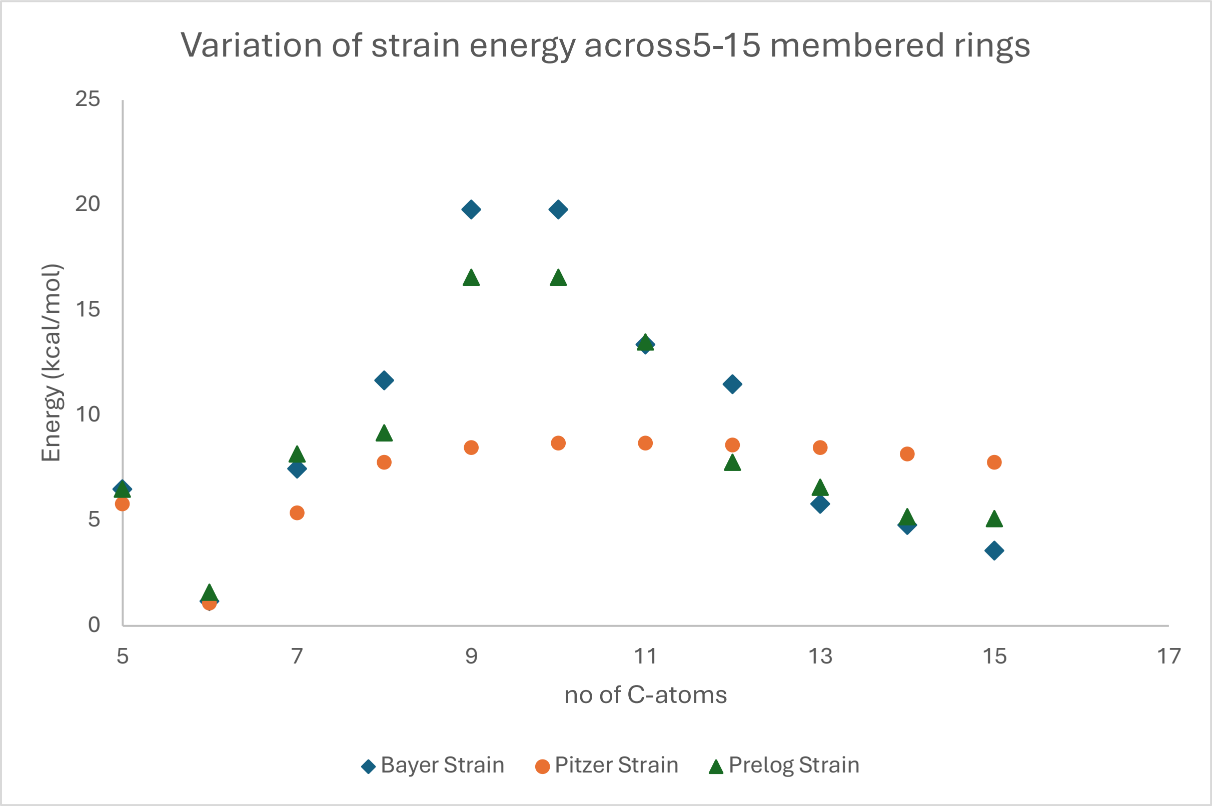


Figure III-5: Variation of strain energy across 5-15 membered rings.

amount of Baeyer,[30] Pitzer[31-33] and Prelog strain[32] are present (Figure III-5), hence making their synthesis challenging. The angle for a tetrahedral carbon atom in medium-sized rings is more than 109.5°. This leads to Baeyer or large angle strain. To avoid transannular interactions medium-rings adopt conformations in which carbon-carbon bonds are eclipsed or partially eclipsed. This gives rise to Pitzer or torsional strain. Prelog strain arises from interactions between non-bonded atoms in medium-sized ring compounds. These unusual properties have made medium-rings an area of great interest in organic chemistry.[32]

Strain Energy: The group of medium-sized carbocycles, consisting of eight to eleven carbon atoms, is characterized by its relatively high ring strain compared to the most prevalent five-, six- and seven membered rings and large rings (+ twelve carbon atoms).[33] The observed conformations of carbocyclic rings are a result of the system trying to minimize angle and torsional strain. In medium-sized rings, additional transannular interactions of ring substituents on non-adjacent carbon atoms can contribute significantly to the ring strain energy (Table III-1).

Table III-1: Strain energy in cycloalkanes.

Strain Energy of cycloalkane							
Ring Size	6	7	8	9	10	11	12
Strain Energy [kcal/mol]	1.4	7.6	11.9	15.5	16.4	15.3	11.8

Synthetic Strategies Towards Macrocyclic Rings:

Given growing interest in the study of medium-sized rings and macrocycles in medicinal chemistry, the development of effective new methods to prepare them is important, especially for oxygen containing compound classes for which existing synthetic methods are limited. Although several methods for the preparation of substituted macrocyclic carbocycles have been reported in the past decades, no generally applicable method has been described. Strategies for accessing macrocyclic carbocycles have been classified into four categories: (1) fragmentation reactions (Gröb Fragmentation), (2) radical ring-expansion/-contraction reactions (Dowd-Beckwith reaction), (3) pericyclic reactions and (4) cyclization reactions of acyclic precursors (RCM).

1. ***Fragmentation Reactions (Gröb fragmentation)***: Grob fragmentation reaction,[34, 35] which is still widely used today is one of the most reliable ways to forge a macrocyclic ring. In this reaction, a molecule of the form **III-18** is heterolytically cleaved into three

fragments: **III-19**, **III-20** and Y (Figure III-6a). The choice of the leaving group Y determines the thermodynamic driving force of this irreversible reaction.

This strong thermodynamic driving force makes the Grob fragmentation a powerful synthetic tool for compensating the high ring strains associated with the formation of medium-sized rings. In recent years, the Grob fragmentation was applied to cascade reactions, thus allowing formation of the fragmentation precursor and fragmentation in one-pot. Molander and co-workers accessed eight-, nine- and ten-membered rings by a samarium diiodide-mediated cyclization/fragmentation cascade of simple

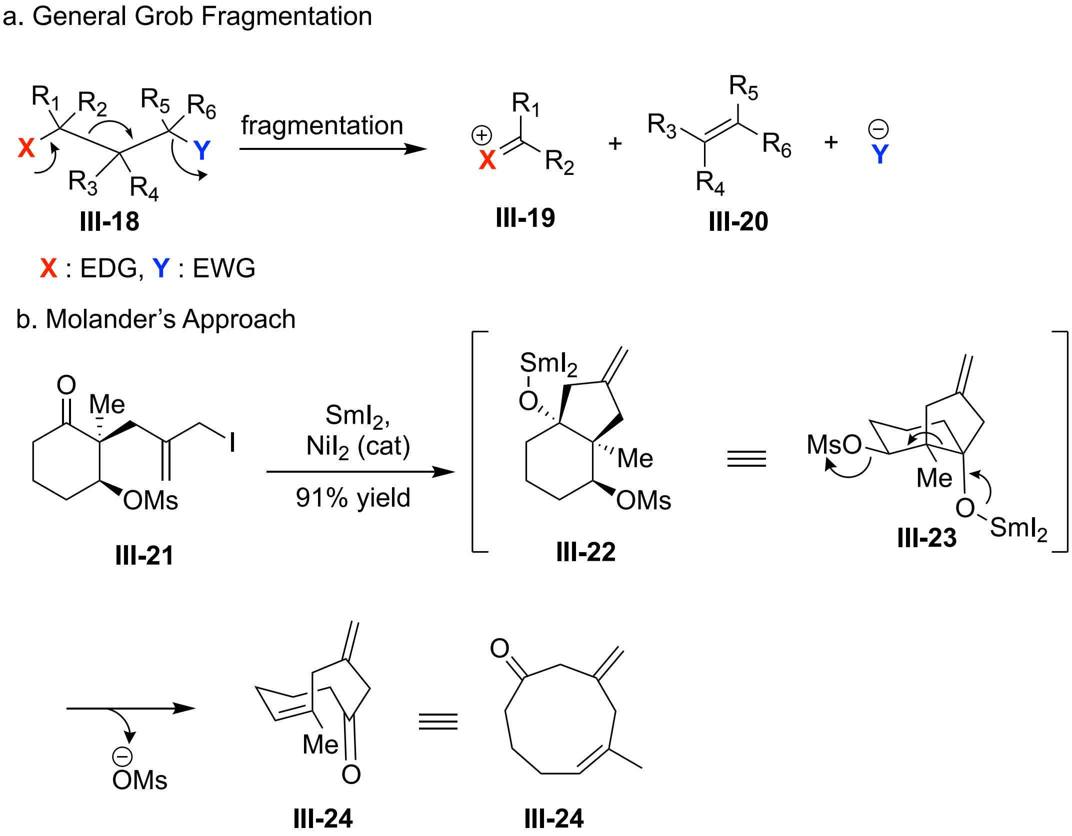
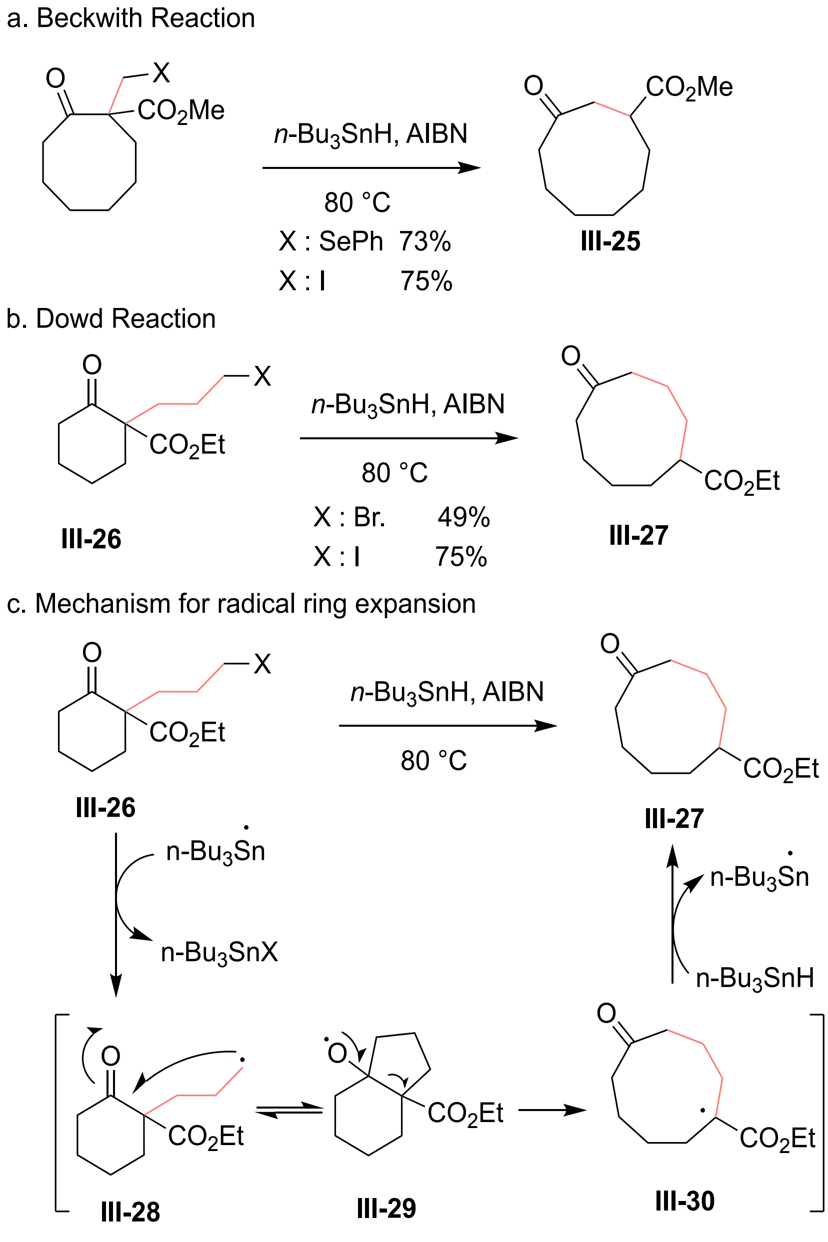


Figure III-6: a. General Grob fragmentation pattern. b. Molander *et al.* cyclization-ring expansion strategy to synthesize macrocycle.

iodocycloalkanones.[36] In this domino reaction, samarium(III) alkoxide **III-22/III-23** was formed by a samarium diioide-mediated intramolecular cyclization of δ-iodoketone **III-21**, which then fragmented to afford cyclononene **III-24** (Figure III-6b).

2. ***Radical ring-expansion/-contraction reactions (Dowd-Beckwith reaction)***: Free



a. Beckwith Reaction

b. Dowd Reaction

c. Mechanism for radical ring expansion

Figure III-7: a. Beckwith Reaction. b. Dowd reaction. c.Mechanism for the Dowd-Beckwith reaction

radical-mediated ring-expansion reactions have been frequently utilized in the synthesis of medium-sized rings in the past.[37] Radical fragmentations can usually be conducted under mild reaction conditions and are operationally simple. Furthermore, a variety of functional groups are tolerated. The drawbacks of radical reactions are the formation of side products. Besides quenching of the generated radical, competing intramolecular [1,5]-H atom abstraction followed by radical quenching is the main undesired reaction pathway.[38] Dowd and Beckwith were the pioneers of radical ring-expansion reactions and their synthetic strategy, known as the Dowd–Beckwith reaction, and variants thereof are the most widely used radical fragmentation strategies. Mechanistically, the reaction commences with the generation of the primary alkyl radical **III-28** from the halide or selenide substituent (Figure III-7). Subsequent intramolecular cyclization results in the

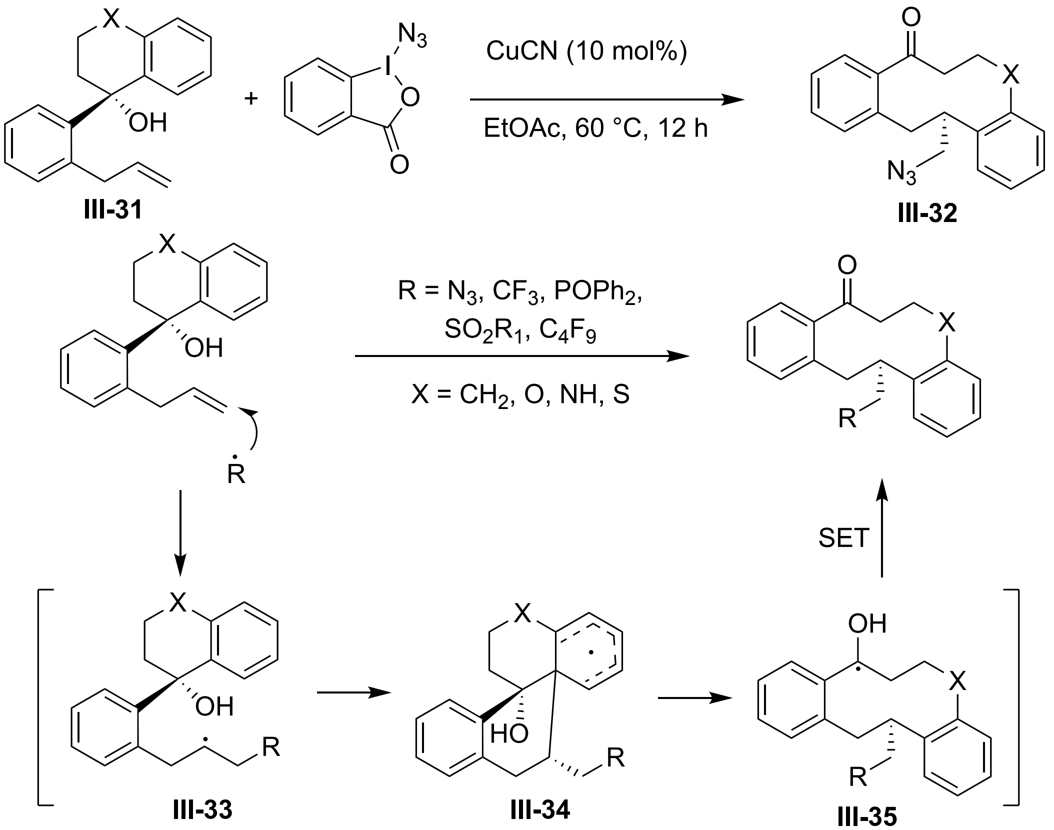


Figure III-8: Radical aryl migration- ring expansion protocol by Liu *et al.*

formation of the high-energy oxygen-centered radical **III-29**. Radical ring-opening of bicycle **III-29** leads to **III-30** with the tertiary radical stabilized by the ester group,[39] providing the driving force for the fragmentation. Hydrogen abstraction from tributyltin hydride finally gives the nine-membered cyclic ketone **III-27** and generates a tributylstannyl radical, which propagates the radical chain reaction. The use of β-keto esters as substrates not only facilitates the preparation of the radical precursors by alkylation, but also renders the cyclic ketone more electron-deficient, and thus, activates it for the radical cyclization.

The Liu group utilized this strategy for the construction of benzannulated medium-sized rings via ring-expansion by using a radical ipso-substitution strategy in 2016.[33] Generation of the radicals was realized by using hypervalent iodine(III) reagents and copper(I) cyanide (R=N_3, CF_3), alkyl or aryl sulfonyl chlorides (R=SO_2R', C_4F_9) and copper(I) iodide, or diphenylphosphine oxide and silver(I) nitrate (R=$P(O)Ph_2$). The first step is the addition of the generated radicals to the terminal alkene substrate **III-31** (Figure

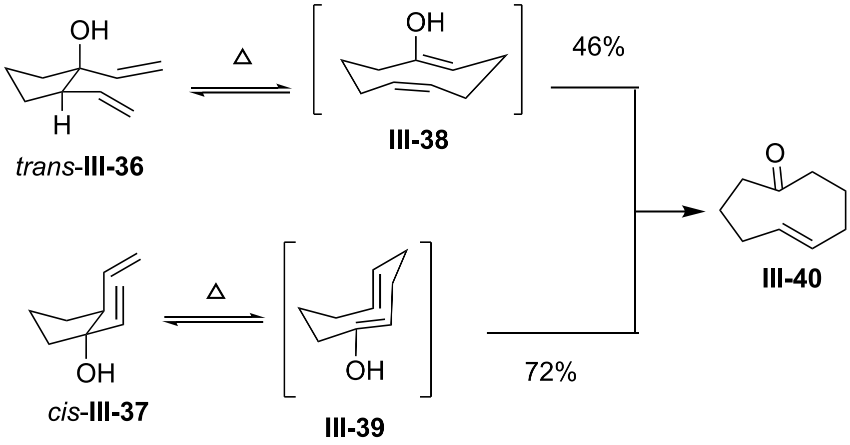


Figure III-9: Thermal oxy-cope rearrangement towards 9-membered macrocyclic ketone.

III-8). The secondary radical **III-33** undergoes a 1,4- or 1,5-aryl migration/ring-expansion sequence to afford the macrocycle **III-32**. The migration presumably proceeds through spiro radical intermediate **III-34**.[40] Oxidation of the tertiary radical **III-35** to the ketone by the copper or silver catalyst and loss of a proton gives the ring-expanded medium-sized cyclic or macrocyclic ketones **III-32**. Furthermore, the authors demonstrated that the use of enantiomerically pure alcohols enabled isolation of enantioenriched medium-sized rings through radical chirality transfer during the ring-expansion.

3. **Pericyclic reactions**: Sigmatropic rearrangements have been utilized for the synthesis of medium-sized rings. The thermal activation (220 °C) of an 81:19 mixture of isomers *trans*-**III-36** and *cis*-**III-37** led to the isolation of (*E*)-5-cyclononen-1-one (**III-40**) as a single isomer in good yield (Figure III-9).[41, 42] The stereochemical outcome of this reaction can be explained by the chair-like transition-state geometries as depicted in Figure III-9. The reaction was later performed as an anionic oxy-Cope rearrangement by treatment of *trans*-**III-36** with potassium hydride at 0 °C to afford the ring expanded product **III-40** in 86% yield.

4. **Cyclization reactions of acyclic precursors (RCM)**: The ring-closing metathesis (RCM) reaction has become one of the most powerful methods to construct medium-sized carbocycles from acyclic precursors. In 2008, the Altmann group described the total synthesis of the Xenia diterpenoid blumiolide C (Figure III-10a).[43] The, Z-configured double bond of the nine-membered ring **III-42** was formed by ring closing metathesis of diene **III-41** (Figure III-10a). Preliminary experiments showed that protection of the allylic alcohol as *p*-methoxy benzyl (PMB) ether was crucial for the success of the reaction. After

final optimizations, the best result was obtained by treatment of **III-41** with Hoveyda–Grubbs II catalyst (50 mol%) in toluene at elevated temperature (90 °C) to give **III-42** in 66% yield. Although RCM has evolved as the preferred technique for the formation of medium to large rings, this methodology suffers at times when multiple double bonds are present. Crimmins *et al.* during the synthesis of (+)-obtusenyne, had to change the synthetic strategy due to the formation of the undesired product **III-45** along with their desired product **III-44**.[44] Protection of the troublesome double bond through epoxidation of **III-46** led to the formation of the desired product **III-47** in 82% yield (Figure III-10b).

