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Hyunmin Park Date

SYNTHESIS OF SMALL MOLECULE THERAPEUTICS AND LIGANDS UTILIZING RHODIUM CARBENOID CHEMISTRY

By

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Doctor of Philosophy

Chemistry

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An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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ABSTRACT

SYNTHESIS OF SMALL MOLECULE THERAPEUTICS AND LIGANDS UTILIZING RHODIUM CARBENOID CHEMISTRY

By Hyunmin Park

The primary objective of this thesis was to utilize the reactions of donor/acceptor substituted rhodium carbenoids for the synthesis of small molecule therapeutics and ligands. The first section of this thesis was to explore novel multi-functional antidepressants with HDAC and monoamine reuptake inhibitors (hydroxamic acid/ 2-aminobenzamide chelator) as potential therapeutic agents for the treatment of depression by utilizing the enantioselective cyclopropanation, reductive amination and amide coupling reaction. Moreover, several effective biological tests were performed and demonstrated that hydroxamic acid analogue with enantioenriched cyclopropane **HM3a-R** has great antidepressant effects in animal models.

The second project was the development of new phosphoric acid ligands as organocatalysts for C-H insertion. In this project, the new phosphoric acid ligands were synthesized for organocatalysis for C-H insertion. As a result, C-H insertion with the phosphoric acid catalyst **12b** has the most effective enatioselectivity of desired C-H insertion products. However, N-H insertion via the photochemistry reaction by using blue LED has no effect on increasing enantioselectivity.

The third section was to develop diverse enantioenriched cyclopropyl amine derivatives for inhibition of EBOV by utilizing the enantioselective cyclopropanation and reductive amination. Furthermore, biological studies (infectivity and cell viability activity) suggested that (*R,S*) enantiomer was much better effect than (*S,R*) enantiomer, as well as secondary amine compounds had a greater effect than tertiary amine compounds. Especially, **HDE-49** is the best for inhibiting EBOV infection with having a significant effect on the cell viability.

In summary, one organocatalysts project for C-H insertion and two different medicinal chemistry projects could be initiated by using enabling technology unique to Davies' group. The multidimensional, multidisciplinary rational approach and collaborative efforts led to the discovery of specific phosphoric acid organocatalysts as well as novel scaffolds for various targets, which might have a greater potential and broader impact in medication development for antidepressant, and ebola virus inhibitors.

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I left South Korea almost five years ago to come to the United States and started this wonderful and precious chemistry journey. I only had my two luggage, two bags with me and many fears. Some of those fears are gone to make place to new ones. But most of them are gone to make place to unforgettable memories. Now I can say that I have more than my luggage with me. Here below I am going to mention the people I mostly feel grateful for and that contributed the most in what I have become.

First of all, I want to say "thank you" to my Ph.D. advisor, **Dr. Huw Davies**. He gave me the great opportunity to study and work organic chemistry, as well as provided endless support during my Ph.D. His dedication to work, his expertise and his approach to deal with scientific topics have been a role model to me. I must honestly admit that the greatest present I could receive from him was not the amount of knowledge transmitted. Indeed, I think I am still light years behind him. The greatest gift and teaching I received from my advisor is not to be afraid of what I DO NOT know, so that I can approach it with enthusiasm and not being discouraged by my ignorance. I guarantee that I am the most fortunate person in the world to be able to perform research with him.

I am grateful to my thesis committee members, Dr. Nathan Jui, and Dr. Hyunsuk Shim. Dr. Nathan Jui did teach me a lot of organic chemistry knowledge and always gave critical thought. Dr. Hyunsuk Shim readily agreed to serve as my committee member for two years without hesitation when I was fourth year graduate student, and also gave me support and advice for me to better understand medicinal chemistry projects. Their constant feedback in yearly reports gave me in the right direction and broad outlook. I also have to thank Dr. Emily Weinert for serving in my research committee for first three years of my graduate study.

Most my Ph.D. research has been collaborative. I have to thank all my collaborators for their constant cooperation and research. I would like to thank Dr. Hyunsuk Shim for antidepressant project. I also have to thank Dr. Mariana Marin and Dr. Gregory Melikian for their collaboration in EBOV project.

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Ac	acetyl
ADP	Adenosine Di-Phosphate
AN-9	privanex
AMP	Ampere
APCI	Atomspheric pressure chemical ionization
aq	aqueous
Ar	Aryl
BEBOV	Bundibugyo Ebola Virus
Blam-Vpr	β-lactamase-viral protein R
Boc	*tert*-butoxycarbonyl
$(Boc)_2O$	di-*tert*-butyldicarbonate
calcd	calculated
CCF4-AM	CCF4 acetoxymethyl ester
CDC	cross dehydrogenative coupling
CDI	1,1'-carbonyldiimidazole
CEBOV	Cote d'Ivpore Ebola Viruss
cm^{-1}	wavenumber(s)
CNS	Central nervous system
conc.	concentrated
CU	connect unit
CuAAC	copper-catalyzed azide-alkyne cycloaddition
CuTC	copper (I) thiphene-2-carboxylate

DA	Dopamine
DAT	Dopamine Transporter
DBU	1,8-diazabicyclo-[5.4.0]-undec-7-ene
DCC	dicyclohexyl carbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DI	deionized
DMAP	4-(N,N-dimethylamino)pyridine
DMEM	Dulbecco modified Eagle medium
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOSP	N-(4-dodecylbenzenesulfonyl)prolinate
EA	ethyl acetate
EBOV	Ebola Virus
EBOVpp	Ebola Virus pseudoparticles
EC_{50}	the half maximal inhibitory concentration
EDC	1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
EHF	Ebola hemorrhagic fever
ELISA	enzyme-linked immunosorbent assay
eq	equivalent
ESI	Electrospray ionization
Et	ethyl

Et_2O	diethyl ether
EVD	Ebola Virus disease
FBS	fetal bovine serum
FDA	Food and Drug Administration
FST	Forced Swim Test
FT-IR	Fourier-transform Infrared
GP	glycoprotein
h or hr	hour(s)
HAT	histone acetyl transferase
HDAC	histone deacetylase
HDACI	histone deacetylase inhibitor
hex	hexane
HIV	The human immunodeficiency virus
HOBt	hydroxybenzotriazole
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
Hz	hertz
IC_{50}	Half maximal inhibitory concentration
i.e.	that is
IgG	Immunoglobulin G
IgM	Immunoglobulin M
in situ	in the reaction mixture
in vacuo	in a vacuum
in vitro	within the glass

in vivo	within the living
I.P.	Intraperitoneal
i-Pr	isopropyl
IR	infrared
J	coupling constant
K_i	binding affinity of the inhibitor
L	RNA-dependent RNA polymerase
LAQ824	dacinostat
LBH589	panobinostat
LC-MS	Liquid chromatography–mass spectrometry
LED	Light-emitting diode
LPS	lipopolysaccharide
Luc	Luciferase
LTQ-FTMS	Linear Trap Quadropole- Fourier Transform Mass Spectrometry
Me	methyl
MGCD0103	mocetinostat
min	minute(s)
mp	melting point
Ms	mesyl (methanesulfonyl)
MS275	entinostat
m/*z*	mass-to-charge ratio (not *m*/*e*)
NAD^+	Nicotinamide adenine dinucleotide
NARI	Noradrenalin Reuptake Inhibitor
NDRI	NET/DAT Reuptake Inhibitor

NE	Norepinephrine
NET	Norepinephrine Transporter
NMR	Nuclear Magnetic Resonance
NP	nucleoprotein
NSI	Nanospray Ionization
NTTL	*N*-1,2-naphthaloyl-*tert*-leucine
OAc	acetate
Oct	octanoate
OTf	triflate
p-ABSA	para-acetamidobenzenesulfonyl azide
PCR	Polymerase chain reaction
Ph	phenyl
PTAD	1-adamantyl-(*N*-phthalimido)acetate
PXD101	belinostat
REBOV	Reston Ebola Virus
R_f	retention factor (in chromatography)
RNA	ribonucleic acid
RT	room temperature
rVSV	the recombinant vesicular stomatitis virus
SAHA	vorinostat
SAR	Structure–activity relationship
SE	Serotonin
SEBOV	Sudan Ebola Virus
SEM	Scanning Electron Microscope

SERT	Serotonin transporter protein
SNRI	Serotonin and norepinephrine reuptake inhibitor
SRM	surface recognition moiety
SSRI	Selective serotonin reuptake inhibitor
STD	sexually transmitted disease
T-705	favipiravir
Temp.	Temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydro-*2H*-pyran
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
t_R	retention time
TRI	triple reuptake inhibitor
TST	tail suspension test
UV	Ultraviolet
VLP	virus-like particles
VP24	minor viral matrix protein
VP30	transcription activator
VP35	polymerase cofactor
VP40	viral matrix protein
VSV	vesicular stomatitis virus
WHO	the World Health Organization
WSC	1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride

ZBG	Zn^{2+} binding group
ZEBOV	Zaire Ebola Virus
5-HT	Serotonin
δ	chemical shift in parts per million
μ	micro
$[\alpha]_D^{20}$	specific optical rotation in 589 nm at 20 °C

Chapter 1: Rational Design of Novel and Multi-functional Antidepressants: Histone Deacetylase (HDAC) and Monoamine Reuptake Inhibitors

1.1. INTRODUCTION

1.1.1. Histone Deacetylases (HDACs) and Histone Deacetylases Inhibitors (HDACIs)

Protein acetylation has significant effects on an important post-translational modification that controls multiple functions, including chromatin remodeling and transcriptional regulation, metabolism, and ageing.[1,2,3] In cells, protein acetylation is retained by two functional enzyme classes: the protein acetylases and deacetylases.[4] Various researches have focused on enzymes that modulate the histone acetylation since these are major components of chromatin and have the important roles in vital cellular functions and in disease.[5,6] Levels of histone acetylation depend on the actions of histone acetyl transferases (HATs) and histone deacetylases (HDACs).[7] Acetylation of lysine residues, catalyzed by HATs, neutralizes the positive charges of ε-amino groups on lysine residues, relaxes chromatin structure, and increases accessibility for the transcription reaction. Whereas, removal of acetyl groups from histones and other nuclear proteins by HDACs induces chromatin condensation and transcriptional repression (**Figure 1.1**).[8,9] In other words, HDACs could remove acetyl groups from histone tails which tighten the bonds between the lysines of histone and the DNA phosphate backbone for transcription.[10] In addition, HDAC can modulate the function of many other proteins

involved in cell survival and proliferation, angiogenesis, inflammation, and immunity. Moreover, since HDACs play an important role in the regulation of gene expression, deregulated HDACs would be associated with treatment of many types of cancers and antidepressant action.[10]

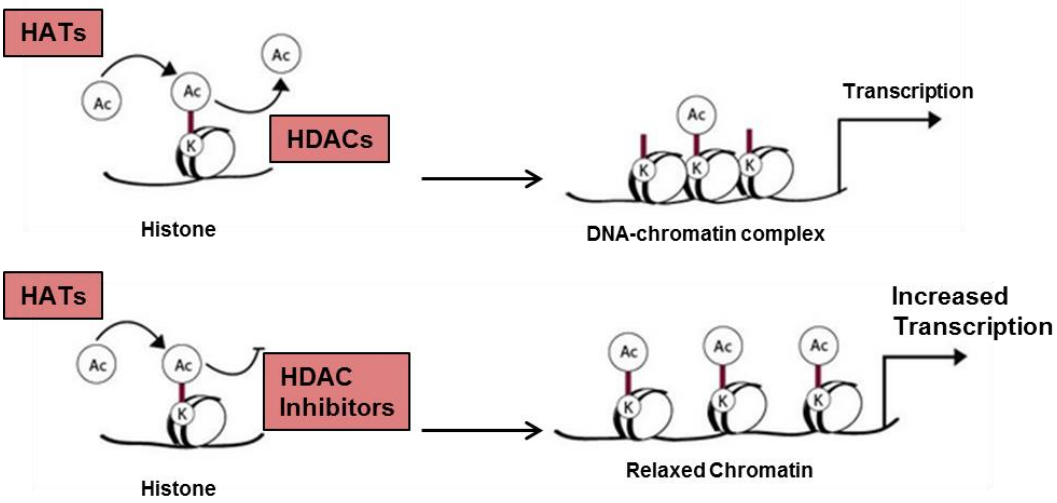


Figure 1.1. Effect of HDAC inhibitors on chromatin remodeling and transcription (adapted from *Nat. Rev. Drug Discov.* (**2008**) 854-868)

HDACs are expressed in all eukaryotic cells, and HDAC activity is essential for cell proliferation, differentiation, and homeostasis. Eighteen HDACs have been identified in humans based on their homology to yeast HDACs. The superfamily of HDACs consists of five main subtypes: Classes I, IIa, IIb, IV, and the structurally distinct Class III.[11,12] Class I includes HDACs 1, 2, 3, and 8 which are all nuclear and generally expressed. Class II, which could go back and forth between the nucleus and the cytoplasm, includes HDACs 4, 5, 6, 7, 9, and 10; within this class, HDACs 6 and 10

(Class IIb) have two catalytic sites, are expressed only in the cytoplasm, and are involved in various biological processes. Class III contains the structurally diverse NAD^+-dependent sirtuin family, which does not act primarily on histones.[13] Finally, the ubiquitously expressed HDAC 11 is the part of Class IV, which has previously been characterized as being part of both Class I and Class II (**Table 1.1**). Class I, II and IV HDACs include the Zn^{2+}-dependent deacetylases, which share significantly structural homology.[14] In contrast, the class III deacetylases, or sirtuins, are structurally and functionally different from other HDACs (**Table 1.1**). Sirtuins are markedly different in their absolute dependence on NAD^+ to carry out catalytic reactions, which include both deacetylase and mono-ADP-transferase activities.[3,15] Overexpression of specific HDACs has been observed in many types of cancer and in the nucleus accumbens of depressed humans studied postmortem.[10,16]

Class I		1, 2, 3	Nuclear	HDAC Zn^{2+}-dependent enzymes
		8	Nuclear/Cytoplasmic	
Class II	IIa	4, 5, 7, 9	Nuclear/Cytoplasmic	
	IIb	6, 10	Mainly/Cytoplasmic	
Class IV		11	Nuclear/Cytoplasmic	
Class III		SIRT 1-7		HDAC NAD^+-dependent enzymes

Table 1.1. The family of the histone deacetylases

Recently, the superfamily of HDACs has been studied as an important therapeutic application for human disorders, particularly for cancer treatment and neuropsychiatric disorders.[17,18] Histone acetylation contributes to the transcriptional activation process by

relaxing a repressive chromatin state, which attribute to the sequestration of the basal transcriptional instrument.[19] Furthermore, expression levels of various HDACs are modulated by antidepressants and mood stabilizers in neuronal and non-neuronal tissue culture systems.[20] Therefore, histone acetylation may represent a key target for antidepressant action. Aberrant activity of HDACs has been found in the nucleus accumbens of depressed humans leading to development of histone deacetylase inhibitors (HDACIs). HDACIs enhance histone acetylation, resulting in inducing chromatin relaxation, modulation of gene expression, and reversing the epigenetic changes.[21]

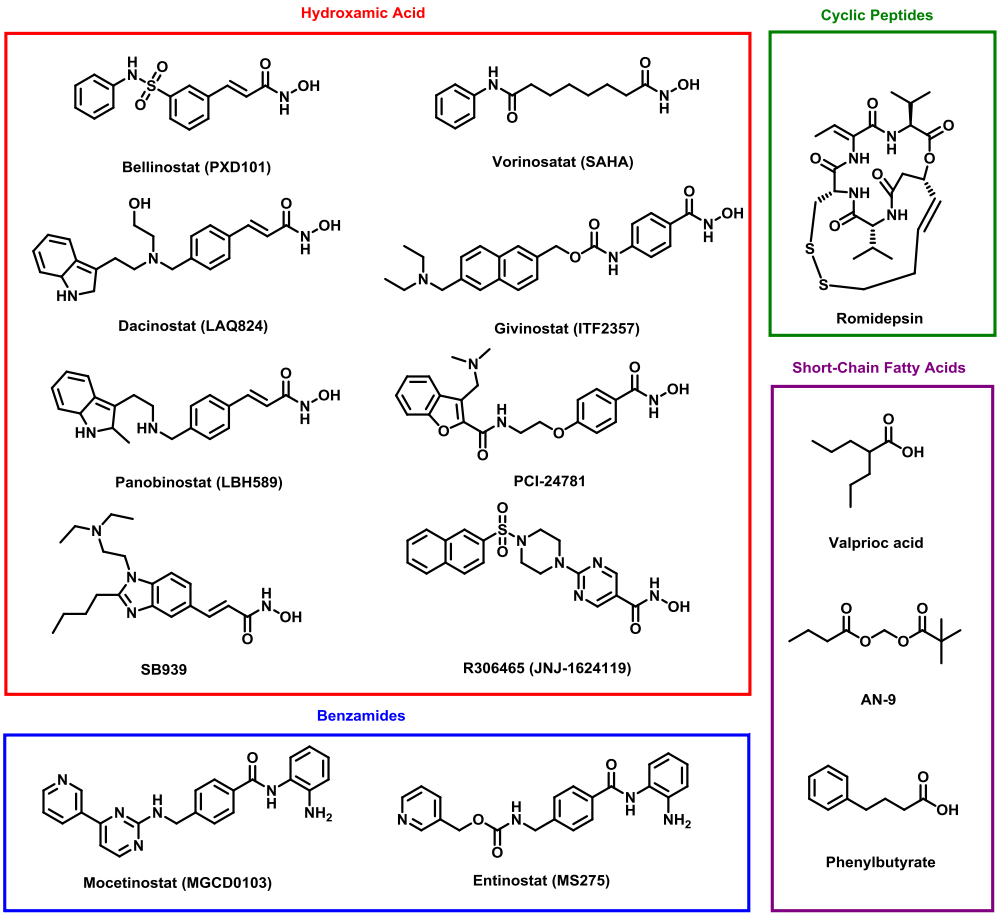


Figure 1.2. Classification of HDAC inhibitors by chemical structure

A lot of effort has been put into the development of HDACIs in recent years.[22,23] Seven structurally distinct classes of inhibitors are known today; inhibitors of four different classes are now in clinical development (**Figure 1.2**). These include the short-chain fatty acids, such as phenylbutyrate, pivanex (pivaloyloxymethyl butyrate; AN-9), and valproic acid. More selective classes include hydroxamic acids such as vorinostat (SAHA), belinostat (PXD101), panobinostat (LBH589), and dacinostat (LAQ824); benzamides including entinostat (MS275) and mocetinostat (MGCD0103); and the cyclic peptides, romidepsin. Suberoylanilide hydroxamic acid (Vorinostat, SAHA) is the first HDACI approved by Food and Drug Administration (FDA) in 2006. Belinostat (PXD101) and panobinostat (LBH589) are also hydroxamate HDACIs which induce acetylation of histone. Entinostat (MS275) is an oral benzamide HDACI and other HDACIs are currently in clinical development.[24] These HDACIs all shared common pharmacophore composed of four portions: [1] Zn^{2+} binding group (ZBG), which chelates Zn^{2+} at the pocket, [2] linker (scaffold), usually hydrophobic which occupies the narrow channel, [3] connect unit (CU), which connects surface recognition moiety (SRM) and linker, [4] SRM, which interacts with residues on the rim of active site (**Figure 1.3**). The general linkers are aliphatic chain, aromatic chain and vinyl-aromatic chain. The most common ZBGs are hydroxamic acid (the most widely explored class of HDACI) and 2-aminobenzamide.[24]

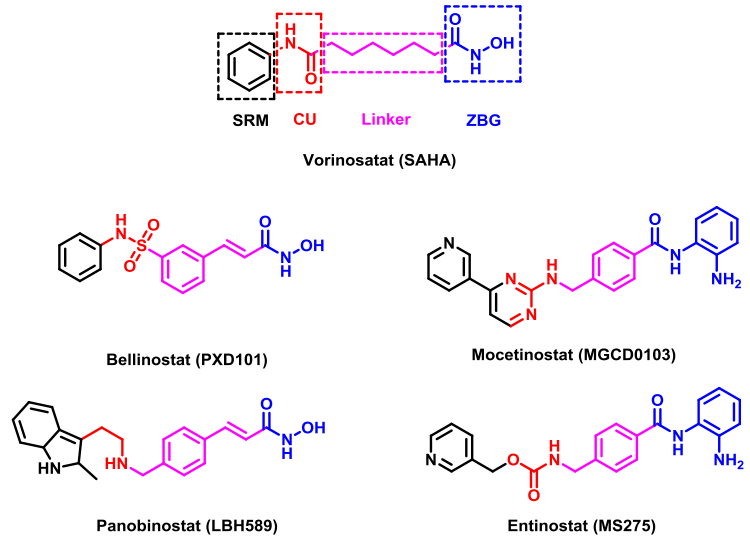


Figure 1.3. Structures and pharmarcophore features of HDAC inhibitors

1.1.2. Monoamine Reuptake Inhibitors

Neuropathic pain is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system".[25] This is a serious health care problem and costs billions of dollars annually in treatment expense in the United States.[26] Recent studies have suggested that up to 30% of adults in the US report suffering from moderate to severe chronic pain.[27] Moreover, this pain condition will have serious impact on quality of life and mood of patients due to the long term of this disease and the lack of effective therapies. The major cause of this health condition is believed to be due to trauma, disease, or injury to the peripheral and/or central sensory neuron system.[28] This abnormality in the sensory neuron system would cause hypersensitivity and unplanned pain.

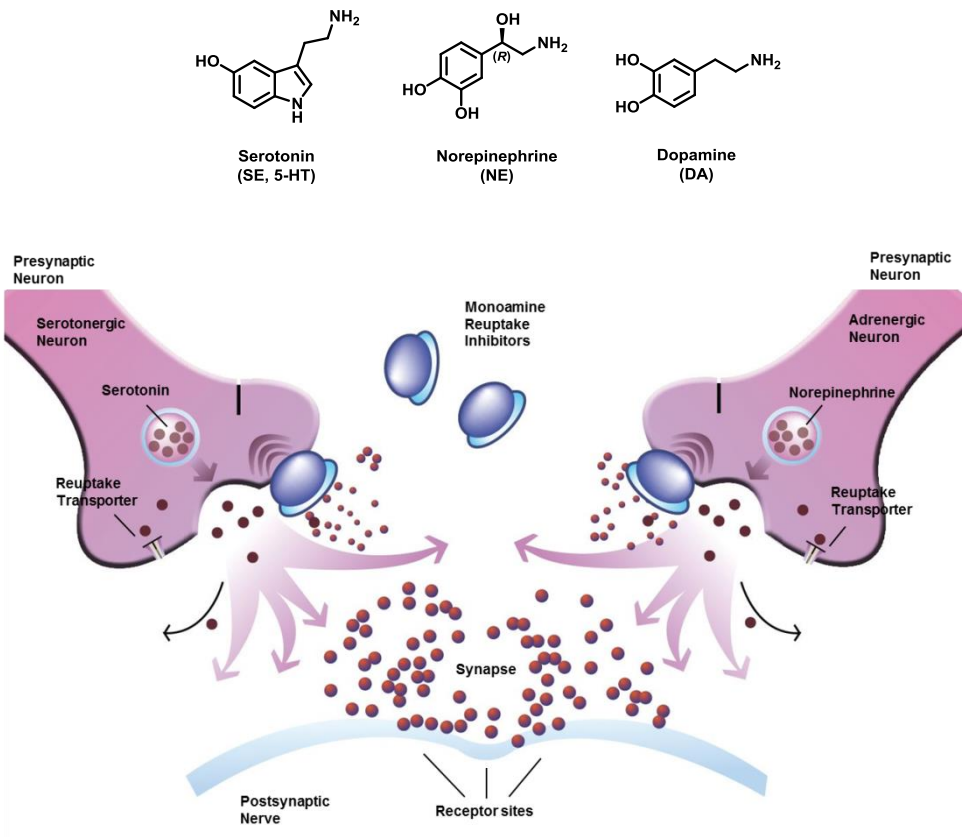


Figure 1.4. Monoamine neurotransmitters (top) and mechanism of monoamine reuptake inhibition action (bottom) (adapted from https://www.youtube.com/watch?v=KBhxTQD4Bsk)

Serotonin (SE) and norepinephrine (NE) in the brain were recognized as the main neurotransmitters involved in the modulation of endogenous pain mechanism.[29] Based on the clinical results, it was suggested that increased concentration of both SE and NE would enhance the pain suppression via multiple postsynaptic receptor mechanisms.[28] There are three different kinds of monoamine neurotransmitters, SE, NE and dopamine (DA) in the human brain that transmit nerve impulses from presynaptic neurons to postsynaptic neurons (**Figure 1.4**). When an impulse gets transmitted, neurotransmitters would be carried back into the presynaptic neuron via monoamine transporter proteins;

Serotonin Transporter (SERT), Norepinephrine Transporter (NET) and Dopamine Transporter (DAT). These transporters have been shown to coordinate sleep, mood, emotion and appetite.[30] Many classes of clinical drugs target these three transporters and thereby have been classified into many groups based on their ability to selectively inhibit serotonin and/or norepinephrine and/or dopamine reuptake into the presynaptic neurons. Monoamine transporter inhibitors are an established drug class that has proven utility for the treatment of the central nervous system (CNS) disorders, especially major depression disorder.[31] Selective serotonin reuptake inhibitors (SSRI's), selective noradrenalin reuptake inhibitors (NARI's), dual SERT/NET reuptake inhibitors (SNRI's) such as duloxetine and milnacipran, dual NET/DAT reuptake inhibitors (NDRIs), and triple reuptake inhibitors (TRI) were found to be effective in treating neuropathic pain but they also showed some adverse side effects such as nausea, vomiting, and dry mouth (**Figure 1.5**).[31,32]

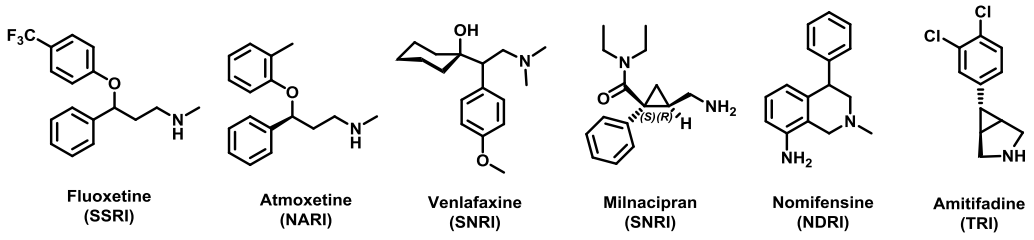


Figure 1.5. Examples of SSRI, NARI, SNRI, NDRI, and TRI

Among those effective monoamine reuptake inhibitors, milnacipran (**Figure 1.6**) is a commercially available antidepressant and FDA approved metarial for the fibramyalgia.[33] It acts as a serotonin (decrease depression) norepinephrin (decrease

chronic pain) reuptake inhibitor (SNRI).[34,35] In addition, thiophene derivatives of milnacipran were found for SNRI. They tested their novel analogues for the treatment of neuropathic pain.[36,37] One of the limitations of using this drug was that this might be the reason for side effects which include itching, nausea, increased anxiety, and sweats. It would be highly desirable to be able to synthesize an alternate drug with all the characteristics of milnacipran but could be easily accessed in enantiomerically pure form to possibly avoid adverse effects or to minimize side effects.