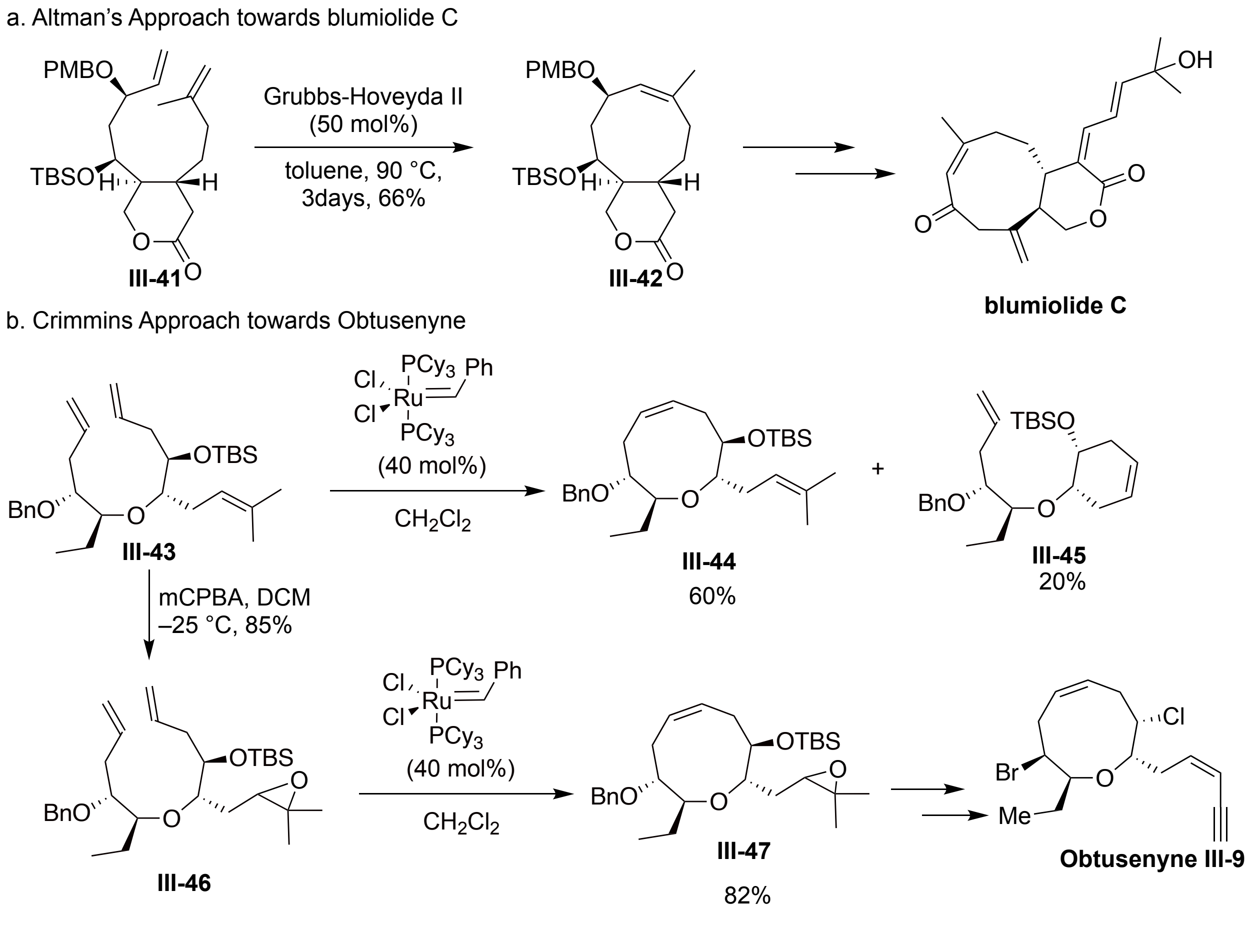
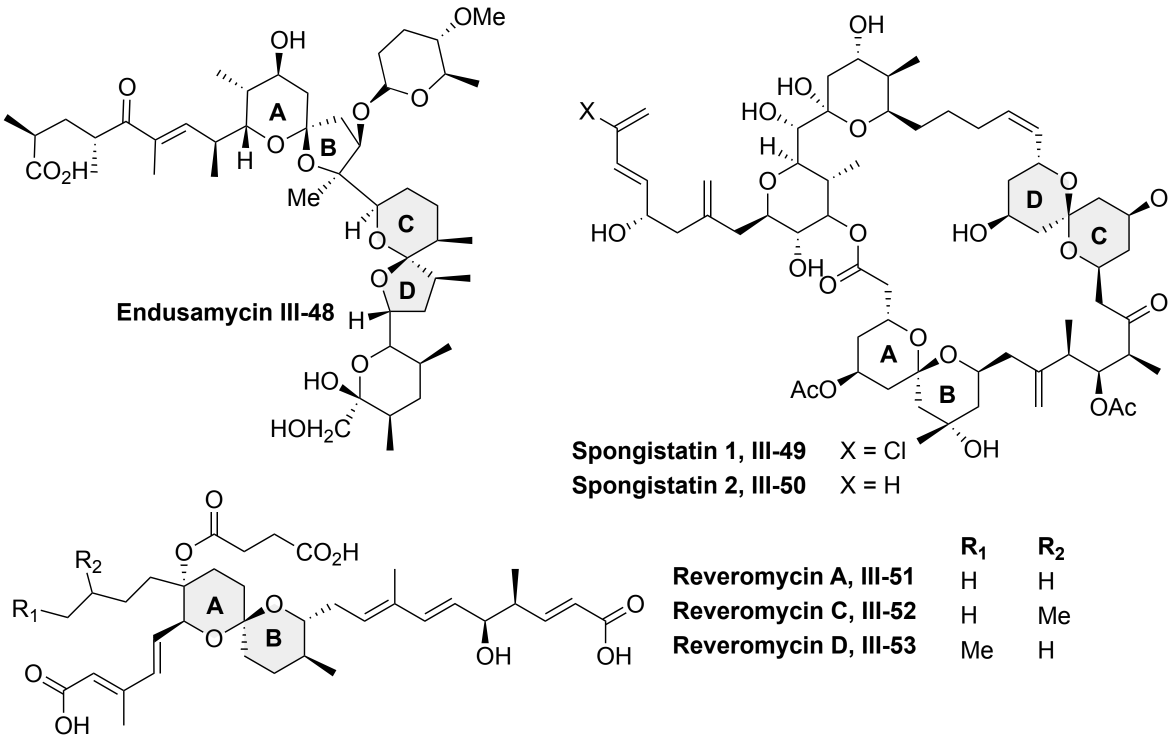


Figure III-10: a. Application of RCM in the total synthesis of blumiolide C. b. Difficulty of RCM during obtusenyne synthesis.

Compound **III-47** was then subsequently converted to the desired natural product Obtusenyne **III-9**.

Single anomeric [contra-thermodynamic] spiroketal:



Endusamycin III-48

Spongistatin 1, III-49 X = Cl

Spongistatin 2, III-50 X = H

	R_1	R_2
Reveromycin A, III-51	H	H
Reveromycin C, III-52	H	Me
Reveromycin D, III-53	Me	H

Figure III-11: Natural product core decorated with single anomeric spiroketal.

In 1993, the research groups of Pettit, Kitagawa/Kobayashi and Fusetani independently reported the isolation, from marine sponges, of a family of related highly oxygenated macrolactones containing highly substituted 6,6-spiroketals and tetrahydropyran rings.[45-47] These molecules were found to be among the most potent cancer cells growth inhibitors tested to date by the U.S. National Cancer Institute on a panel of 60 human carcinoma cell lines, with GI_{50} values in the nanomolar and picomolar ranges. Despite these promising properties, further biological investigations were precluded by the extremely low quantities that were obtained by extraction of marine organisms and the unacceptable ecological impact of larger scale isolation of the producing sponges to generate **III-49** and **III-50**. This scarce abundance, combined with remarkable structural complexity, prompted many research groups to address the challenge of the synthesis of these macrolides. Non-anomeric spiroketals are common in insect pheromones, polyketide antibiotics and marine toxins (Figure III-11). Endusamycin **III-48** belongs to a class of polyketide ionophore antibiotics which are microbial metabolites produced by Streptomyces.[48] Biological properties are related to ion transportations across biological membranes.

General Techniques Used For The Synthesis Of Singly Anomeric Spiroketals

Since this class of molecules lack the additional anomeric stabilization, their synthesis is dependent on certain parameters. Unless the mono-anomeric configuration is locked by ring fusion or suitably placed equatorial substituents on the six-membered ring, ring flipping will quickly transform the singly anomeric structure into the more stable anomeric structure. It is perhaps not surprising that nearly all mono-anomeric spiroketals bear an alkyl substituent in the 6-position of the tetrahydropyran ring. Ring flipping is prevented in these cases since it would place the substituent and the spiroketal oxygen in a sterically encumbered 1,3-diaxial setting (Figure III-12).[49] In natural products the

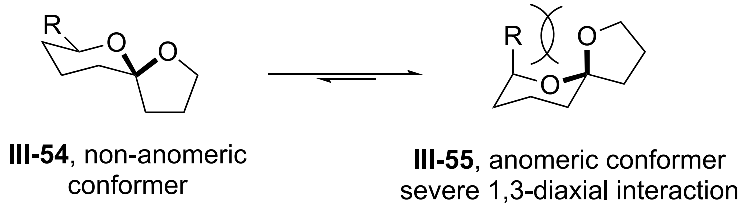
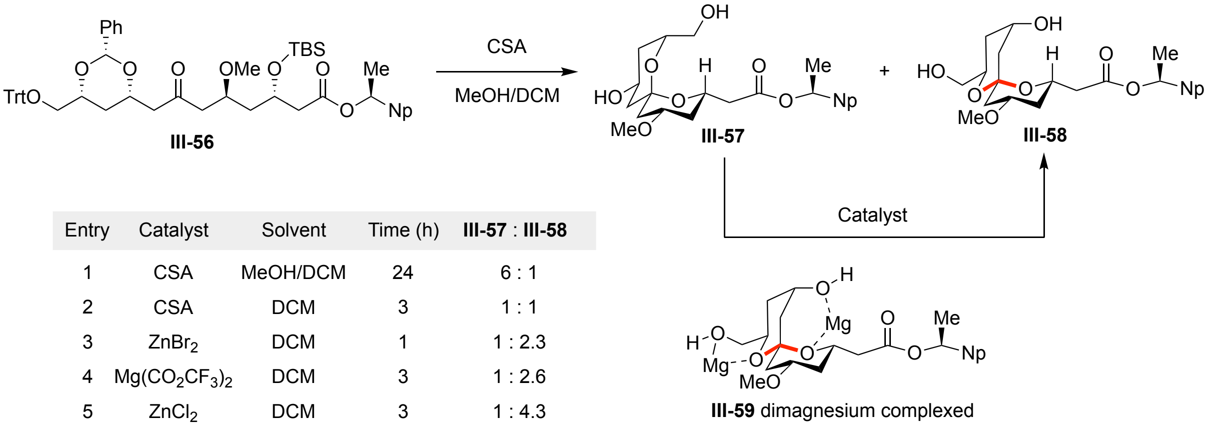


Figure III-12: Unfavourable 1,3 diaxial interaction between the 6-position alkyl group and the axial oxygen of spiroketal.

singly anomeric configuration may be stabilized by additional factors, which override the thermodynamic preference for the anomeric configuration. For example, intramolecular hydrogen bonding may contribute greatly to the stability of the mono-anomeric configuration. In addition, the constraints imposed by the macrocyclic structures may favor the mono-anomeric configuration.

Previous Synthetic Strategies For The Generation Of Singly-Anomeric Spiroketals:

1. ***Spongistatins***: Structurally, the spongistatins possess a striking array of diversity, including a 42-membered macrolactone incorporating two spiroketal moieties. A particularly interesting feature is the CD spiroketal unit possessing only one anomeric relationship (Figure III-11). In the case of spongistatins it has been proposed that the mono-anomeric configuration of the CD spiroketal unit is stabilized by intramolecular hydrogen bonding. In addition, conformational constraints imposed by the macrocyclic structure most likely favor the mono-anomeric configuration.



Entry	Catalyst	Solvent	Time (h)	**III-57** : **III-58**
1	CSA	MeOH/DCM	24	6 : 1
2	CSA	DCM	3	1 : 1
3	$ZnBr_2$	DCM	1	1 : 2.3
4	$Mg(CO_2CF_3)_2$	DCM	3	1 : 2.6
5	$ZnCl_2$	DCM	3	1 : 4.3

Figure III-13: Evans protocol to synthesize the [C,D] spiroketal ring in spongistatin.

Evans Protocol: The first total synthesis of the spongistatins was published by Evans and co-workers.[50] In the CD spiroketal synthesis removal of the oxygen protecting groups and spontaneous spirocyclization of **III-56** furnished a 6:1 mixture of two isomeric spiroketals **III-57** and **III-58** (Figure III-13). Formation of the desired mono-anomeric spiroketal **III-58** was accomplished by equilibration of the doubly anomeric spiroketal **III-57** using different Lewis acid catalysts (see table). A series of conditions was explored to determine ways to control the equilibration (Figure III-13).[51] It was postulated that an internal chelate is formed between the C25 hydroxyl group, the metal cation, and the C27 anomeric oxygen (**III-59**, dimagnesium complex), which then stabilizes the mono-anomeric structure in the thermodynamic equilibration.

Lau Protocol: Lau and co-workers published a synthesis for the CD spiroketal segment of spongistatin where the strategy was simply to utilize Lewis acid catalysis in the equilibration (Figure III-14).[52] Open-chained ketone precursor **III-60** underwent cyclization when treated with hydrofluoric acid to furnish a mixture of spiroketal isomers **III-61** and **III-62** in a ratio of 1:4.6. Upon further treatment with $ZnBr_2$, the ratio reversed (3.4:1), favoring the desired spiroketal **III-62**.

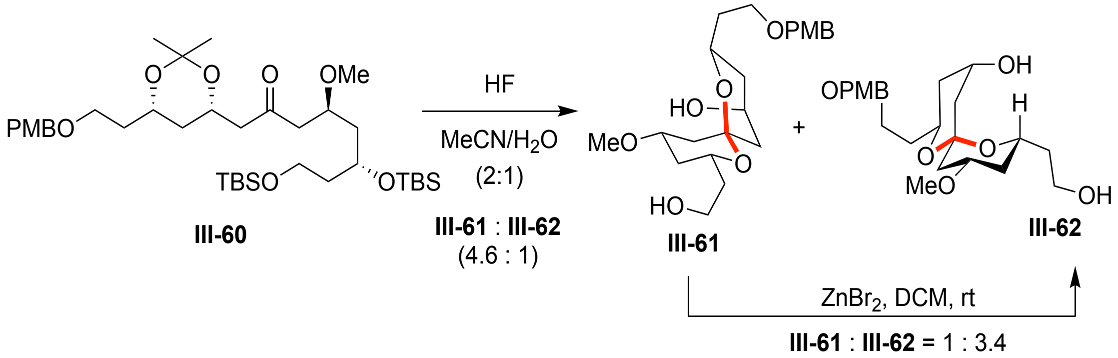
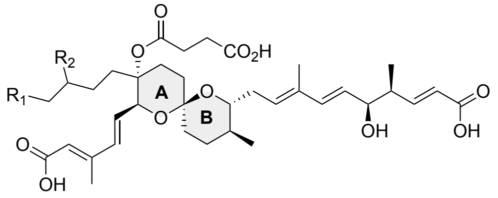


Figure III-14: Strategy to synthesize the [C,D] spiroketal ring in spongistatin by Lau *et al.*

2. ***Reveromycin***: Reveromycins A-D (**III-51–III-53**) are a family of polyketide-type antibiotics isolated from the genus Streptomyces.[53] The spiroketal moeties in reveromycins are mono-anomeric. Nakata and co-workers obtained a 1:2 mixture of the mono-anomeric spiroketal **III-65** and the doubly anomeric spiroketal **III-64** (Figure III-15).[54] In this approach when the open chain compound **III-63** was treated with camphor sulfonic acid in a mixture of two polar solvents MeOH and Chloroform the desired single anomeric spiroketal **III-65** was isolated in 27% yield. The reason for this was hypothesized as the disfavoured interaction of the *ax*-H and the bulky *ax*-$CH_2OTBDPS$ betwwen the two spiroketal rings in **III-64**. This synthetic strategy also illustrates the two basic features stated earlier. First, the presence of steric congestion and secondly, the requirement of polar solvents for the synthesis of the contra-thermodynamic spiroketal core.

3. ***Spirofungins***: Spirofungins (**III-66**) A and B are polyketide spiroketal type antibiotics that were isolated as a 4:1 mixture from the culture filtrate and extracts of *Streptomyces violaceusniger Tu¨ 4113*.[55] Dias and co-workers showed supporting evidence for the

a. General Structure of reveromycin



	R1	R2
Reveromycin A, III-51	H	H
Reveromycin C, III-52	H	Me
Reveromycin D, III-53	Me	H

b. Synthesis of the contra thermodynamic spiroketal ring in reveromycin by Nakata group

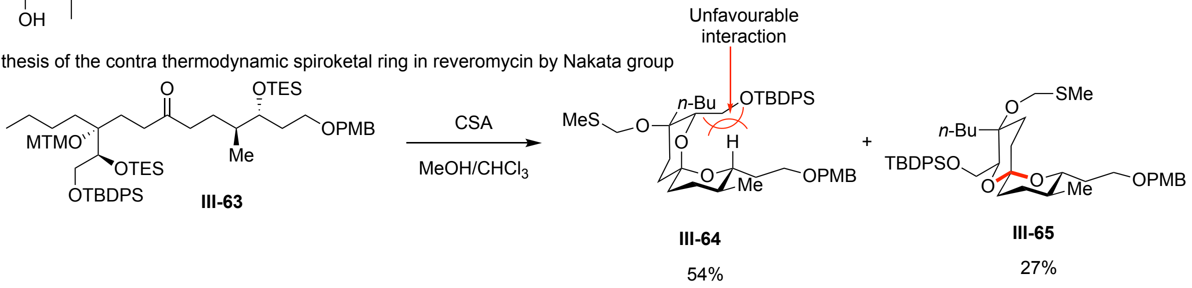
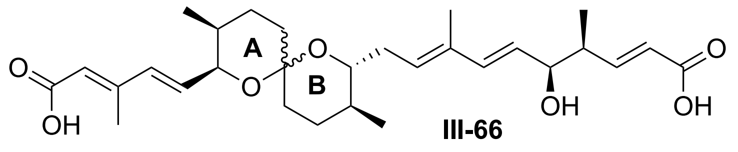


Figure III-15: Synthetic strategy to generate the [A,B] spiroketal ring in Reveromycin.

a. General Structure of Spirofungin



b. Synthesis of the [A,B] spiroketal ring in spirofungin by Dias *et al.*

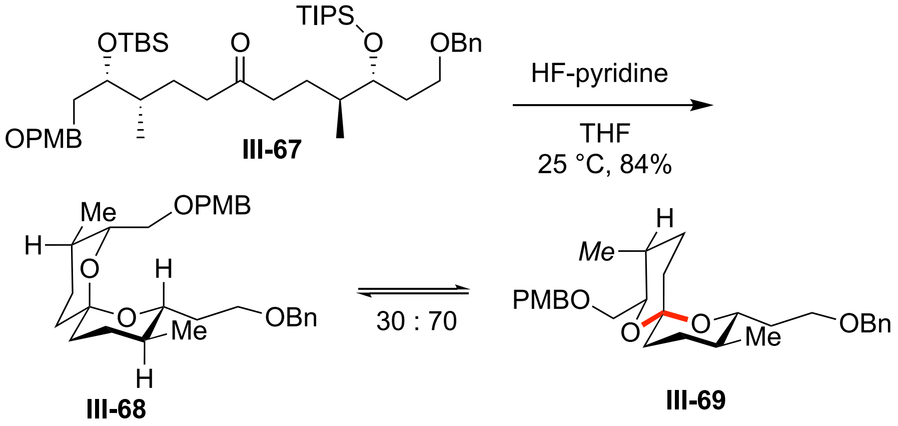


Figure III-16: Synthetic strategy to generate the [A,B] spiroketal ring in Spirofungin.

configuration of the epimeric C15 carbon in spirofungin B by developing an efficient synthetic method that gives access to both spirofungin spiroketals (Figure III-16).[56] Open-chain intermediate **III-67** was subjected to acid deprotection and concomitant spiroketalization by treatment with HF-pyridine gave a 30:70 mixture of spiroketals **III-68** and **III-69**.

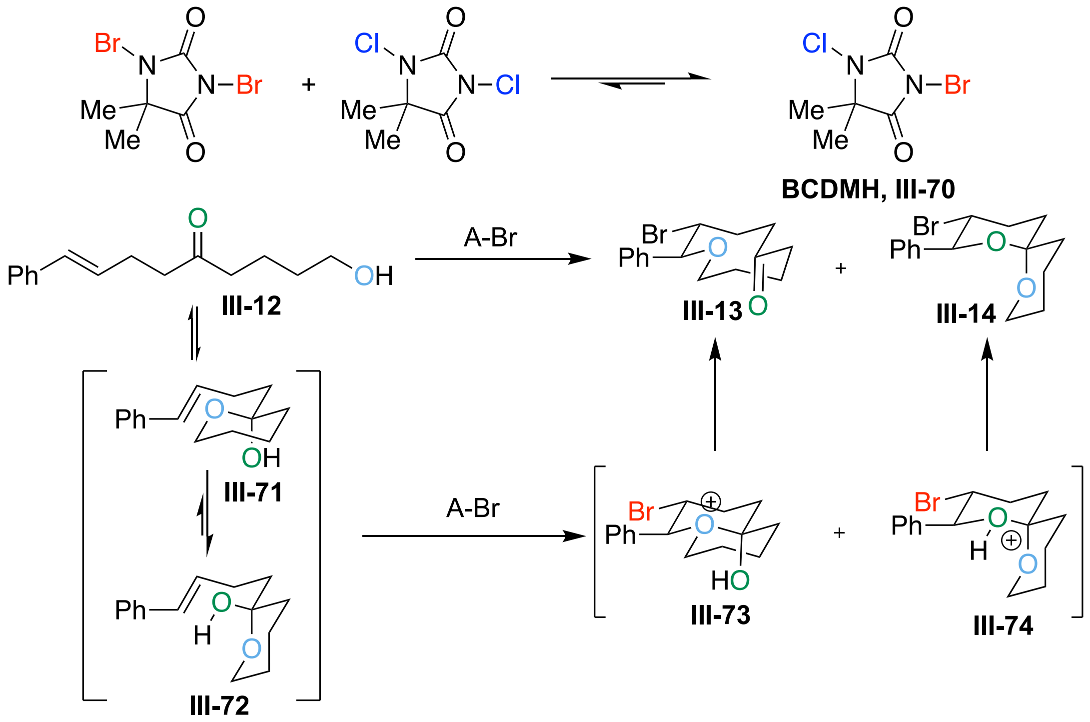
Natural products containing halogens are exceedingly common, for both medium-sized ethers and spiroketals. Despite excellent advances in the last decade, synthesis of halogenated macrocyclic ether/spiroketals has not been well explored. Thus, development of a single protocol to access these scaffolds by simply altering the reaction condition could be extremely beneficial for the development of the chemical space.

Reaction development and Optimization Studies

During the development of the protocol for the synthesis of double anomerically stabilized spiroketal **III-14**, we observed that when the free alcohol **III-12** was treated in the presence of the equimolar quantity of DBDMH and DCDMH, the macrocyclic ether **III-13** was obtained as the major product whereas the spiroketal **III-14** was only obtained as

a. Initial result

b. Probable mechanistic explanation



c. Control experiment

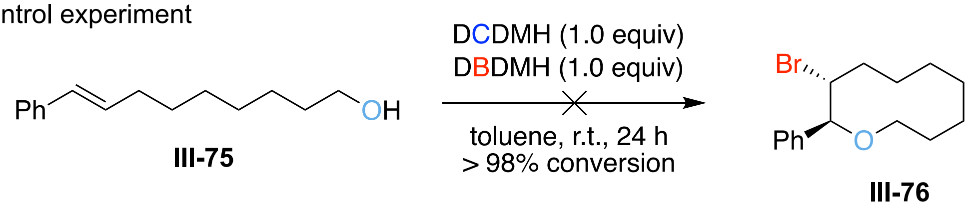


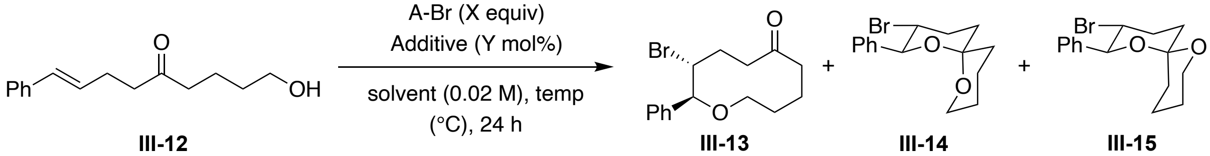
Figure III-17: Optimization studies for the synthesis of the macrocycle.

the minor product (Figure III-17). Since the major focus at that time was the synthesis of the spirocycle **III-14**, we investigated conditions that would improve the efficacy of the methodology and generated the spiroketal in great yield and excellent diastereoselectivity.[15]

But the diversity of the natural product family and the challenges to synthesize the macrocycle and the singly anomeric spiroketal always motivated us to better understand and develop a protocol for the synthesis of macrocyclic ethers and the contra-thermodynamic spiroketal. With this initial result in hand, we sought out to understand how the macrocycle would have resulted from the given reaction. We postulated, as depicted in Figure III-17, the free alcohol exists in an equilibrium between substrate **III-12** and its hemiacetal forms **III-71** and **III-72**. If the hydroxy group intercepted during the bromo functionalization of hemiacetal **III-74** it will produce the desired spiroketal **III-14.** However, if the interception proceeds through the pyranyl oxygen embedded in the six-membered ring, **III-73**, it would yield the macrocycle **III-13**. Presence of the hemiacetals **III-71** and **III-72** is in agreement with Carreira's report during the disclosure of their spiroketalization reaction.[57] To justify the hypothesis that the macrocycle originated from the hemiacetal intermediate, compound **III-75** was synthesized and was subjected to the same reaction condition. Nonetheless, **III-75** failed to generate the desired bromo-macroether **III-76**. The only difference between the alcohol and the keto-alcohol is the presence of the ketone moiety on the alkyl chain of keto-alcohol **III-12** (Figure III-17). The ketone functionality in **III-12** can provide a route to facilitate the entropically less favorable pathway that leads to macrocycle **III-13**. The presence of the equilibrating hemiacetal reduces the entropic barrier in comparison to the direct macrocyclization of **III-76**.

Following this initial result, we conducted an extensive set of optimization studies that would result in the formation of the macrocyclic ether. During our pursuit we were able to take advantage of the existing equilibrium and tune the reaction conditions that would either solely yield the macroether **III-13**, or the double anomerically stabilized spiroketal **III-14**, or the more challenging singly anomeric **III-15** product. Table III-2 briefly summarizes the results. We began our optimization by treating the free alcohol **III-12** with 1.0 equiv of DCMDH and DBDMH that led to the formation of the macroether as the major product along with the double anomerically stabilized spiroketal **III-14** and a trace amount (7%) of the single anomerically stabilized spiroketal **III-15** (Table III-2, entry 1). In order to circumvent this problem, other brominating agents such as NBS and *N*-bromosaccharin were tried (enties 2-4) but these were not effective in inducing higher selectivity towards one product, as well as they led to sub-par conversion of the starting material. When 1 M HCl was used as catalyst (entry 5), the reaction was completed in 6 h but this led to an equimolar formation of all the three products. This outcome can be rationalized from the fact that addition of HCl not only activates the bromonium ion but also helps in the pre-organization of the keto-alkenol substrate **III-12** towards the formation of the hemi-acetal. Similar observations were noted during the recording of NMR for these substrates in $CDCl_3$ vs CD_3OD. $CDCl_3$ being slightly acidic would result in the significant amount of the hemi-acetal form vs the linear chain alkenol. These results were in line with the observations made by Carriera's and Denmark's group where the selective formation of linear chain alkenol was observed in CD_3OD.[57, 58] Switching to Lewis acids improved the reaction. Among the multiple Lewis acids that were tried $ZnBr_2$ and $InCl_3$ generated the best results. When $ZnBr_2$ was used in addition to DBDMH as the brominating agent it generated the double anomerically stabilized spiroketal **III-14** as the sole product (entries 10, 11). Although we wanted to drive the equilibrium towards the formation of **III-13** and **III-15**, the latter reaction condition generated **III-14** as the only product. Increasing the

Table III-2: Optimization Table for the synthesis of macroether and spiroketals.



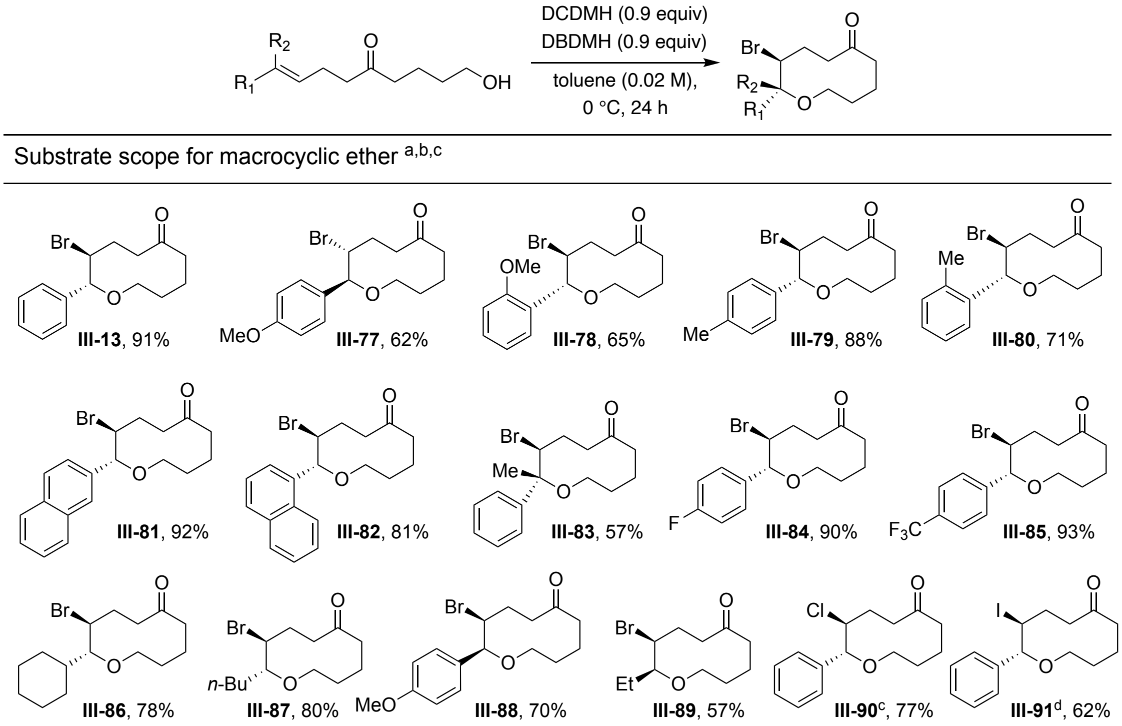
Entry[a]	A-Br (X equiv.)	Additive (Y equiv.)	Solvent	Temp (°C)	Coversion (%)[b]	Relative Yield (%)[b] **III-13** : **III-14** : **III-15**
1	DBDMH (1.0)	DCDMH (1.0)	Toluene	rt	100	1.1 : 1.0 : 0.2
2	NBS (1.0)	–	Toluene	rt	55	1.0 : 1.0 : 0.3
3	NBSacc (1.0)	–	DCM	rt	80	1.0 : 1.0 : 0.3
4	NBS (2.0)	–	Toluene	rt	95	1.0 : 0.9 : 0.2
5[c]	NBS (2.0)	HCl (1M) (0.2)	Toluene	rt	100	1.0 : 1.0 : 0.7
6	DBDMH (2.5)	DCDMH (2.5)	Toluene	rt	100	1.0 : 1.3 : 1.0
7	DBDMH (5.0)	DCDMH (5.0)	Toluene	rt	100	1.0 : 2.0 : 1.0
8	DBDMH (2.5)	HCl (1M) (0.25)	Toluene	rt	100	1.0 : 1.5 : 1.0
9[d]	DBDMH (2.5)	Quinuclidine (0.25)	Toluene	rt	30	–
10[e]	DBDMH (2.0)	$ZnBr_2$ (1.0)	Toluene	rt	100	0.0 : 1.0 : 0.0
11[e]	DBDMH (1.2)	$ZnBr_2$ (1.0)	Toluene	rt	100	0.0 : 1.0 : 0.0
12	DBDMH (0.5)	DCDMH (0.5)	Toluene	rt	70	2.0 : 0.5 : 0.3
13	DBDMH (0.75)	DCDMH (0.75)	Toluene	rt	100	10.0 : 1.0 : 1.0
14	DBDMH (0.75)	DCDMH (0.75)	Toluene	0	90	20.0 : 1.0 : 1.0
15	DBDMH (0.75)	DCDMH (0.75)	Toluene	–20	60	50.0 : 1.0 : 1.0
16	DBDMH (0.90)	DCDMH (0.90)	Toluene	0	100	40.0 : 1.0 : 1.0
17	DBDPH (0.90)	DCDPH (0.90)	Toluene	0	100	40.0 : 1.0 : 1.0
18	DBDMH (0.90)	DCDMH (0.90)	Chlorobenzene	0	100	40.0 : 1.0 : 1.0
19[e]	DBDMH (0.90)	DCDMH (0.90)	DMF	0	100	0.0 : 1.0 : 10.0
20[e]	DBDMH (0.90)	DCDMH (0.90)	DMSO	0	100	0.0 : 1.0 : 8.0

[a] All reactions were performed at 0.3 mmol scale under the standard reaction condition. [b] Conversion and relative ratios were evaluated on crude ^1H NMR with MTBE as internal standard. [c] reaction completed in 6 h. [d] reaction time was 48 h. [e] reaction completed in 2 h.

amount of DCDMH and DBDMH, led to a near equimolar ratio for the formation of all the three products (entries 6-8). Thus, we wanted to see the effects of the bromo-functional on going sub-stoichiometric amounts of DCDMH and DBDMH. Indeed, when half equiv of DCDMH and DBDMH were used, the macroether **III-13** was formed as the major product although the conversion was only 70% after 24 h. Use of 0.75 equiv led to complete consumption of the starting alkenol and generated the macroether **III-13** in 74% isolated yield (entry 13). Further reduction of temperature allowed the formation of the macroether as the major product with only trace amounts of spiroketal formation. Nonetheless, the reaction was slow with reduced temperature and at –20 °C and only 60% conversion was seen after 24h (entries 13-15). Increased loading to 0.90 equiv of DCDMH and DBDMH generated macroether **III-13** as the sole product with trace amount of the spiroketal formation (entry 16). The same result was observed when DBDPH and DCDPH were employed as the bromine source (entry 17). Chlorobenzene as the solvent was also equally effective in promoting the reaction of alkenol to yield the macrocyclic ether **III-13** (entry 18). When more polar solvents were employed, the equilibrium switched to favour the formation of the single anomerically stabilized spiroketal **III-15** as the major product (entries 19, 20). This was in accordance with the literature reports by Lau and Ley group for the synthesis of spongistatins (discussed in the previous section).[52] Since this class of molecules lack the additional anomeric stabilization, their synthesis is dependent on solvent, reaction condition, and sometimes use of chelating agents. Thus, in the presence of 0.9 equiv of DCDMH and DBDMH in DMF as the solvent at 0 °C, the single anomerically stabilized spiroketal **III-15** was isolated in 80% yield (10:1 *dr*).

Substrate Scope:

Macrocyclic ether: With the optimized reaction condition in hand, the scope of the reaction was investigated (Figure III-X). *Trans*-disubstituted substrates with different *p*-substituted arenes were well tolerated, providing products **III-13** and **III-77** – **III-85** in high yields (>60%) as a single diastereomer. The relative stereochemistry in these halogenated macrocycles was established unequivocally by the crystal structure of the product **III-13** and **III-97**. Both EDG as well as EWG irrespective of their electronic demands provided the corresponding products in good to excellent yields. Tri-substituted alkenol **III-135** generated the corresponding product **III-83** in good yield. Alkyl substrates were well tolerated and formed the corresponding macrocyclic keto-ethers in great yields

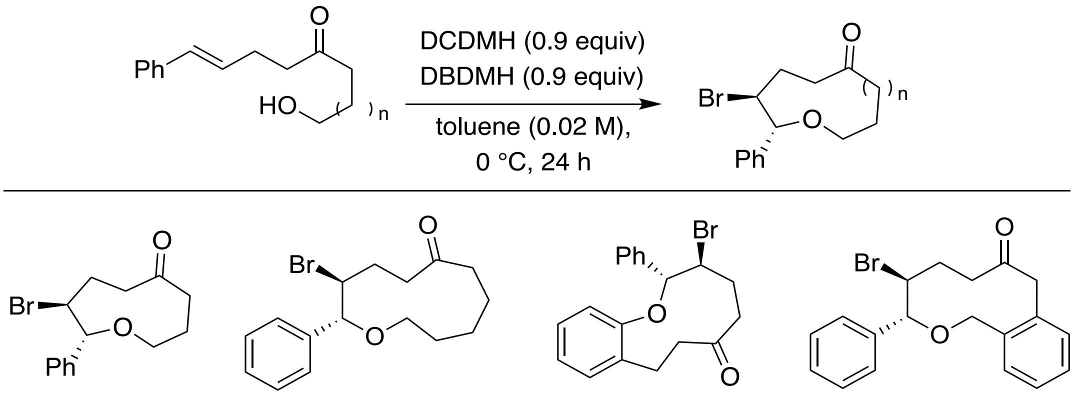


[a] Unless otherwise mentioned all reactions were performed on 0.3 mmol scale at 0.02 M concentration for 2h at 0 °C in toluene as solvent. [b] Isolated yield [c] NCS (2.0 equiv) was only used [d] NIS (2.0 equiv) was used as the iodinating agent

Figure III-18: Substrate scope studies for the synthesis of the macrocycle.

(**III-86** and **III-87**). The corresponding chloro **III-90** and iodo-macrocycles **III-91** were also synthesized with the same methodology in great yields as a single diastereomer (Figure III-18).

When the chain length was altered, the corresponding 9-membered and 11-membered macrocycles were obtained in moderate yields but in low *dr* (Figure III-19). When phenolic alcohol was used as the substrate, it generated the corresponding product **III-95** as a single diastereomer in good yield. When the free alcoholic group was switched to a benzyl alcohol, the corresponding macrocycle **III-97** was obtained as a single diastetreomer in great yield.



III-92, 56%[a,b]
dr 3:1

III-93, 43%[a,b]
dr 1:1

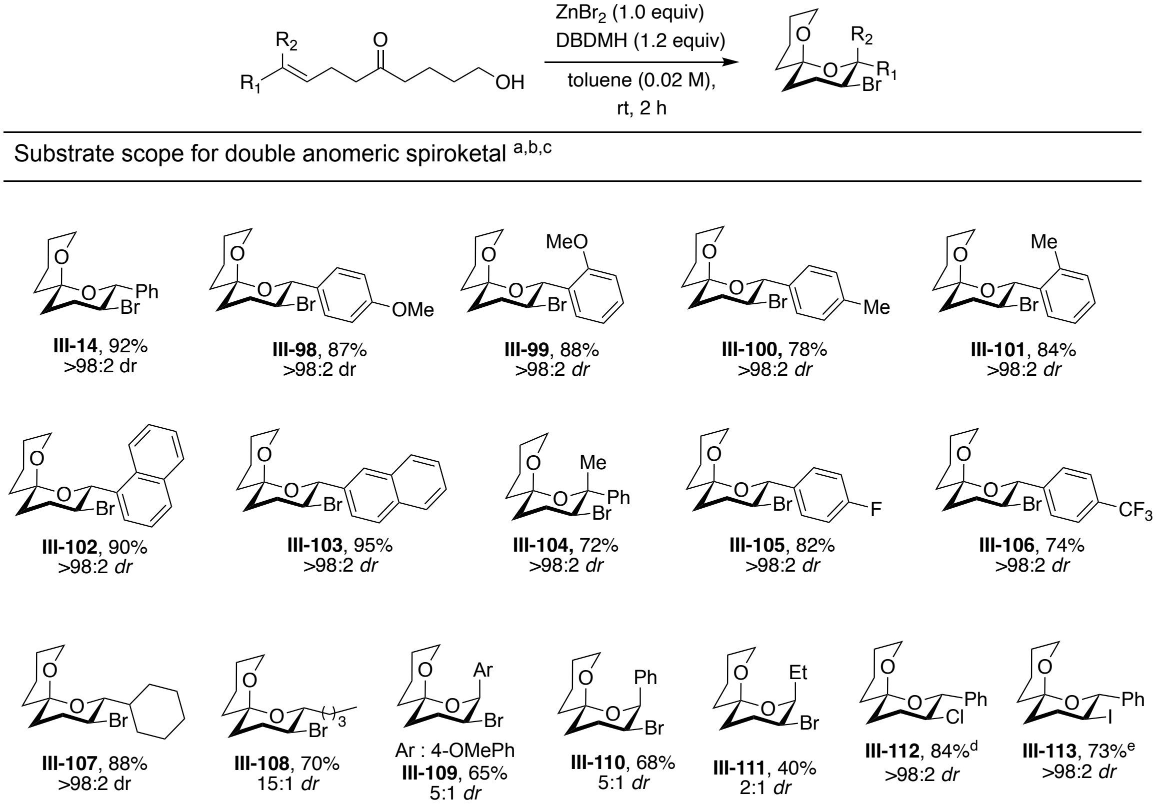
III-95, 65%
single diastereomer

III-97, 95%
single diastereomer

[a] Unless otherwise mentioned all reactions were performed on 0.3 mmol scale at 0.02 M concentration for 2 h at 0 °C in toluene as solvent. [b] Isolated yield.

Figure III-19: Substrate scope for different ring sized macrocycle and switch in the reactivity of the free alcohol.

Double-anomeric Spiroketal: The generality of the bromospiroketalization reaction was examined with various keto-alkeneols (Figure III-20). *Trans*-disubstituted substrates with different *p*-substituted arenes were well tolerated, providing products **III-14** and **III-98** – **III-106** in high yields (>75%), excellent *dr* (>98:2). Even the *trans*-substituted alkyl substrates were well tolerated and generated the corresponding products **III-107** & **III-108**



Substrate scope for double anomeric spiroketal [a,b,c]

III-14, 92% >98:2 dr

III-98, 87% >98:2 dr

III-99, 88% >98:2 *dr*

III-100, 78% >98:2 *dr*

III-101, 84% >98:2 *dr*

III-102, 90% >98:2 *dr*

III-103, 95% >98:2 *dr*

III-104, 72% >98:2 *dr*

III-105, 82% >98:2 *dr*

III-106, 74% >98:2 *dr*

III-107, 88% >98:2 dr

III-108, 70% 15:1 *dr*

Ar : 4-OMePh **III-109**, 65% 5:1 *dr*

III-110, 68% 5:1 *dr*

III-111, 40% 2:1 *dr*

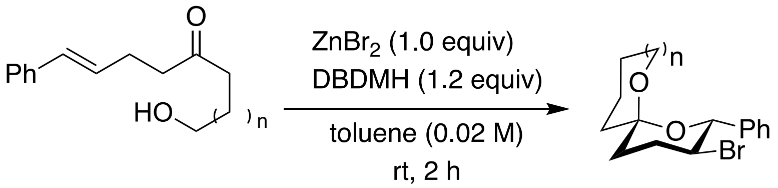
III-112, 84%[d] >98:2 *dr*

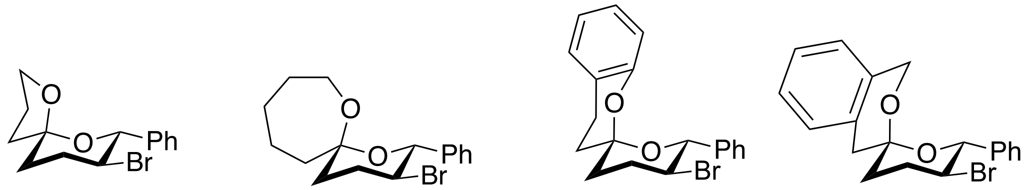
III-113, 73%[e] >98:2 *dr*

[a] Unless otherwise mentioned all reactions were performed on 0.3 mmol scale at 0.02 M concentration for 2 h at 0 °C in toluene as solvent. [b] Isolated yield. [c] *dr* was calculated from the crude ^{1}H NMR [d] DCDMH was only used. [e] NIS was used as the iodinating agent.