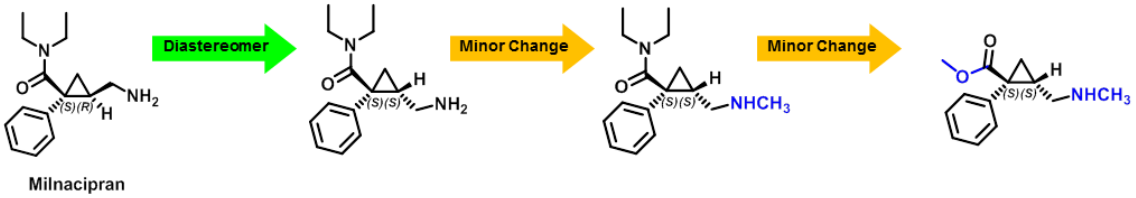


Figure 1.6. Structures of SNRIs based on asymmetric cyclopropanes (Milnacipran)

Recently, Davies's lab has synthesized various asymmetric cyclopropanes based on milnacipran by utilizing dirhodium catalysts, particularly chiral dirhodium catalysts for enantioselective transformations (**Figure 1.6**).[32] One such dirhodium tetracarboxylate catalyst is Rh_2(*S*-DOSP)$_4$ or Rh_2(*R*-DOSP)$_4$.[38,39,40] The reactions of donor/acceptor carbenoids with allylic species in the presence of chiral dirhodium catalysts such as Rh_2(*S*-DOSP)$_4$ or Rh_2(*R*-DOSP)$_4$ is an effective way to synthesize chiral cyclopropanes (**Figure 1.7**).[39,40,41]

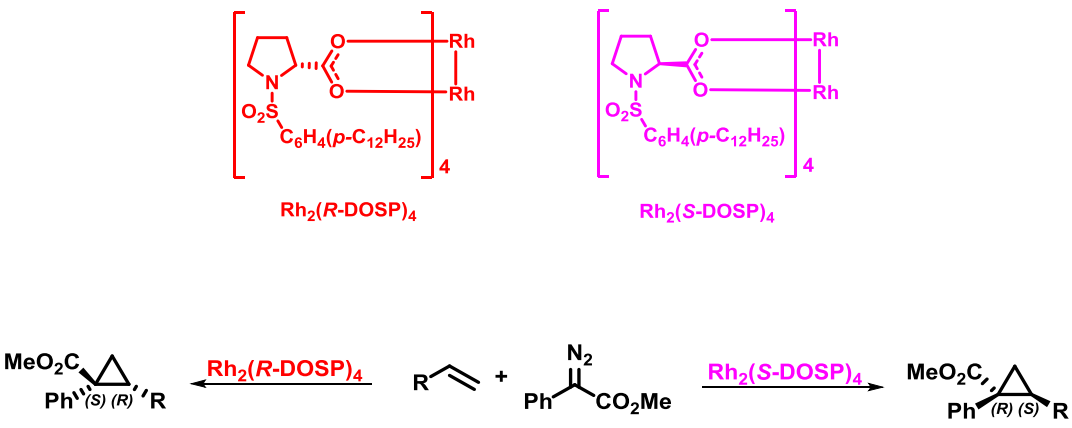


Figure 1.7. Structures of $Rh_2(DOSP)_4$ and scheme of rhodium-catalyzed asymmetric cyclopropanation

In addition, these enantioenriched cyclopropane compounds have been prepared for treatment of neuropathic pain. First, diastereomer of milnacipran was synthesized and radioligand binding assays at SERT, NET, and DAT were performed in rat brain membranes to confirm K_i value of these cyclopropyl compounds. The results showed that this diastereomer (*R* form >10k) was inactive against all monoamine transporters. And also, minor change from amine to methylamine was not effective either like this. However, after minor change from amide to ester, binding affinity of this compound was comparable to milnacipran and 2 fold more potent in binding to SERT than milnacipran (**Figure 1.8**).[32]

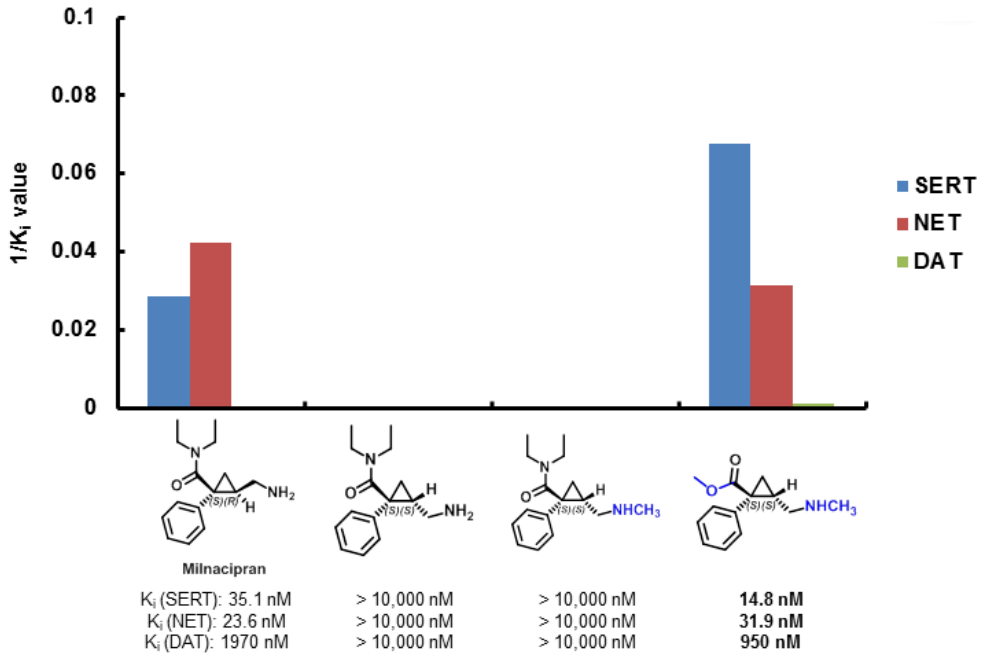


Figure 1.8. Bioactivity of milnacipran analogues (K_i values in nM ± SEM)[32]

Based on above compound, many derivatives of *S,S*-enantioselective asymmetric cyclopropyl compounds were prepared, such as 4-bromo, 3,4-dichloro, 3,4-dibromo and biphenyl (**Figure 1.9**). And also, these *R,R*-enantiomers were also synthesized to observe enantioselective bioactivity between those enantiomers. First, this *S,S* enantiomer case, binding affinity of 4-Br, 3,4-diCl, and 3,4-diBr was comparable to 4-H compound. And 3,4-diCl and 3,4-diBr are 7 fold more potent in binding to NET than 4-H compound (**Figure 1.9**). The interesting result was that *R* form was 20 fold more potent and selective as compared to *S* form, and this *R* form is 100 fold potent than milnacipran. Therefore, these data showed that isomer with *R* form is more bioactive than *S* form. And also, a substituent at 4 position such as 4-Br comes under NET selective category. In addition, substituents at 3,4 position such as 3,4-diCl and 3,4-diBr can come under SERT/NET selective category. Finally, bulky substituent at 4 position such as 4-Ph

comes under SERT selective category and all compounds were relatively inactive towards DAT.[32]

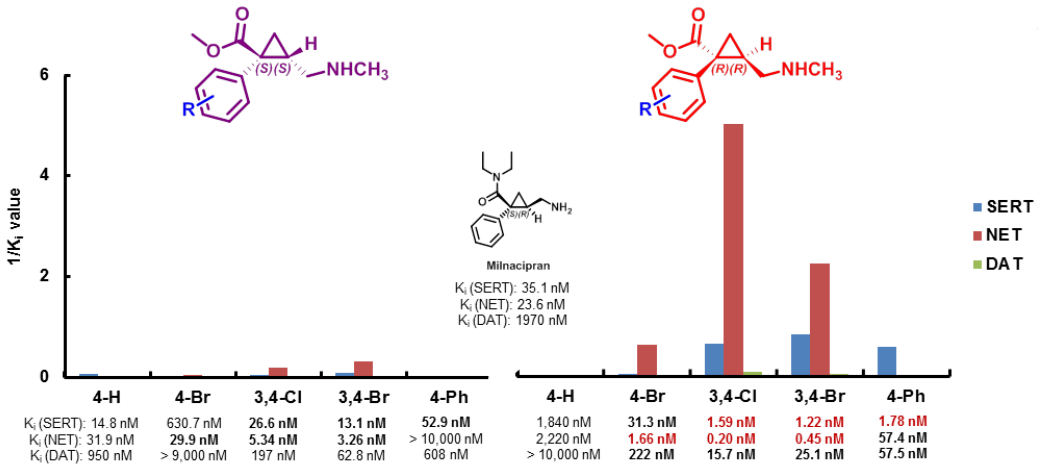


Figure 1.9. K_i values (nM ± SEM) for novel aryl cyclopropylamines in radioligand binding assay at SERT, NET, and DAT in rat brain membranes.[32]

1.1.3. Design of Novel Antidepressants with HDAC and Monoamine Reuptake Inhibitors

Recently, a number of HDACIs have been developed by modifying of SRM, linker and ZBG, as well as have focused on varying linker portion. Moreover, expression levels of various HDACs are modulated by antidepressants and mood stabilizers such as SAHA and MS275.[20] However, antidepressants have shown limited efficacy against neuropathic pain when given intrathecally.[32] In order to develop novel antidepressants with HDACIs as safe antidepressants without side effects such as fatigue and neuropathic pain, SNRIs based on milnacipran, which has the cyclopropyl ring and is known to be effective treatment for neuropathic pain,[30] would be designed with HDACIs moieties

including hydroxamic acid and 2-aminobenzamide chelator as Zn^{2+} binding site.[20] Furthermore, additional hypothesis was that the bioactivity for both enantiomers would be different because of the difference in their 3-D formation in the receptor active site which can be exploited to achieve the selectivity.[32]

Therefore, for development of new multi-functional antidepressants, two materials, enantiomerically enriched cyclopropane aldehyde compounds and hydroxamic acid/2-aminobenzamide chelator, will be combined to investigate novel antidepressants without side effects because asymmetric cyclopropanes could release neuropathic pain since cyclopropanes might be able to possibly avoid adverse effects or to minimize side effects by controlling monoamine reuptake in nerve cell, as well as hydroxamic acid and 2-aminobenzamide chelator would have a significant effect on antidepressant activity by chelating Zn^{2+} ions. Moreover, these structurally unique enantiomers scaffolds could be synthesized by utilizing Rh(II) carbene-mediated catalytic asymmetric intermolecular cyclopropanation.[40,41]

On the basis of these effective properties for antidepressants without neuropathic pain, novel and multifunctional antidepressants could be designed with asymmetric cyclopropanes as monoamine reuptake inhibitors, as well as hydroxamic acid and 2-aminobenzamide as Zn^{2+} chelator as HDACIs. Finally, structurally unique chiral cyclopropane scaffolds could be potential pharmaceutical agents in drug discovery (**Figure 1.10**).[32] The same molecule itself could not inhibit both, but these antidepressants could inhibit HDACs, while others could inhibit monoamine reuptake. Therefore it is possible to inhibit both monoamine reuptake and histone deacetylation at the same time.

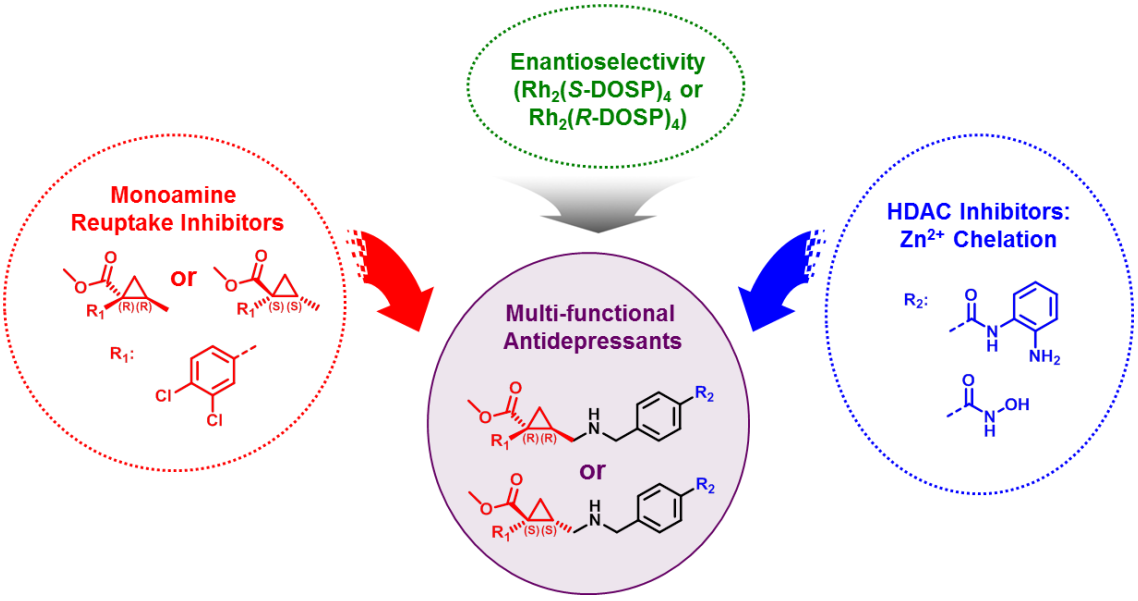


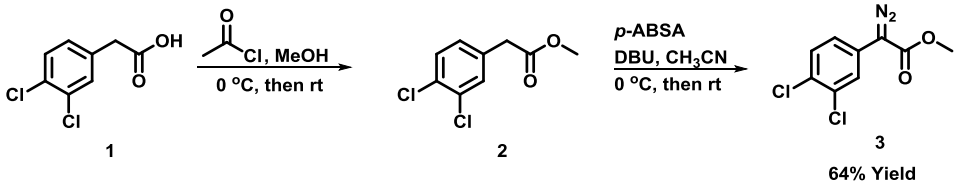
Figure 1.10. Rational structure-based design principle (incorporation approach) of multi-functional antidepressants

1.2. RESULTS AND DISCUSSION

1.2.1. Chemistry

The goal of this project is to synthesize novel antidepressants based on enantiopure milnacipran analogues that could potentially treat neuropathic pain by controlling monoamine reuptakes, and hydroxamic acid/ 2-aminobenzamide chelator analogues that could inhibit histone deacetylation by chelating Zn^{2+} ion.[24,32] As a part of this project, these new potential antidepressants would be synthesized to send for bioanalysis such as abilities of HDACIs and monoamine reuptake inhibition.

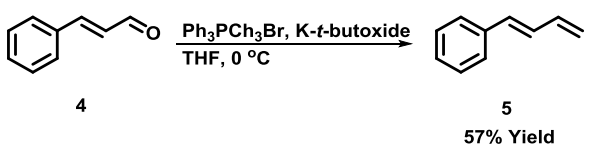
1.2.1.1. Synthesis of Dichloro Aryl Diazoacetate



Scheme 1.1. Synthesis of dichloro aryl diazoacetate

The donor/acceptor diazo compound (**3**) was first synthesized (**Scheme 1.1**).[32] The esterification of 2-phenylacetic acid (**1**) in the presence of acetyl chloride in methanol gave the corresponding ester (**2**) in quantitative yield. A diazo transfer reaction in the presence of pacetamidobenzenesulfonyl azide (*p*-ABSA) and the base 1,8-diazabicyclo-[5,4,0]-undec-*7*-ene (DBU) in acetonitrile yielded the corresponding diazo compound (**3**) in good to excellent yield. This reaction was performed in large scale to synthesize enough diazo compound, which could be used for both racemic and enantioselective synthesis.

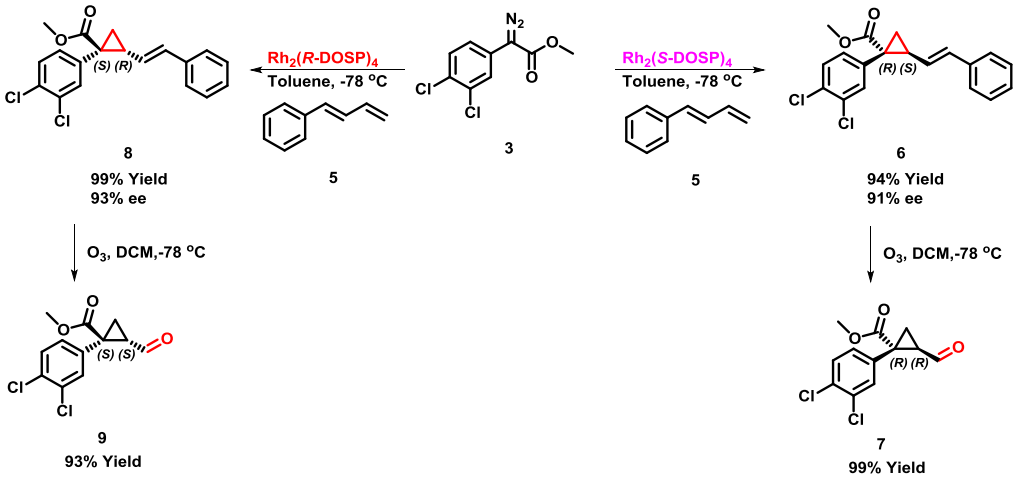
1.2.1.2. Synthesis of (*E*)-Buta-1,3-dienylbenzene



Scheme 1.2. Synthesis of (*E*)-buta-1,3-dienylbenzene

(*E*)-Buta-1,3-dienylbenzene was used for cyclopropanation reaction throughout this project. (*E*)-Buta-1,3-dienylbenzene (**5**) was synthesized via a Wittig reaction where *trans*-cinnamaldehyde (**4**) was reacted with triphenyl phosphine methyl bromide and potassium *tert*-butoxide. The resultant crude product was distilled to give a colorless liquid (**Scheme 1.2**).[32]

1.2.1.3. Synthesis of Enantiomers of Arylcyclopropylaldehyde Compounds



Scheme 1.3. Synthesis of enantiomers of arylcyclopropylaldehyde compounds

After diazo compound was synthesized, enantiomer synthesis of aryl cyclopropylaldehydes was pursued. These reactions were performed using both enantiomers of the catalyst. A Set of enantiopure compound consists of chloride substitutions at 3 and 4 position. Intermolecular asymmetric cyclopropanation reaction of the 3,4-dichloro phenyl diazoacetate (**3**) with (*E*)-buta-1,3-dienylbenzene (**5**) in the

presence of 1 mol% chiral catalysts; Rh_2(*S*-DOSP)$_4$ or Rh_2(*R*-DOSP)$_4$ gave the desired cyclopropane products in good yield. Typically, > 91% ee was observed. The enantiomerically enriched esters (**6**, **8**) were subjected to ozonolysis conditions to get the corresponding aldehydes (**7**, **9**) (**Scheme 1.3**).[32]

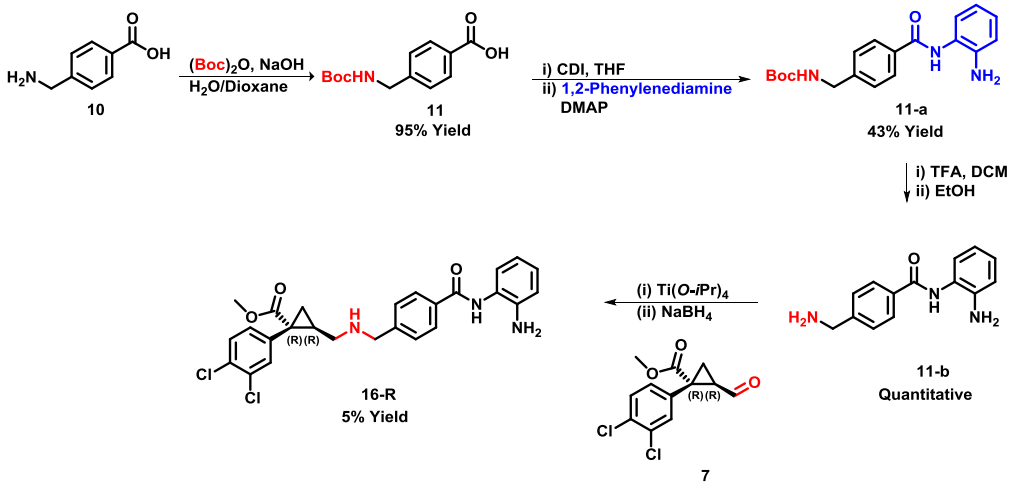
1.2.1.4. Synthesis of Multi-functional Antidepressants with 2-Aminobenzamide

1.2.1.4.1. INEFFICIENT Reaction of Antidepressants with 2-Aminobenzamide

1.2.1.4.1.1. Synthesis of Primary Amine Intermediate with 2-Aminobenzamide

First, in order for the reasonable and promising synthesis of the multi-functional antidepressants with 2-aminobenzamide, one possible scheme was designed (**Scheme 1.4.**). The amino group of 4-(aminomethyl) benzoic acid (**10**) was protected as its *tert*-butyloxy carbamate (**11**) in 95% yield by reaction with di-*tert*-butyl dicarbonate and 1M aqueous sodium hydroxide in a mixture of dioxane and water.[42,43] This intermediate (**11**) was directly converted from carboxylic acid to benzamide (**11-a**) by addition of 1,2-phenylenediamine in the presence of 1,1'-carbonyldiimidazole (CDI) and 4-(dimethylamino)pyridine (DMAP) coupling reagent.[44,45] Deprotection of the Boc group with trifluoroacetic acid (TFA) and EtOH at room temperature (RT) gave the amine compound with 2-aminobenziamide (**11-b**).[42,46] Finally, reaction of the cyclopropyl aldehydes (**7**) with the amine compound with benziamide (**11-b**) in the presence of titanium(IV) isopropoxide generated the imine *in situ*, which was then reduced using sodium borohydride to get the multi-functional cyclopropane compound with 2-

aminobenziamide (**16-R**).[32] However, in this reaction, the yield was too low (~ 5%) and even though some of final product could be synthesized. Therefore, another scheme was examined to obtain the final compound.

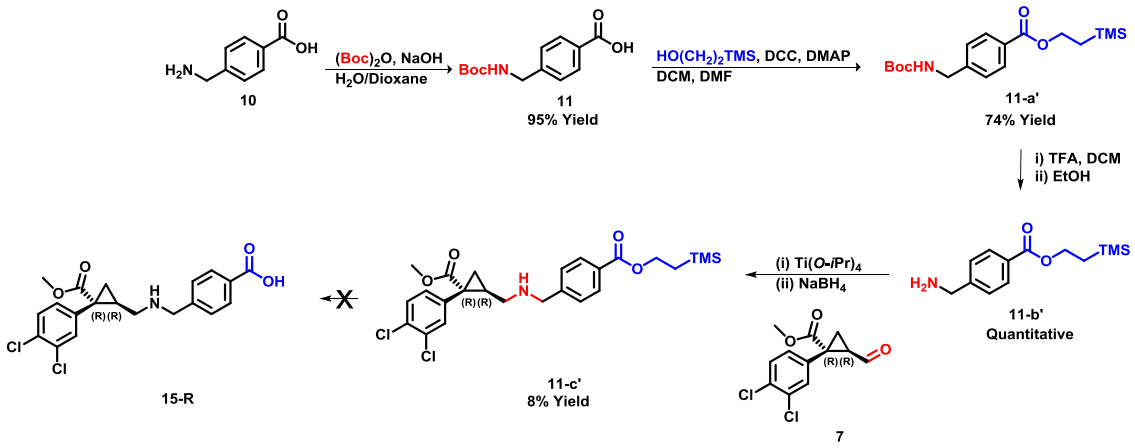


Scheme 1.4. Inefficient reaction of multi-functional antidepressants with 2-aminobenzamide

1.2.1.4.1.2. Synthesis of Secondary Amine Intermediate with *O*-Protection of TMS

A second scheme was designed to generate the desired compound, relying on *O*-TMS protection (**Scheme 1.5**). The amino group of 4-(aminomethyl) benzoic acid (**10**) was first *N*-protected as the *tert*-butyloxy carbamate (**11**),[42,43] and then was *O*-protected as the 2-(trimethylsilyl)ethanol (**11-a'**) by reaction with dicyclohexyl carbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in DMF and DCM.[47,48] After removal of the Boc *N*-protecting group with trifluoroacetic acid (TFA) (**11-b'**),[42,46] reaction of the aldehydes with amine in the presence of titanium(IV) isopropoxide generated the imine *in*

situ, which was then reduced using sodium borohydride to get the desired amine compound with *O*-protection of TMS (**11-c'**).[32] Still, in this reaction, the yield was remained low (~ 7%) even in the presence of high concentration of catalysts. Therefore, this method was not considered to be sufficiently practical to move forward.



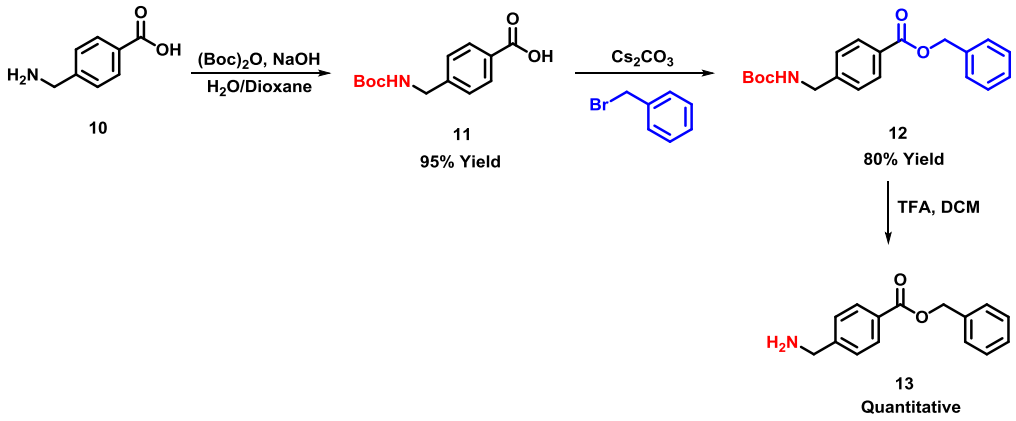
Scheme 1.5. Inefficient reaction (TMS protection) for multi-functional antidepressants with 2-aminobenzamide

1.2.1.4.2. EFFICIENT Reaction of Antidepressants with 2-Aminobenzamide

1.2.1.4.2.1. Synthesis of Methylamine Intermediate with Benzyl Ester

Finally, for reasonable and promising synthesis of the multi-functional antidepressants with 2-aminobenzamide, the methylamine intermediate **13** was prepared by *O*-protection with benzyl ester instead of TMS group (**Scheme 1.6**). Methylamine intermediate (**13**) began from 4-(aminomethyl) benzoic acid (**10**), which was *N*-protected

using di-*tert*-butyl dicarbonate in dioxane/water giving acid **11**.[42,43] Acid intermediate **11** was then converted into benzyl ester **12**, using benzyl bromide and Cs_2CO_3 in DMF.[49] Finally, the removal of the Boc group via TFA gave the desired methylamine intermediate **13**.[42,46] This simple procedure gave **13** as a solid pure enough for use after recrystallization.

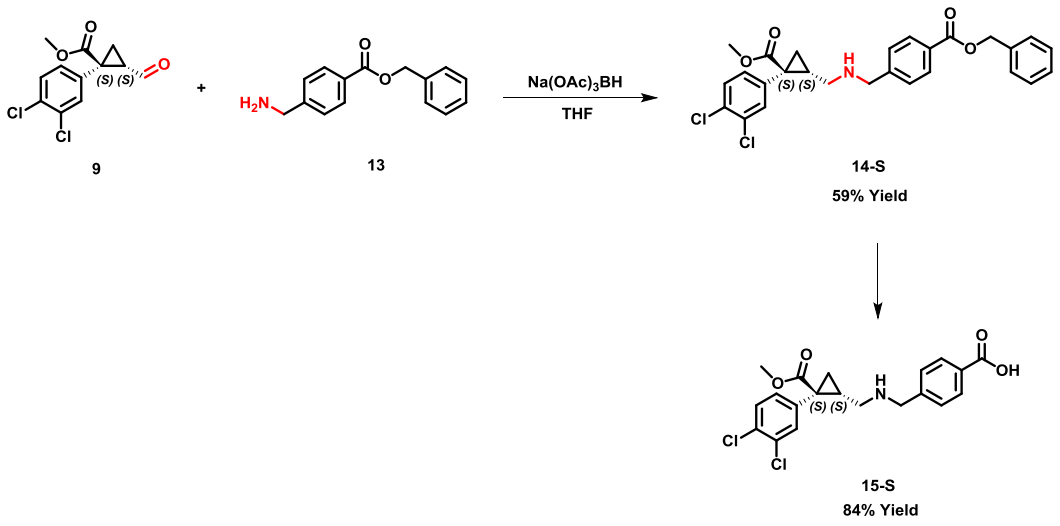


Scheme 1.6. Synthesis of methylamine intermediate with benzyl ester

1.2.1.4.2.2. Synthesis of Secondary Amine Intermediate

In order to synthesize the desired secondary amine compound, reductive amination between aldehyde **9** and amine **13** was performed (**Scheme 1.7**). First, sodium borohydride was used as reducing agent with titanium(IV) isopropoxide in MeOH.[32] This reaction was first stirred with **9** and titanium(IV) isopropoxide overnight and then $NaBH_4$ and amine were added to obtain secondary amine as its benzyl ester (**14-S**) in 35% yield.[32] In addition, to optimizing this reductive amination for high yield with $NaBH_4$, other mild reducing agents were used.[50] $Na(OAc)_3BH$ was a good alternative reducing

agent because $Na(OAc)_3BH$ is a mild reducing agent that will only reduce the imine, and it gave **14-S** in 59% yield.[50] $Na(CN)BH_3$ could also be used as and it gave **14-S** in 40% yield. The next step was the hydrogenolysis of the benzyl ester. This was achieved using catalytic 10% Pd/C with H_2 in methanol giving, after filtration and purification, the desired acid (**15-S**).[51,52,53,54]

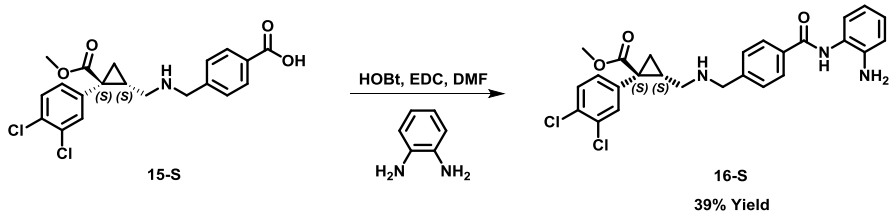


Scheme 1.7. Synthesis of secondary amine intermediate with benzyl ester and the hydrogenolysis of the benzyl ester

1.2.1.4.2.3. Synthesis of Novel Antidepressant with 2-Aminobenzamide

Last step is the coupling reaction for amide to generate multi-functional antidepressant with 2-aminobenzamide (**16-S**) (**Scheme 1.8**). In terms of this coupling reaction for amide, several paper introduced the amide coupling reaction in the presence of 1,1'-carbonyldiimidazole (CDI), 4-dimethylaminopyridine (DMAP)[45] or CDI, TFA[24,44] as coupling agents. But, the product was difficult to isolate from this reaction and was not

pure enough to carry out further experiment. Therefore, amide coupling reaction with CDI was unsuccessful to synthesize **16-S**. This might be because the secondary amine would be nucleophilic enough to react with CDI intermediates. An alternative approach for the synthesis of **16-S** would be an amide coupling reaction with hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC).[55] This new coupling reaction with HOBt and EDC was performed to generate **16-S**. This product 16-S required purification by column chromatography (SiO_2, EA 100%) followed by preparative TLC and was obtained in 39% yield. These studies showed that the optimum approach for the synthesis of **16-S** was the sequence of reductive amination with $Na(OAc)_3BH$ and amide coupling reaction with HOBt and EDC. In addition, based on this procedure, **16-R** enantiomer was synthesized as well in 37% yield.

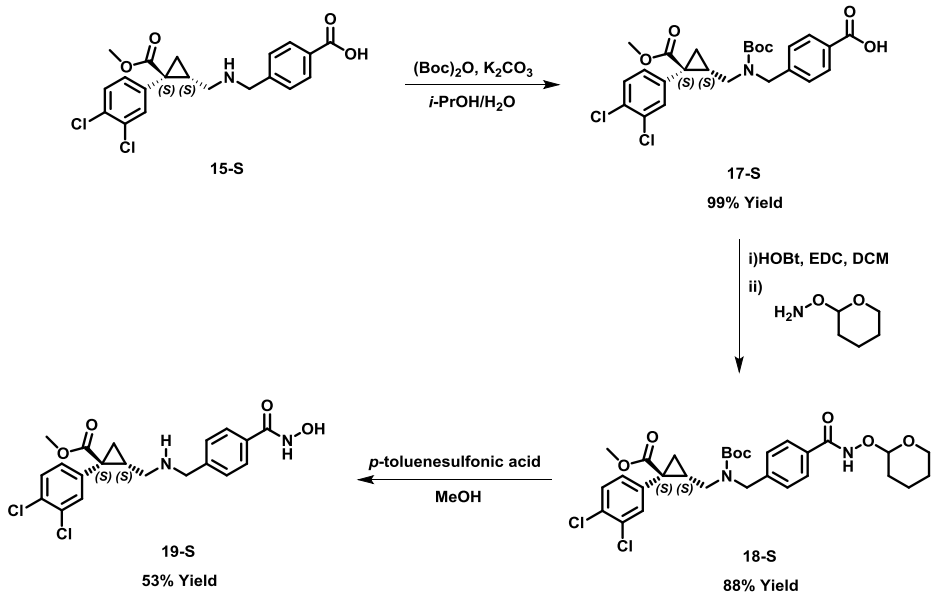


Scheme 1.8. Synthesis of multi-functional antidepressant with 2-aminobenzamide

1.2.1.5. Synthesis of Multi-functional Antidepressant with Hydroxamic Acid

The synthesis of another multi-functional antidepressant with hydroxamic acid (**19-S**) is shown in **Scheme 1.9**. First, this desired acid (**15-S**) was *N*-protected using di-*tert*-butyl dicarbonate in *i*-PrOH/H_2O with K_2CO_3 giving acid **17-S** in 99% yield.[21] Second, this *N*-protected acid (**17-S**) was *O*-protected by condensation reaction with *O*-(tetrahydro-2H-pyran-2yl)hydroxylamine via the mixed anhydride in the presence of

EDC and HOBt to give the protected *N*-hydroxybenzamide derivative (**18-S**).[21, 56, 57] This **18-S** was finally deprotected by *p*-toluenesulfonic acid to give **19-S** in 53% yield.[58] In addition, based on this procedure, **19-R** enantiomer was synthesized as well in 54% yield.



Scheme 1.9. Synthesis of multi-functional antidepressant with hydroxamic acid

1.2.2. Biological Analysis

1.2.2.1. *In Vitro* Data for HDACI Activity

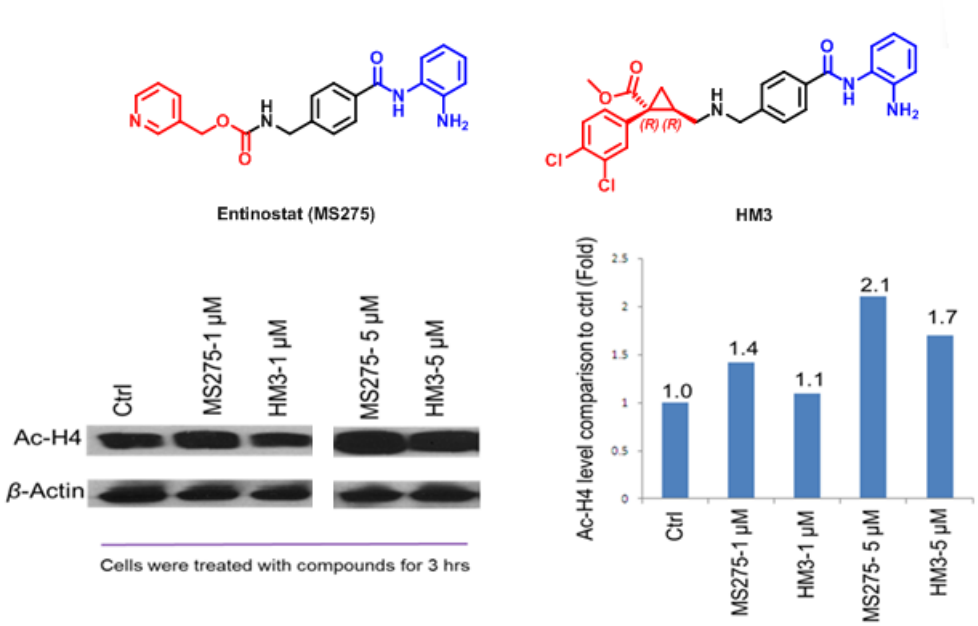


Figure 1.11. Effects of **HM3** and **MS-275** (3 hrs) for HDACI activity

Considering the clinical importance of this study, the multi-functional antidepressant compound with 2-aminobenzamide **HM3** (**16-R**) was sent to Dr. Shim's laboratory for *in vitro* testing for HDACI activity using the 9L rat glioma cell line as a model. All *in vitro* studies were performed in Dr. Shim's laboratory at Winship Cancer Institute. Western blot analyses were performed to detect the effects of **HM3** (1 µM or 5 µM, 3 hrs) on histone H4 acetylation, a well characterized HDACI target. **MS-275** (1 µM or 5 µM, 3 hrs), a well-known HDACI, was used as a positive control. Data depicted in **Figure 1.11** show that both **MS-275** and **HM3** were able to increase histone H4

acetylation. In addition, **MS-275** yielded a signal slightly higher than **HM3** (Western blot analyses were performed with specific antibodies for histone H4 acetylation as well as for *β*-actin. *β*-Actin is used as a loading control, and reported as fold change compared with control underneath each band; Control=DMSO). This data showed that **HM3** has HDAC inhibitory properties that can be used for antidepressants.

1.2.2.2. *In Vivo* Data for Anti-inflammation Activity

In addition, for the clinical study, the anti-inflammation activity was performed with multi-functional antidepressant compounds with hydroxamic acid **HM3a-R** (**19-R**) and **HM3a-S** (**19-S**) since inflammation causes several harmful stimuli such as irritants, damaged cells, and thermal or mechanical injury of homeostasis[59, 60] and hydroxamic acids are a class of compound with significant biological importance as strong metal chelators for antibacterial, anti-inflammatory and anti-asthmatic behavior.[61-63] Dr. Shim's laboratory at Winship Cancer Institute performed *in vivo* testing for anti-inflammation activity using the xylene-induced mouse ear edema method.[64] Adult Swiss albino mice (~ 20g) were randomly selected. And then, hydroxamic acid compounds **HM3a-R** (**19-R**) or **HM3a-S** (**19-S**) were injected into mice. After 30 min, mice treated 30 μl of xylene on the anterior and posterior surfaces of the right ear lobe, the left ear was considered as control. One hour later, two ear punches (6-8 mm diameter) were taken from mice for checking the ear weight, and the percentage of ear edema was calculated based on the weight of another ear without xylene. Data depicted in **Figure 1.12** shows that both **HM3a-R** and **HM3a-S** were able to suppress xylene-induced ear edema in mice. In addition, this data said that **HM3a-R** (**19-R**) was more effective than **HM3a-S** (**19-S**)

against xylene-induced ear inflammation. The observation that one enantiomer of **19** is more effective than the other is an indication that the effect of these compounds is due to some form of specific binding.

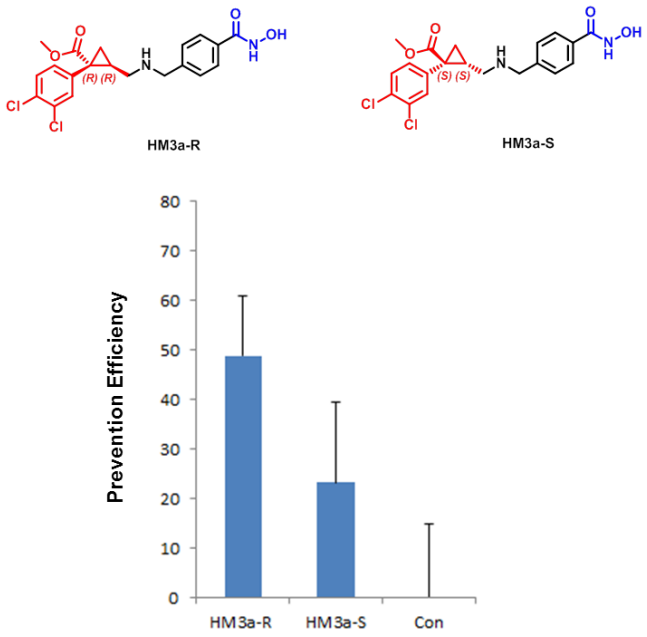


Figure 1.12. Effects of **HM3a-R** and **HM3a-S** for anti-inflammation activity (I.P. injection; does 10 mg/Kg)

1.2.2.3. *In Vivo* Data for Antidepressant Activity (Tail Suspension Test)

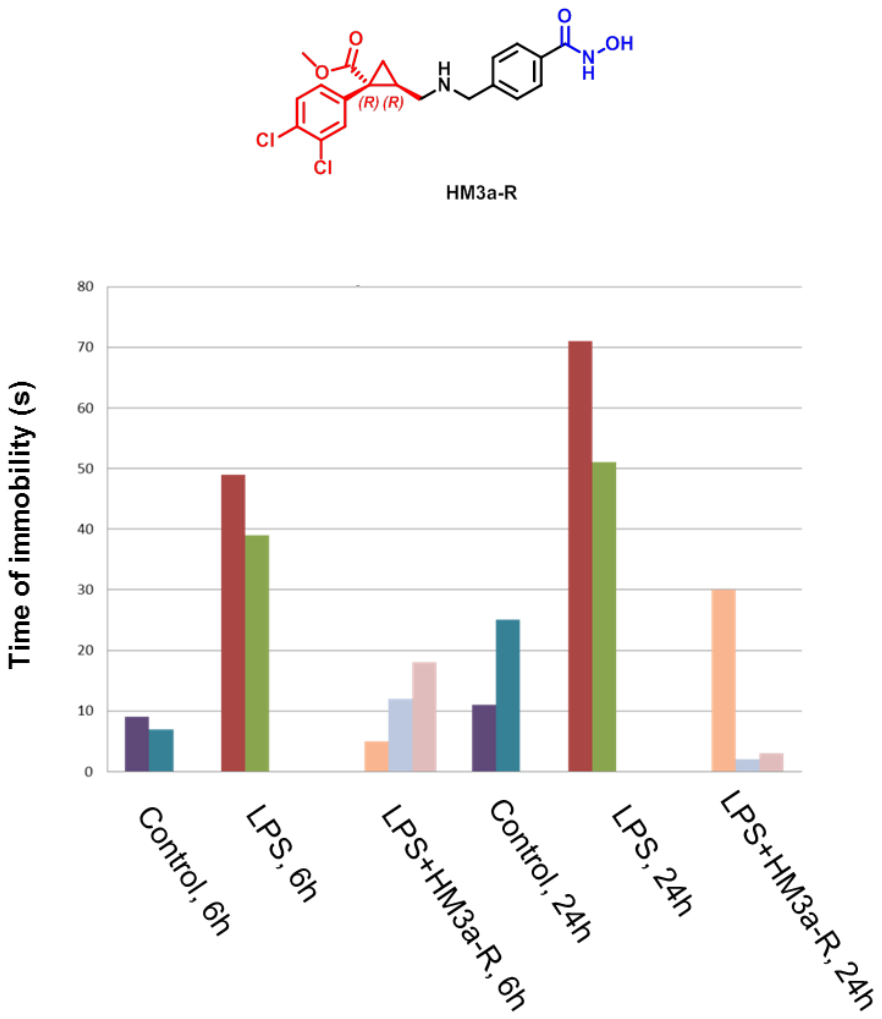


Figure 1.13. Effect of **HM3a-R** for antidepressant activity (I.P. injection; does 10 mg/Kg; Each bars indicate a singlicate data. e.g. Control and LPS were carried out in duplicate, and LPS+**HM3a-R** was carried out in triplicate)

The tail suspension test (TST) was performed as a preliminary test for assessing antidepressant activity in mice because it is an established tool for screening of potential

antidepressant materials. The test is based on the fact that animals subjected to the short term, inescapable stress of being suspended by their tail, would develop an immobile posture.[65] The extent of the immobility correlates with level of depression. An animal subjected to an antidepressant will tend to be more mobile in this test. Using this TST method, the *in vivo* test for antidepressant activity was performed with the proposed multi-functional antidepressant compound with **HM3a-R** (**19-R**). The reference compound lipopolysaccharide (LPS) was used to generate the depression model in the mice because LPS is an endotoxin that causes depression activity. **Figure 1.13** shows the effects of **HM3a-R** antidepressants with hydroxamic acid. Control and LPS condition did not significantly change the immobility time at any of the time tested. However, **HM3a-R** significantly decreased the duration of immobility when **HM3a-R** exists even in the presence of LPS. In conclusion, these preliminary results showed that time of immobility decreased after adding **HM3a-R**. Therefore, the results of this initial screen are an indication that **HM3a-R** has antidepressant activity, and also the enantiomerically enriched (*R, R*) cyclopropane aldehyde with hydroxamic acid is a crucial part of chemical structures for antidepressant.

1.2.2.4. *In Vivo* Data for Antidepressant Activity (Forced Swim Test)

The forced swim test (FST) was performed to evaluate the antidepressant potential of **HM3a-R**, in this study. This is a relatively simple test, and involves taking the mice, after they have been treated, and placing them from their housing chamber into a beaker filled with water at a temperature of 25 +/- 0.5 degrees Celsius. The mice, once

they are placed into this beaker, will float and will attempt to swim in an effort to swim out of the beaker. Studies have shown that mice that spend less time swimming (i.e. more time spent immobile and are simply floating in the beaker) correlate to social defeat/stress, and are linked to depressive behaviors. Thus, we can compare two groups of mice and those who spend more time swimming (i.e. less time spent immobile) correlate with antidepressant behavior compared to mice that spend less time swimming (i.e. more time spent immobile). For this study, we had 8 pairs of control/**HM3a-R**-treated 16 mice that were subject to FST. Mice that received **HM3a-R** were injected intraperitoneally (I.P.) with 100 μL of **HM3a-R** (control mice received 100 μL DMSO IP injection) at a concentration of 75mg/kg and were treated 6 hours prior to conducting FTS, because in our experience, a 6 hour treatment period showed the greatest effect. Two 2-liter beakers were filled approximately 75% with water at 25 +/- 0.5 degrees Celsius. Two camcorders were placed, respectively, directly across from each beaker and every trial was recorded in this manner. While the beakers were adjacent to each other, they were encapsulated by cardboard boxes to prevent the mice from any visual distractions that might perturb the results. Each mice were assigned a letter from A-P by one lab member and their identity with respect to treatment group were blinded to the second lab member analyzing the results. The lab member assigning the letters for the mice took the mice in pairs (i.e. one control mouse and one treated mouse) and simultaneously placed them into their two respective beakers. Each pair of mice was placed into the beaker for 10 minutes and was then placed back into their housing chamber where the next control-treated mice pair was placed. This was done for all 8 control-treated pairs.

After completion of the test, a second lab member who was blinded to the identities of the control-treated mice pairs calculated the time spent immobile for each mice pair. This was done by taking a stopwatch and summing up the time intervals in which the mice were immobile (i.e. only floating and not actively swimming. "Actively swimming" is defined as using both hindlegs in a manner that is more proactive than wading or floating). For each 10-minute trial, the summed time spent immobile were divided into 2-minute intervals (i.e. minutes 0-2, minutes 2-4, minutes 4-6, minutes 6-8, minutes 8-10). After calculating the time spent immobile for all 16 mice, the second lab member was unblinded to the identity of the mice. The time spent immobile for all 8 control mice and all 8 treated mice were averaged and plotted for minutes 2-8 and minutes 2-10, respectively. These *in vivo* results indicate that compared to control mice, **HM3a-R** treated mice spent significantly less time immobile (i.e. were more actively swimming) (**Figure 1.14**). This correlates to the **HM3a-R** treated mice demonstrating more antidepressant behavior than their control pairs. Results from this study support **HM3a-R**'s antidepressant effect in a depressive mouse model. Therefore, the results of this initial screen are an indication that **HM3a-R** has antidepressant activity, and also the enantiomerically enriched (*R, R*) cyclopropane aldehyde with hydroxamic acid is a crucial part of chemical structures for antidepressant.