Figure III-20: Substrate scope studies for the synthesis of the double anomeric spiroketal.

in high yields (>75%) and excellent *dr* (>98:2). The *cis*-substituted alkenols transpired to their corresponding spiroketals **III-109** – **III-111** in moderate yields but low *dr*. A plausible explanation for this observation could be derived from the fact that these derivatives suffer considerable 1,3-diaxial interaction and hence results in the decreased diastereoselectivity. When the *trans*-alkenol was reacted in the presence of DCDMH the corresponding chloro-spiroketal **III-112** was formed in high yield and diastereoslectivity. The same was true for iodo-spiroketal **III-113**, synthesized by using NIS as the halogen source.





III-114, 92%[a]
>98:2 *dr*

III-115, 80%
>98:2 *dr*

III-116, 80%
>98:2 *dr*

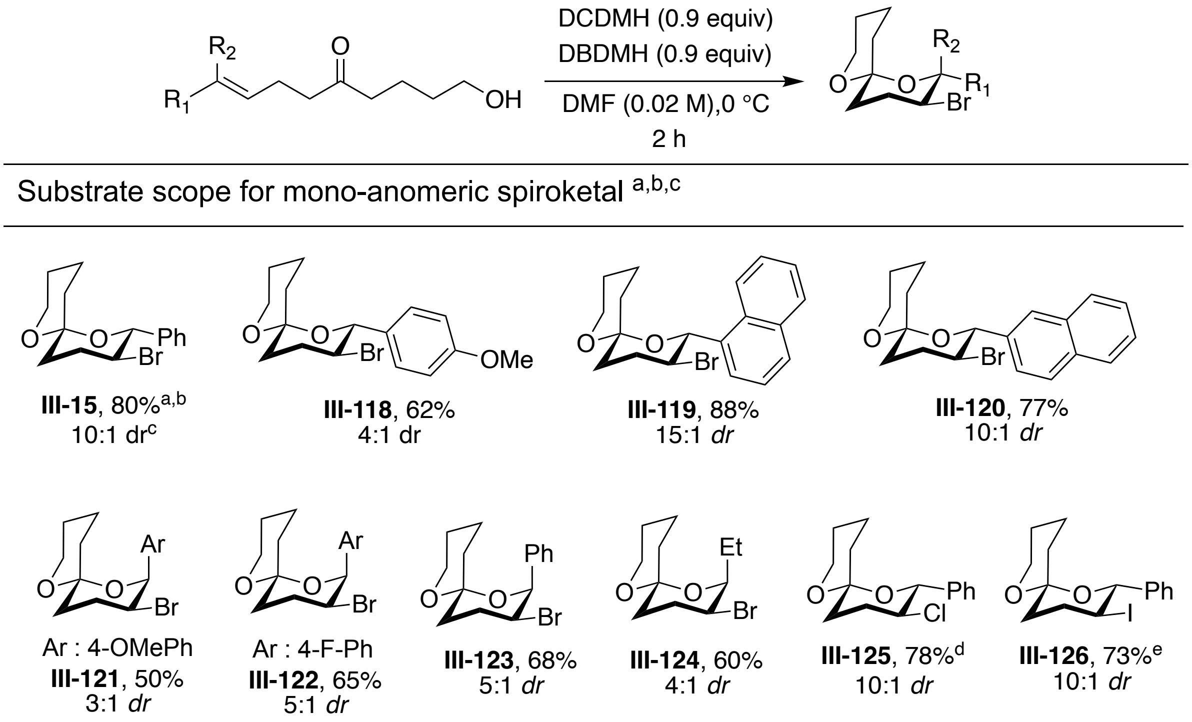
III-117, 92%
>98:2 *dr*

[a] Unless otherwise mentioned all reactions were performed on 0.3 mmol scale at 0.02 M concentration for 2 h at 0 °C in toluene as solvent. [b] Isolated yield

Figure III-21: Substrate scope for different ring sized double anomeric spiroketal and switch in the reactivity of the free alcohol.

In order to exploit the generality of the optimized condition, the reaction was peroformed with different alkenol chain lengths. The corresponding [6,5] and [6,7] spiroketals **III-114** and **III-115** were formed in good yield and excellent diastereoselectivity. When the alkyl alcohol was to the less reactive phenolic group the substrate was well tolerated under the reaction condition. It transpired to the corresponding product **III-116** in good yield and excellent diastereoselectivity (Figure III-21). Similar observations were made when the free alcohol was switched to a benzyl alcohol. The corresponding product **III-117** was obtained with excellent yield and distereoselective.

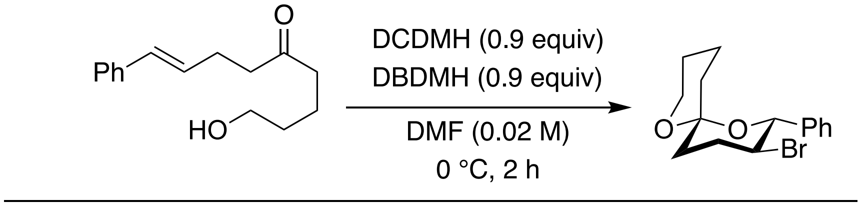
Single-anomeric Spiroketal: Figure III-22 summarizes the results for a handful of keto-alkenols that were subjected to the optimized conditions for single-anomeric-bromospiroketalization. Most of these substrates irrespective of their electronic properties were well tolerated and generated the desired product in good yields and excellent diastereoselection. The relative stereochemistry in these halogenated spiroketals was established unequivocally by the crystal structure of **III-15**. Both [6,6] and [6,5]-spiroketals were formed in great yields with good *dr*, but the *cis*-alkenols transpired to their corresponding products in moderate yields and low *dr* (Figure III-22). The above protocol was also successful in generating the corresponding chloro and the iodo-spiroketals **III-125**, **III-126** respectivey in great yields and good *dr*. When the alkyl-alcohol was switched

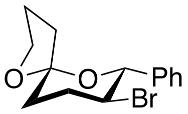


[a] Unless otherwise mentioned all reactions were performed on 0.3 mmol scale at 0.02 M concentration for 2 h at 0 °C in DMF as solvent. [b] Isolated yield. [c] *dr* was calculated from the crude ^{1}H NMR [d] DCDMH was used as the chlorinating agent. [e] NIS was used as the iodinating agent

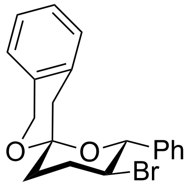
Figure III-22: Substrate scope studies for the synthesis of the mono-anomeric spiroketal.

to a benzyl alcohol, the corresponding bromo-spiroketal **III-128** was formed in high yield with 10:1 *dr* (Figure III-23).





III-127, 81%[a,b]
10:1 *dr*



III-128, 80%[a,b]
10:1 *dr*

[a] Unless otherwise mentioned all reactions were performed on 0.3 mmol scale at 0.02 M concentration for 2 h at 0 °C in DMF as solvent. [b] Isolated yield.

Figure III-23: Substrate scope for different ring sized single anomeric spiroketal and switch in the reactivity of the free alcohol.

General Remarks

All reactions were performed in flame-dried glassware under an atmosphere of nitrogen gas unless otherwise indicated. Unless otherwise specified, all solvents were strictly dried before use: dichloromethane was distilled over calcium hydride under a stream of nitrogen gas; tetrahydrofuran, and toluene were distilled from sodium and benzophenone. Hexanes and ethyl acetate were ACS grade and were used as purchased.

Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Varian Unity Plus 500 MHz spectrometer was used to record the ^{1}H NMR and ^{13}C NMR spectra using $CDCl_3$ as solvent. The residual peak of $CDCl_3$ or TMS was used as the internal standard for both ^{1}H NMR ($\delta = 7.26$ ppm for $CDCl_3$ or $\delta = 0$ ppm for TMS) and ^{13}C NMR ($\delta = 77.0$ ppm). Chemical shifts were reported in parts per million (ppm). Analytical thin-layer chromatography (TLC) was performed on Silicycle silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, or by staining with phosphomolybdic acid in ethanol. Column chromatography was performed with silica gel 60 (230 – 450 mesh). Infrared spectra were recorded on a JASCO FT/IR-6600. High Resolution Mass Spectrometry was performed in the Department of Chemistry at Michigan State University Mass Facility.

Experimental Section

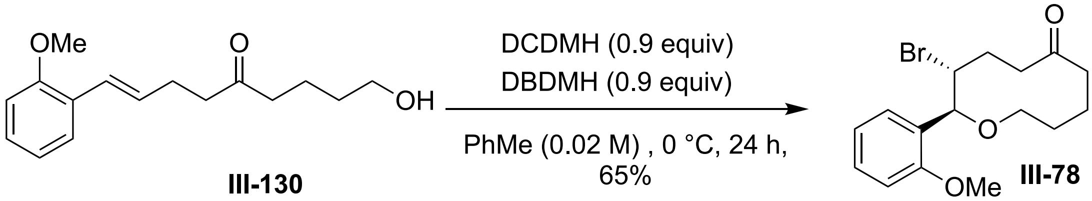
General Procedure for the bromo macroetherification of keto-alkenols (GP I):

Synthesis of 3-bromo-2-phenyloxecan-6-one (III-13): In a clean, dry 50 mL round bottom was taken DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) and DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv). The flask was kept under vacuum and backfilled with argon before the addition of dry toluene (5 mL). The reaction mixture was stirred at rt for 10 minutes before transferring to an ice bath precooled to 0 °C.

In a separate 25 mL round bottom was added the corresponding keto-alkenol (III-12) (69.6 mg, 0.30 mmol, 1.0 equiv). This flask was kept under vacuum and backfilled with argon before the addition of dry toluene (10 mL). The mixture was then immediately transferred to an ice bath for 15 minutes at 0 °C.

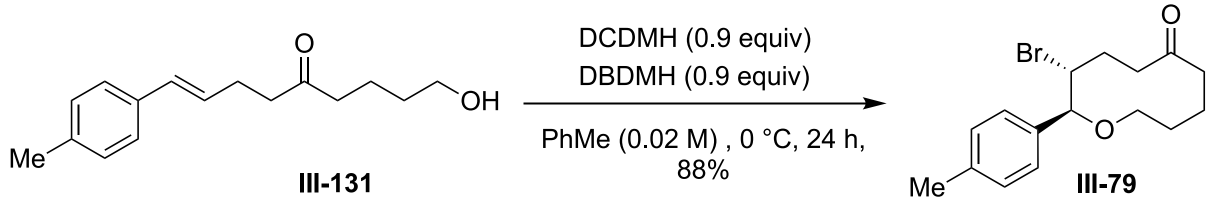
After pre-cooling the contents of both flasks, the solution containing the keto-alkenol was added dropwise to the solution of DCDMH and DBDMH. The resulting mixture was then stirred for 24 h at 0 °C whereupon TLC showed complete consumption of the starting material. The reaction mixture was quenched with Na_2SO_3 (3 mL), extracted with EtOAc (3 X 5 mL) and dried over Na_2SO_4. The volatiles were removed under reduced pressure and the crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent). Compound **III-13** was obtained as a white solid in 91% yield (85 mg, 0.27 mmol).

Analytical data for III-13: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 3H), 7.29 – 7.25 (m, 2H), 4.08 – 4.00 (m, 2H), 3.13 (dt, J = 8.2, 4.0 Hz, 1H), 2.83 (td, J = 9.1, 4.3 Hz, 1H), 2.80 - 2.67 (m, 3H), 2.59 – 2.49 (m, 1H), 2.48 – 2.40 (m, 1H), 2.25 (dd, J = 15.3, 6.7 Hz, 1H), 2.10 (dddd, J = 13.0, 11.2, 7.5, 3.1 Hz, 1H), 1.65 – 1.57 (m, 1H), 1.55 – 1.39 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.28, 139.88, 128.42, 128.27, 127.92, 85.50, 69.61, 55.78, 42.27, 42.08, 32.99, 29.43, 22.18. IR (cm^{-1}): 2938, 2885, 2868, 1710, 1443, 1366, 1350, 1260, 991, 744. HRMS: TOF MS AP$^+$ ($C_{15}H_{19}BrO_2$): Calc. [M + H]$^+$: 311.0646, Found [M + H]$^+$: 311.0647.



Compound **III-78** was synthesized from **III-130** (78.7 mg, 0.30 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-78** was isolated as a colorless solid in 65% yield (66.6 mg, 0.195 mmol).

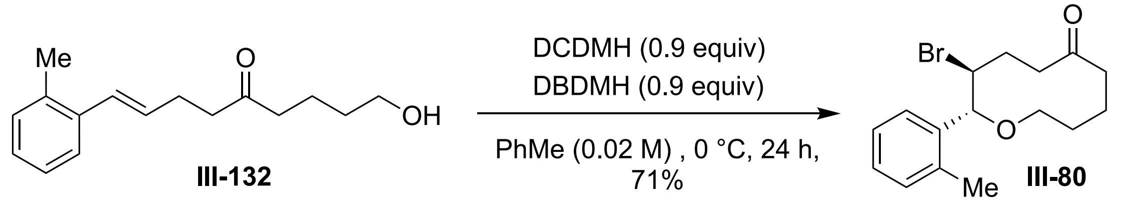
Analytical data for III-78: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.21 (m, 2H), 6.96 (td, J = 7.5, 1.1 Hz, 1H), 6.86 (dd, J = 8.3, 1.1 Hz, 1H), 4.71 – 4.56 (m, 1H), 4.27 – 4.08 (m, 1H), 3.82 (s, 3H), 3.13 (dt, J = 7.7, 3.6 Hz, 1H), 2.90 (ddd, J = 11.0, 8.9, 1.9 Hz, 1H), 2.80-2.70 (m, 2H), 2.65 (ddd, 15.4, 12.1, 1.8 Hz, 1H), 2.43 (d, J = 12.6 Hz, 2H), 2.28 (ddd, J = 15.4, 7.5, 1.8 Hz, 1H), 2.08 (dtdd, J = 14.0, 12.0, 3.3, 1.9 Hz, 1H), 1.67-1.59 (m, 1H), 1.55-1.47 (m, 1H), 1.42 (dtt, J = 14.8, 11.5, 3.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.10, 158.35, 139.30, 129.29, 120.79, 110.93, 89.50, 69.41, 55.79, 55.24, 42.73, 42.54, 33.00, 29.51, 22.42. IR (cm^{-1}): 3107, 3030, 2915, 2878, 1709, 1554, 1310, 1175, 870. HRMS: TOF MS AP$^+$ ($C_{15}H_{21}BrO_3$): Calc. [M + H]$^+$: 341.0752, Found [M + H]$^+$: 341.0749.



Compound **III-79** was synthesized from **III-131** (73.9 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-79** was isolated as a white solid in 88% yield (85.9 mg, 0.26 mmol).

Analytical data for compound III-79: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.17-7.12 (m, 4H), 4.04 (ddd, J = 13.0, 9.7, 3.4 Hz, 1H), 3.99 (d, J = 9.9 Hz, 1H), 3.13 (dt, J = 8.2, 2.9 Hz, 1H), 2.81 (ddd, J = 10.9, 8.9, 1.8 Hz, 1H), 2.76-2.65 (m, 3H), 2.56-2.48 (m, 1H), 2.47-2.39 (m, 1H), 2.34 (s, 3H), 2.24 (ddd, J = 15.5, 7.3, 1.9 Hz, 1H), 2.09 (dtdd, J = 14.8, 12.9, 3.9, 2.3 Hz, 1H), 1.64-1.56 (m, 1H), 1.54-1.48 (m, 1H), 1.48-1.38 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 208.30, 140.43, 138.18, 136.92, 129.04, 127.85, 85.33, 69.53, 56.04, 42.31, 33.04, 29.47, 22.23, 21.39. IR (cm^{-1}): 3108, 2906, 2855, 1725, 1523, 1379, 1300, 871. HRMS: TOF MS AP$^+$ ($C_{16}H_{21}BrO_2$): Calc. [M + H]$^+$: 325.0803, Found [M + H]$^+$: 325.0807.

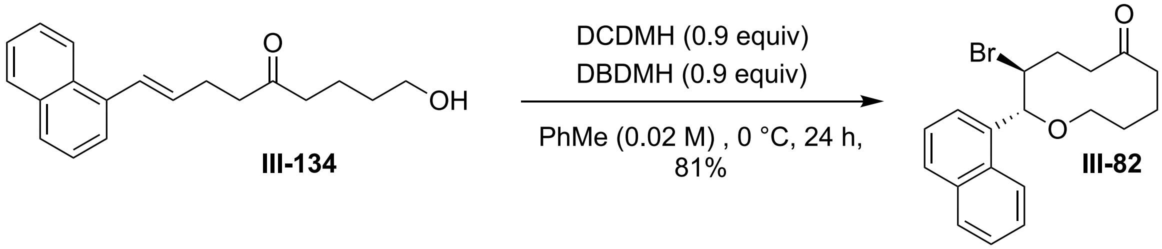
Compound **III-80** was synthesized from **III-132** (73.9 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-80** was isolated as a white solid in 71% yield (69.3 mg, 0.21 mmol).



Analytical data for compound III-80: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30-7.26 (m, 1H), 7.23-7.15 (m, 2H), 7.12-7.09 (m, 1H), 4.38 (d, J = 9.9 Hz, 1H), 4.15-4.04 (m, 1H), 3.07 (dt, J = 8.7, 3.3 Hz, 1H), 2.83 (ddd, J = 10.9, 8.8, 1.7 Hz, 1H), 2.80-2.74 (m, 2H), 2.69 (t, J = 13.8 Hz, 1H), 2.53-2.41 (m, 2H), 2.39 (s, 3H), 2.29-2.22 (m, 1H), 2.14-2.04 (m, 1H), 1.53-1.35 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 208.13, 137.43, 130.24, 127.99, 126.35, 81.22, 69.19, 52.06, 42.56, 42.41, 33.32, 29.54, 22.28, 19.99, 14.29. IR (cm^{-1}): 3108, 2906, 2855, 1725, 1523, 1379, 1300, 871. HRMS: TOF MS AP$^+$ ($C_{16}H_{21}BrO_2$): Calc. [M + H]$^+$: 325.0803, Found [M + H]$^+$: 325.0809.

Compound **III-81** was synthesized from **III-133** (84.7 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-81** was isolated as a white solid in 92% yield (100 mg, 0.28 mmol).

Analytical data for compound III-81: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.6, 3.8 Hz, 3H), 7.71 (s, 1H), 7.53 – 7.44 (m, 2H), 7.41 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.25 – 4.06 (m, 2H), 3.13 (dt, *J* = 8.9, 3.3 Hz, 1H), 2.88 (ddd, *J* = 11.3, 9.0, 2.5 Hz, 1H), 2.84 – 2.69 (m, 3H), 2.63 – 2.53 (m, 1H), 2.47 (dd, *J* = 13.8, 9.0 Hz, 1H), 2.27 (ddd, *J* = 15.6, 7.4, 1.9 Hz, 1H), 2.18 – 2.05 (m, 1H), 1.68 – 1.58 (m, 1H), 1.54 – 1.35 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.33, 137.20, 133.52, 132.97, 128.37, 128.22, 128.04, 127.86, 126.32, 126.27, 124.72, 85.75, 69.79, 55.50, 42.39, 33.10, 31.74, 29.47, 25.42, 22.81, 22.23, 14.28. IR (cm^{-1}): 3110, 3008, 2917, 2869, 1717, 1510, 1350, 1319, 980. HRMS: TOF MS AP$^+$ ($C_{19}H_{21}BrO_2$): Calc. $[M + H]^+$: 361.0803, Found $[M + H]^+$: 361.0803.



Compound **III-82** was synthesized from **III-134** (84.7 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-82** was isolated as a white solid in 81% yield (87.8 mg, 0.24 mmol).

Analytical data for compound III-82: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.60 – 7.38 (m, 4H), 3.10 (dt, *J* = 8.9, 3.4 Hz, 1H), 2.92 (td, *J* = 9.1, 3.5 Hz, 1H), 2.88 – 2.78 (m, 2H), 2.77 – 2.51 (m, 3H), 2.30 (dd, *J* = 15.7, 6.8 Hz, 1H), 2.19 – 2.06 (m, 1H), 1.68 – 1.57 (m, 1H), 1.51 – 1.15 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.45, 132.07, 130.99, 129.11, 129.06, 128.96, 126.12, 125.69, 125.14, 123.91, 86.74, 69.64, 60.56, 42.24, 33.02, 30.10, 29.59, 22.81, 22.21. IR (cm^{-1}): 3110, 3008, 2917, 2869, 1717, 1510, 1350, 1319, 980. HRMS: TOF MS AP$^+$ ($C_{19}H_{21}BrO_2$): Calc. [M + H]$^+$: 361.0803, Found [M + H]$^+$: 361.0809.

Compound **III-83** was synthesized from **III-135** (74 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-83** was isolated as a white solid in 57% yield (55.6 mg, 0.17 mmol).

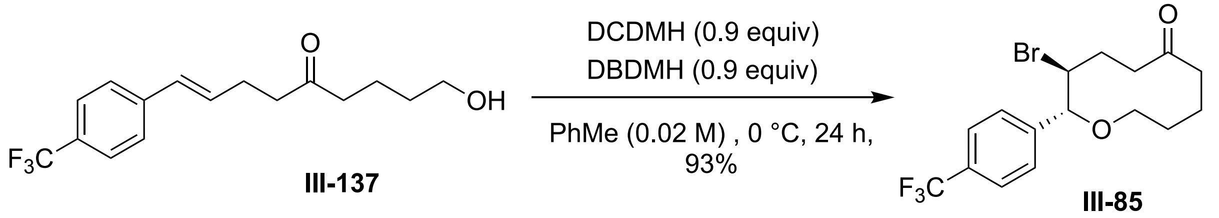
Analytical data for compound III-83: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 2H), 7.33 (t, J = 7.2 Hz, 2H), 7.29 (d, J = 7.2 Hz, 1H), 4.05 (dd, J = 11.3, 1.9 Hz, 1H), 3.20 (ddd, J = 10.9, 8.5, 2.0 Hz, 1H), 2.97-2.89 (m, 2H), 2.89-2.82 (m, 1H), 2.61 (ddd, J = 14.3, 11.9, 1.7 Hz, 1H), 2.39-2.33 (m, 1H), 2.33-2.28 (m, 1H), 2.27-2.21 (m, 1H), 2.05-2.00 (m, 1H), 1.72 (s, 3H), 1.61-1.56 (m, 1H), 1.29-1.25 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.61, 144.23, 127.98, 127.75, 126.83, 82.22, 64.05, 63.55, 44.47, 30.83, 30.12, 29.86, 23.09, 14.95. IR (cm^{-1}): 3108, 2906, 2855, 1725, 1523, 1379, 1300, 871. HRMS: TOF MS AP$^+$ ($C_{16}H_{21}BrO_2$): Calc. [M + H]$^+$: 325.0803, Found [M + H]$^+$: 325.0810.

Compound **III-84** was synthesized from **III-136** (75 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-84** was isolated as a white solid in 90% yield (88.9 mg, 0.27 mmol).

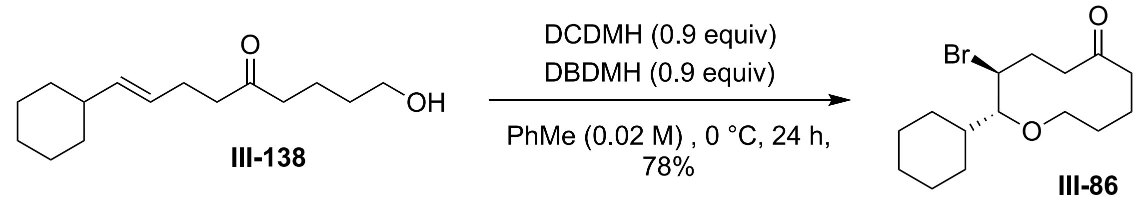
Analytical data for compound III-84: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.21 (m, 2H), 7.08 – 6.98 (m, 2H), 4.06 – 3.94 (m, 2H), 3.13 (d, *J* = 9.1 Hz, 1H), 2.87 – 2.78 (m, 1H), 2.77 – 2.66 (m, 2H), 2.52 (dd, *J* = 14.9, 3.2 Hz, 1H), 2.45 (dd, *J* = 14.0, 3.2 Hz, 1H), 2.26 (dd, *J* = 15.6, 7.3 Hz, 1H), 2.15 – 2.05 (m, 1H), 1.68 – 1.57 (m, 2H), 1.50 – 1.39 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.36, 161.73, 129.53, 115.35, 115.18, 84.84, 69.67, 55.90, 31.74, 29.45, 22.81, 22.20, 14.29. ^{19}F NMR (470 MHz, $CDCl_3$) δ -113.71.

Compound **III-85** was synthesized from **III-137** (90.1 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-85** was isolated as a white solid in 93% yield (105.8 mg, 0.28 mmol).

Analytical data for compound III-85: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.57 (m, 2H), 7.57 – 7.54 (m, 2H), 4.72 (d, J = 8.1 Hz, 1H), 3.70 (ddd, J = 9.5, 8.0, 4.0 Hz, 1H), 3.22 (dt, J = 10.2, 3.5 Hz, 1H), 2.87 (td, J = 10.0, 3.7 Hz, 1H), 2.57 – 2.47 (m, 2H), 2.47 – 2.43

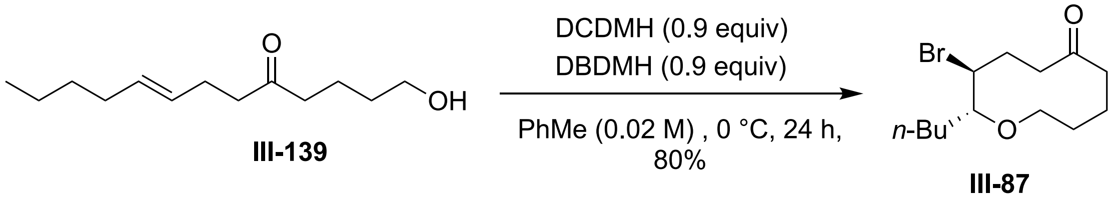


(m, 2H), 2.30 – 2.23 (m, 1H), 2.19 – 2.08 (m, 1H), 1.90-1.77 (m, 2H), 1.46-1.38 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 212.03, 152.87, 129.35, 125.89, 125.58, 125.54, 85.55, 75.93, 55.11, 45.61, 36.81, 31. 96, 28.74, 23.63. ^{19}F NMR (470 MHz, CDCl$_3$) δ -62.64.



Compound **III-86** was synthesized from **III-138** (71.5 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-86** was isolated as a white solid in 78% yield (74.2 mg, 0.234 mmol).

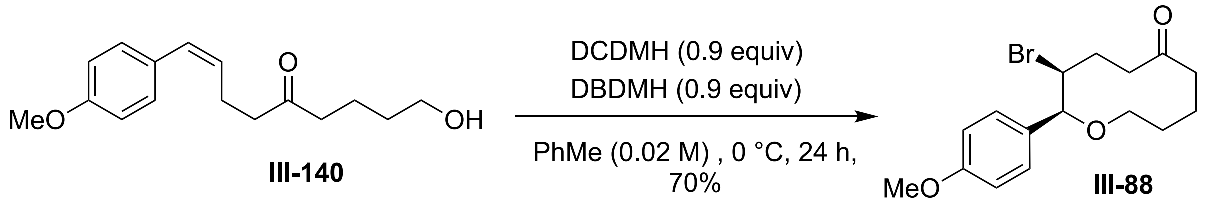
Analytical data for compound III-86: ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.01 (dt, J = 9.7, 3.7 Hz, 1H), 3.83 (dd, J = 7.8, 3.7 Hz, 1H), 3.46-3.40 (m, 1H), 3.23-3.16 (m, 1H), 2.58-2.50 (m, 1H), 2.48-2.40 (m, 2H), 2.38-2.29 (m, 2H), 2.20-2.11 (m, 1H), 1.95-1.88 (m, 2H), 1.83-1.71 (m, 3H), 1.69-1.59 (m, 4H), 1.35-1.10 (m, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 212.58, 80.93, 74.54, 66.77, 44.98, 39.96, 37.03, 32.22, 31.28, 28.99, 28.90, 26.38, 36.35, 25.93, 23.85. IR (cm^{-1}): 1722, 1279, 1240, 1145, 910, 812. HRMS: TOF MS AP$^+$ ($C_{15}H_{25}BrO_2$): Calc. [M + H]$^+$: 317.1111, Found [M + H]$^+$: 317.1118.



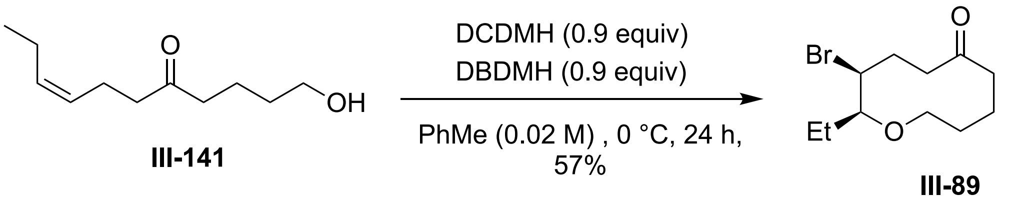
Compound **III-87** was synthesized from **III-139** (71.5 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-87** was isolated as a white solid in 78% yield (74.2 mg, 0.234 mmol).

Analytical data for compound III-87: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (dd, J = 10.2, 3.6 Hz, 1H), 4.09 – 4.03 (m, 1H), 4.03 – 3.91 (m, 1H), 3.86 (dddd, *J* = 10.0, 7.5, 4.1, 2.1 Hz, 1H), 2.19 (dddd, J = 15.1, 10.2, 2.2, 0.8 Hz, 1H), 2.02 – 1.95 (m, 2H), 1.94 – 1.88 (m, 3H), 1.61 – 1.56 (m, 1H), 1.55 – 1.50 (m, 1H), 1.47 – 1.38 (m, 2H), 1.38 – 1.27 (m, 3H), 1.19 – 0.99 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H), 0.91 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.32, 71.87, 65.09, 54.36, 44.78, 43.51, 40.09, 35.41, 29.90, 26.92, 22.23, 14.06. IR (cm^{-1}): 1710, 1395, 1310, 1195, 1125, 1005, 915, 878. HRMS: TOF MS AP$^+$ ($C_{13}H_{23}BrO_2$): Calc. [M + H]$^+$: 291.0954, Found [M + H]$^+$: 291.0959.

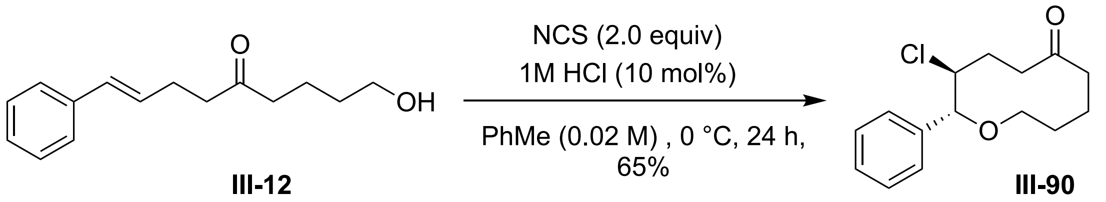
Compound **III-88** was synthesized from **III-140** (78.7 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-88** was isolated as a white solid in 70% yield (71.7 mg, 0.21 mmol).



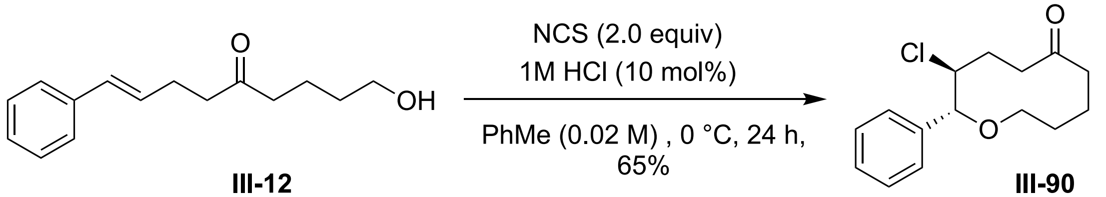
Analytical data for compound III-88: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.11 (dt, J = 7.2, 3.2 Hz, 1H), 4.03-4.00 (m, 1H), 3.81 (s, 3H), 3.44 (dt, J = 9.1, 3.2 Hz, 1H), 3.34 (dd, J = 16.0, 11.7 Hz, 1H), 2.95 (dt, J = 13.3, 3.4 Hz, 1H), 2.86-2.76 (m, 2H), 2.33 (dd, J = 15.3, 6.5 Hz, 1H), 2.20-2.05 (m, 3H), 1.74-1.56 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.86, 159.39, 131.62, 128.46, 113.55, 82.40, 69.03, 61.55, 55.37, 43.26, 38.79, 31.67, 29.48, 22.39. IR (cm^{-1}): 3110, 3045, 2915, 2880, 1710, 1521, 1305, 1145, 871. HRMS: TOF MS AP$^+$ ($C_{15}H_{21}BrO_3$): Calc. [M + H]$^+$: 341.0752, Found [M + H]$^+$: 341.0757.



Compound **III-89** was synthesized from **III-141** (78.7 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-89** was isolated as a white solid in 57% yield (71.7 mg, 0.21 mmol).



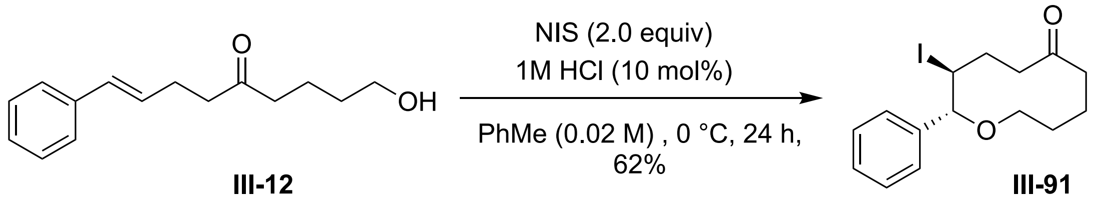
Analytical data for compound III-89: 1H NMR (500 MHz, $CDCl_3$) δ 4.09 (dt, *J* = 10.0, 3.8 Hz, 1H), 3.91 (ddd, *J* = 10.3, 4.8, 2.9 Hz, 1H), 3.51 – 3.42 (m, 1H), 3.24 (ddd, *J* = 10.1, 8.7, 4.6 Hz, 1H), 2.59 – 2.41 (m, 3H), 2.33 (dt, *J* = 13.4, 5.6 Hz, 1H), 2.15 – 2.06 (m, 2H), 1.96 (ddd, *J* = 14.7, 7.3, 3.0 Hz, 1H), 1.93 – 1.85 (m, 2H), 1.75 – 1.66 (m, 1H), 1.63 (tdd, *J* = 10.7, 6.2, 2.7 Hz, 2H), 1.05 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.19, 84.52, 74.42, 60.51, 45.77, 37.38, 28.85, 28.63, 26.75, 23.53, 12.74. IR (cm^{-1}): 1708, 1366, 1345, 1181, 1090, 870, 791. HRMS: TOF MS AP^+ ($C_{11}H_{19}BrO_2$): Calc. $[M + H]^+$: 263.0641, Found $[M + H]^+$: 263.0649.



III-12 **III-90**

Compound **III-90** was synthesized from **III-12** (78.7 mg, 0.3 mmol), NCS (80.1 mg, 0.6 mmol, 2.0 equiv) and 1 M HCl (30 *μ*L, 0.03 mmol, 0.10 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-90** was isolated as a white solid in 65% yield (51.7 mg, 0.195 mmol).

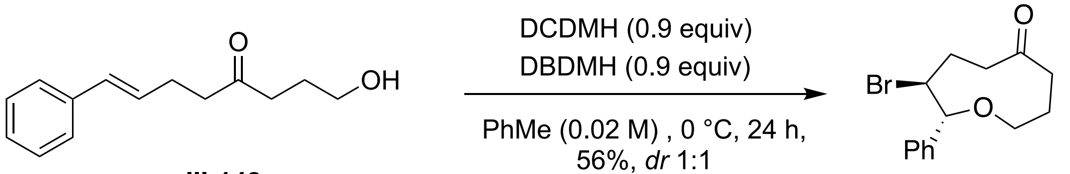
Analytical data for compound III-90: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 3.98 – 3.84 (m, 2H), 3.16 (dt, *J* = 9.3, 3.5 Hz, 1H), 2.82 (ddd, *J* = 11.0, 8.9, 1.9 Hz, 1H), 2.72 (dddd, *J* = 15.4, 11.4, 5.7, 3.5 Hz, 2H), 2.62 (m, 1H), 2.49 – 2.36 (m, 2H), 2.30 – 2.22 (dd, 1H), 2.15 – 2.05 (m, 1H), 1.67 – 1.58 (m, 1H), 1.52 – 1.40 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.30, 145.77, 128.54, 128.29, 127.96, 79.85, 74.47, 62.07, 36.79, 31.59, 28.22, 25.34, 18.10. IR (cm^{-1}): 3110, 2840, 1712, 1548, 1312, 1105. HRMS: TOF MS AP^+ ($C_{15}H_{19}ClO_2$): Calc. $[M + H]^+$: 267.1147, Found $[M + H]^+$: 311.0647.



Compound **III-91** was synthesized from **III-12** (78.7 mg, 0.3 mmol), NIS (135 mg, 0.6 mmol, 2.0 equiv) and 1 M HCl (30 μL, 0.03 mmol, 0.10 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-91** was isolated as a white solid in 62% yield (71.7 mg, 0.19 mmol).

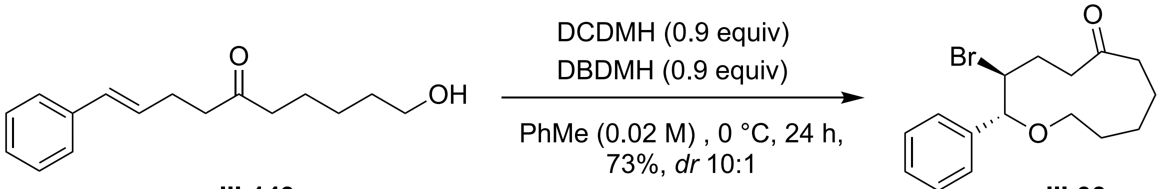
Analytical data for compound III-91: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35-7.26 (m, 3H), 7.26-7.22 (m, 2H), 4.22 (td, J = 9.7, 3.4 Hz, 1H), 4.09 (d, J = 10.2 Hz, 1H), 3.08 (dt, J = 8.4, 2.7 Hz, 1H), 2.83 (ddd, J = 11.1, 8.4, 2.2 Hz, 2H), 2.75 (dd, J = 13.1, 10.2 Hz, 2H), 2.69 – 2.60 (m, 1H), 2.34 (dd, J = 15.4, 9.3 Hz, 1H), 2.23 (ddd, J = 15.4, 7.3, 1.9 Hz, 1H), 2.10 (ddd, J = 14.1, 3.9, 1.9 Hz, 1H), 1.65 – 1.59 (m, 1H), 1.52 – 1.37 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 208.34, 141.04, 128.54, 128.27, 127.94, 86.31, 69.88, 44.37, 42.15, 37.00, 35.09, 29.59, 22.25. IR (cm^{-1}): 3135, 2950, 2820, 1703, 1510, 1300, 1050, 871. HRMS: TOF MS AP$^+$ ($C_{15}H_{19}IO_2$): Calc. [M + H]$^+$: 359.0503, Found [M + H]$^+$: 359.0500.

Compound **III-92** was synthesized from **III-142** (78.7 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-92** was isolated as a white solid in 56% yield (49.7 mg, 0.168 mmol).



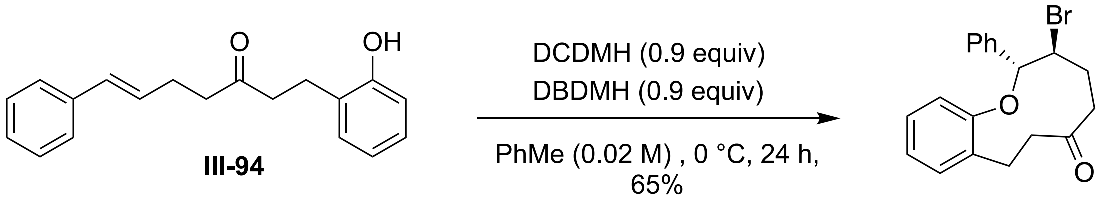
III-142

Analytical data for compound III-92: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45 – 7.36 (m, 1H), 7.35 – 7.28 (m, 4H), 4.41 (td, *J* = 7.9, 2.6 Hz, 1H), 4.15 – 4.01 (m, 1H), 3.64 (dt, *J* = 9.9, 4.8 Hz, 1H), 3.19 (ddd, *J* = 10.3, 7.2, 6.1 Hz, 1H), 2.71 – 2.56 (m, 2H), 2.49 (dd, *J* = 6.9, 5.9 Hz, 1H), 2.32 – 2.06 (m, 3H), 2.01 – 1.87 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 200.60, 140.12, 128.37, 127.72, 126.08, 86.65, 73.62, 55.10, 40.91, 34.25, 27.52, 21.84. IR (cm^{-1}): 3010, 2945, 2808, 1705, 1570, 1548, 1448, 1276, 1075. HRMS: TOF MS AP$^+$ ($C_{14}H_{17}BrO_2$): Calc. [M + H]$^+$: 297.0485, Found [M + H]$^+$: 297.0481.



III-143 **III-93**

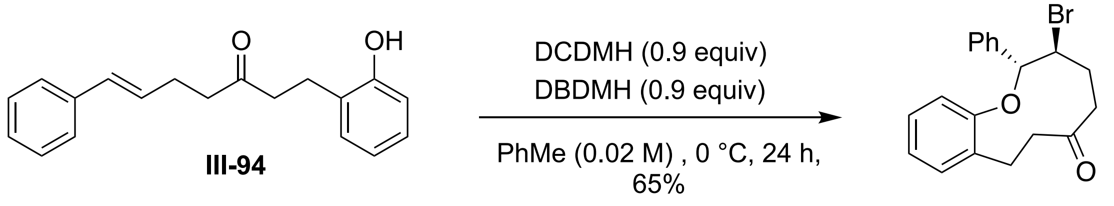
Compound **III-93** was synthesized from **III-143** (78.7 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-93** was isolated as a white solid in 73% yield (71.1 mg, 0.22 mmol).