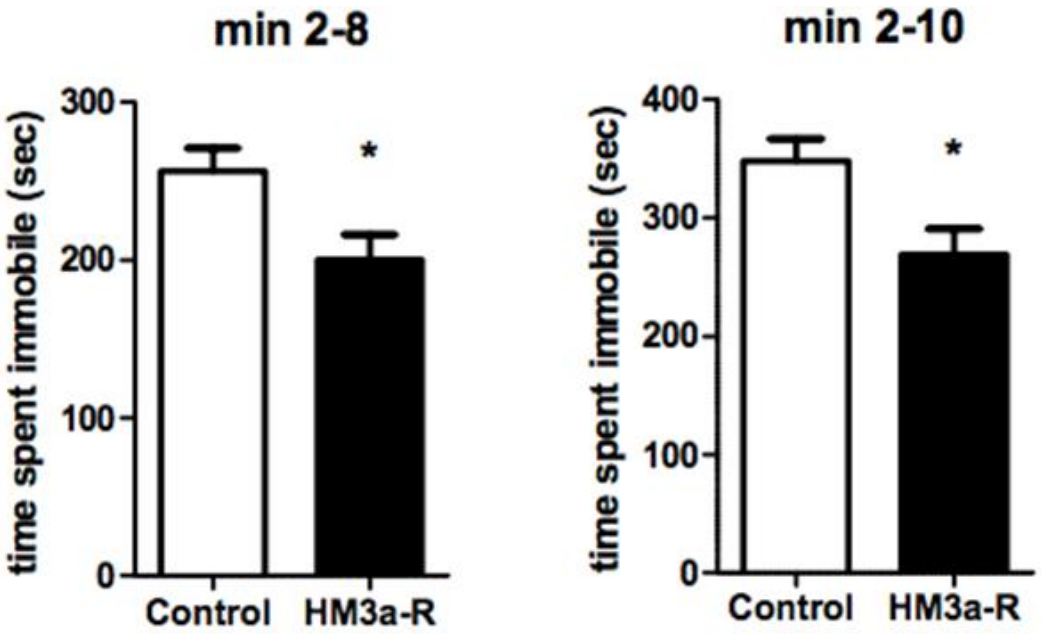


Figure 1.14. Effect of **HM3a-R** for antidepressant activity via forced swim test

1.3. CONCLUSIONS

In summary, multi-functional antidepressants with HDAC and monoamine reuptake inhibitors were designed based on enantiopure milnacipran analogues that could potentially treat neuropathic pain by controlling monoamine reuptake in nerve cell, and hydroxamic acid/ 2-aminobenzamide chelator analogues that could inhibit histone deacetylation by chelating Zn^{2+} ions. These compounds were synthesized by utilizing the enantioselective cyclopropanation with carbenoids derived from donor-acceptor diazo compound in the presence of Rh_2(*S*-DOSP)$_4$ or Rh_2(*R*-DOSP)$_4$ as the key step. An optimized synthetic scheme was developed to convert the initial cyclopropane to the potential multifunctional antidepressants **19-R** and **19-S**.

Initial *in vitro* studies showed that **16-R** has a HDAC inhibitory ability. The *in vivo* studies described herein showed that **19-R** showed positive activity in both an anti-inflammation and antidepressant test. The results demonstrate that the multifunctional antidepressant **19-R**, which contains the enantiomerically enriched (*R, R*) cyclopropane aldehyde with hydroxamic acid, does retain antidepressant activity and would be worth further biological evaluation.

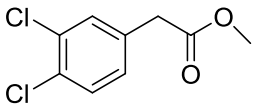
1.4. EXPERIMENTAL SECTION

General Methods

All experiments were performed under anhydrous conditions in an atmosphere of argon except where stated, using oven-dried glassware. Hexane, pentane, THF, toluene, acetonitrile, and methylenechloride were dried by a solvent purification system. Unless otherwise noted, all other reagents were obtained from commercial sources and used as received. ^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded at 400 MHz on an INOVA-400, or Varian-400. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ H 7.26 for the residual protons in $CDCl_3$, 3.31 in CD_3OD, or 2.50 in DMSO), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, etc), coupling constant (J/Hz), integration. Coupling constants were taken directly from the spectra and are uncorrected. ^{13}C NMR spectra were recorded at 100 MHz, and all chemical shift values are reported in ppm on the δ scale, with an internal reference of δ C 77.16 for $CDCl_3$, 49.00 for CD_3OD, or 39.52 for DMSO. Melting points were measured with electrothermal melting point apparatus model 1001D and by Barnstead International (Volts: 120, AMPs: 1.6, Watts: 200, Hz: 50/60, Phase: 1)

and were uncorrected. Optical rotations were measured on a PerkinElmer Model 341 Polarimeter. Infrared (IR) spectra were collected on a Nicolet iS10 FT-IR spectrometer. High Resolution Mass spectra (HRMS) were taken on a Thermo Finnigan LTQ-FTMS spectrometer with APCI, ESI or NSI, and Liquid Chromatography Mass spectra (LC-MS) was measured on Agilent Technologies 6120 Quadrupole LC/MS spectrometer. Thin layer chromatographic analysis was performed with silica gel plates, visualizing with UV light. Flash column chromatography was performed on silica gel 60 Å (230-400 mesh). Analytical enantioselective chromatographies were measured on Varian Prostar instrument and used isopropanol/hexane as gradient.

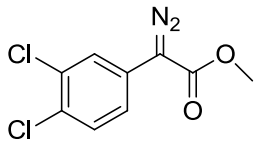
Methyl 2-(3,4-dichlorophenyl)acetate (2)



Methyl 2-(3,4-dichlorophenyl)acetate (**2**) was prepared by known method.[32] 3,4-dichlorophenylacetic acid (5.4 g, 26.8 mmol) and methanol (50 mL) was added into 100 mL round bottom flask with a stir bar. The reaction flask was cooled down to 0 ^{o}C, and then acetyl chloride (4.2 g, 53.7mmol) was added dropwise at 0 ^{o}C. The reaction was stirred at RT overnight. The reaction mixture was poured into saturated ammonium chloride solution and extracted with diethyl ether (3 x 40 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The material was taken on to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 6.0 Hz, 1H), 7.39 (s, 1H),

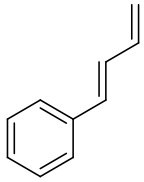
7.14 (dd, *J* = 8.4, and 2.0 Hz, 1H), 3.71 (s, 3H), 3.59 (s, 2H). The spectroscopic data matches what was previously reported in the literature.[32]

Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (3)



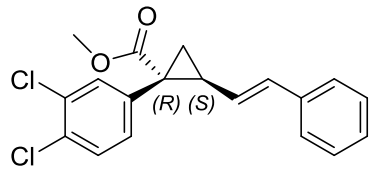
Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (**3**) was prepared by known method.[32] **2** and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (7.3 g, 30.4 mmol) were dissolved in acetonitrile (20 mL) and cooled to 0 ^{o}C. 1,8-Diazabicyclo-[*5,4,0*]-undec-7-ene (DBU) (7.4 g, 48.7 mmol) in acetonitrile (10 mL) was added dropwise at 0 ^{o}C, and the reaction was stirred at RT overnight. The reaction mixture was poured into saturated ammonium chloride solution and extracted with diethyl ether (2 x 100 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The product was purified by flash chromatography (silica gel, 3:1 hexanes:diethyl ether) to obtain an orange solid (4.8 g, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 2.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.29 (dd, *J* = 8.4, and 2.0 Hz, 1H), 3.89 (s, 3H). The spectroscopic data matches what was previously reported in the literature.[32]

(*E*)-Buta-1,3-dienylbenzene (5)



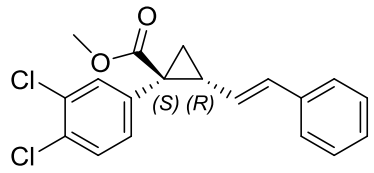
(*E*)-Buta-1,3-dienylbenzene (**5**) was prepared by known method.[32] Methyltriphenylphosphine bromide (17.9 g, 50 mmol) and THF (100 mL) was added into 500 mL round bottom flask with a stir bar. The reaction flask was cooled down to 0 ^{o}C, and then potassium *tert*-butoxide (8.4 g, 75 mmol) was added. The reaction was stirred for 5h at 0 ^{o}C under an atmosphere of argon. (*E*)-3-phenylacrylaldehyde (6.6 g, 170 mmol) in THF (14 mL) was added dropwise over 1h, and the reaction was stirred overnight. The reaction mixture was poured into H_2O (200 mL) and extracted into pentane (3 x 40 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$. Hexane (100 mL) was added to the combined organic layers to precipitate triphenyl phosphine oxide. The reaction mixture was filtered through silica gel and the solvent was removed under reduced pressure. The product was purified by Kugelrohr distillation (85 ^{o}C) to obtain a colorless liquid (3.5 g, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.31 (t, 2H), 7.22 (t, 1H), 6.78 (dd, *J* = 15.6, and 10.4 Hz, 1H), 6.60 - 6.48 (m, 2H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* = 10.0 Hz, 1H). The spectroscopic data matches what was previously reported in the literature.[32]

Methyl (*1R,2S*)-1-(3,4-dichlorophenyl)-2-((*E*)-styryl)cyclopropane-1-carboxylate (6)



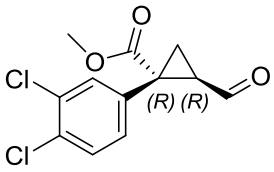
Methyl (*1R,2S*)-1-(3,4-dichlorophenyl)-2-((*E*)-styryl)cyclopropane-1-carboxylate (**6**) was prepared by known method.[32] To an oven dried 100 mL round bottom flask with a stir bar was added (*E*)-buta-1,3-dienylbenzene (781 mg, 6 mmol), Rh_2(*S*-DOSP)$_4$ (28 mg, 1% mol), and dry, degassed toluene (4 mL). The reaction vessel was cooled to -78 ^oC in a dry ice and acetone bath. The diazo compound **3** (490 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2h at -78 ^oC under an atmosphere of argon. The reaction was stirred and allowed to warm to room temperature overnight. The solvent was removed under reduced pressure and the product was purified by flash chromatography (silica gel, 8:1 hexanes:ethyl acetate) to obtain 94% yield (654.2 mg). HPLC analysis: 91% ee (OD-H column, 1% 2-propanol in hexanes, 1.0 mL/min, t_R = 6.58 (major) and 9.77 (minor) min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.26 - 7.12 (m, 6H), 6.61(d, *J* = 15.6 Hz, 1H), 5.19 (dd, *J* = 16.0, and 9.6 Hz, 1H), 3.66 (s, 3H), 2.78 (ddd, *J* = 9.2, 9.2, and 6.8 Hz, 1H), 2.09 (dd, *J* = 8.8, and 4.8 Hz, 1H), 1.44 (dd, *J* = 6.8, and 4.8 Hz, 1H). The spectroscopic data matches what was previously reported in the literature.[32]

Methyl (*1S,2R*)-1-(3,4-dichlorophenyl)-2-((*E*)-styryl)cyclopropane-1-carboxylate (8)



Synthesis of the enantiomer of **8** was carried out using Rh_2(*R*-DOSP)$_4$ (1% mol) as catalyst in the same reaction conditions as described above to obtain 99% yield. HPLC analysis: 93% ee (OD-H column, 1% 2-propanol in hexanes, 1.0 mL/min, t_R = 6.01 (minor) and 8.24 (major) min). NMR spectroscopic data is same as **6**.

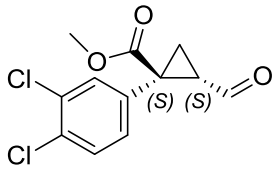
Methyl (*1R,2R*)-1-(3,4-dichlorophenyl)-2-formylcyclopropane-1-carboxylate (7)



Methyl (*1R,2R*)-1-(3,4-dichlorophenyl)-2-formylcyclopropane-1-carboxylate (**7**) was prepared by known method.[32] In a 100 mL round bottom flask with a stir bar, **6** (345.7 mg, 1 mmol) was dissolved in dichloromethane (20 mL) and flushed with argon. This solution was then cooled to -78 ^{o}C through an acetone and dry ice bath. Ozone was bubbled through the solution until a blue color persisted, and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine (262.3 mg, 1 mmol) was added to quench the reaction and stirred overnight while warming to room temperature. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (silica gel, 8:1 hexanes : ethyl acetates) to give the product as a colorless

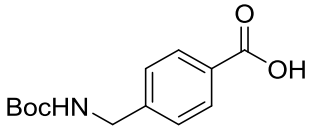
oil (268 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 5.6 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.42 (s, 1H), 7.13 (dd, *J* = 8.4, and 2.4 Hz, 1H), 3.69 (s, 3H), 2.81 (ddd, *J* = 8.8, 6.0, and 6.0 Hz, 1H), 2.15 (dd, *J* = 8.8, and 4.8 Hz, 1H), 2.09 - 2.05 (m, 1H). The spectroscopic data matches what was previously reported in the literature.[32]

Methyl (*1S,2S*)-1-(3,4-dichlorophenyl)-2-formylcyclopropane-1-carboxylate (9)



Synthesis of the enantiomer of **9** was carried out using **8** as starting material in the same reaction conditions as described above to obtain in 93% yield of product. NMR spectroscopic data is same as **7**.

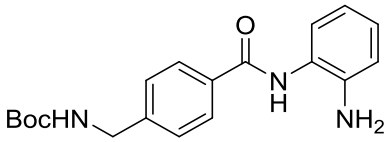
4-(((*tert*-Butoxycarbonyl)amino)methyl)benzoic acid (11)



4-(((*tert*-Butoxycarbonyl)amino)methyl)benzoic acid (**11**) was prepared by know method.[42,43] 4-(Aminomethyl)benzoic acid (2.0 g, 13.1 mmol, 1 eq) was dissolved in dioxane (32 mL) and water (16 mL) at RT. 1M NaOH (aq) (16 mL, 15.7 mmol, 1.2 eq) was added and the solution was cooled to 4 °C in an ice bath. Di-*tert*-butyl dicarbonate (3.1 g, 14.4 mmol, 1.1 eq) was added and the solution was allowed to warm slowly to

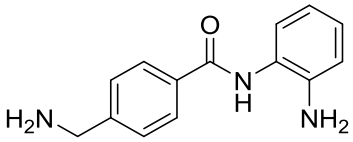
room temperature. After 15 hours, the dioxane was removed under reduced pressure. The remaining aqueous solution was acidified to pH 2 with 10% $KHSO_4$ (aq) and extracted with EA. The organic layer was dried over Na_2SO_4, filtered and condensed to give **11** as a white solid (3.2 g, 95%). ^{1}H NMR (400 MHz, DMSO) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.48 (t, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.18 (d, *J* = 6.4 Hz, 2H), 1.39 (s, 9H). The spectroscopic data matches what was previously reported in the literature.[42,43]

***tert*-Butyl (4-((2-aminophenyl)carbamoyl)benzyl)carbamate (11-a)**



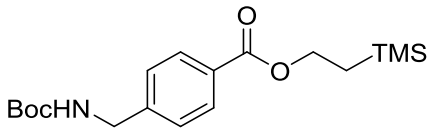
tert-Butyl (4-((2-aminophenyl)carbamoyl)benzyl)carbamate (**11-a**) was prepared by known method.[44,45] Into **11** (927.5 mg, 3.7 mmol, 1 eq) in anhydrous tetrahydrofuran (THF, 22 mL) was added 1,1'-carbonyldiimidazole (719.9 mg, 4.44 mmol, 1.2 eq) at RT. The mixture was heated to reflux for 3 h. A mixture of 1,2-phenylenediamine (600.2 mg, 5.55 mmol, 1.5 eq) and 4-dimethylaminopyridine (DMAP, 90.4 mg, 0.74 mmol, 0.2 eq) in THF (60 mL) was added dropwise into the resulting clear solution at 40 ^{o}C. After the mixture was stirred for 2 h, the solvent was removed. The residue was triturated with water and filtered to give a white-yellowish solid (543.8 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.10 (t, 1H), 6.87 - 6.83 (m, 2H), 4.39 (d, *J* = 6.0 Hz, 2H), 1.47 (s, 9H). The spectroscopic data matches what was previously reported in the literature.[44,45]

4-(Aminomethyl)-*N*-(2-aminophenyl)benzamide (11-b)



Trifluoroacetic acid (2.4 mL, 31.8 mmol, 20 eq) was added dropwise to a stirred solution of **11-a** (543.8 mg, 1.59 mmol, 1 eq) in CH_2Cl_2 (20 mL). The mixture was stirred at RT for 2 h, evaporated to dryness under reduced pressure, and coevaporated twice with absolute EtOH (20 mL × 2) to afford **11-b** as a brown solid (quantitative). mp 97 - 100 ^{o}C; IR (neat) ν (cm^{-1}) 2915, 2629, 1669, 1531, 1194, 1137, 723; ^{1}H NMR (400 MHz, DMSO) δ 9.96 (s, 1H), 8.29 (brs, 2H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.10 (t, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.86 (t, 1H), 4.15 (d, *J* = 5.6 Hz, 2H). The spectroscopic data matches what was previously reported in the literature.[66]

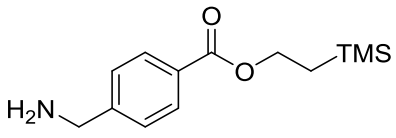
2-(Trimethylsilyl)ethyl 4-(((*tert*-butoxycarbonyl)amino)methyl)benzoate (11-a')



In A mixture of **11** (2.5 g, 22.0 mmol, 1.0 eq), 2-(trimethylsilyl)ethanol (3.9 g, 33.0 mmol, 1.5 eq) and 4-(dimethylamino)pyridine (268.9 mg, 2.2 mmol, 0.1 eq in DCM (26 mL)) were stirred in DMF (22 mL) and DCM (88 mL) and cooled down at 0 ^{o}C. Then,

dicyclohexyl carbodiimide (5.0 g, 24.2 mmol, 1.1 eq in DCM (22 mL)) was added into the solution, stirred overnight for 18 hrs, and allowed to warm to RT over that time. The precipitate was removed by filteration, washing with diethyl ether. The filterate was concentrated to give the crude product, which was further purified by column chromatography (SiO_2, Hexane:EA = 3:1) to give **11-a'** as a white powder (5.7 g, 75%). mp: 63 - 64 ^oC; IR (neat) ν (cm^{-1}): 3364, 2954, 1713, 1515, 1270, 1248, 1171, 1100, 837, 755; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.39 (m, 4H), 1.48 (s, 9H), 1.11 (ddd, *J* = 7.2, 4.4, and 4.0 Hz, 2H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 156.1, 144.2, 130.0, 129.8, 127.3, 79.9, 63.4, 44.5, 28.5, 17.5, 1.3; HRMS (ESI): *m/z* calcd for $C_{12}H_{18}NO_4Si^+$ ($M+H^+$): 268.1005, found: 268.0997.

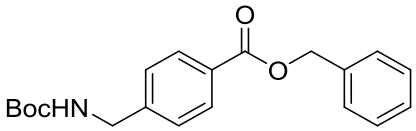
2-(Trimethylsilyl)ethyl 4-(aminomethyl)benzoate (11-b')



Trifluoroacetic acid (12.4 mL, 162.0 mmol, 10 eq) was added dropwise to a stirred solution of **11-a'** (5.7 g, 16.2 mmol, 1 eq) in CH_2Cl_2 (90 mL). The mixture was stirred at RT for 2 h, evaporated to dryness under reduced pressure, and coevaporated twice with absolute EtOH (180 mL × 2) to afford **11-b'** as a brown solid (quantitative). mp 136 - 140 ^oC; IR (neat) ν (cm^{-1}) 2954, 1673, 1315, 1201, 1181, 1137, 838; ^1H NMR

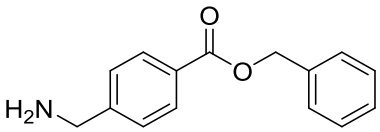
(400 MHz, DMSO) δ 8.39 (brs, 2H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 4.38 (t, 2H), 4.13 (d, *J* = 4.8 Hz, 2H), 1.07 (t, 2H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, DMSO) δ 165.4, 139.2, 138.8 (impurity), 130.8 (impurity), 130.0, 129.5 (impurity), 129.3, 129.1, 128.9 (impurity), 62.9, 41.9, 16.8, 1.4; HRMS (ESI): *m/z* calcd for $C_{13}H_{22}NO_2Si^+$ ($M+H^+$): 252.1420, found: 252.1412.

Benzyl 4-(((*tert*-butoxycarbonyl)amino)methyl)benzoate (12)



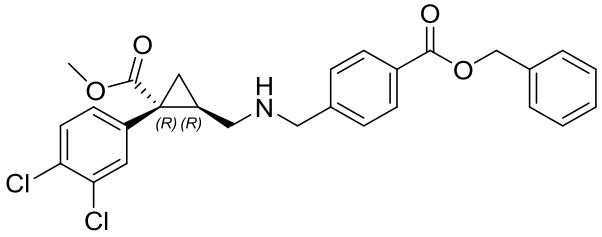
A mixture of **11** (2.7 g, 10.5 mmol, 1.0 eq), benzyl bromide (1.8 g, 10.5 mmol, 1.0 eq) and Cs_2CO_3 (3.8 g, 11.6 mmol, 1.1 eq) in DMF (20 mL) was stirred at RT for 1 h. Then the solution was poured into water (20 mL), extracted with EA (30 mL × 2), and dried over $MgSO_4$. The organic layer was concentrated to give the crude product, which was further purified by column chromatography (SiO_2, Hexane: EA = 4:1) to give **12** as a white powder (2.9 g, 81%). mp 74 - 77 ^{o}C; IR (neat) ν (cm^{-1}) 3362, 2976, 1694, 1507, 1366, 1267, 1164, 1099, 752, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.47 - 7.34 (m, 7H), 5.37 (s, 2H), 4.37 (d, *J* = 6.0 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 156.1, 144.6, 136.2, 130.2, 129.3, 128.8, 128.4, 128.3, 127.4, 80.0, 66.9, 44.5, 28.6; HRMS (ESI): *m/z* calcd for $C_{20}H_{23}NO_4Na^+$ ($M+Na^+$): 364.1525, found: 364.1528.

Benzyl 4-(aminomethyl)benzoate (13)



Trifluoroacetic acid (6.4 mL, 83.0 mmol) was added dropwise to a stirred solution of **12** (2.8 g, 8.3 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at RT for 2 h, evaporated to dryness under reduced pressure, and coevaporated twice with absolute EtOH (100 mL × 2) to afford **13** as a light yellow solid (quantitative). mp 115 - 117 ^oC; IR (neat) ν (cm^{-1}) 3427, 2891, 1670, 1273, 1200, 1182, 1130, 722; ^1H NMR (400 MHz, DMSO) δ 8.28 (brs, 2H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.49 - 7.34 (m, 5H), 5.36 (s, 2H), 4.14 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 166.3, 139.5, 136.1, 129.6, 129.5, 129.2, 128.6, 128.2, 128.0, 66.4, 41.9; HRMS (ESI): *m/z* calcd for $C_{15}H_{16}NO_2^+$ ($M+H^+$): 242.1181, found: 242.1199.

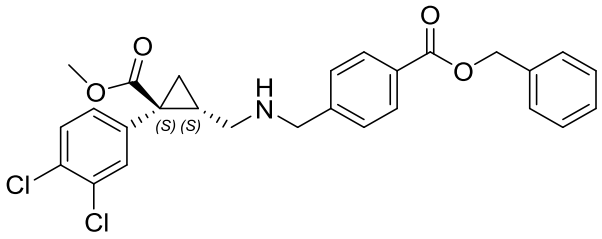
Benzyl 4-(((((*1R,2R*)-2-(3,4-dichlorophenyl)-2-(methoxycarbonyl)cyclopropyl)-methyl)-amino)methyl)benzoate (14-R)



In a 100 mL round bottom flask equipped with a magnetic stir bar, **7** (73.7 mg, 0.27 mmol, 1 eq.) was dissolved in THF (5 mL) and flushed with argon. This solution

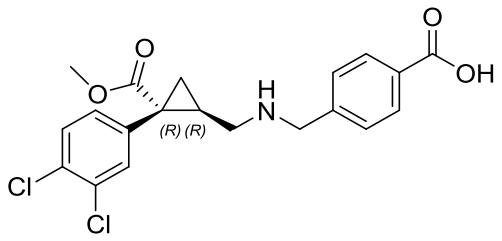
was treated with **13** (130.3 mg, 0.54 mmol in 5 mL THF, 2 eq.) and $Na(OAc)_3BH$ (86.9 mg, 0.41 mmol, 1.5 eq) and stirred at RT for 3 h under argon. After the allotted time had passed, the reaction was quenched with aqueous saturated $NaHCO_3$, and the product was extracted with EA. The EA extract was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, ethyl acetate: Hexane = 4:1) to give a colorless oil in 58% yield (77.9 mg). IR (neat) ν (cm^{-1}) 3317, 3032, 2950, 2822, 1714, 1474, 1378, 1267, 1173, 1097, 1030, 908, 752, 728, 696; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.35 (m, 7H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.15 (dd, *J* = 8.0, and 2.0 Hz, 1H), 5.37 (s, 2H), 3.78 (d, *J* = 13.6 Hz, 1H), 3.67 (d, *J* = 14.0 Hz, 1H), 3.63 (s, 3H), 2.27 (d, *J* = 6.8 Hz, 2H), 2.11 - 2.04 (m, 1H), 1.74 (dd, *J* = 9.2, and 4.4 Hz, 1H), 1.17 (dd, *J* = 6.8, and 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 166.5, 145.5, 136.3, 136.1, 133.2, 132.2, 131.7, 130.7, 130.2, 130.0, 129.1, 128.8, 128.4, 128.3, 128.0, 66.8, 53.7, 52.8, 49.5, 33.0, 28.6, 20.2; HRMS (ESI): *m/z* calcd for $C_{27}H_{26}Cl_2NO_4^+$ ($M+H^+$): 498.1239, found: 498.1241.