III-94

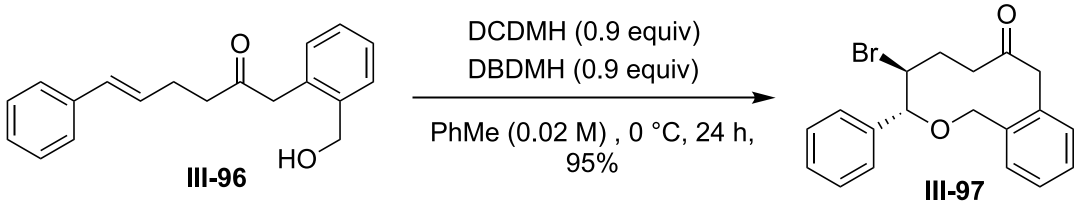
III-95

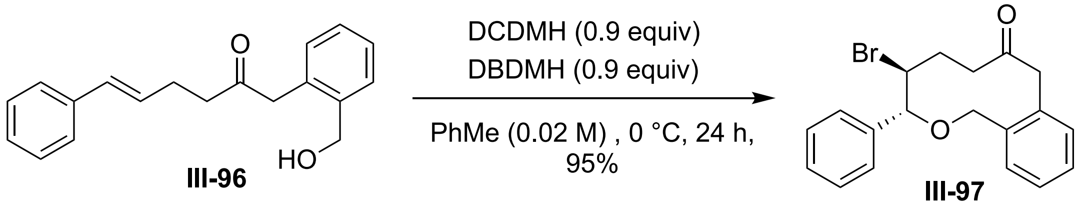
Analytical data for compound III-93: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41-7.37 (m, 2H), 7.37-7.32 (m, 2H), 7.32-7.28 (m, 1H), 4.81 (dt, J = 10.2, 3.2 Hz, 1H), 4.11 (td, J = 10.2, 5.3 Hz, 1H), 3.46-3.41 (m, 1H), 3.22-3.14 (m, 1H), 2.65-2.57 (m, 1H), 2.05-1.88 (m, 3H), 1.85 (dd, J = 11.6, 1.7 Hz, 1H), 1.73-1.64 (m, 1H), 1.65-1.55 (m, 2H), 1.52-1.40 (m, 2H), 1.36 (td, J = 13.2, 4.1 Hz, 1H), 1.31-1.24 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 208.03, 139.63, 128.17, 128.01, 127.66, 85.25, 69.35, 55.52, 42.01, 41.82, 32.73, 29.17, 21.93. IR (cm^{-1}): 3035, 2980, 2805, 1708, 1556, 1330, 1315, 1105, 1030, 980. HRMS: TOF MS AP$^+$ ($C_{16}H_{21}BrO_2$): Calc. [M + H]$^+$: 325.0798, Found [M + H]$^+$: 325.0799.



III-95

Compound **III-95** was synthesized from **III-94** (78.7 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **III-95** was isolated as a white solid in 65% yield (71.7 mg, 0.17 mmol).

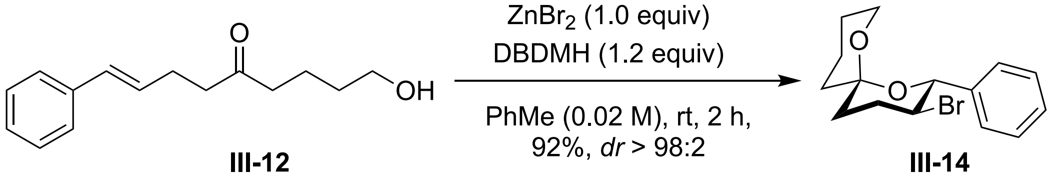




Compound **III-97** was synthesized from **III-96** (78.7 mg, 0.3 mmol), DBDMH (77.2 mg, 0.27 mmol, 0.90 equiv), DCDMH (53.2 mg, 0.27 mmol, 0.90 equiv) according to GP I. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-97** was isolated as a white solid in 95% yield (71.7 mg, 0.17 mmol).

Analytical data for compound III-97: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 1H), 7.38 – 7.36 (m, 2H), 7.34 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.29 (td, *J* = 7.5, 1.4 Hz, 1H), 7.23 – 7.14 (m, 2H), 6.94 (dd, *J* = 7.5, 1.4 Hz, 1H), 4.32 (dd, *J* = 9.2, 6.7 Hz, 2H), 4.26 – 4.17 (m, 2H), 4.13 (d, *J* = 16.4 Hz, 1H), 3.68 (d, *J* = 16.4 Hz, 1H), 2.83 (dddd, *J* = 14.7, 9.9, 3.7, 1.7 Hz, 1H), 2.75 (ddd, *J* = 13.9, 9.5, 1.5 Hz, 1H), 2.57 (ddd, *J* = 13.9, 9.8, 1.6 Hz, 1H), 2.50 (dddd, *J* = 15.2, 9.6, 5.7, 1.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.62, 138.73, 135.15, 134.59, 132.42, 128.82, 128.76, 128.60, 128.49, 128.06, 127.07, 84.69, 71.39, 55.82, 47.17, 39.19, 32.77. IR (cm^{-1}): 3150, 3085, 2975, 2810, 1720, 1521, 1301, 1170, 1050. HRMS: TOF MS AP$^+$ ($C_{19}H_{19}BrO_2$): Calc. [M + H]$^+$: 359.0641, Found [M + H]$^+$: 359.0649.

General Procedure for the double-anomeric bromo spiroketals from keto-alkenols (GP II):

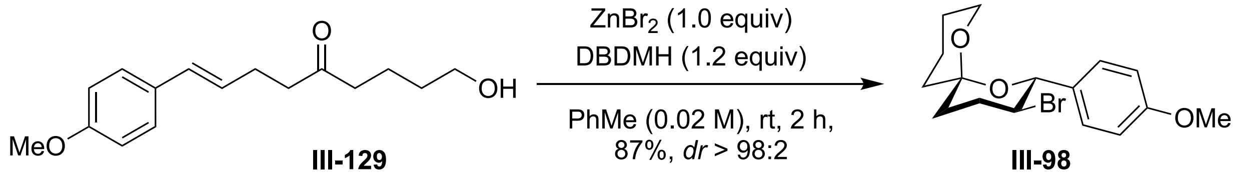


III-12 **III-14**

A clean dry 50 mL round bottom was charged with $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) and DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv). The flask was kept under vacuum and backfilled with argon before the addition of dry toluene (5 mL). The reaction mixture was stirred at rt for 10 minutes.

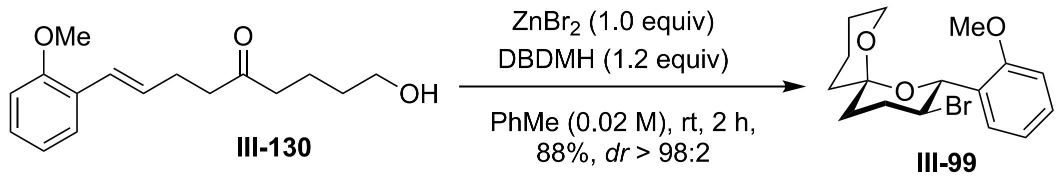
In a separate 25 mL round bottom was added the corresponding keto-alkenol (**III-12**) (69.6 mg, 0.30 mmol, 1.0 equiv). This flask was kept under vacuum and backfilled with argon before the addition of toluene (10 mL). The reaction mixture containing the keto-alkenol was added immediately to the rb containing $ZnBr_2$ and DBDMH. The resulting mixture was stirred at rt for 2 h whereupon TLC showed complete consumption of the starting material. The reaction mixture was then quenched with Na_2SO_3 (3 mL), extracted with EtOAc (3 X 5 mL) and dried over Na_2SO_4. The volatiles are removed under reduced pressure and the crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane: ethyl acetate as eluent). Compound **III-14** was obtained as a pale yellowish liquid in 92% yield (86.1 mg, 0.28 mmol).

Analytical data for compound III-14: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.41 (m, 2H), 7.40-7.31 (m, 3H), 4.68 (d, J = 10.3 Hz, 1H), 4.02 (ddd, J = 12.0, 10.3, 4.5 Hz, 1H), 3.73-3.64 (m, 2H), 2.52 (qd, J = 12.8, 5.0 Hz, 1H), 2.29 (dtd, J = 12.9, 4.4, 2.9 Hz, 1H), 1.84-1.66 (m, 4H), 1.64-1.54 (m, 1H), 1.53-1.44 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.81, 128.46, 128.23, 128.12, 96.13, 76.48, 60.93, 52.54, 37.79, 35.02, 31.39, 25.15, 18.49. IR (cm^{-1}): 3065, 2900, 1440, 1263, 1176, 1081. HRMS: TOF MS ES$^+$ ($C_{15}H_{20}BrO_2$): Calc. [M + H]$^+$: 311.0647, Found [M + H]$^+$: 311.0645.



Compound **III-98** was synthesized from **III-129** (78.7 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-98** was isolated as a yellow liquid in 87% yield (89 mg, 0.26 mmol).

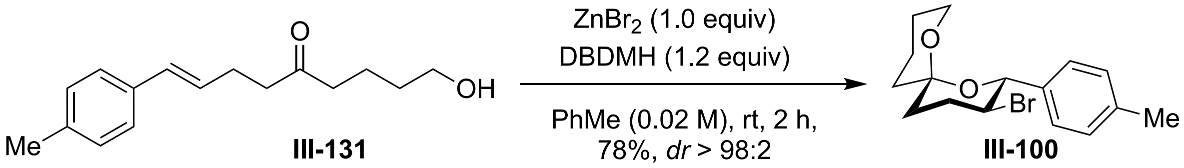
Analytical data for compound III-98: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.32 (m, 2H), 6.92-6.88 (m, 2H), 4.63 (d, J = 10.4 Hz, 1H), 4.00 (ddd, J = 12.1, 10.3, 4.5 Hz, 1H), 3.82 (s, 3H), 3.72-3.62 (m, 1H), 2.51 (qd, J = 12.8, 4.9 Hz, 1H), 2.27 (dtd, J = 12.8, 4.5, 2.7 Hz, 1H), 1.83-1.69 (m, 3H), 1.69-1.63 (m, 1H), 1.52-1.42 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.61, 132.15, 129.20, 113.61, 96.15, 75.99, 60.92, 55.36, 52.93, 37.80, 35.03, 31.43, 25.17, 18.50. IR (cm^{-1}): 3035, 2905, 2835, 1465, 1378, 1335, 1276, 1145, 1100, 1080, 987, 787. HRMS: TOF MS ES$^+$ ($C_{16}H_{22}BrO_3$): Calc. [M + H]$^+$: 341.0752, Found [M + H]$^+$: 341.0741.



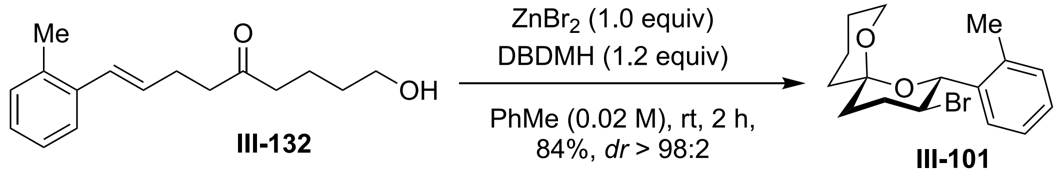
Compound **III-99** was synthesized from **III-130** (78.7 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-99** was isolated as a yellow liquid in 88% yield (90.1mg, 0.264 mmol).

Analytical data for compound III-99: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, J = 7.6, 1.7 Hz, 1H), 7.31 (ddd, J = 8.3, 7.4, 1.7 Hz, 1H), 7.00 (td, J = 7.4, 1.1 Hz, 1H), 6.93 (dd, J = 8.3, 1.1 Hz, 1H), 5.30 (d, J = 10.6 Hz, 1H), 4.21 (td, J = 11.5, 4.4 Hz, 1H), 3.86 (s, 3H), 3.84-3.77 (m, 1H), 3.72-3.66 (m, 1H), 2.54 (qd, J = 12.8, 4.9 Hz, 1H), 2.28 (dtd, J = 12.7, 4.3, 2.8 Hz, 1H), 1.82-1.68 (m, 4H), 1.66-1.56 (m, 2H), 1.50-1.42 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.84, 129.42, 128.25, 128.21, 120.85, 111.28, 96.12, 60.77, 55.85, 51.46, 37.98, 35.06, 31.44, 25.24, 18.56. IR (cm^{-1}): 3095, 2965, 2800, 1561, 1280, 1115, 1071, 878. HRMS: TOF MS ES$^+$ ($C_{16}H_{22}BrO_3$): Calc. [M + H]$^+$: 341.0752, Found [M + H]$^+$: 341.0751.

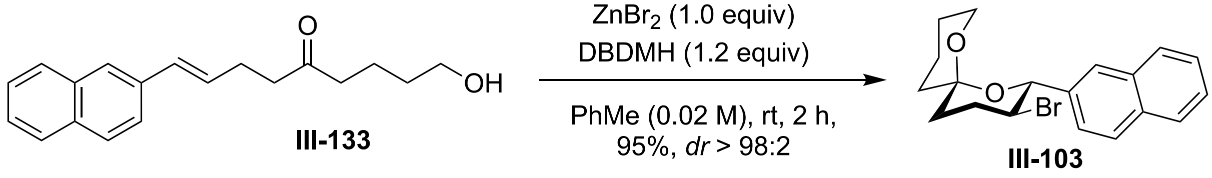
Compound **III-100** was synthesized from **III-131** (73.9 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-100** was isolated as a yellow liquid in 78% yield (76.1 mg, 0.234 mmol).



Analytical data for compound III-100: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 4.65 (d, J = 10.3 Hz, 1H), 4.02 (ddd, J = 12.0, 10.3, 4.5 Hz, 1H), 3.77-3.58 (m, 2H), 2.51 (tdd, J = 13.0, 12.0, 5.0 Hz, 1H), 2.37 (s, 3H), 2.27 (dtd, J = 13.0, 4.5, 2.9 Hz, 1H), 1.83-1.64 (m, 4H), 1.51-1.42 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 138.21, 136.92, 128.99, 128.00, 96.13, 76.27, 60.91, 52.69, 37.81, 35.03, 31.42, 25.16, 21.44, 18.48. IR (cm^{-1}): 3010, 2939, 2869, 1517, 1440, 1175, 1040, 998, 968, 811. HRMS: TOF MS AP$^+$ ($C_{16}H_{22}BrO_2$): Calc. [M + H]$^+$: 325.0803, Found [M + H]$^+$: 325.0803.



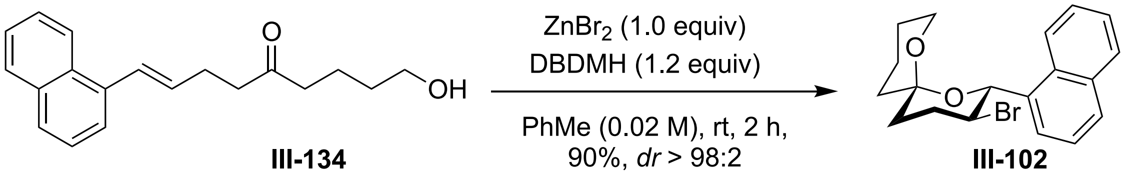
Compound **III-101** was synthesized from **III-132** (73.9 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), ZnBr$_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-101** was isolated as a yellow liquid in 84% yield (82 mg, 0.252 mmol).



Analytical data for compound III-101: 1H NMR (500 MHz, Chloroform-*d*) δ 7.40 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.20 – 7.14 (m, 1H), 5.05 (d, *J* = 10.4 Hz, 1H), 4.10 (ddd, *J* = 12.0, 10.4, 4.5 Hz, 1H), 3.74 – 3.63 (m, 2H), 2.58 – 2.50 (m, 1H), 2.49 (s, 3H), 2.28 (dtd, *J* = 12.9, 4.4, 2.9 Hz, 1H), 1.85 – 1.59 (m, 5H), 1.52 – 1.42 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.50, 136.61, 130.28, 128.11, 126.26, 96.10, 72.30, 60.86, 53.25, 37.89, 35.08, 31.48, 25.16, 20.36, 18.46. IR (cm^{-1}): 3084, 2915, 2869, 1556, 1440, 1390, 1148, 1070, 975, 968, 811. HRMS: TOF MS AP$^+$ ($C_{16}H_{22}BrO_2$): Calc. [M + H]$^+$: 325.0803, Found [M + H]$^+$: 325.0810.

Compound **III-103** was synthesized from **III-133** (84.7 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-103** was isolated as a yellow liquid in 95% yield (103 mg, 0.285 mmol).

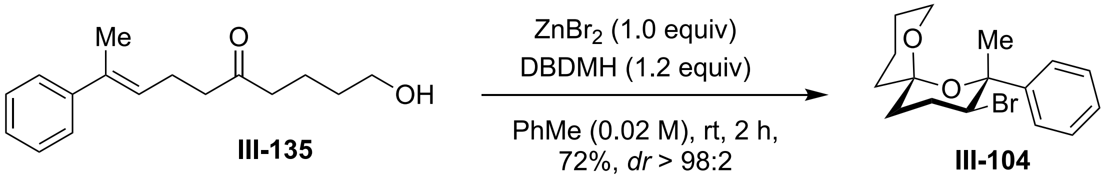
Analytical data for compound III-103: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.82 (m, 4H), 7.56 (dd, J = 8.5, 1.7 Hz, 1H), 7.52-7.45 (m, 2H), 4.85 (d, J = 10.3 Hz, 1H), 4.14 (ddd, J = 12.0, 10.3, 4.5 Hz, 1H), 3.77-3.67 (m, 2H), 2.57 (qd, J = 12.5, 5.6 Hz, 1H), 2.32 (dtd, *J* = 12.5, 4.5, 3.0 Hz, 1H), 1.88-1.79 (m, 2H), 1.77-1.67 (m, 2H), 1.64-1.56 (m, 1H), 1.52-1.43 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.18, 133.55, 133.12, 128.30, 128.04, 127.86, 127.70, 126.19, 125.53, 96.23, 76.70, 61.02, 52.41, 37.84, 35.04, 31.43, 25.16, 18.51. IR (cm^{-1}): 3054, 2939, 2869, 1448, 1375, 1349, 1270, 1080. HRMS: TOF MS AP$^+$ ($C_{19}H_{22}BrO_2$): Calc. [M + H]$^+$:361.0803, Found [M + H]$^+$: 361.0803.



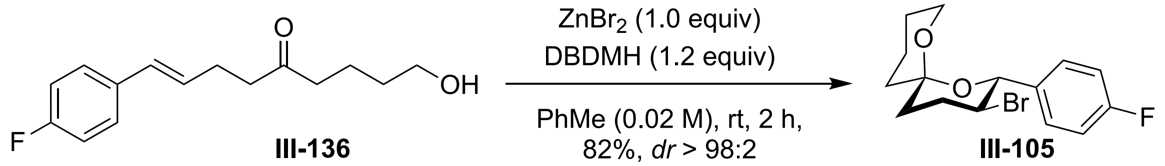
Compound **III-102** was synthesized from **III-134** (84.7 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-102** was isolated as a yellow liquid in 90% yield (97.5 mg, 0.27 mmol).

Analytical data for compound III-102: ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 8.5 Hz, 1H), 7.90-7.83 (m, 2H), 7.64 (d, J = 7.1 Hz, 1H), 7.56-7.46 (m, 2H), 5.60-5.42 (m, 1H), 4.45-4.30 (m, 1H), 3.79-3.73 (m, 1H), 3.73-3.67 (m, 1H), 2.69-2.58 (m, 1H), 2.36 (dq, J = 13.0, 3.9 Hz, 1H), 1.92-1.86 (m, 2H), 1.76-1.71 (m, 1H), 1.67 (tt, J = 12.1, 3.6 Hz, 1H), 1.62-1.57 (m, 1H), 1.54-1.39 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.03, 129.00, 125.99, 125.55, 125.37, 96.33, 76.25, 61.10, 52.79, 37.92, 35.16, 31.70, 25.13, 18.47. IR (cm^{-1}): 3054, 2939, 2869, 1448, 1375, 1349, 1270, 1080. HRMS: TOF MS AP^+ ($C_{19}H_{22}BrO_2$): Calc. $[M + H]^+$:361.0803, Found $[M + H]^+$: 361.0803.

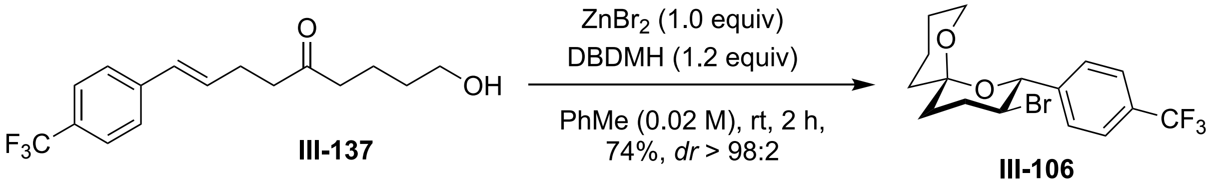
Compound **III-104** was synthesized from **III-135** (73.9 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-104** was isolated as a yellow liquid in 72% yield (70.2 mg, 0.216 mmol).



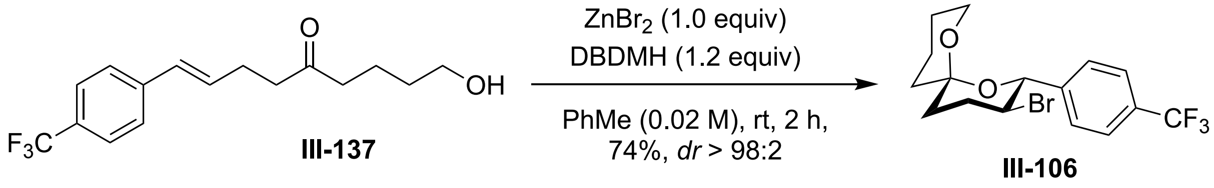
Analytical data for compound III-104: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59-7.55 (m, 2H), 7.38-7.32 (m, 3H), 4.03 (dd, J = 12.9, 3.9 Hz, 1H), 3.89-3.82 (m, 1H), 3.64-3.58 (m, 1H), 2.62 (qd, J = 13.2, 4.0 Hz, 1H), 2.16-2.10 (m, 1H), 2.02 (s, 3H), 1.95-1.89 (m, 1H), 1.87-1.81 (m, 1H), 1.81-1.73 (m, 2H), 1.55-1.51 (m, 2H), 1.51-1.45 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.39, 127.80, 127.49, 126.35, 96.54, 78.77, 61.55, 59.61, 39.44, 37.52, 28.35, 25.44, 18.97, 18.63.