Benzyl 4-(((((*1S,2S*)-2-(3,4-dichlorophenyl)-2-(methoxycarbonyl)cyclopropyl)-methyl)-amino)methyl)benzoate (14-S)



Synthesis of the enantiomer of **14-S** was carried out using **9** as starting material in the same reaction conditions as described above to obtain in 59% yield of product. NMR spectroscopic data is same as **14-R**.

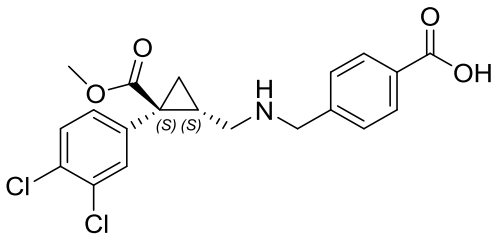
4-(((((*1R,2R*)-2-(3,4-dichlorophenyl)-2-(methoxycarbonyl)cyclopropyl)methyl)-amino)-methyl)benzoic acid (15-R)



A mixture of **14-R** (167.8 mg, 0.34 mmol, 1 eq) and Pd/C (10% wt, 3.6 mg, 0.034 mmol, 0.1 eq.) were dissolved in MeOH (30 mL). The solution was deoxygenated by purging with Ar for 10 min, and then this solution was hydrogenated at RT, and the progress of the reaction was monitored by TLC (Hex: EA = 1:8). The solid residues were removed by filtration over celite, and washed with MeOH. After filtration, the organic layer was evaporated to dryness to give the corresponding acids. Concentration *in vacuo* gave crude product, which was further purified by column chromatography (SiO_2, DCM: MeOH = 4:1) to obtain **15-R** as a white powder (116.5 mg, 85%). mp 161 - 165 ^{o}C; IR (neat) ν (cm^{-1}) 2915, 2629, 1669, 1531, 1194, 1137, 724; ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.29 (dd, *J* = 8.4, and 2.4 Hz, 1H), 4.16 (d, *J* = 4.4 Hz, 2H), 3.66 (s, 3H), 2.35 - 2.26 (m, 1H), 2.22 - 2.13 (m, 2H), 1.85 (dd, *J* = 8.4, and 5.2 Hz, 1H), 1.59 (dd, *J* = 6.4, and 5.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 174.6, 174.3, 141.5 (impurity),

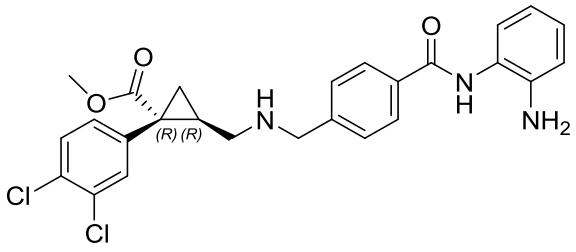
138.5, 138.2 (impurity), 136.8, 136.2, 134.5, 133.4, 133.1, 132.3, 131.7, 131.1, 130.8 (impurity), 130.5, 129.3 (impurity), 53.5, 52.3, 49.7, 34.2, 24.5, 21.5; LC-MS: *m/z* calcd for $C_{20}H_{20}Cl_2NO_4$ ($M+H^+$): 408.1, found: 408.1; HRMS (ESI): *m/z* calcd for $C_{20}H_{20}Cl_2NO_4$ ($M+H^+$): 408.0769, found: 408.0763.

4-(((((*1S,2S*)-2-(3,4-dichlorophenyl)-2-(methoxycarbonyl)cyclopropyl)methyl)-amino)-methyl)benzoic acid (15-S)



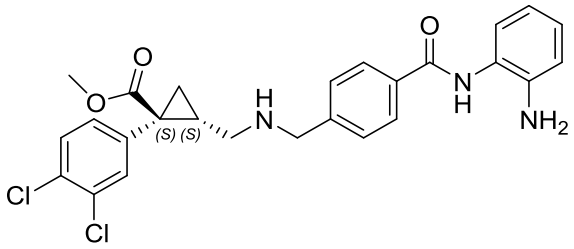
Synthesis of the enantiomer of **15-S** was carried out using **14-S** as starting material in the same reaction conditions as described above to obtain in 84% yield of product. NMR spectroscopic data is same as **15-R**.

Methyl (*1R,2R*)-2-(((4-((2-aminophenyl)carbamoyl)benzyl)amino)methyl)-1-(3,4-dichloro-phenyl)cyclopropane-1-carboxylate (16-R)



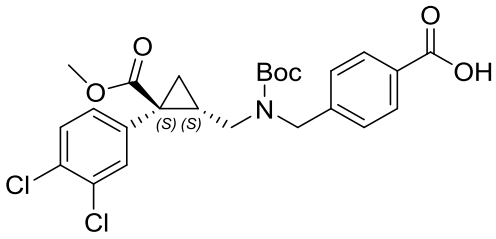
To a solution of 1,2-phenylenediamine (75.7 mg, 0.7 mmol, 2 eq.) in DMF (3 mL) was added **15-R** (144.3 mg, 0.35 mmol, 1 eq.), then 1-hydroxybenzotriazole (HOBt, 71.6 mg, 0.53 mmol, 1.5 eq.) and finally 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (EDC or WSC, 101.6 mg, 0.53 mmol, 1.5 eq.), and the mixture stirred at room temperature for 14 hrs. The reaction mixture was diluted with EtOAc (50 mL), washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated. This filtered yellow solution was purified by column chromatography (SiO_2, EA 100%; Biotage Isolera). The crude product was purified by preparative TLC on silica gel (SiO_2, EA: MeOH = 4:1), affording a **16-R** (68.5 mg, 39%). mp 146 - 148 ^oC; $[\alpha]_D^{20}$ = - 13.4 ^{o} (C 0.41, $CHCl_3$); IR (neat) ν (cm^{-1}) 3288, 2924, 1719, 1651, 1605, 1522, 1453, 1318, 1273, 748; ^1H NMR (400 MHz, CD_3OD): δ 7.92 (d, *J* = 10.8 Hz, 2H), 7.52 (d, *J* = 2.8 Hz, 1H), 7.43 - 7.38 (m, 2H), 7.32 - 7.29 (m, 1H), 7.23 (dd, *J* = 10.8, and 2.8 Hz, 1H), 7.17 (dd, *J* = 10.0, and 1.2 Hz, 1H), 7.09 (t, 1H), 6.92 (dd, *J* = 10.8, and 1.6 Hz, 1H), 6.77 (t, 1H), 3.81 (ddd, *J* = 32.8, 18.0, and 14.8 Hz, 2H), 3.62 (s, 3H), 2.59 (ddd, *J* = 38.0, 16.0, and 6.8 Hz, 1H), 2.20 - 2.09 (m, 2H), 1.74 (dd, *J* = 11.6, and 6.4 Hz, 1H), 1.36 (dd, *J* = 14.8, and 8.4 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 175.1, 168.6, 143.9, 139.2, 137.8, 134.5, 133.0, 132.6, 132.3, 131.4, 130.8, 129.9, 129.2, 128.7, 127.8, 125.4, 119.8, 118.9, 53.7, 53.2, 50.1, 34.1, 28.3, 21.1; LC-MS: *m/z* calcd for $C_{26}H_{26}Cl_2N_3O_3$ ($M+H^+$): 498.1, found: 498.1; HRMS (ESI): *m/z* calcd for $C_{26}H_{26}Cl_2N_3O_3$ ($M+H^+$): 498.1351, found: 498.1344.

Methyl (*1S,2S*)-2-(((4-((2-aminophenyl)carbamoyl)benzyl)amino)methyl)-1-(3,4-dichloro-phenyl)cyclopropane-1-carboxylate (16-S)



Synthesis of the enantiomer of **16-S** was carried out using **15-S** as starting material in the same reaction conditions as described above to obtain in 39% yield of product. NMR spectroscopic data is same as **16-R**.

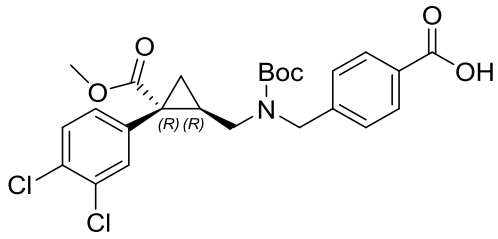
4-(((*tert*-Butoxycarbonyl)(((*1S,2S*)-2-(3,4-dichlorophenyl)-2-(methoxycarbonyl)-cyclopropyl)methyl)amino)methyl)benzoic acid (17-S)



15-S (87.0 mg, 0.21 mmol, 1 eq.) was dissolved in *i*-propanol (3 mL) and water (3 mL) at RT. K_2CO_3 (31.8 mg, 0.231 mmol, 1.1 eq.) and di-*tert*-butyl dicarbonate (59.6 mg, 0.273 mmol, 1.3 eq.) were added and the solution was stirred for 17h at RT. After 17 hours, the reaction mixture was concentrated under reduced pressure. This was dissolved in EA (10 mL), washed with 2N HCl (5 mL), and dried over Na_2SO_4. The organic layer was filtered and condensed to give **17-S** as colorless oil (105.7 mg, 99%). IR (neat) ν

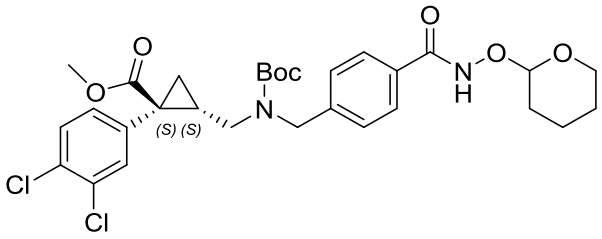
(cm^{-1}) 2977, 1722, 1691, 1476, 1411, 1249, 1170, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.37 - 7.03 (m, 5H), 4.60 - 4.36 (m, 2H), 3.61 (s, 3H), 2.47 - 2.37 (brm, 1H), 2.10 - 2.07 (m, 2H), 1.72 - 1.65 (brm, 1H), 1.40 (s, 9H), 1.29 - 1.26 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.5, 171.5, 155.7, 135.6, 133.1, 132.5, 132.0, 131.3, 131.2, 130.7, 130.4, 129.6 (impurity), 129.5 (impurity), 128.6 (impurity), 128.4 (impurity), 128.0, 127.7, 80.8, 52.9, 28.5, 26.4, 21.2, 14.4; HRMS (ESI): *m/z* calcd for $C_{25}H_{26}Cl_2NO_6$ ($M-H^+$): 506.1137, found: 506.1148.

4-(((*tert*-Butoxycarbonyl)(((*1R,2R*)-2-(3,4-dichlorophenyl)-2-(methoxycarbonyl)-cyclopropyl)methyl)amino)methyl)benzoic acid (17-R)



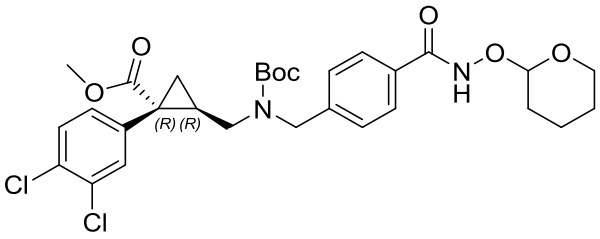
Synthesis of the enantiomer of **17-R** was carried out using **15-R** as starting material in the same reaction conditions as described above to obtain in 92% yield of product. NMR spectroscopic data is same as **17-S**.

Methyl (*1S,2S*)-2-(((tert-butoxycarbonyl)(4-(((tetrahydro-2H-pyran-2-yl)oxy)-carbamoyl) benzyl)amino)methyl)-1-(3,4-dichlorophenyl)cyclopropane-1-carboxylate (18-S)



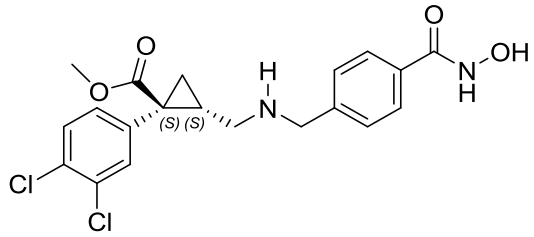
EDC (77.6 mg, 0.41 mmol, 1.5 eq.) and HOBt (47.4 mg, 0.35 mmol, 1.3 eq.) were added to a solution of **17-S** (139.4 mg, 0.27 mmol, 1.0 eq.) in CH_2Cl_2 (15 ml). The reaction mixture was stirred for 1 hr at room temperature and then NH_2OTHP (79.1 mg, 0.68 mmol, 2.5 eq.) was added. The solution was maintained for 8 h at 50°C. $NaHCO_3$ (1N) was added and the solution was extracted EA and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The resulting crude material was purified by column chromatography (Hex: EA 3:2) to give **18-S** as a white powder (147 mg, 89%). mp 70 - 73 ^oC; IR (neat) ν (cm^{-1}) 3239, 2948, 1723, 1614, 1475, 1248, 1166, 1150, 1033, 905, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.29 - 7.28 (brm, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.05 - 7.02 (brm, 1H), 5.07 (s, 1H), 4.70 - 4.23 (m, 2H), 3.99 (t, 1H), 3.64 - 3.60 (m, 1H), 3.59 (s, 3H), 2.40 - 2.34 (m, 1H), 2.11 - 2.07 (m, 1H), 1.88 - 1.81 (m, 4H), 1.71 - 1.58 (m, 5H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 172.3, 155.9, 135.6, 133.1, 132.5, 132.0, 131.2, 130.6, 130.4, 127.7 (two aromatic signals overlapping), 127.1, 102.9, 80.7, 62.9, 60.6, 52.9, 44.3, 28.5, 28.3, 26.4, 25.2, 21.2, 18.8, 14.4; HRMS (ESI): *m/z* calcd for $C_{30}H_{37}Cl_2N_2O_7$ ($M+H^+$): 607.1978, found: 607.1980.

Methyl (*1R,2R*)-2-(((tert-butoxycarbonyl)(4-(((tetrahydro-2H-pyran-2-yl)oxy)-carbamoyl) benzyl)amino)methyl)-1-(3,4-dichlorophenyl)cyclopropane-1-carboxylate (18-R)



Synthesis of the enantiomer of **18-R** was carried out using **17-R** as starting material in the same reaction conditions as described above to obtain in 93% yield of product. NMR spectroscopic data is same as **18-S**.

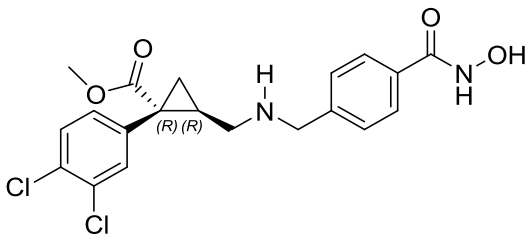
Methyl (*1S,2S*)-1-(3,4-dichlorophenyl)-2-(((4-(hydroxycarbamoyl)benzyl)amino)-methyl) cyclopropane-1-carboxylate (19-S)



p-Toluenesulfonic acid (32.3 mg, 0.17 mmol, 1.0 eq.) was added to a solution of **18-S** (100.8 mg, 0.17 mmol, 1.0 eq.) in MeOH (20 mL). The solution was stirred for 17 h at 80°C. The reaction mixture was monitored by TLC (Eluent: Hex: EA = 3:2). The reaction mixture was concentrated, extracted with saturated $NaHCO_3$ (50 mL) and EA (50 mL x 2). The organic layer was dried over Na_2SO_4, filtered and condensed. The crude

product was purified by preparative TLC on silica gel (SiO_2, EA: MeOH = 4:1), affording a **19-S** (37.0 mg, 53%). $[\alpha]_D^{20}$ = + 1.6 ^{o} (C 1.00, $CHCl_3$); IR (neat) ν (cm^{-1}) 3246, 2923, 2851, 1717, 1614, 1557, 1474, 1434, 1271, 1031, 898; ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 - 7.68 (m, 2H), 7.51 (s, 1H), 7.42 - 7.41 (m, 1H), 7.30 - 7.17 (m, 3H), 3.72 - 3.69 (m, 2H), 3.61 (s, 3H), 2.42 - 2.40 (brm, 1H), 2.08 - 2.06 (brm, 2H), 1.71 - 1.70 (brm, 1H), 1.35 - 1.31 (brm, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.3, 167.8, 144.4, 137.9, 134.5, 133.0, 132.5, 132.3, 131.3, 129.6, 128.9, 128.2, 54.1, 53.2, 34.1, 29.7, 28.9, 21.1; HRMS (ESI): *m/z* calcd for $C_{20}H_{21}Cl_2N_2O_4$ ($M+H^+$): 423.0878, found: 423.0874.

Methyl (*1R,2R*)-1-(3,4-dichlorophenyl)-2-(((4-(hydroxycarbamoyl)benzyl)amino)-methyl) cyclopropane-1-carboxylate (19-R)



Synthesis of the enantiomer of **19-R** was carried out using **18-R** as starting material in the same reaction conditions as described above to obtain in 54% yield of product. NMR spectroscopic data is same as **19-S**.

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Chapter 2: Development of New Phosphoric Acid Ligands as Organocatalysts for C-H Insertion

2.1. INTRODUCTION

2.1.1. C-H Insertion and Phosphoric Acid Ligands for Organocatalysis for Enantioselective C-H Insertion

The direct C-H insertion is one of the most powerful synthesis research areas for organic chemistry, and this has been used as a very useful tool for the rapid synthesis of natural products and pharmaceutical targets.[1, 2] Although many studies have been performed in this area, the reaction selectivity such as regioselectivity and enantioselectivity is still a challenge because most of the C-H bonds are usually strong bonds of similar energy.[3, 4] Until now, transition-metal catalyzed enantioselective C-H insertion has been shown to be effective; however, most of these reactions need complex chiral ligands and neighboring directing groups that can tolerate harsh reaction conditions.[5] Therefore, the development of effective and accessible catalysts should be studied further.

Recently, various organocatalysis studies have been successfully applied to realize the effective enantioselective C-H functionalization reactions, such as cross dehydrogenative coupling reactions, 1,5-hydride transfer reactions, β-functionalization of carbonyl compounds, and intra or intermolecular C-H insertion.[6, 7] For these reactions, a lot of papers have been researched by using phosphoric acid ligands as organocatalysts. One example of this type of reaction is the asymmetric cross dehydrogenative coupling

(CDC) reaction, which lead to an enantioselective C-H amination (**Figure 2.1**).[8] The reaction with a chiral phosphoric acid **catalyst 1**, oxidant **2**, and Na_3PO_4 converted the amide **1** to the tetracyclic product **3** in 81% yield and 94% ee.

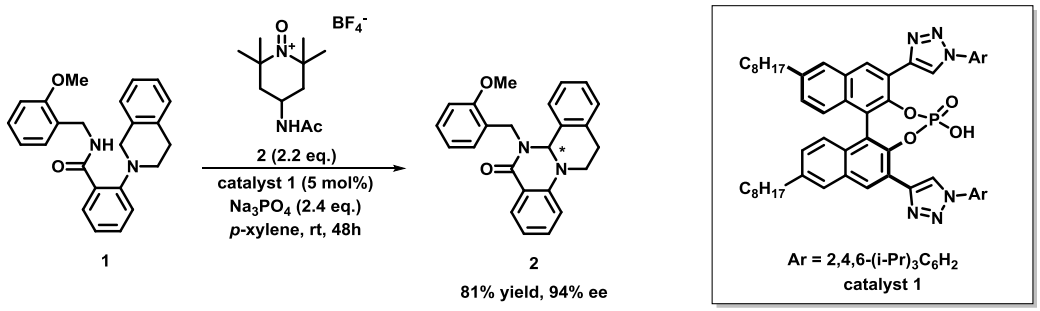


Figure 2.1. Asymmetric organocatalytic intramolecular cross dehydrogenative coupling reaction

A second example is the asymmetric organocatalytic 1,5-hydride transfer/ring closure reaction catalyzed by chiral phosphoric acid. Benzylidene malonate **4** was used as the substrate and the chiral phosphoric acid **catalyst 2** was used as the optimal organocatalyst at RT for this transformation. The asymmetric 1,5-hydride transfer/ring closure reaction by merging **catalyst 2** with Lewis acid such as $MgCl_2$ or $Mg(BF_4)_2$ gave substrate **5** (**Figure 2.2 a**).[9, 10] In addition to the synthesis of tetrahydroquinolines, **8** has been synthesized using a similar strategy. Chiral bisphosphoric acid **catalyst 3** was used as a catalyst for asymmetric 1,5-hydride transfer/ring closure reaction. The desired product **8** was afforded in up to 81% yield, 11:1 dr and 84% ee (**Figure 2.2 b**).[11]

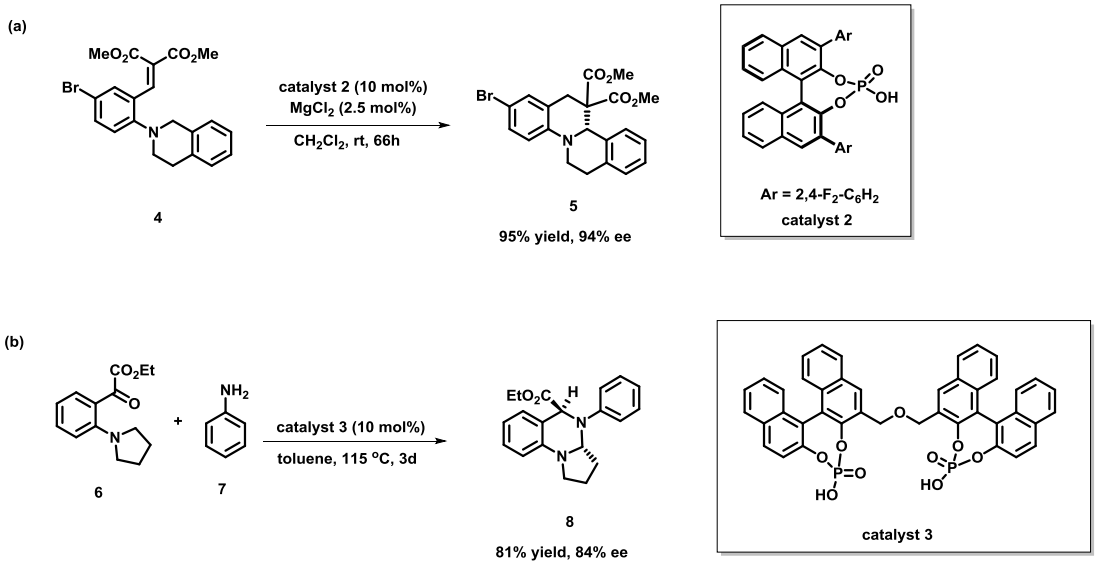


Figure 2.2. (a) Chiral phosphoric acid catalytic asymmetric 1,5-hydride transfer/ring closure reaction; (b) Chiral bisphosphoric acid catalytic asymmetric 1,5-hydride transfer/ring closure reaction

2.1.2. Design of New Phosphoric Acid Ligands for Organocatalysis for C-H Insertion

Recently, Davies's lab has synthesized various chiral dirhodium(II) complexes to catalyze the reaction of methyl phenyldiazoacetate **14** with 1,2-dimethyl indole **22** for the development of enantioselective carbenoid-mediated C-H functionalization of indoles because of the wide existence of indole structures in natural products and biologically active molecules (**Figure 2.3**). In the presence of Rh_2(*S*-DOSP)$_4$ catalyst, the desired transformation is very efficient, yielding the 3-alkylation product **23** in 95% yield, however, with negligible asymmetric induction (<5% ee) because the lack of asymmetric

induction may be resulted from an achiral enol **14B**, which is generated from the zwitterionic intermediate **14A** via a rapid proton transfer.[12]