Compound **III-105** was synthesized from **III-136** (75.1 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-105** was isolated as a yellow liquid in 82% yield (81 mg, 0.246 mmol).

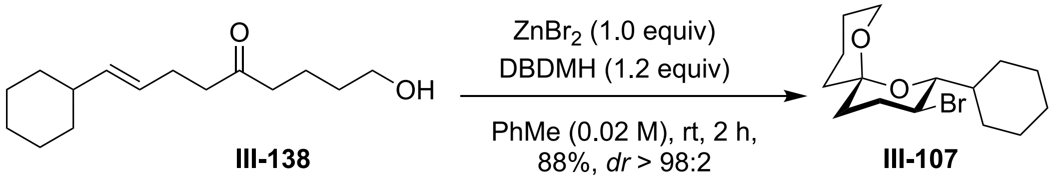


Analytical data for compound III-105: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.37 (m, 2H), 7.08-7.02 (m, 2H), 4.66 (d, J = 10.3 Hz, 1H), 3.94 (ddd, J = 12.0, 10.3, 4.5 Hz, 1H), 3.72-3.67 (m, 1H), 3.66-3.60 (m, 1H), 2.50 (tdd, J = 13.0, 12.0, 4.8 Hz, 1H), 2.27 (dtd, J = 13.0, 4.5, 2.8 Hz, 1H), 1.83-1.65 (m, 4H),1.63-1.56 (m, 1H), 1.53-1.44 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.71, 135.75, 129.75, 115.20, 96.21, 75.80, 60.98, 52.70, 37.75, 34.98, 31.33, 25.12, 18.49. ^{19}F NMR (470 MHz, $CDCl_3$) δ -113.91.



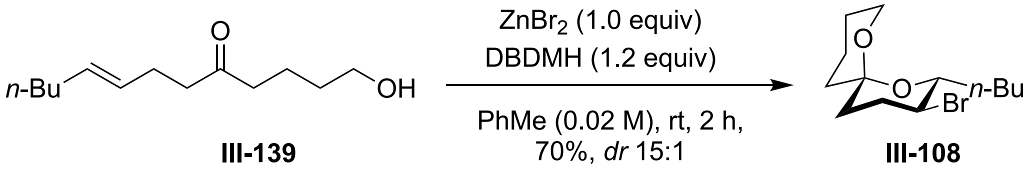
Compound **III-106** was synthesized from **III-137** (90.1 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-106** was isolated as a yellow liquid in 74% yield (84.2 mg, 0.222 mmol).

Analytical data for compound III-106: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H), 4.56 (d, J = 10.1 Hz, 1H), 3.99 – 3.90 (m, 2H), 3.68-3.62 (m, 1H), 2.51-2.41 (m, 2H), 2.33 – 2.15 (m, 1H), 1.91-1.83 (m, 2H), 1.66-1.56 (m, 3H), 1.52-1.45 (m, 1H), 1.44-1.36 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.65, 138.62, 128.52, 125.20, 125.17, 96.25, 75.94, 61.05, 52.03, 37.71, 34.94, 31.26, 25.07, 18.46. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.53.

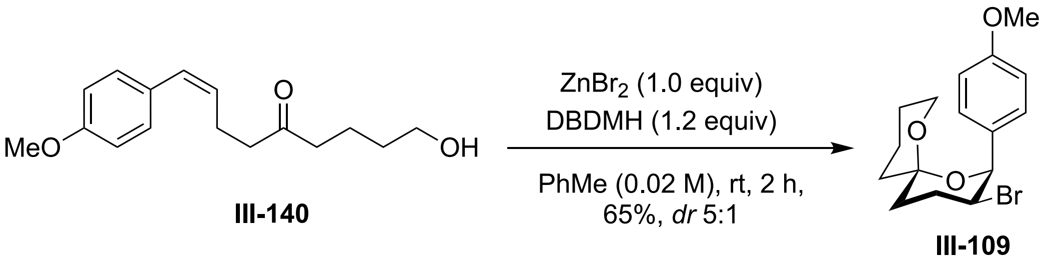


Compound **III-107** was synthesized from **III-138** (71.5 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-107** was isolated as a yellow liquid in 88% yield (83.8 mg, 0.264 mmol).

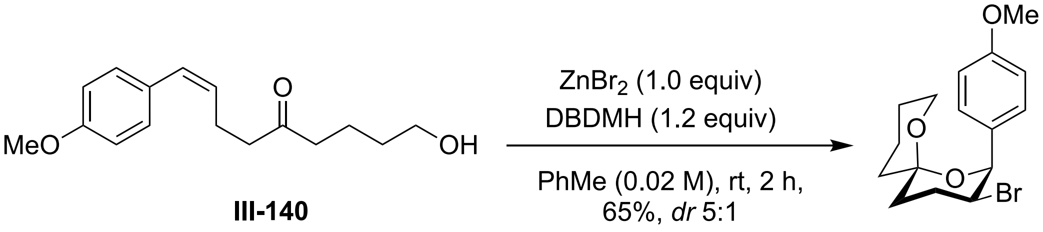
Analytical data for compound III-107: ^1H NMR (500 MHz, $CDCl_3$) δ 4.37 – 4.24 (m, 1H), 3.96-3.70 (m, 2H), 3.64-3.56 (m, 1H), 2.27-2.16 (m, 1H), 2.05-1.91 (m, 2H), 1.90-1.84 (m, 1H), 1.84-1.73 (m, 5H), 1.72-1.67 (m, 2H), 1.67-1.60 (m, 3H), 1.47-1.36 (m, 1H), 1.37-1.22 (m, 4H), 1.22-1.10 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 106.58, 79.91, 69.24, 67.54, 41.03, 40.35, 38.39, 37.23, 33.86, 32.16, 31.79, 31.05, 29.24, 28.67, 27.30, 20.38.



Compound **III-108** was synthesized from **III-139** (63.7 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-108** was isolated as a yellow liquid in 70% yield (61.2 mg, 0.21 mmol) with a diastereomeric ratio of 15:1.



Analytical data for compound III-108: ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.91 (dd, *J* = 10.2, 4.6 Hz, 1H), 4.49 (dd, *J* = 8.9, 8.0 Hz, 1H), 4.33 – 4.23 (m, 1H), 4.07 – 3.97 (m, 1H), 3.29 (dddd, *J* = 9.8, 7.4, 4.2, 3.2 Hz, 1H), 2.60 – 2.43 (m, 2H), 2.17 (ddd, *J* = 13.6, 9.9, 4.6 Hz, 1H), 2.03 (d, *J* = 7.6 Hz, 1H), 1.96 – 1.81 (m, 3H), 1.55 – 1.49 (m, 1H), 1.45 – 1.29 (m, 5H), 0.92 (td, *J* = 7.2, 3.4 Hz, 5H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 107.02, 71.78, 65.15, 59.45, 47.88, 44.67, 40.61, 35.38, 29.85, 27.04, 25.89, 22.22, 14.05.

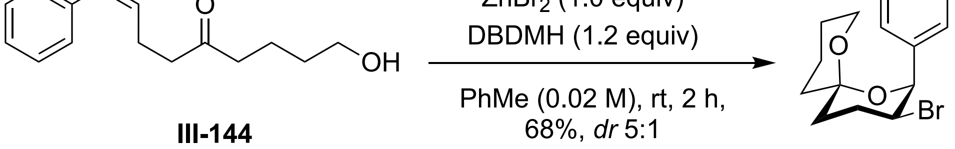


III-140

III-109

Compound **III-109** was synthesized from **III-140** (78.7 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), ZnBr$_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-109** was isolated as a yellow liquid in 65% yield (66.5 mg, 0.195 mmol) with a diastereomeric ratio of 5:1.

Analytical data for compound III-109: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.38 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 4.46 (d, *J* = 10.1 Hz, 1H), 4.04-3.93 (m, 2H), 3.82 (s, 3H), 3.65-3.59 (m, 1H), 2.50-2.40 (m, 2H), 2.28-2.20 (m, 1H), 1.90-1.80 (m, 2H), 1.65-1.57 (m, 3H), 1.50-1.43 (m, 1H), 1.42-1.33 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.71, 131.91, 129.10, 113.62, 97.74, 79.60, 61.98, 55.37, 52.47, 37.94, 32.59, 28.18, 25.34, 18.09.

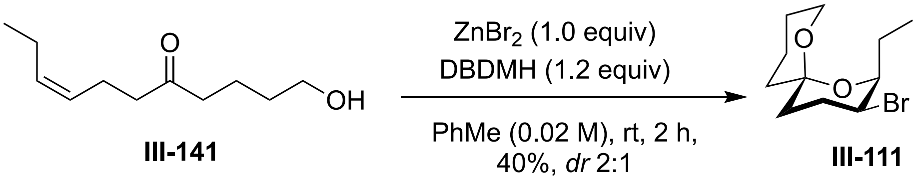


III-144

III-110

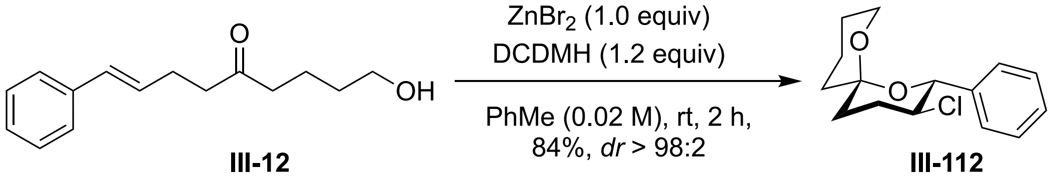
Compound **III-110** was synthesized from **III-144** (69.7 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-110** was isolated as a yellow liquid in 68% yield (63.5 mg, 0.204 mmol) with a diastereomeric ratio of 5:1.

Analytical data for compound III-110: ^1H NMR (500 MHz, $CDCl_3$) δ 7.48-7.44 (m, 2H), 7.36-7.26 (m, 3H), 4.92 (d, J = 6.2 Hz, 1H), 4.54 (dt, *J* = 8.0, 5.7 Hz, 1H), 3.91 (td, *J* = 11.3, 3.5 Hz, 1H), 3.65-3.57 (m, 1H), 2.07-1.81 (m, 4H), 1.76-1.70 (m, 2H), 1.70-1.64 (m, 2H), 1.63-1.59 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.64, 128.62, 128.56, 106.63, 81.05, 62.03, 57.79, 37.50, 33.57, 28.43, 25.34, 20.37.



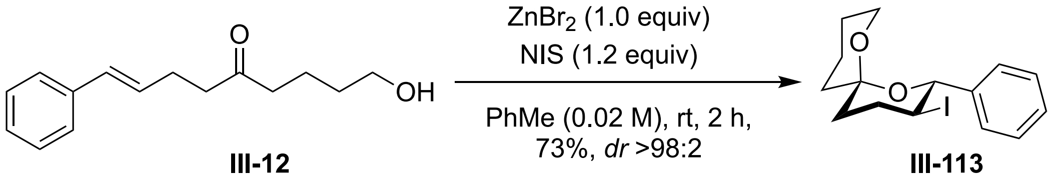
Compound **III-111** was synthesized from **III-141** (55.3 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-111** was isolated as a yellow liquid in 40% yield (31.6 mg, 0.12 mmol) with a diastereomeric ratio of 2:1.

Analytical data for compound III-111: ^1H NMR (500 MHz, $CDCl_3$) δ 4.29-4.20 (m, 1H), 4.02-3.91 (m, 2H), 3.62 (ddt, J = 11.2, 4.1, 1.9 Hz, 1H), 2.08-2.00 (m, 2H), 1.97-1.82 (m, 3H), 1.80-1.63 (m, 5H), 1.63-1.50 (m, 2H), 1.10 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 105.63, 83.47, 63.09, 61.94, 38.95, 33.69, 27.78, 27.34, 25.28, 20.22, 12.07.



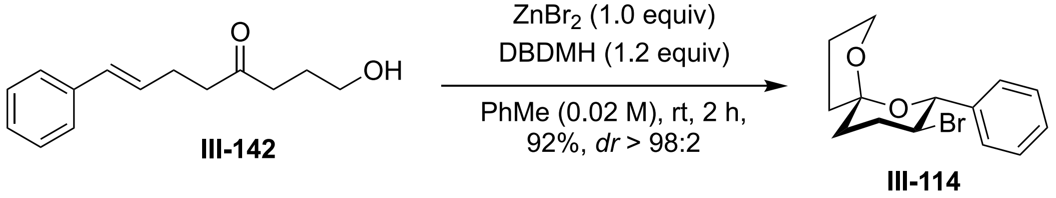
Compound **III-112** was synthesized from **III-12** (69.7 mg, 0.3 mmol), DCDMH (71 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-112** was isolated as a yellow liquid in 84% yield (67.2 mg, 0.252 mmol) with a diastereomeric ratio of >98:2.

Analytical data for compound III-112: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.44 (m, 2H), 7.41-7.31 (m, 3H), 4.39 (d, J = 9.9 Hz, 1H), 4.03-3.96 (m, 1H), 3.88 (ddd, J = 11.4, 9.9, 4.8 Hz, 1H), 3.67-3.61 (m, 1H), 2.50-2.43 (m, 1H), 2.35 (dq, J = 13.3, 4.4 Hz, 1H), 2.08 (tdd, J = 13.3, 11.4, 5.2 Hz, 1H), 1.93-1.81 (m, 2H), 1.68-1.57 (m, 3H), 1.50-1.44 (m, 1H), 1.43-1.35 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 128.54, 128.28, 127.95, 97.70, 79.85, 62.07, 59.58, 36.79, 31.59, 28.21, 25.33, 18.10.



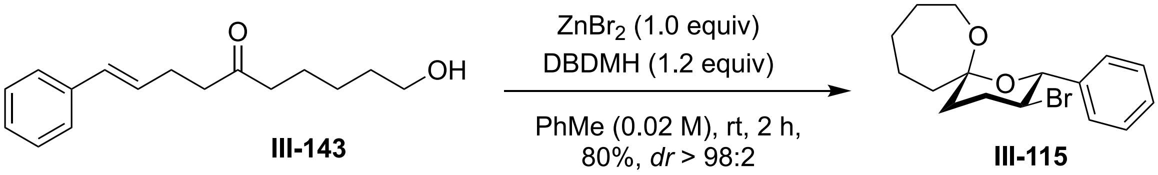
Compound **III-113** was synthesized from **III-12** (69.7 mg, 0.3 mmol), NIS (81 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-113** was isolated as a yellow liquid in 73% yield (78.5 mg, 0.22 mmol) with a diastereomeric ratio of >98:2.

Analytical data for compound III-113: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.32 (m, 5H), 4.77 (d, J = 10.7 Hz, 1H), 4.17 (ddd, J = 12.4, 10.7, 4.3 Hz, 1H), 3.73-3.63 (m, 2H), 2.71 (tdd, J = 13.2, 12.4, 4.4 Hz, 1H), 2.41 (dtd, J = 13.2, 4.4, 2.7 Hz, 1H), 1.79-1.70 (m, 2H), 1.70-1.67 (m, 1H), 1.67-1.61 (m, 2H), 1.50-1.42 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.68, 128.54, 128.24, 128.12, 96.41, 77.38, 60.91, 38.98, 35.31, 33.75, 32.80, 25.18, 18.39.



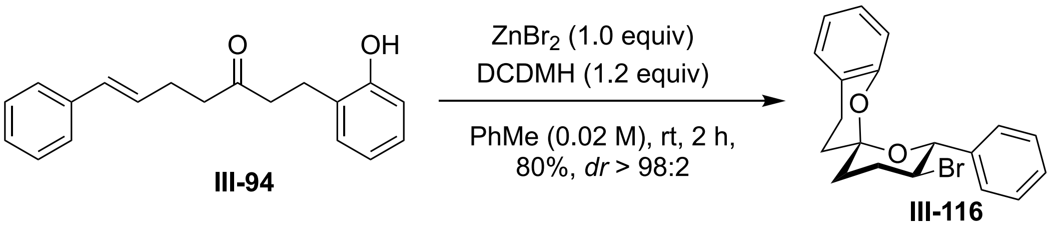
Compound **III-114** was synthesized from **III-142** (65.5 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), $ZnBr_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-114** was isolated as a yellow liquid in 92% yield (82.1 mg, 0.28 mmol) with a diastereomeric ratio of >98:2. The structure was confirmed via X-ray crystallography.

Analytical data for compound III-114: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.37 (m, 2H), 7.38-7.33 (m, 2H), 7.33-7.29 (m, 1H), 4.83 (d, J = 10.4 Hz, 1H), 4.03 (ddd, J = 12.0, 10.4, 4.6 Hz, 1H), 3.99-3.87 (m, 2H), 2.51 (qd, J = 13.3, 4.6 Hz, 1H), 2.40 (dtd, J = 12.8, 4.6, 2.8 Hz, 1H), 2.09 (td, J = 13.3, 4.5 Hz, 1H), 2.04-1.95 (m, 2H), 1.88-1.81 (m, 2H), 1.77-1.70 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.87, 128.48, 128.29, 128.07, 106.31, 77.64, 67.52, 52.21, 37.34, 35.35, 32.86, 23.78.k

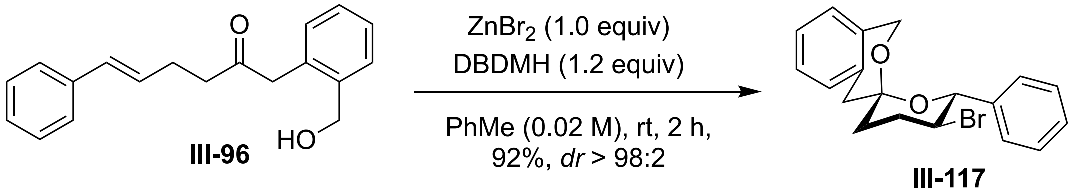


Compound **III-115** was synthesized from **III-143** (73.9 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), ZnBr$_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-115** was isolated as a yellow liquid in 80% yield (78.1 mg, 0.24 mmol) with a diastereomeric ratio of >98:2.

Analytical data for compound III-115: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.43-7.39 (m, 2H), 7.39-7.34 (m, 2H), 7.34-7.30 (m, 1H), 4.77 (d, J = 10.4 Hz, 1H), 4.03 (ddd, J = 11.9, 10.4, 4.6 Hz, 1H), 3.79-3.67 (m, 2H), 2.48 (qd, J = 12.9, 4.1 Hz, 1H), 2.28 (dq, J = 12.6, 4.1 Hz, 1H), 2.05 (dt, J = 13.5, 3.6 Hz, 1H), 1.91 (dd, J = 15.0, 7.9 Hz, 1H), 1.85-1.76 (m, 2H), 1.73-1.61 (m, 4H), 1.43-1.33 (m, 1H), 1.31-1.26 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.92, 128.51, 128.35, 128.11, 101.18, 77.39, 62.05, 52.79, 40.84, 37.59, 31.73, 30.64, 29.86, 22.77.



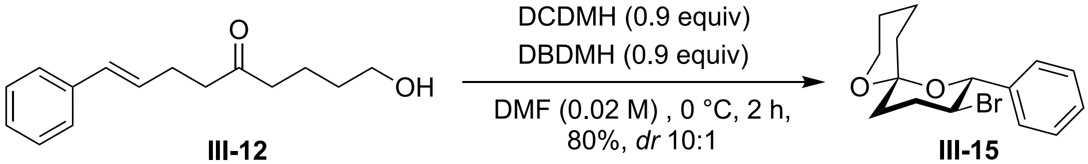
Compound **III-116** was synthesized from **III-94** (84.1 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), ZnBr$_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-116** was isolated as a yellow liquid in 80% yield (86.2 mg, 0.24 mmol) with a diastereomeric ratio of >98:2.



Compound **III-117** was synthesized from **III-96** (84.1 mg, 0.3 mmol), DBDMH (102.9 mg, 0.36 mmol, 1.2 equiv), ZnBr$_2$ (67.6 mg, 0.30 mmol, 1.0 equiv) according to GP II. The crude product was purified via column chromatography (20 X 250 mm, 99:1 hexane:ethyl acetate as eluent) and compound **III-117** was isolated as a yellow liquid in 92% yield (99.2 mg, 0.28 mmol) with a diastereomeric ratio of >98:2.

Analytical data for compound III-117: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36-7.32 (m, 2H), 7.32-7.27 (m, 3H), 7.20-7.12 (m, 3H), 6.96 (d, J = 7.2 Hz, 1H), 4.99 (d, J = 14.5 Hz, 1H), 4.68 (d, J = 14.5 Hz, 1H), 4.60 (d, J = 10.0 Hz, 1H), 4.05 (ddd, 11.3, 10.0, 4.8 Hz, 1H), 3.41 (d, J = 16.5 Hz, 1H), 2.99 (d, J = 16.5 Hz, 1H), 2.57 (dq, J = 13.5, 4.3 Hz, 1H), 2.35 (dddd, J = 13.5, 12.3, 11.4, 5.1 Hz, 1H), 2.07-1.95 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.22, 134.32, 130.56, 128.78, 128.17, 127.91, 126.79, 126.33, 125.94, 124.09, 97.87, 80.31, 63.30, 51.87, 37.23, 32.55, 32.50.