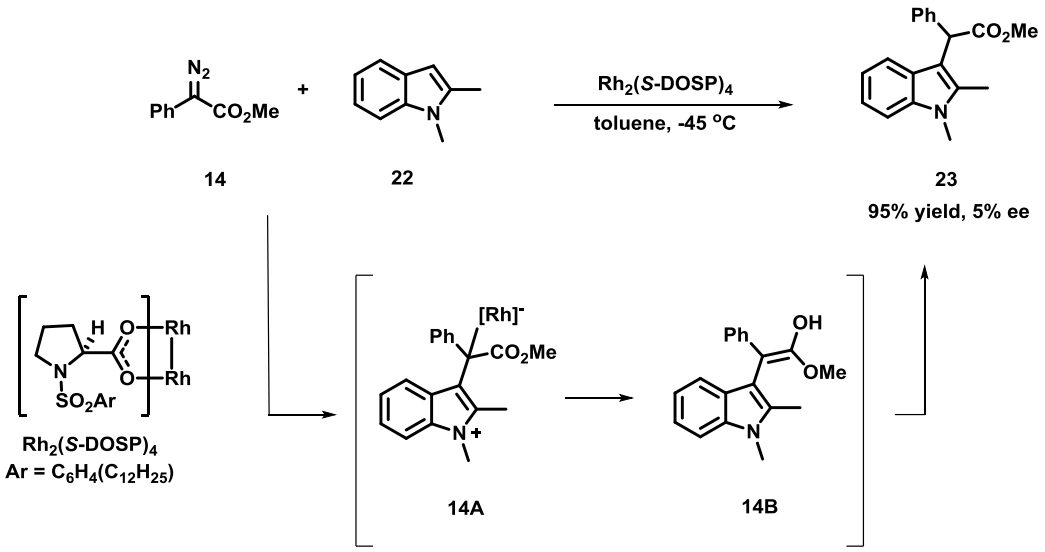


Figure 2.3. C-H insertion of methyl phenyldiazoacetate and 1,2-dimethyl indole with Rh_2(*S*-DOSP)$_4$

In addition, rhodium and chiral phosphoric acids as organocatalysts have been studied to achieve highly enantioselective products.[13, 14] The use of chiral phosphoric acids is not only activated the imine substrate by trapping process and suppressed unwanted side reactions, but also provided an efficient chiral environment for enantioselective control. By applying the rhodium and chiral phosphoric acids system, chiral phosphoric acid **catalyst 4** was successfully developed for a highly enantioselective C-H Insertion of indoles with phenyl diazo esters. In the presence of $Rh_2(OAc)_4$ and **catalyst 4**, *N*-methyl indole **13** reacted with methyl phenyldiazoacetate **14** to afford the 3-alkylation product **15** in 96% yield with 92% ee (**Figure 2.4**). A number

of indoles including *N*-alkyl, aryl, silyl, and a number of α-aryl-α-diazoesters were well tolerated, affording the desired products in good results.[15]

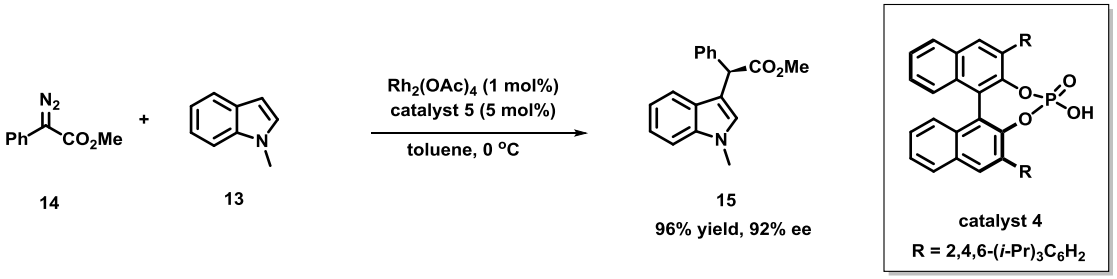


Figure 2.4. C-H insertion of methyl phenyldiazoacetate and *N*-methyl indole with $Rh_2(OAc)_4$

Previously, Davies lab has studied donor/acceptor-substituted rhodium carbenoids, especially, Rh_2(*S*-DOSP)$_4$, that proceed via zwitterionic intermediates. At that time, they studied with methyl phenyldiazoacetate as the precursor to the donor/acceptor carbenoid with Rh_2(*S*-DOSP)$_4$. Although Rh_2(*S*-DOSP)$_4$ reaction of methyl phenyldiazoacetate with 1,2-dimethylindole is very efficient to generate the alkylation product in 95% yield, enantioselectivity of product is poor (**Figure 2.3**). However, using $Rh_2(OAc)_4$ and chiral phosphoric acids system with *N*-methyl indole and methyl phenyldiazoacetate successfully gave a highly enantioselective C-H insertion in 96% yield with 92% ee (**Figure 2.4**). Now, for novel organocatalysts for C-H insertion with methyl phenyldiazoacetate and *N*-methyl indole or 1,2-dimethyl indole, the simple enantioselective chiral phosphoric acid catalyst with cyclopropane moiety (**12a**) was designed based on **catalyst 4** (**Figure 2.5**). Since trapping active intermediates with different electrophiles gave only negligible enantioselectivity when using a chiral

rhodium catalyst, using chiral phosphoric acid could contribute to the creation of a strong chiral environment and also activate the reaction component and suppress other side reaction pathways. Furthermore, a variety of phosphoric acid catalysts were also designed to expand and organize phosphoric acid library, and also synthesized via cyclopropanation between phosphate diazo compounds and many types of styrene substrates including *o*-Br, *m*-Br, *p*-Br, *o*-Cl, *m*-Cl, *p*-Cl, 2-6-diCl styrene or 1,1-diphenylethylene to check the efficiency of enentioselectivity for C-H insertion depending on the substrate size and steric hindrance effects of the ligands since **catalyst 4** including 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$ is a big size of phosphoric acid catalyst and has the steric hindrance effect when C-H insertion happened. Therefore, these different types of the enantioselective chiral cyclopropyl phosphate intermediates were designed for the combination of a rhodium catalyst and a chiral phosphoric acid organocatalyst would be synthesized from the designed enantioselective chiral cyclopropyl phosphate intermediates (**Figure 2.5**). This is a promising strategy in the development of new and valuable reactions as it is possible that unprecedented transformations may not be achievable using one catalyst alone.

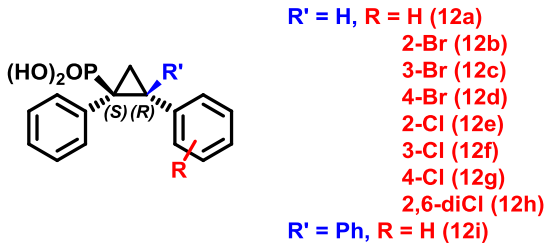


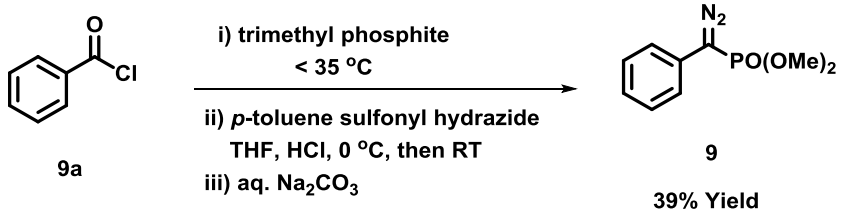
Figure 2.5. Diverse novel enantioselective chiral phosphoric acid catalysts with cyclopropane for C-H insertion

2.2. RESULTS AND DISCUSSION

2.2.1. Chemistry

The goal of this project is to synthesize novel phosphoric acid catalysts as organocatalysts for C-H insertion based on cyclopropyl phosphoric acid analogues that could potentially be used to obtain enantioenriched C-H insertion products. As a part of this project, these new potential organocatalysts would be synthesized to check another synthesis method such as N-H insertion with photochemistry.

2.2.1.1. Synthesis of Diazophosphate (9)

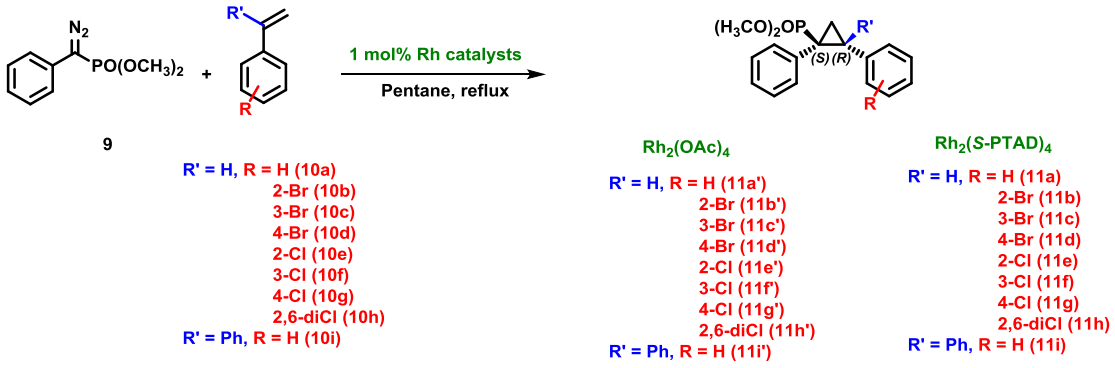


Scheme 2.1. Synthesis of diazophosphate (**9**)

The diazophosphate compound (**9**) was first synthesized using an established approach (**Scheme 2.1**).[16-18] The reaction of benzoyl chloride (**9a**) in the presence of trimethyl phosphite gave the corresponding phosphate intermedate. A diazo transfer reaction in the presence of *p*-toluene sulfonyl hydrazide in THF and HCl system, and the treatment of an aqueous solution of Na_2CO_3 generated the desired diazophosphate compound (**9**) in moderate yield (39%). This reaction was performed in large scale to

synthesize enough diazo compound, which could be used for both racemic and enantioselective synthesis.

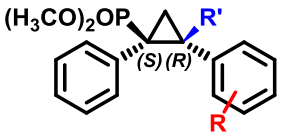
2.2.1.2. Synthesis of Diverse Enantioselective Cyclopropyl Phosphonate Intermediates



Scheme 2.2. Synthesis of diverse enantioselective cyclopropyl phosphonate intermediates

For new chiral phosphoric acid catalyst, the main steps are cyclopropanation with diazophosphonate, styrene substrates, and rhodium catalysts such as $Rh_2(OAc)_4$ or Rh_2(*S*-PTAD)$_4$,[17, 18] and synthesis of phosphoric acid from phosphonate. First, using $Rh_2(OAc)_4$, racemic cyclopropyl phosphate intermediate **11** series (R = H, **11a'**; R = 2-Br, **11b'**; R = 3-Br, **11c'**; R = 4-Br, **11d'**; R = 2-Cl, **11e'**; R = 3-Cl, **11f'**; R = 4-Cl, **11g'**; R = 2,6-diCl, **11h'**; or R' = diPh, **11i'**) were synthesized as control standards for chiral HPLC via cyclopropanation with diazophosphonate **9** and styrene substrates **10** series (styrene, **10a**; 2-bromostyrene, **10b**; 3-bromostyrene, **10c**; 4-bromostyrene, **10d**; 2-chlorostyrene, **10e**; 3-chlorostyrene, **10f**; 4-chlorostyrene, **10g**; 2,6-dichlorostyrene, **10h**; or 1,1-

diphenylethylene, **10i**) in pentane as a solvent under reflux condition (**Scheme 2.2**). Using Rh_2(*S*-PTAD)$_4$, enantioselective cyclopropyl phosphate intermediate **11** series (R = H, **11a**; R = 2-Br, **11b**; R = 3-Br, **11c**; R = 4-Br, **11d**; R = 2-Cl, **11e**; R = 3-Cl, **11f**; R = 4-Cl, **11g**; R = 2,6-diCl, **11h**; or R' = diPh, **11i**) were synthesized via cyclopropanation with diazophosphonate **9** and styrene substrates **10** series (styrene, **10a**; 2-bromostyrene, **10b**; 3-bromostyrene, **10c**; 4-bromostyrene, **10d**; 2-chlorostyrene, **10e**; 3-chlorostyrene, **10f**; 4-chlorostyrene, **10g**; 2,6-dichlorostyrene, **10h**; or 1,1-diphenylethylene, **10i**) in pentane as a solvent under reflux condition (**Scheme 2.2**). $Rh_2(OAc)_4$-catalyzed reaction could give the racemic standard compounds as moderate yield except for **11h**'. On the other hands, Rh_2(*S*-PTAD)$_4$-catalyzed cyclopropanation reaction was effective to obtain desired cyclopropyl phosphate intermediates with good yields (> 76%) and high enantioselectivity (> 94% ee) (**Scheme 2.3**).



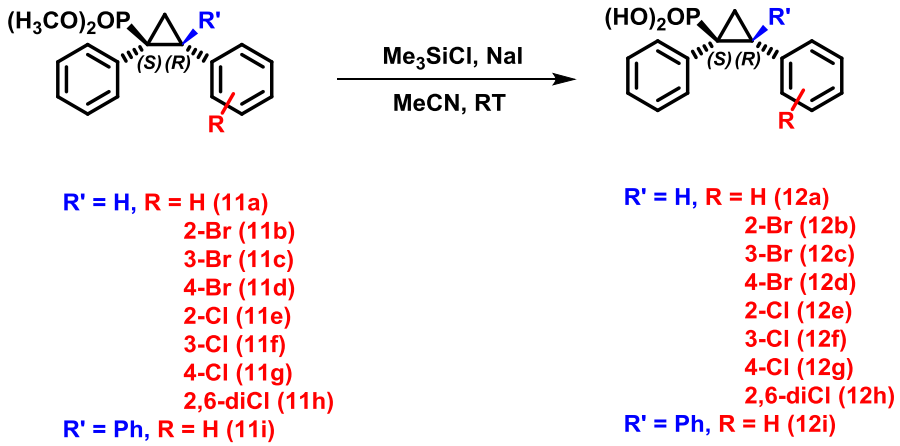
R = 2-Br, 3-Br, 4-Br
2-Cl, 3-Cl, 4-Cl, 2,6-diCl
R' = H, Ph

	$Rh_2(OAc)_4$	Rh_2(*S*-PTAD)$_4$
R' = H, R = H	11a' (98%/ racemic)	11a (98%/ 97% ee)
2-Br	11b' (45%/ racemic)	11b (77%/ 96% ee)
3-Br	11c' (68%/ racemic)	11c (96%/ 96% ee)
4-Br	11d' (50%/ racemic)	11d (87%/ 95% ee)
2-Cl	11e' (75%/ racemic)	11e (80%/ 96% ee)
3-Cl	11f' (64%/ racemic)	11f (86%/ 94% ee)
4-Cl	11g' (61%/ racemic)	11g (97%/ 97% ee)
2,6-diCl	11h' (24%/ racemic)	11h (76%/ 95% ee)
R' = Ph, R = H	11i' (65%/ racemic)	11i (87%/ 99% ee)

Scheme 2.3. Yields and ee values of diverse enantioselective cyclopropyl phosphonate intermediates

2.2.1.3. Synthesis of Diverse Phosphoric Acids with Cyclopropane

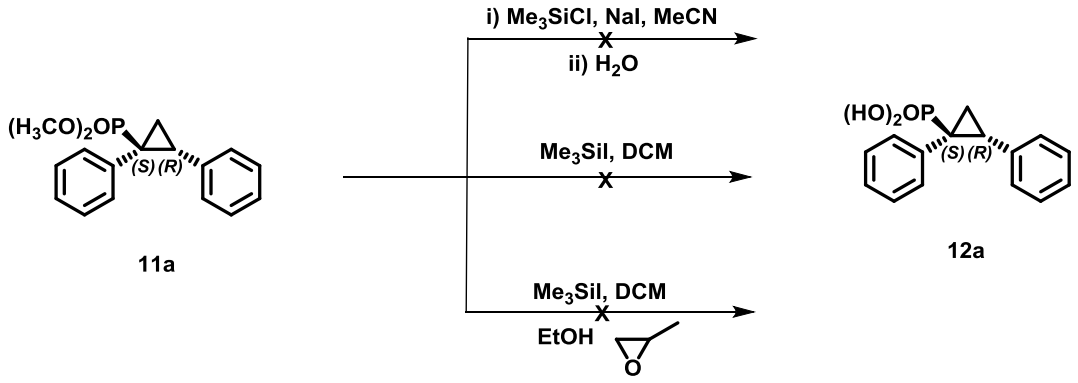
The desired cyclopropyl phosphoric acids were synthesized from the enenantioenriched cyclopropyl phosphonate intermediates. Using reduction and hydrolysis with chlorotrimethylsilane and sodium iodide in acetonitrile condition, cyclopropyl phosphonate intermediates **11** series (R = H, **11a**; R = 2-Br, **11b**; R = 3-Br, **11c**; R = 4-Br, **11d**; R = 2-Cl, **11e**; R = 3-Cl, **11f**; R = 4-Cl, **11g**; R = 2,6-diCl, **11h**; or R' = diPh, **11i**) could undergo facile cleavage to obtain desired phosphoric acid catalyst **12** series (R = H, **12a**; R = 2-Br, **12b**; R = 3-Br, **12c**; R = 4-Br, **12d**; R = 2-Cl, **12e**; R = 3-Cl, **12f**; R = 4-Cl, **12g**; R = 2,6-diCl, **12h**; or R' = diPh, **12i**) in essentially quantitative yield (**Scheme 2.4**).



Scheme 2.4. Synthesis of diverse phosphoric acids with cyclopropane

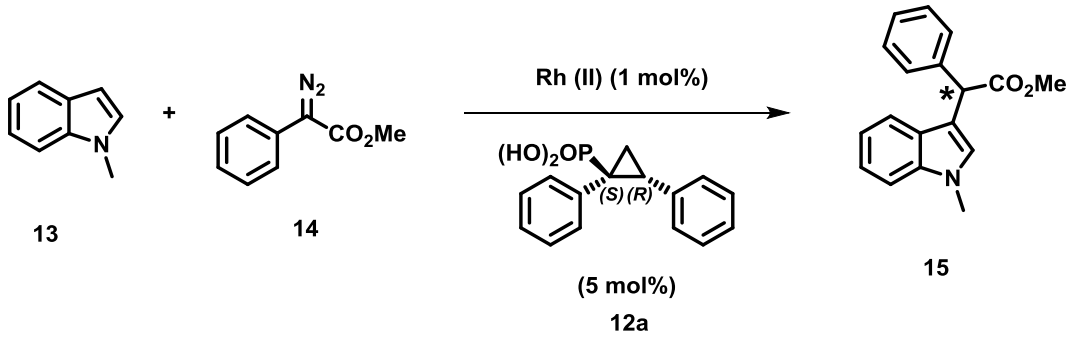
Other hydrolysis conditions were explored of **11a** to form **12a**, but they were not successful. These include hydrolysis with chlorotrimethylsilane and sodium iodide in aqueous acetonitrile, hydrolysis with chlorotrimethylsilane, sodium iodide in acetonitrile,

and treatment with propylene oxide in ethanol, and treatment with three equivalents of trimethylsilyl iodide in dichloromethane at room temperature with or without the addition of propylene oxide (**Scheme 2.5**).[19, 20]



Scheme 2.5. Inefficient reaction for phosphoric acid with cyclopropane compound

2.2.1.4. Synthesis and Optimization of C-H Insertion with Methyl Indole, Diazoacetate and Organocatalyst (12a) in High Yield and Enantioselectivity



Scheme 2.6. Synthesis of C-H insertion product (**15**) between methyl indole (**13**) and methyl phenyl diazoacetate (**14**)

The asymmetric C-H insertion of indoles from Rh (II) and chiral phosphoric acid co-catalyzed reactions of aryl diazoacetates with indoles was investigated. We initially carried out the C-H insertion experiments with *N*-methyl indole (**13**) and methyl phenyldiazoacetate (**14**) to obtain desired C-H insertion product methyl 2-(1-methyl-*1H*-indol-3-yl)-2-phenylacetate (**15**) in order to check enantioselectivity when designed chiral phosphoric acid catalyst **12a** was treated (**Scheme 2.6**). In this reaction, $Rh_2(OAc)_4$ or $Rh_2(Oct)_4$ catalyzed diazo decomposition of a aryl diazoacetate generates a metal carbenoid and reaction of the metal carbenoid with an indole at C-3 position produces a zwitterionic intermediate. Therefore, the chiral phosphoric acids can serve as a chiral proton shuttle and help the proton transfer process via an enantioselective protonation to finish the reaction in high yield and enantioselectivity.

Entry	Solvent	Temp (°C)	Rh (II)	Catalyst	% yield	ee (%)
1	Toluene	0	$Rh_2(OAc)_4$	X	39	racemic
2	Toluene	0	$Rh_2(OAc)_4$	O	40	9
3	Toluene	-41	$Rh_2(Oct)_4$	O	64	11
4	DCM	-41	$Rh_2(Oct)_4$	O	66	11
5	TFT	-41	$Rh_2(Oct)_4$	O	60	11
6	Hexane	-41	$Rh_2(Oct)_4$	O	69	5
7	$CHCl_3$	-41	$Rh_2(Oct)_4$	O	18	2
8	THF	-41	$Rh_2(Oct)_4$	O	95	18

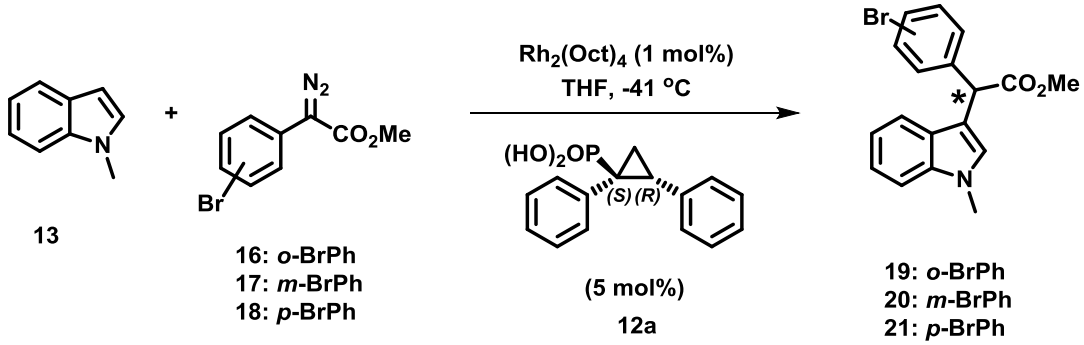
Table 2.1. Optimization of C-H insertion product (**15**) between methyl indole (**13**) and methyl phenyl diazoacetate (**14**)

In order to synthesize desired C-H insertion product methyl 2-(1-methyl-*1H*-indol-3-yl)-2-phenylacetate (**15**), diverse conditions were used to optimize C-H insertion

reaction in high yield and enantioselectivity of **15** based on **Scheme 2.6** (**Table 2.1**). First, C-H insertion of **13** and **14** with $Rh_2(OAc)_4$ (1 mol%) in toluene at 0 ^oC without phosphoric acid catalyst **12a** was performed to obtain the racemic compound, and desired racemic product was generated in 39% yield. Interestingly, the reaction with phosphoric acid catalyst **12a** (5 mol%) gave in 40% yield and 9% ee, and this result showed that the reaction with phosphoric acid catalyst **12a** does give a small amount of asymmetric induction. To optimize the reaction conditions, first, temperature was changed from 0 ^oC to -41 ^oC and $Rh_2(Oct)_4$ was used instead of $Rh_2(OAc)_4$ because $Rh_2(Oct)_4$ is much more reactive at -41 ^oC condition compared to $Rh_2(OAc)_4$. The result showed that low temperature was a little bit more effective yield and enantioselectivity (64% yield, 11% ee) than 0 ^oC. After that, many different types of solvent system under -41 ^oC were carried out to optimize C-H insertion reaction in high yield and enantioselectivity of **15**. When DCM and TFT were performed as the solvent system of C-H insertion, the results were almost similar as toluene condition (DCM: 66% yield, 11% ee; TFT: 60% yield, 11% ee). On the other hands, hexane solvent system showed the lower enantioselectivity than other solvent systems (69% yield, 5% ee), and even worse yield and enantioselectivity under the $CHCl_3$ system (18% yield, 2% ee). Finally, the best condition of C-H insertion was found under THF solvent system condition and showed high yield and enantioselevtivity compared to other conditions (95% yield, 18% ee). These whole results indicate that using the phosphoric acid catalyst **12a** has an effect on increasing the yield and enantioselectivity of desired C-H insertion product, as well as the THF solvent condition under -41 ^oC would be the best C-H insertion condition between *N*-methyl

indole and methyl phenyldiazoacetate in the presence of $Rh_2(Oct)_4$. But still, there is not a major increase of enantioselectivity.

2.2.1.5. Synthesis of C-H Insertion with Methyl Indole, Diazoacetate with Br or Cl, and Organocatalyst (12a)



Scheme 2.7. Synthesis of C-H insertion products **19**, **20** and **21**

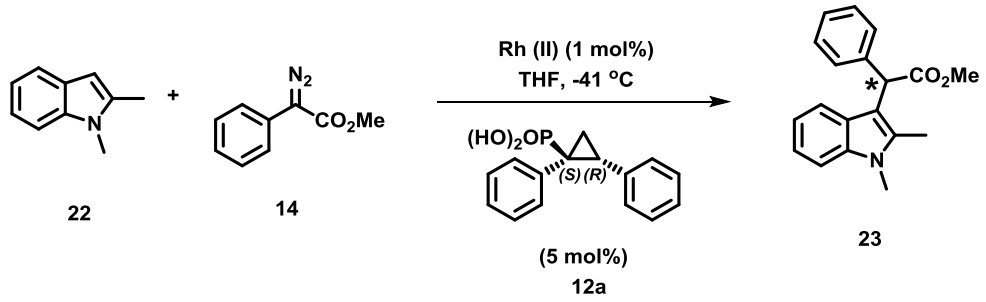
Another asymmetric C-H insertion in the presence of $Rh_2(Oct)_4$ and chiral phosphoric acid **12a** was carried out to check enantioselectivity of bromophenyl diazoacetates with indoles because diazoacetates with bromophenyl moieties can make electron-deficient environment and bromide makes bulky-diazoacetates compared to only phenyl diazoacetates. Therefore, these environmental changes such as size and density of electron would give the desired C-H insertion products in excellent or poor enantioselectivity. In order to prove the influence on enantioselectivity ability of the bromide substitute, C-H insertion experiments with *N*-methyl indole (**13**) and diverse methyl bromophenyl diazoacetates (**16**, **17**, or **18**) were performed to obtain desired C-H

insertion product methyl 2-(2 or 3 or 4-bromophenyl)-2-(1-methyl-*1H*-indol-3-yl)acetate (**19**, **20**, or **21**) (**Scheme 2.7, Table 2.2**). The $Rh_2(Oct)_4$-catalyzed reaction in the presence of phosphoric acid catalyst **12a** was conducted at the optimized condition using THF solvent at -41 ^oC. First, C-H insertion of **13** and **16** with $Rh_2(Oct)_4$ (1 mol%) in THF at -41 ^oC without phosphoric acid catalyst **12a** was performed to obtain the racemic compound, and desired racemic product **19** was generated in 71% yield. In contract, the reaction with phosphoric acid catalyst **12a** (5 mol%) gave some asymmetric induction (6% ee) and improved yield. C-H Insertion reactions were also carried out with methyl *m*-bromo- or *p*-bromo-phenyldiazoacetates and these diazo compounds gave slightly higher enantioselevtivity compared to the *o*-bromo-phenyldiazoacetates (*m*-BrPh: 84% yield, 15% ee; *p*-BrPh: 82% yield, 19% ee). These results indicate that C-H insertion with *p*-bromo-phenyldiazoacetates in the presence of phosphoric acid catalyst **12a** and $Rh_2(Oct)_4$ has the most effective enatioselectivity of desired C-H insertion product compared with *o*-bromo or *p*-bromo-phenyldiazoacetates. But still, there is not significant increase of enantioselectivity.

Entry	R	Rh (II)	Catalyst	% yield	ee (%)
1	*o*-BrPh	$Rh_2(Oct)_4$	X	71	racemic
2	*o*-BrPh	$Rh_2(Oct)_4$	O	90	6
3	*m*-BrPh	$Rh_2(Oct)_4$	O	84	15
4	*p*-BrPh	$Rh_2(Oct)_4$	O	82	19

Table 2.2. Catalytic effect of C-H insertion products (**19**, **20**, and **21**)

2.2.1.6. Synthesis of C-H Insertion with Dimethyl Indole, Diazoacetate, and Organocatalyst (12a)



Scheme 2.8. Synthesis of C-H insertion product (**23**) between dimethyl indole (**22**) and methyl phenyl diazoacetate (**14**)

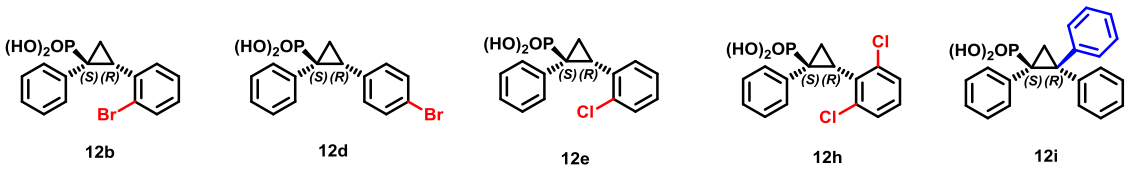
Finally, C-H insertion with methyl phenyldiazoacetate and 1,2-dimethylindole has been studied (**Scheme 2.8**; **Table 2.3**). Even though the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of methyl phenyldiazoacetate with 1,2-dimethylindole is very efficient, generating the desired product **23** in 95% yield, negligible enantioselectivity was observed (5% ee). However, the highly enantioselective C-H insertion of indoles with phenyl diazoesters was developed by applying chiral phosphoric acid as zwitterionic intermediate trapping, and the reaction between *N*-methyl indole and methyl phenyldiazoacetate in the presence of $Rh_2(OAc)_4$ and chiral phosphoric acid gave the 3-alkylation product in 96% yield with 92% ee. Therefore, I assume that the novel chiral phosphoric acid with cyclopropane catalyst would be effective on enantioselectivity of C-H insertion with methyl phenyldiazoacetate and 1,2-dimethylindole compared to C-H insertion without organocatalyst because the Rh_2(*S*-DOSP)$_4$-catalyzed reaction without phosphoric acid catalyst **12a** has negligible enantioselectivity (5% ee). In order to check the increase of

enantioselectivity of C-H insertion, first C-H insertion of **22** and **14** with $Rh_2(Oct)_4$ (1 mol%) in THF at -41 ^oC without phosphoric acid catalyst **12a** was performed to obtain the racemic compound, and desired racemic product **27** was generated in 73% yield. Next, the reaction with phosphoric acid catalyst **12a** (5 mol%) gave the product in 80% yield and 17% ee, and this result showed that the reaction with phosphoric acid catalyst **12a** has more effective yield than the reaction without phosphoric acid catalyst **12a**, but the enantioselectivity is still very low. C-H Insertion reactions with $Rh_2(S\text{-DOSP})_4$ were also carried out. C-H Insertion of **22** and **14** with $Rh_2(S\text{-DOSP})_4$ (1 mol%) in THF at -41 ^oC without phosphoric acid catalyst **12a** gave the racemic compound in 35% yield, and C-H reaction with phosphoric acid catalyst **12a** in the presence of $Rh_2(S\text{-DOSP})_4$ gave high enantioselevtivity (60% yield, 21% ee). These results indicate that C-H insertion with phosphoric acid catalyst **12a** has an effect on enantioselectivity of desired C-H insertion product, but the effect is modest.

Entry	Rh (II)	Catalyst	% yield	ee (%)
1	$Rh_2(Oct)_4$	X	73	racemic
2	$Rh_2(Oct)_4$	O	80	17
3	$Rh_2(S\text{-DOSP})_4$	X	35	racemic
4	$Rh_2(S\text{-DOSP})_4$	O	60	21

Table 2.3. Catalytic effect of C-H insertion product (**23**) between dimethyl indole (**22**) and methyl phenyl diazoacetate (**14**)

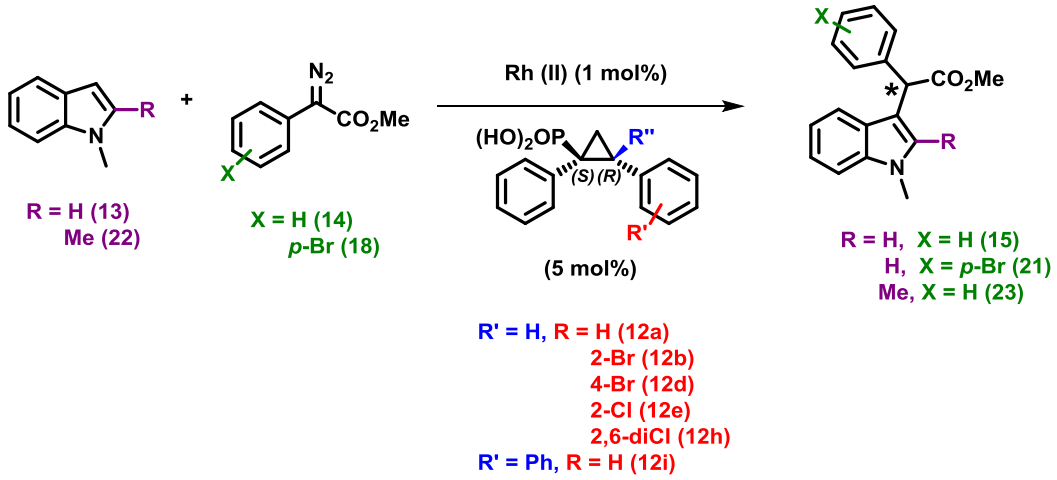
2.2.1.7. Synthesis of C-H Insertion with Diverse Organocatalysts (12 series)



Scheme 2.9. Selected organocatalysts (**12b**, **12d**, **12e**, **12h**, and **12i**) for C-H insertion

A variety of phosphoric acid catalysts including *o*-Br, *m*-Br, *p*-Br, *o*-Cl, *m*-Cl, *p*-Cl, 2-6-diCl styrene or 1,1-diphenylethylene were designed and completely synthesized to expand and organize phosphoric acid organocatalysts library, and also previous data showed that simple phosphoric acid catalyst **12a** has an effect on enantioselectivity of desired C-H insertion product even in the presence of $Rh_2(Oct)_4$ although there is not significant increase of enantioselectivity. Based on this data, five different phosphoric acid organocatalysts (R = 2-Br, **12b**; R = 4-Br, **12d**; R = 2-Cl, **12e**; R = 2,6-diCl, **12h**; and R' = diPh, **12i**) were selected and used into C-H insertion reaction to confirm and compare to the efficiency of enentioselectivity depending on the substrate size and steric hindrance effects of the organocatalysts when C-H insertion happened. Therefore, these various types of chiral cyclopropyl phosphoric acid catalysts were chosen (**Scheme 3.9**). This is because bromine is the second biggest halogen atom and compared with chlorine as the size effect. And also, *o*-Br (**12b**) and *p*-Br (**12d**)/ *o*-Cl (**12e**) and 2,6-diCl (**12h**)

could compare as the steric hindrance effect individually. Finally, simple phosphoric acid catalyst could compare with diPh (**12i**).

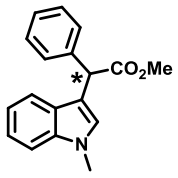


Scheme 2.10. Selected three C-H insertion reactions with diverse oragnocatalysts (**12** series)

Next, in order to compare with enantioselectivity of asymmetric C-H insertion in the presence of $Rh_2(Oct)_4$ and selected five different phosphoric acid organocatalysts (R = 2-Br, **12b**; R = 4-Br, **12d**; R = 2-Cl, **12e**; R = 2,6-diCl, **12h**; and R' = diPh, **12i**), three varied C-H insertion reactions (C-H insertion between 1. methyl indole and methyl phenyl diazoacetate; 2. methyl indole and methyl *p*-bromophenyl diazoacetate; 3. 1,2-dimethylindole and methyl phenyl diazoacetate) were chosen (**Scheme 2.10**). This is largely because these three C-H insertion reactions with chiral phosphoric acid **12a** gave increasing and reasonable enantioselectivity of C-H insertion (~20%). Therefore, in order for verification the enantioselectivity ability of C-H insertion depending on size and

density of organocatalysts, C-H insertion experiments with *N*-methyl indole (**13**), dimethyl indole (**22**), methyl phenyl diazoacetate (**14**), and *p*-bromo methyl phenyl diazoacetate (**18**) were performed to obtain desired C-H insertion products (**15**, **21**, or **23**). Since using THF solvent condition under -41 ^{o}C would be the best C-H insertion condition in the presence of $Rh_2(Oct)_4$, this best condition was carried out. First, C-H insertion between **13** and **14** with $Rh_2(Oct)_4$ (1 mol%) and phosphoric acid catalysts (5 mol%) in THF at -41 ^{o}C was performed to obtain the enantioselective compound. Individually, the reaction with phosphoric acid catalyst **12b**, **12d**, **12e**, **12h**, or **12i** gave in 96% yield and 31% ee (**12b**), 93% yield and 29% ee (**12d**), 99% yield and 24% ee (**12e**), 96% yield and 13% ee (**12h**), or 97% yield and 17% ee (**12i**). These results showed that the reaction with phosphoric acid catalyst **12b** has more effective enantioselectivity than the reaction with other phosphoric acid catalysts such as **12d**, **12e**, **12h**, or **12i**, as well as **12a** (**Scheme 2.11**). In addition, another C-H insertion reaction with **13** and methyl *p*-bromo phenyl diazoacetate (**18**) was carried out and these results showed that the 2-Br organocatalyst (**12b**) gave the highest enantioselevtivity compared to other organocatalysts (**12b**: 85% yield, 26% ee; **12d**: 85% yield, 18% ee; **12e**: 91% yield, 20% ee; **12h**: 89% yield, 13% ee; **12i**: 90% yield, 18% ee), as well as C-H insertion reaction with **22** and methyl phenyl diazoacetate (**14**) gave the similar result (**12b**: 91% yield, 30% ee; **12d**: 88% yield, 21% ee; **12e**: 83% yield, 19% ee; **12h**: 63% yield, 28% ee; **12i**: 99% yield, 19% ee) (**Scheme 3.11**). These results indicate that 2-Br organocatalyst (**12b**) had the better eantioselectivity than 4-Br (**12d**) or 2-Cl (**12e**) organocatalysts. In other words, those data showed that the changes of substrate size and steric hindrance effects of the organocatalysts may be possible to affect the increase of enantioselectivity because 2-Br

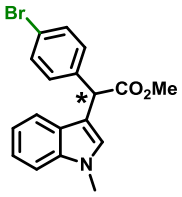
and 4-Br case, 2-Br organocatalyst (**12b**) was located more steric hindrance than 4-Br organocatalyst, as well as 2-Br and 2-Cl case, Br is bigger atom size than Cl so that 2-Br organocatalyst (**12b**) has greater enantioselectivity than 2-Cl organocatalyst (**12e**). 2,6-diCl (**12h**) and diPh (**12i**) case, these organocatalysts was expected to increase enantioselectivity of C-H insertion because of size and steric hindrance. The results, however, showed that **12h** and **12i** have less effect on enantioselectivity of C-H insertion than other organocatalysts even though these organocatalysts has two Cl atoms at orth position or has two phenyl groups instead of one phenyl group. Therefore, C-H insertion with the phosphoric acid catalyst **12b** has the most effective enantioselectivity of desired C-H insertion products. Although there is an only minor increase in enantioselectivity, this approach could still be a promising strategy for the development of new and valuable reactions as it is possible that unprecedented transformations may not be achievable using one catalyst alone.



15

Rh (II) / Catalyst / Yield / ee

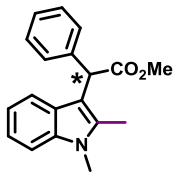
$Rh_2(Oct)_4$ / H / 95% / 18% ee
$Rh_2(Oct)_4$ / 2-Br / 96% / 31% ee
$Rh_2(Oct)_4$ / 4-Br / 93% / 29% ee
$Rh_2(Oct)_4$ / 2-Cl / 99% / 24% ee
$Rh_2(Oct)_4$ / 2,6-diCl / 96% / 13% ee
$Rh_2(Oct)_4$ / diPh / 97% / 17% ee



21

Rh (II) / Catalyst / Yield / ee

$Rh_2(Oct)_4$ / H / 82% / 19% ee
$Rh_2(Oct)_4$ / 2-Br / 85% / 26% ee
$Rh_2(Oct)_4$ / 4-Br / 85% / 18% ee
$Rh_2(Oct)_4$ / 2-Cl / 91% / 20% ee
$Rh_2(Oct)_4$ / 2,6-diCl / 89% / 13% ee
$Rh_2(Oct)_4$ / diPh / 90% / 18% ee



23

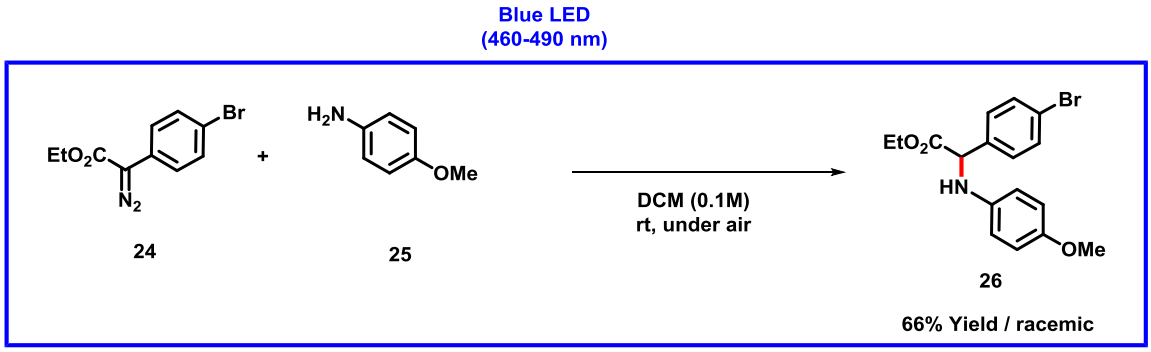
Rh (II) / Catalyst / Yield / ee

$Rh_2(Oct)_4$ / H / 80% / 17% ee
$Rh_2(Oct)_4$ / 2-Br / 91% / 30% ee
$Rh_2(Oct)_4$ / 4-Br / 88% / 21% ee
$Rh_2(Oct)_4$ / 2-Cl / 83% / 19% ee
$Rh_2(Oct)_4$ / 2,6-diCl / 63% / 28% ee
$Rh_2(Oct)_4$ / diPh / 99% / 19% ee

Scheme 2.11. Yields and ee values of C-H insertion

2.2.1.8. Photochemistry of Aryldiazoacetates

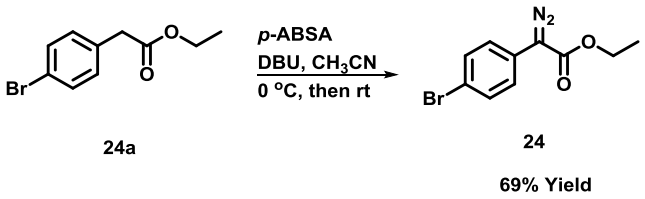
The Davies group has demonstrated that the aryldiazoacetates will undergo N-H insertion under photochemical condition. The N-H insertion is an attractive transformation and important for synthesis of valuable amines in bioactive targets.[21-26] As these reactions may involve enol intermediates, it would be interesting to determine if these reactions could be rendered enantioselective by using the chiral phosphoric acid derivatives. The photochemistry of aryldiazoacetate was conducted using blue LED (460nm ~ 490nm) in order to achieve N-H insertion reaction.[27, 28] For instance, N-H insertion between 4-bromophenyl ethyl diazoacetate (**24**) and 4-methoxyaniline (**25**) in DCM at RT under air condition without Rh catalysts gave the desired N-H insertion racemic compound **26** in 66% yield, and there were no reactions in the absence of blue LED light (**Scheme 2.12**).



Scheme 2.12. N-H insertion reaction with blue LED as photochemistry

2.2.1.8.1. Synthesis of 4-Bromophenyl Ethyl Diazoacetate

In order to confirm the enantioselectivity of asymmetric N-H insertion, the donor/acceptor diazo compound (**24**) were first synthesized (**Scheme 2.13**).[29] A diazo transfer reaction of ethyl 2-(4-bromophenyl)acetate (**24a**) in the presence of *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and the base 1,8-diazabicyclo-[5,4,0]-undec-*7*-ene (DBU) in acetonitrile yielded the corresponding 4-bromophenyl ethyl diazoacetate (**24**) in good yield. This reaction was performed in large scale to synthesize enough diazo compound, which could be used for both racemic and enantioselective synthesis.

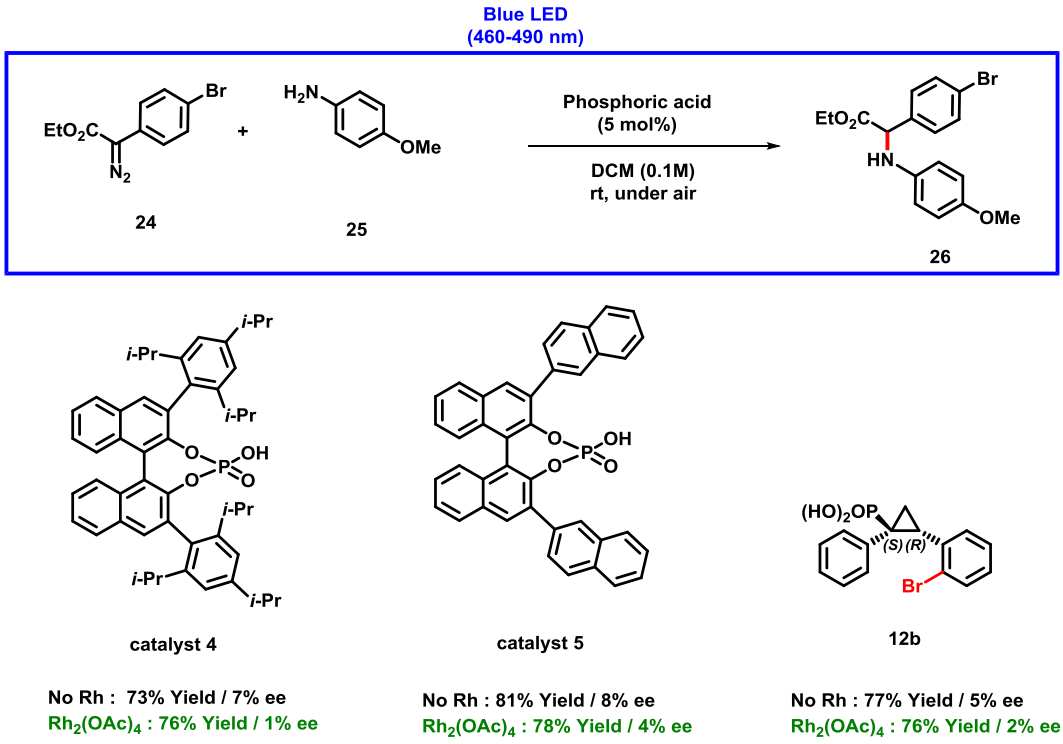


Scheme 2.13. Synthesis of 4-bromophenyl ethyl diazoacetate

2.2.1.8.2. Synthesis of N-H Insertion with Diverse Organocatalysts via Photochemistry

Finally, N-H insertion between 4-bromophenyl ethyl diazoacetate (**24**) and 4-methoxyaniline (**25**) in the presence of the phosphoric acid organocatalyst **12b** was performed (**Scheme 2.14**). Since the rhodium-catalyzed C-H insertion gave the highest level of enantioselectivity with the phosphoric acid catalyst **12b**, it was used in the photochemical N-H insertion test reaction. Furthermore, **catalyst 4** and **catalyst 5** were

utilized as control catalysts because these catalysts have proven to increase the enantioselectivity in the rhodium-catalyzed C-H insertion products.[15] For N-H insertion with **24** and **25**, the standard condition was DCM at RT under air condition with blue LED (460nm ~ 490nm) based on previous study. N-H insertion without $Rh_2(OAc)_4$ and phosphoric acid catalyst generated desired N-H insertion racemic compound **26** in 66% yield. Also, N-H insertion between **24** and **25** with organocatalysts **catalyst 4**, **catalyst 5**, or **12b** (5 mol%) gave **26** in 73% yield and 7% ee (**catalyst 4**), 81% yield and 8% ee (**catalyst 4**), or 77% yield and 5% ee (**12b**) individually (**Scheme 2.14**). Moreover, even though $Rh_2(OAc)_4$ (1 mol%) was treated in N-H insertion reaction, these results showed that the reaction with organocatalysts in the presence of $Rh_2(OAc)_4$ has no effect on increasing enantioselectivity for N-H insertion (**catalyst 4**: 76% yield, 1% ee; **catalyst 5**: 78% yield, 4% ee; **12b**: 76% yield, 2% ee). Therefore, compared to C-H insertion with organocatalyst **12b**, phosphoric acid catalysts couldn't develop the enantioselectivity of N-H insertion.



Scheme 2.14. N-H insertion reaction with diverse organocatalysts via blue LED as photochemistry

2.3. CONCLUSIONS

In order to develop the new phosphoric acid ligands for organocatalysis for enantioselecive C-H insertion, novel enantioselective chiral phosphoric acid catalysts with cyclopropane were developed. For new chiral phosphoric acids, the diverse phosphate intermediates were synthesized via cyclopropanation with Rh_2(*S*-PTAD)$_4$, diazophosphonate and styrene derivatives in pentane under reflux condition. After that, the desired phosphoric acid catalysts (**12a**, **12b**, **12c**, **12d**, **12e**, **12f**, **12g**, **12h**, and **12i**) were synthesized through the reaction between phosphate intermediate and TMSCl in the presence of sodium iodide in acetonitrile. Using these new catalysts, C-H insertion reactions with Rh(II) without/with organocatalysts were performed to check the

enantioselectivity of C-H insertion. Optimization data of the C-H insertion reaction showed that the best condition of C-H insertion was under THF solvent system condition with $Rh_2(Oct)_4$ (1 mol%) and phosphoric acid catalysts (5 mol%) at -41 ^oC in high yield. In addition, another asymmetric C-H insertion in the presence of $Rh_2(Oct)_4$ and chiral phosphoric acid **12a** was carried out to check enantioselectivity of bromophenyl diazoacetates with indoles. The results of C-H insertion reactions with methyl *o*-bromo-, *m*-bromo- or *p*-bromo-phenyldiazoacetates showed better enantioselevtivity of *p*-bromo compared to *o*-bromo or *m*-phenyldiazoacetates. Finally, C-H insertion with methyl phenyldiazoacetate and 1,2-dimethylindole was carried out with $Rh_2(Oct)_4$ or $Rh_2(S\text{-}DOSP)_4$, and this reaction with phosphoric acid catalyst **12a** gave the best enantioselevtivity. These results showed that using phosphoric acid catalyst **12a** has an effect on increasing the yield and enantioselectivity of desired C-H insertion product, as well as the THF solvent condition under -41 ^oC would be the best C-H insertion condition.