General Procedure for the single-anomeric bromo spiroketals from keto-alkenols (GP III):



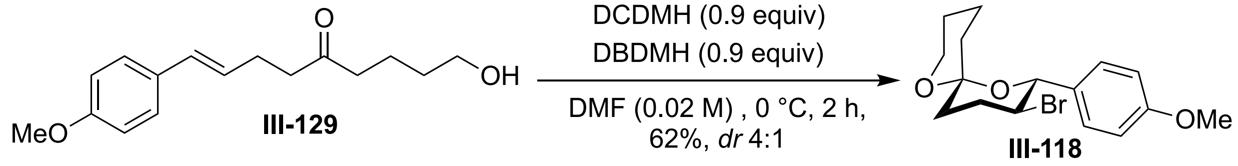
III-12 **III-15**

A clean dry 25 mL round bottom was charged with DCDMH (26.6 mg, 0.135 mmol, 0.90 equiv) and DBDMH (38.6 mg, 0.135 mmol, 0.90 equiv). The flask was kept under vacuum and backfilled with argon before the addition of dry N,N-dimethylformamide (2.5 mL). The reaction mixture was stirred at rt for 10 minutes before transferring to an ice bath precooled at 0 °C.

In a separate 10 mL round bottom was added the corresponding keto-alkenol (III-12) (34.8 mg, 0.15 mmol, 1.0 equiv). This flask was kept under vacuum and backfilled with argon before the addition of dry *N,N*-dimethylformamide (5 mL). The mixture was then immediately transferred to an ice bath for 15 minutes at 0 °C.

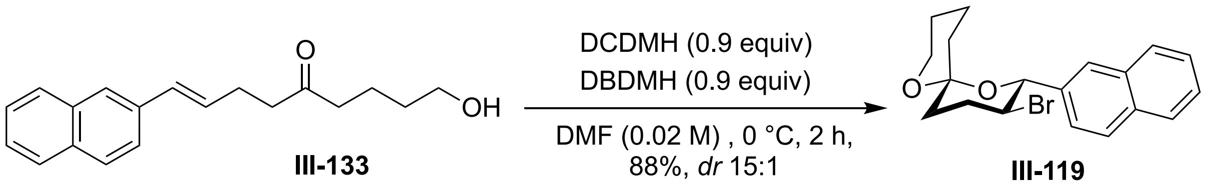
After pre-cooling the contents of both flasks, the solution containing the keto-alkenol was added dropwise to the solution of DCDMH and DBDMH. The resulting mixture was then stirred for 2 h at 0 °C before quenching with Na_2SO_3 (1 mL), extracted with EtOAc (3 X 5 mL) and dried over Na_2SO_4. The volatiles were removed under reduced pressure and crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent). Compound **III-15** was obtained as a colourless solid in 80% yield (37.3 mg, 0.12 mmol). The structure of **III-15** was confirmed through X-ray crystallography.

Analytical data for compound III-15: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.43 (m, 2H), 7.40-7.32 (m, 3H), 4.50 (d, J = 10.1 Hz, 1H), 4.05-3.94 (m, 2H), 3.66-3.59 (m, 1H), 2.52-2.41 (m, 2H), 2.24 (dtd, J = 13.7, 11.6, 6.3 Hz, 1H), 1.91-1.82 (m, 2H), 1.68-1.57 (m, 3H), 1.51-1.43 (m, 1H), 1.43-1.34 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.57, 128.59, 128.27, 128.00, 97.75, 80.05, 62.01, 52.05, 37.90, 32.57, 28.19, 25.33, 18.09.



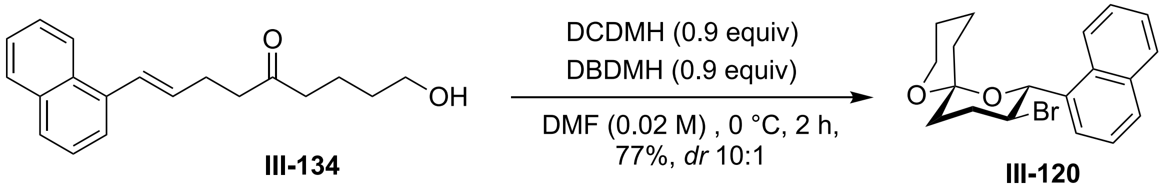
Compound **III-118** was synthesized from **III-129** (39.4 mg, 0.15 mmol), DBDMH (38.6 mg, 0.135 mmol, 0.90 equiv), DCDMH (26.6 mg, 0.135 mmol, 0.90 equiv) according to GP III. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **III-118** was isolated as a colourless solid in 62% yield (31.7 mg, 0.09 mmol).

Analytical data for compound III-118: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.6 Hz, 1H), 6.90 (d, J = 8.7 Hz, 1H), 4.46 (d, J = 10.2 Hz, 1H), 4.03-3.93 (m, 2H), 3.82 (s, 2H), 3.65-3.59 (m, 1H), 2.50-2.40 (m, 2H), 2.28-2.16 (m, 1H), 1.87-1.80 (m, 2H), 1.67-1.56 (m, 3H), 1.50-1.44 (m, 1H), 1.41-1.33 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.71, 131.90, 129.10, 113.62, 97.74, 79.60, 61.98, 55.37, 52.47, 37.94, 32.59, 28.17, 25.34, 18.09.



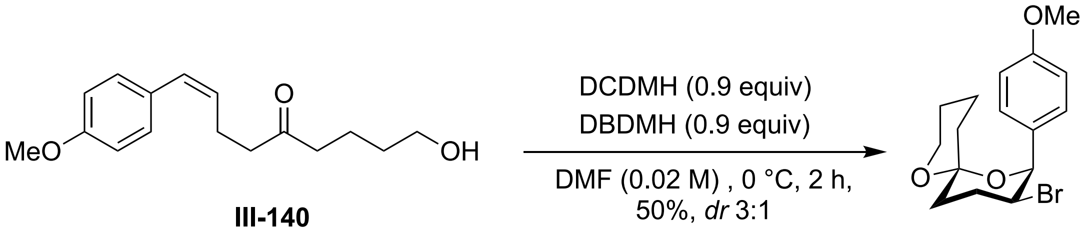
Compound **III-119** was synthesized from **III-133** (42.4 mg, 0.15 mmol), DBDMH (38.6 mg, 0.135 mmol, 0.90 equiv) DCDMH (26.6 mg, 0.135 mmol, 0.90 equiv) according to GP III. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-119** was isolated as a colourless solid in 88% yield (47.7 mg, 0.132 mmol).

Analytical data for compound III-119: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93-7.90 (m, 1H), 7.90-7.82 (m, 3H), 7.60 (dd, J = 8.4, 1.7 Hz, 1H), 7.52-7.45 (m, 2H), 4.67 (d, J = 10.2 Hz, 1H), 4.13 (ddd, J = 11.7, 10.2, 4.8 Hz, 1H), 4.02-3.93 (m, 1H), 3.67-3.61 (m, 1H), 2.56-2.46 (m, 2H), 2.29 (qd, J = 12.7, 5.3 Hz, 1H), 1.97-1.84 (m, 2H), 1.70-1.56 (m, 3H), 1.50-1.37 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 136.94, 133.59, 133.13, 128.32, 128.06, 127.85, 127.44, 126.28, 126.23, 125.52, 97.87, 80.27, 62.06, 51.96, 37.98, 32.63, 28.22, 25.32, 18.13.



Compound **III-120** was synthesized from **III-134** (42.4 mg, 0.15 mmol), DBDMH (38.6 mg, 0.135 mmol, 0.90 equiv) DCDMH (26.6 mg, 0.135 mmol, 0.90 equiv) according to GP III. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **III-120** was isolated as a white solid in 77% yield (41.7 mg, 0.116 mmol).

Analytical data for compound III-120: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 7.1 Hz, 1H), 7.57-7.53 (m, 1H), 7.53-7.47 (m, 2H), 5.33 (d, J = 10.0 Hz, 1H), 4.47 (td, J = 10.6, 4.7 Hz, 1H), 3.87-3.79 (m, 1H), 3.56 (dd, J = 11.1, 4.7 Hz, 1H), 2.65-2.59 (m, 1H), 2.60-2.53 (m, 1H), 2.41-2.30 (m, 1H), 2.02-1.90 (m, 2H), 1.73-1.56 (m, 3H), 1.46 (td, J = 13.3, 4.7 Hz, 1H), 1.43-1.37 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.20, 129.05, 126.15, 125.61, 125.36, 97.98, 62.01, 51.37, 37.82, 34.81, 32.56, 28.56, 25.27, 18.29.

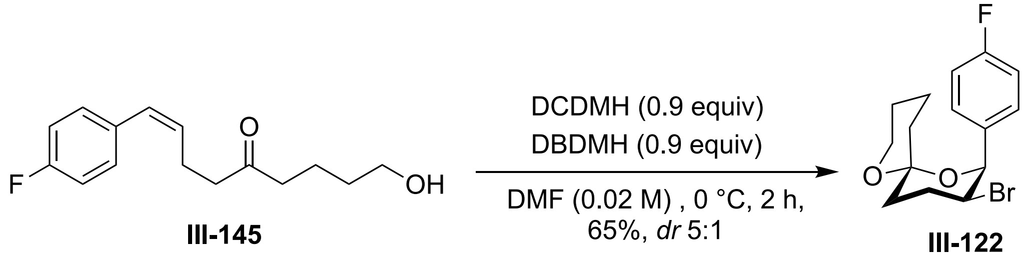


III-140

III-121

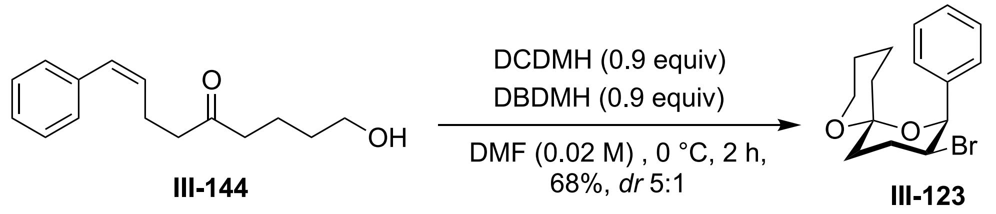
Compound **III-121** was synthesized from **III-140** (39.4 mg, 0.15 mmol), DBDMH (38.6 mg, 0.135 mmol, 0.90 equiv) DCDMH (26.6 mg, 0.135 mmol, 0.90 equiv) according to GP III. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-121** was isolated as a semi-solid in 50% yield (25.6 mg, 0.075 mmol).

Analytical data for compound III-121: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 4.82-4.78 (m, 1H), 4.52-4.44 (m, 1H), 3.81 (s, 3H), 3.62-3.57 (m, 2H), 2.65-2.55 (m, 1H), 2.15-2.03 (m, 2H), 2.02-1.93 (m, 1H), 1.93-1.85 (m, 1H), 1.66-1.53 (m, 5H).^{13}C NMR (126 MHz, $CDCl_3$) δ 158.93, 133.05, 126.94, 113.49, 96.41, 70.99, 61.09, 56.85, 55.37, 35.29, 30.16, 28.85, 25.27, 18.55.



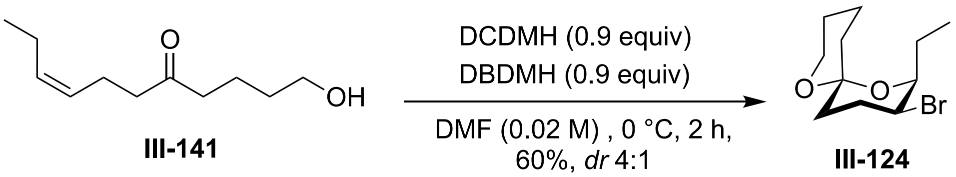
Compound **III-122** was synthesized from **III-145** (37.5 mg, 0.15 mmol), DBDMH (38.6 mg, 0.135 mmol, 0.90 equiv) DCDMH (26.6 mg, 0.135 mmol, 0.90 equiv) according to GP III. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-122** was isolated as a colourless solid in 65% yield (32.1 mg, 0.098 mmol).

Analytical data for compound III-122: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.40-7.35 (m, 2H), 7.06-6.98 (m, 2H), 4.88 (d, J = 9.3 Hz, 1H), 4.66-4.59 (m, 1H), 4.12-4.05 (m, 1H), 3.74-3.66 (m, 1H), 2.04-1.99 (m, 1H), 1.97-1.87 (m, 1H), 1.76-1.66 (m, 6H), 1.62-1.56 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 129.97, 126.49, 115.95, 106.47, 83.83, 62.35, 58.99, 39.15, 33.66, 28.72, 25.44, 20.34. ^{19}F NMR (470 MHz, CDCl$_3$) δ -112.72.



Compound **III-123** was synthesized from **III-144** (34.8 mg, 0.15 mmol), DBDMH (38.6 mg, 0.135 mmol, 0.90 equiv), DCDMH (26.6 mg, 0.135 mmol, 0.90 equiv) according to GP III. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-123** was isolated as a colourless solid in 68% yield (31.7 mg, 0.102 mmol).

Analytical data for compound III-123: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.36 (m, 2H), 7.36-7.27 (m, 3H), 4.89 (d, J = 9.5 Hz, 1H), 4.72-4.64 (m, 1H), 4.15-4.08 (m, 1H), 3.74-3.67 (m, 1H), 2.06-1.98 (m, 1H), 1.98-1.82 (m, 2H), 1.76-1.72 (m, 2H), 1.71-1.68 (m, 2H), 1.67-1.57 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.49, 128.89, 128.72, 128.18, 106.42, 83.84, 62.34, 39.19, 33.67, 28.72, 25.46, 25.42, 20.36.

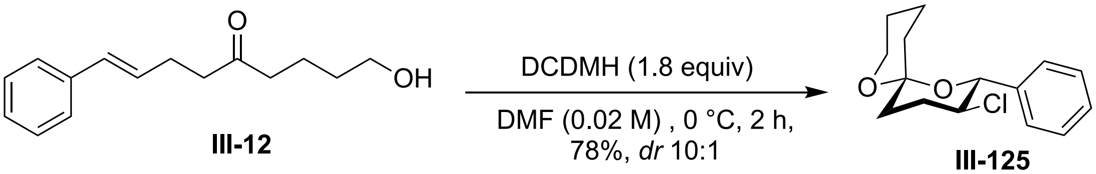


III-141

III-124

Compound **III-124** was synthesized from **III-141** (27.6 mg, 0.15 mmol), DBDMH (38.6 mg, 0.135 mmol, 0.90 equiv), DCDMH (26.6 mg, 0.135 mmol, 0.90 equiv) according to GP III. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane:ethyl acetate as eluent) and compound **III-124** was isolated as a colourless liquid in 60% yield (23.4 mg, 0.09 mmol).

Analytical data for compound III-124: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (dt, *J* = 9.0, 4.6 Hz, 1H), 3.96 (dt, *J* = 9.5, 4.0 Hz, 1H), 3.89 – 3.78 (m, 1H), 3.64 – 3.54 (m, 1H), 2.50 (dt, *J* = 13.6, 7.3 Hz, 1H), 2.21 – 2.10 (m, 2H), 1.98 – 1.90 (m, 2H), 1.90 – 1.84 (m, 2H), 1.84 – 1.78 (m, 2H), 1.78 – 1.71 (m, 3H), 1.08 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.03, 77.41, 77.16, 76.91, 62.13, 61.89, 47.07, 33.35, 30.10, 28.11, 27.76, 25.38, 20.36, 12.74.

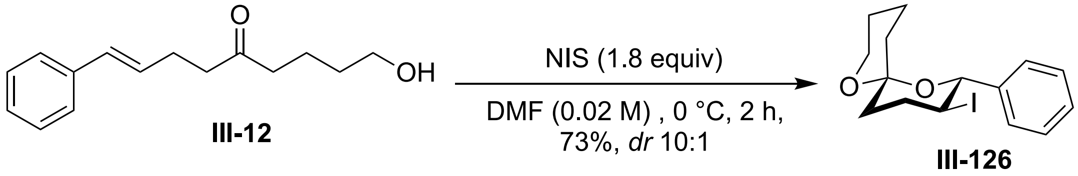


III-12

III-125

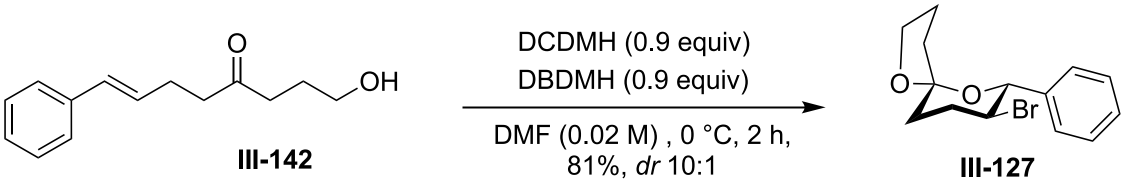
Compound **III-125** was synthesized from **III-12** (34.8 mg, 0.15 mmol), DCDMH (53.2 mg, 0.27 mmol, 1.80 equiv) according to GP III. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **III-125** was isolated as a yellow liquid in 78% yield (31.2 mg, 0.117 mmol).

Analytical data for compound III-125: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.49 – 7.42 (m, 2H), 7.41 – 7.30 (m, 3H), 4.39 (d, *J* = 9.9 Hz, 1H), 4.04 – 3.96 (m, 1H), 3.88 (ddd, *J* = 11.4, 9.9, 4.8 Hz, 1H), 3.67 – 3.60 (m, 1H), 2.49-2.43 (m, 1H), 2.35 (dq, *J* = 13.2, 4.4 Hz, 1H), 2.08 (tdd, *J* = 13.3, 11.4, 5.2 Hz, 1H), 1.93 – 1.81 (m, 2H), 1.68 – 1.57 (m, 3H), 1.43 – 1.32 (m, 1H), 1.50-1.44 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 140.43, 128.39, 128.13, 127.80, 92.74, 79.70, 61.92, 36.64, 33.51, 31.43, 28.06, 25.19, 17.95.



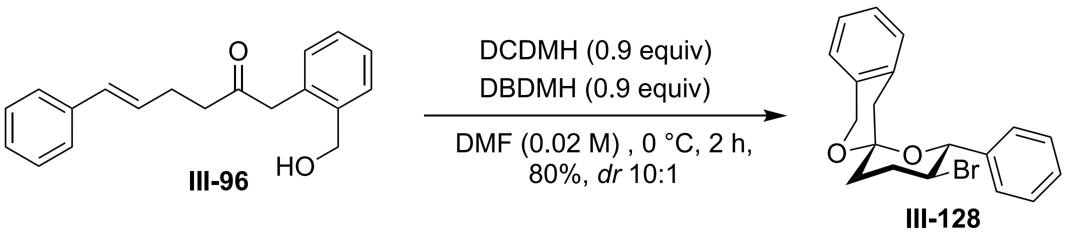
Compound **III-126** was synthesized from **III-12** (34.8 mg, 0.15 mmol), NIS (60.7 mg, 0.27 mmol, 1.8 equiv) according to GP III. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **III-126** was isolated as a greenish liquid in 73% yield (39.2 mg, 0.11 mmol).

Analytical data for compound III-126: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.46-7.42 (m, 2H), 7.40-7.31 (m, 3H), 4.59 (d, J = 10.6 Hz, 1H), 4.13 (ddd, J = 12.1, 10.6, 4.7 Hz, 1H), 4.00-3.93 (m, 1H), 3.65-3.57 (m, 1H), 2.56 (dtd, J = 13.9, 4.6, 3.4 Hz, 1H), 2.51-2.36 (m, 2H), 1.85 (td, J = 13.5, 4.6 Hz, 1H), 1.70 (dt, J = 13.5, 3.8 Hz, 1H), 1.67-1.57 (m, 3H), 1.51-1.42 (m, 1H), 1.42-1.33 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 140.27, 128.66, 128.27, 128.05, 97.86, 81.18, 61.86, 39.34, 35.05, 32.11, 28.11, 25.33, 18.05.



Compound **III-127** was synthesized from **III-142** (32.7 mg, 0.15 mmol), DBDMH (38.6 mg, 0.135 mmol, 0.90 equiv), DCDMH (26.6 mg, 0.135 mmol, 0.90 equiv) according to GP III. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **III-127** was isolated as a colourless solid in 81% yield (36.1 mg, 0.122 mmol).

Analytical data for compound III-127: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.44-7.39 (m, 2H), 7.38-7.29 (m, 3H), 4.49 (d, J = 10.1 Hz, 1H), 4.05-3.97 (m, 2H), 3.92 (q, J = 7.4 Hz, 1H), 2.59-2.52 (m, 1H), 2.47 (ddd, J = 12.6, 8.0, 4.5 Hz, 1H), 2.22-2.10 (m, 3H), 2.04-1.93 (m, 1H), 1.91-1.73 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.32, 128.64, 128.35, 128.00, 108.36, 82.02, 68.30, 51.77, 36.18, 34.50, 32.25, 24.39.



Compound **III-128** was synthesized from **III-96** (42.1 mg, 0.15 mmol), DBDMH (38.6 mg, 0.135 mmol, 0.90 equiv), DCDMH (26.6 mg, 0.135 mmol, 0.90 equiv) according to GP III. The crude product was purified via column chromatography (20 X 250 mm, 98:2 hexane: ethyl acetate as eluent) and compound **III-128** was isolated as a colourless solid in 80% yield (43.1 mg, 0.12 mmol).

Analytical data for compound III-128: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39-7.35 (m, 2H), 7.34-7.27 (m, 3H), 7.14-7.06 (m, 2H), 7.04-6.99 (m, 1H), 6.99-6.94 (m, 1H), 4.80 (d, J = 14.7 Hz, 1H), 4.79 (d, J = 10.3 Hz, 1H), 4.72 (d, J = 14.7 Hz, 1H), 4.08 (ddd, J = 12.0, 10.3, 4.5 Hz, 1H), 2.95 (d, J = 16.8 Hz, 1H), 2.85 (d, J = 16.8 Hz, 1H), 2.70-2.59 (m, 1H), 2.43-2.36 (m, 1H), 2.03-1.98 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 130.98, 128.77, 128.61, 128.27, 128.10, 126.73, 125.94, 124.03, 96.57, 96.57, 77.81, 61.88, 51.92, 38.04, 37.20, 31.58.

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