Moreover, based on this data, five different phosphoric acid organocatalysts (R = 2-Br, **12b**; R = 4-Br, **12d**; R = 2-Cl, **12e**; R = 2,6-diCl, **12h**; and R' = diPh, **12i**) were selected and used into C-H insertion reaction to check and compare to the efficiency of enentioselectivity depending on the substrate size and steric hindrance effects of the organocatalysts when C-H insertion happened. As a result, C-H insertion with the phosphoric acid catalyst **12b** has the most effective enatioselectivity of desired C-H insertion products. In addition, N-H insertion between **24** and **25** in the presence of the phosphoric acid organocatalyst **12b** was performed to reveal the enantiolselectivity of N-H insertion when **12b** was treated in the photochemistry reaction by using blue LED (460nm ~ 490 nm). In conclusion, even though $Rh_2(OAc)_4$ was used in N-H insertion

reaction, these results showed that the organocatalyst has no effect on increasing enantioselectivity for N-H insertion.

In summary, although so far the level of enantioselectivity for C-H insertion is relatively low, the cyclopropyl phosphoric acids are readily obtained in enantiomerically pure form and would be worth exploring further as chiral acid catalysts.

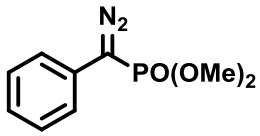
2.4. EXPERIMENTAL SECTION

General Methods

All experiments were performed under anhydrous conditions in an atmosphere of argon except where stated, using oven-dried glassware. Hexane, pentane, THF, toluene, acetonitrile, and methylenechloride were dried by a solvent purification system. Unless otherwise noted, all other reagents were obtained from commercial sources and used as received. ^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded at 400 MHz, 500 MHz, or 600 MHz on an INOVA-400, Varian-400, INOVA-500, or BRUKER-600. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ H 7.26 for the residual protons in $CDCl_3$, 3.31 in CD_3OD, or 2.50 in DMSO), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, etc), coupling constant (J/Hz), integration. Coupling constants were taken directly from the spectra and are uncorrected. ^{13}C NMR spectra were recorded at 100 MHz, 125 MHz, or 150 MHz, and all chemical shift values are reported in ppm on the δ scale, with an internal reference of δ C 77.16 for $CDCl_3$, 49.00 for CD_3OD, or 39.52 for DMSO. Melting points were measured with electrothermal melting point apparatus model 1001D and by Barnstead International (Volts: 120, AMPs: 1.6, Watts: 200, Hz: 50/60, Phase: 1)

and were uncorrected. Optical rotations were measured on a PerkinElmer Model 341 Polarimeter. Infrared (IR) spectra were collected on a Nicolet iS10 FT-IR spectrometer. High Resolution Mass spectra (HRMS) were taken on a Thermo Finnigan LTQ-FTMS spectrometer with APCI, ESI or NSI, and Liquid Chromatography Mass spectra (LC-MS) was measured on Agilent Technologies 6120 Quadrupole LC/MS spectrometer. Thin layer chromatographic analysis was performed with silica gel plates, visualizing with UV light. Flash column chromatography was performed on silica gel 60 Å (230-400 mesh). Analytical enantioselective chromatographies were measured on Varian Prostar instrument and used isopropanol/hexane as gradient.

Dimethyl (diazo(phenyl)methyl)phosphonate (9)

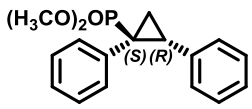


Dimethyl (diazo(phenyl)methyl)phosphonate (**9**) was prepared by known method.[16-18] Benzoyl chloride (**9a**; 10.5 g, 75 mmol) was placed in a 100 mL round bottom flask and placed under argon atmosphere. Then, trimethyl phosphite was added dropwise, keeping the reaction temperature below 35 ^{o}C and stirred for 2 hrs. The reaction materials was stirred at RT overnight and then purified by vacuum distillation using the Kugelrohr distillation equipment to give a phosphate intermediate as yellow oil.

To a 0 ^{o}C solution of *p*-toluene sulfonyl hydrazide (13.2 g, 71 mmol) in THF (500 mL) was added conc. HCl (3 mL, 36 mmol). Then, the phosphate intermediate was added dropwise over 5 min, and stirred for 5 hrs, warming to RT. After that, the solution was

concentrated to give an off-white solid. This crude intermediate was suspended in an aqueous solution of Na_2CO_3 and stirred overnight at RT. The mixture was extracted with Et_2O (2 x 100 mL). The organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography (ether 100%) to give an orange solid. This contained an impurity, so the diazophosphate was dissolved in pentane (600 mL) and the remaining white/orange solid was filtered to generate desired diazophosphate (6.2 g, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8.8, and 7.2 Hz, 2H), 7.17 - 7.13 (m, 3H), 3.83 (s, 3H), 3.80 (s, 3H); ^{31}P NMR (160 MHz, $CDCl_3$) δ 21.49. The spectroscopic data matches what was previously reported in the literature. [16-18]

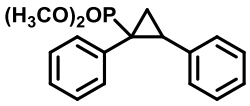
Dimethyl ((*1S,2R*)-1,2-diphenylcyclopropyl)phosphonate (11a)



Dimethyl ((*1S,2R*)-1,2-diphenylcyclopropyl)phosphonate (**11a**) was prepared by known method.[18] A stirred mixture of styrene (**10a**, 122.9 mg, 1.18 mmol, 5.9 eq.) and Rh_2(*S*-PTAD)$_4$ (3.1 mg, 1 mol %, 0.002 eq.) in pentane (5 mL) was heated under reflux under an argon atmosphere. To this solution was added the dimethyl (diazo(phenyl)methyl) phosphonate (**9**) (45.2 mg, 0.2 mmol, 1.0 eq.) in pentane (15 mL) via syringe pump over 8 h, and the mixture was then stirred for an additional 4 h. The mixture was then concentrated *in vacuo*, and the residue was purified on silica (SiO_2, EA 100%) to obtain 98% yield (97% ee) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 - 7.10 (m, 3H), 7.07 - 7.04 (m, 5H), 6.74 (ddd, *J* = 4.0, 2.8, and 2.4 Hz, 2H), 3.75 (d, *J* = 10.5 Hz, 3H), 3.69 (d, *J* = 10.5 Hz, 3H), 3.02 (ddd, *J* = 16.0, 8.8, and 8.4 Hz, 1H),

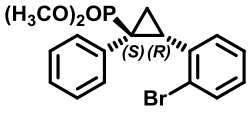
2.07 (ddd, *J* = 17.6, 9.2, and 5.2 Hz, 1H), 1.73 (ddd, *J* = 12.4, 6.4, and 5.2 Hz, 1H); ^{31}P NMR (160 MHz, $CDCl_3$) δ 30.81. The enantiomeric excess was determined by HPLC using the published procedure and the spectroscopic data matches what was previously reported in the literature.[18]

Dimethyl (1,2-diphenylcyclopropyl)phosphonate (11a')



Synthesis of the racemic compound of **11a'** was carried out using $Rh_2(OAc)_4$ (1% mol) as catalyst in the same reaction conditions as described above to obtain 98% yield. NMR spectroscopic data is same as **11a**.

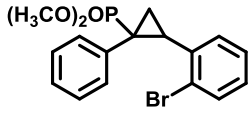
Dimethyl ((*1S,2R*)-2-(2-bromophenyl)-1-phenylcyclopropyl)phosphonate (11b)



Dimethyl ((*1S,2R*)-2-(2-bromophenyl)-1-phenylcyclopropyl)phosphonate (**11b**) was prepared by known method.[18] A stirred mixture of 2-bromostyrene (**10b**, 216.0 mg, 1.18 mmol, 5.9 eq.) and Rh_2(*S*-PTAD)$_4$ (3.1 mg, 1 mol %, 0.002 eq.) in pentane (5 mL) was heated under reflux under an argon atmosphere. To this solution was added the dimethyl (diazo(phenyl)methyl)phosphonate (**9**) (45.2 mg, 0.2 mmol, 1.0 eq.) in pentane (15 mL) via syringe pump over 8 h, and the mixture was then stirred for an additional 4 h. The mixture was then concentrated *in vacuo*, and the residue was purified on silica (SiO_2,

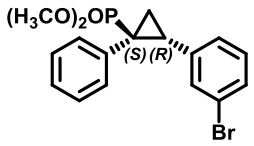
EA 100%) to obtain 77% yield (96% ee) as a white powder. IR (neat) ν (cm^{-1}) 2952, 1736, 1445, 1372, 1246, 1183, 1029, 944, 849, 826, 752, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.0, and 1.6 Hz, 1H), 7.10 - 7.06 (m, 5H), 6.92 (ddd, *J* = 7.6, 7.2, and 2.0 Hz, 1H), 6.85 (ddd, *J* = 7.6, 7.6, and 1.2 Hz, 1H), 6.35 (dd, *J* = 7.6, and 1.6 Hz, 1H), 3.84 (d, *J* = 10.4 Hz, 3H), 3.69 (d, *J* = 10.4 Hz, 3H), 3.32 (ddd, *J* = 16.0, 8.8, and 6.8 Hz, 1H), 2.05 (ddd, *J* = 17.2, 8.8, and 5.2 Hz, 1H), 1.88 (ddd, *J* = 12.0, 6.8, and 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.8, 132.7, 132.0 (d, J_{CP} = 4.0 Hz), 130.2, 128.1 (dd, J_{CP} = 4.5 and 2.2 Hz), 127.9 (d, J_{CP} = 1.5 Hz), 127.4 (d, J_{CP} = 2.7 Hz), 126.9, 126.8, 53.9 (d, J_{CP} = 8.1 Hz), 53.5 (d, J_{CP} = 5.4 Hz), 30.5, 28.0, 15.5 (d, J_{CP} = 3.0 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 29.25; LC-MS: *m/z* calcd for $C_{17}H_{19}BrO_3P$ ($M+H^+$): 381.0, found: 381.0; HRMS (ESI): *m/z* calcd for $C_{17}H_{19}BrO_3P$ ($M+H^+$): 381.0255, found: 381.0252; HPLC analysis: 96% ee (OJ column, 1% 2-propanol in hexanes, 1.0 mL/min, 230 nm, t_R = 25.18 (minor) and 35.31 (major) min).

Dimethyl (2-(2-bromophenyl)-1-phenylcyclopropyl)phosphonate (11b')



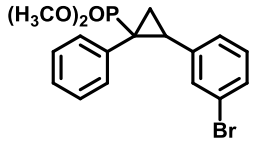
Synthesis of the racemic compound of **11b'** was carried out using $Rh_2(OAc)_4$ (1% mol) as catalyst in the same reaction conditions as described above to obtain 45% yield. NMR spectroscopic data is same as **11b**.

Dimethyl ((*1S,2R*)-2-(3-bromophenyl)-1-phenylcyclopropyl)phosphonate (11c)



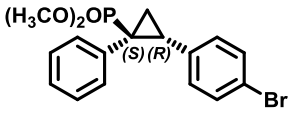
Dimethyl ((*1S,2R*)-2-(3-bromophenyl)-1-phenylcyclopropyl)phosphonate (**11c**) was prepared by known method.[18] A stirred mixture of 3-bromostyrene (**10c**, 216.0 mg, 1.18 mmol, 5.9 eq.) and Rh_2(*S*-PTAD)$_4$ (3.1 mg, 1 mol %, 0.002 eq.) in pentane (5 mL) was heated under reflux under an argon atmosphere. To this solution was added the dimethyl (diazo(phenyl)methyl)phosphonate (**9**) (45.2 mg, 0.2 mmol, 1.0 eq.) in pentane (15 mL) via syringe pump over 8 h, and the mixture was then stirred for an additional 4 h. The mixture was then concentrated *in vacuo*, and the residue was purified on silica (SiO_2, EA 100%) to obtain 96% yield (96% ee) as a white powder. IR (neat) ν (cm^{-1}) 2952, 1737, 1596, 1565, 1492, 1446, 1373, 1245, 1029, 948, 850, 828, 778, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 - 7.13 (m, 4H), 7.08 - 7.04 (m, 2H), 6.93 (t, 1H), 6.89 (t, 1H), 6.57 (d, *J* = 7.6 Hz, 1H), 3.72 (d, *J* = 10.8 Hz, 3H), 3.68 (d, *J* = 10.8 Hz, 3H), 2.95 (ddd, *J* = 16.0, 8.8, and 6.4 Hz, 1H), 2.07 (ddd, *J* = 17.2, 8.8, and 5.2 Hz, 1H), 1.70 (ddd, *J* = 12.0, 6.4, and 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8 (d, J_{CP} = 2.6 Hz), 133.2 (d, J_{CP} = 1.6 Hz), 132.3 (d, J_{CP} = 4.0 Hz), 131.4, 129.5, 129.3, 128.2 (d, J_{CP} = 2.4 Hz), 127.7 (d, J_{CP} = 2.7 Hz), 126.5, 122.0, 53.5 (t), 29.9 (d, J_{CP} = 186.2 Hz), 26.7 (d, J_{CP} = 1.3 Hz), 17.0 (d, J_{CP} = 3.0 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 29.16; LC-MS: *m/z* calcd for $C_{17}H_{19}BrO_3P$ ($M+H^+$): 381.0, found: 381.0; HRMS (ESI): *m/z* calcd for $C_{17}H_{19}BrO_3P$ ($M+H^+$): 381.0255, found: 381.0253; HPLC analysis: 96% ee (OJ column, 3% 2-propanol in hexanes, 1.0 mL/min, 230 nm, t_R = 22.98 (minor) and 28.05 (major) min).

Dimethyl (2-(3-bromophenyl)-1-phenylcyclopropyl)phosphonate (11c')



Synthesis of the racemic compound of **11c'** was carried out using $Rh_2(OAc)_4$ (1% mol) as catalyst in the same reaction conditions as described above to obtain 68% yield. NMR spectroscopic data is same as **11c**.

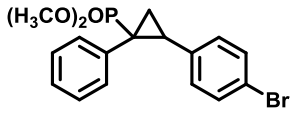
Dimethyl ((*1S,2R*)-2-(4-bromophenyl)-1-phenylcyclopropyl)phosphonate (11d)



Dimethyl ((*1S,2R*)-2-(4-bromophenyl)-1-phenylcyclopropyl)phosphonate (**11d**) was prepared by known method.[18] A stirred mixture of 4-bromostyrene (**10d**, 216.0 mg, 1.18 mmol, 5.9 eq.) and Rh_2(*S*-PTAD)$_4$ (3.1 mg, 1 mol %, 0.002 eq.) in pentane (5 mL) was heated under reflux under an argon atmosphere. To this solution was added the dimethyl (diazo(phenyl)methyl)phosphonate (**9**) (45.2 mg, 0.2 mmol, 1.0 eq.) in pentane (15 mL) via syringe pump over 8 h, and the mixture was then stirred for an additional 4 h. The mixture was then concentrated *in vacuo*, and the residue was purified on silica (SiO_2, EA 100%) to obtain 87% yield (95% ee) as a white powder. IR (neat) ν (cm^{-1}) 3477, 2951, 1736, 1491, 1446, 1245, 1182, 1027, 940, 856, 825, 766, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 - 7.14 (m, 5H), 7.07 - 7.03 (m, 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 3.71 (d, *J* = 10.4 Hz, 3H), 3.67 (d, *J* = 10.4 Hz, 3H), 2.95 (ddd, *J* = 16.0, 9.2, and 6.8 Hz, 1H), 2.07

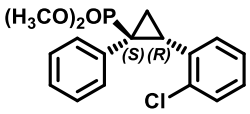
(ddd, J = 17.2, 8.8, and 5.2 Hz, 1H), 1.67 (ddd, J = 12.4, 6.8, and 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4 (d, J_{CP} = 2.6 Hz), 133.3 (d, J_{CP} = 1.5 Hz), 132.2 (d, J_{CP} = 4.1 Hz), 130.9, 129.7, 128.2 (d, J_{CP} = 2.4 Hz), 127.6 (d, J_{CP} = 2.8 Hz), 120.3, 53.5 (t), 29.8 (d, J_{CP} = 186.3 Hz), 26.6 (d, J_{CP} = 1.4 Hz), 16.7 (d, J_{CP} = 3.1 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 29.27; LC-MS: *m/z* calcd for $C_{17}H_{19}BrO_3P$ ($M+H^+$): 381.0, found: 381.0; HRMS (ESI): *m/z* calcd for $C_{17}H_{19}BrO_3P$ ($M+H^+$): 381.0255, found: 381.0253; HPLC analysis: 95% ee (OD-H column, 1% 2-propanol in hexanes, 1.0 mL/min, 230 nm, t_R = 45.75 (minor) and 49.36 (major) min).

Dimethyl (2-(4-bromophenyl)-1-phenylcyclopropyl)phosphonate (11d')



Synthesis of the racemic compound of **11d'** was carried out using $Rh_2(OAc)_4$ (1% mol) as catalyst in the same reaction conditions as described above to obtain 50% yield. NMR spectroscopic data is same as **11d**.

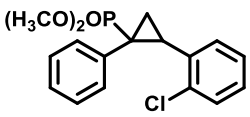
Dimethyl ((*1S,2R*)-2-(2-chlorophenyl)-1-phenylcyclopropyl)phosphonate (11e)



Dimethyl ((*1S,2R*)-2-(2-chlorophenyl)-1-phenylcyclopropyl)phosphonate (**11e**) was prepared by known method.[18] A stirred mixture of 2-chlorostyrene (**10e**, 163.5 mg,

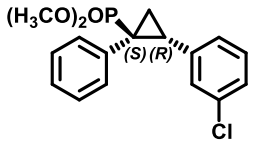
1.18 mmol, 5.9 eq.) and Rh_2(*S*-PTAD)$_4$ (3.1 mg, 1 mol %, 0.002 eq.) in pentane (5 mL) was heated under reflux under an argon atmosphere. To this solution was added the dimethyl (diazo(phenyl)methyl)phosphonate (**9**) (45.2 mg, 0.2 mmol, 1.0 eq.) in pentane (15 mL) via syringe pump over 8 h, and the mixture was then stirred for an additional 4 h. The mixture was then concentrated *in vacuo*, and the residue was purified on silica (SiO_2, EA 100%) to obtain 80% yield (96% ee) as a white powder. IR (neat) ν (cm^{-1}) 2952, 1740, 1482, 1445, 1248, 1182, 1050, 1029, 961, 945, 850, 827, 754, 728, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.0, and 1.2 Hz, 1H), 7.11 - 7.07 (m, 5H), 7.00 (ddd, *J* = 7.6, 7.6, and 1.6 Hz, 1H), 6.81 (ddd, *J* = 8.0, 8.0, and 1.2 Hz, 1H), 6.36 (dd, *J* = 7.6, and 1.2 Hz, 1H), 3.83 (d, *J* = 10.8 Hz, 3H), 3.67 (d, *J* = 10.8 Hz, 3H), 3.34 (ddd, *J* = 15.6, 8.4, and 6.4 Hz, 1H), 2.05 (ddd, *J* = 17.2, 8.8, and 5.2 Hz, 1H), 1.86 (ddd, *J* = 12.0, 6.8, and 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 133.9 (d, J_{CP} = 2.4 Hz), 133.8 (d, J_{CP} = 1.8 Hz), 131.8 (d, J_{CP} = 3.9 Hz), 129.3, 128.0 (d, J_{CP} = 2.3 Hz), 127.8, 127.7, 127.4 (d, J_{CP} = 2.7 Hz), 126.2, 53.8 (d, J_{CP} = 6.5 Hz), 53.3 (d, J_{CP} = 6.6 Hz), 29.3 (d, J_{CP} = 187.2 Hz), 25.3 (d, J_{CP} = 1.3 Hz), 15.1 (d, J_{CP} = 3.3 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 29.47; LC-MS: *m/z* calcd for $C_{17}H_{19}ClO_3P$ ($M+H^+$): 337.0, found: 337.0; HRMS (ESI): *m/z* calcd for $C_{17}H_{19}ClO_3P$ ($M+H^+$): 337.0760, found: 337.0755; HPLC analysis: 96% ee (OJ-H column, 1% 2-propanol in hexanes, 1.0 mL/min, 230 nm, t_R = 32.40 (minor) and 43.07 (major) min).

Dimethyl (2-(2-chlorophenyl)-1-phenylcyclopropyl)phosphonate (11e')



Synthesis of the racemic compound of **11e'** was carried out using $Rh_2(OAc)_4$ (1% mol) as catalyst in the same reaction conditions as described above to obtain 75% yield. NMR spectroscopic data is same as **11e**.

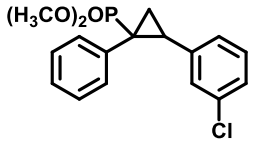
Dimethyl ((*1S,2R*)-2-(3-chlorophenyl)-1-phenylcyclopropyl)phosphonate (11f)



Dimethyl ((*1S,2R*)-2-(3-chlorophenyl)-1-phenylcyclopropyl)phosphonate (**11f**) was prepared by known method.[18] A stirred mixture of 3-chlorostyrene (**10f**, 163.5 mg, 1.18 mmol, 5.9 eq.) and Rh_2(*S*-PTAD)$_4$ (3.1 mg, 1 mol %, 0.002 eq.) in pentane (5 mL) was heated under reflux under an argon atmosphere. To this solution was added the dimethyl (diazo(phenyl)methyl)phosphonate (**9**) (45.2 mg, 0.2 mmol, 1.0 eq.) in pentane (15 mL) via syringe pump over 8 h, and the mixture was then stirred for an additional 4 h. The mixture was then concentrated *in vacuo*, and the residue was purified on silica (SiO_2, EA 100%) to obtain 86% yield (94% ee) as a white powder. IR (neat) ν (cm^{-1}) 2952, 1598, 1571, 1446, 1247, 1182, 1027, 952, 850, 827, 783, 750, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 - 7.12 (m, 3H), 7.05 - 7.02 (m, 3H), 6.95 (t, 1H), 6.76 (t, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 3.72 (d, *J* = 10.8 Hz, 3H), 3.67 (d, *J* = 10.8 Hz, 3H), 2.96 (ddd, *J* = 15.6, 8.8, and 6.4 Hz, 1H), 2.07 (ddd, *J* = 17.2, 8.8, and 5.2 Hz, 1H), 1.70 (ddd, *J* = 12.4, 6.8, and 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5 (d, J_{CP} = 3.0 Hz), 133.8, 133.2, 132.3 (d, J_{CP} = 4.4 Hz), 129.0, 128.5, 128.2 (d, J_{CP} = 2.5 Hz), 127.7 (d, J_{CP} = 3.3 Hz), 126.6, 126.2, 53.6 (d, J_{CP} = 6.8 Hz), 53.5 (d, J_{CP} = 6.8 Hz), 29.8 (d, J_{CP} = 186.8 Hz), 26.8 (d, J_{CP}

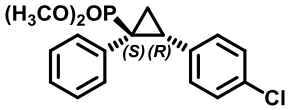
= 1.9 Hz), 16.9 (d, J_{CP} = 3.8 Hz); ^{31}P NMR (200 MHz, $CDCl_3$) δ 29.19; LC-MS: *m/z* calcd for $C_{17}H_{19}ClO_3P$ ($M+H^+$): 337.0, found: 337.0; HRMS (ESI): *m/z* calcd for $C_{17}H_{19}ClO_3P$ ($M+H^+$): 337.0760, found: 337.0754; HPLC analysis: 94% ee (OJ column, 1% 2-propanol in hexanes, 1.0 mL/min, 230 nm, t_R = 39.94 (minor) and 57.15 (major) min).

Dimethyl (2-(3-chlorophenyl)-1-phenylcyclopropyl)phosphonate (11f')



Synthesis of the racemic compound of **11f'** was carried out using $Rh_2(OAc)_4$ (1% mol) as catalyst in the same reaction conditions as described above to obtain 64% yield. NMR spectroscopic data is same as **11f**.

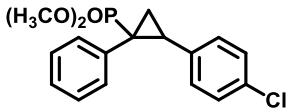
Dimethyl ((*1S,2R*)-2-(4-chlorophenyl)-1-phenylcyclopropyl)phosphonate (11g)



Dimethyl ((*1S,2R*)-2-(4-chlorophenyl)-1-phenylcyclopropyl)phosphonate (**11g**) was prepared by known method.[18] A stirred mixture of 4-chlorostyrene (**10g**, 163.5 mg, 1.18 mmol, 5.9 eq.) and Rh_2(*S*-PTAD)$_4$ (3.1 mg, 1 mol %, 0.002 eq.) in pentane (5 mL) was heated under reflux under an argon atmosphere. To this solution was added the dimethyl (diazo(phenyl)methyl)phosphonate (**9**) (45.2 mg, 0.2 mmol, 1.0 eq.) in pentane

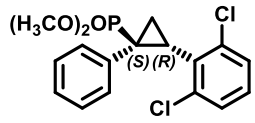
(15 mL) via syringe pump over 8 h, and the mixture was then stirred for an additional 4 h. The mixture was then concentrated *in vacuo*, and the residue was purified on silica (SiO_2, EA 100%) to obtain 97% yield (97% ee) as a white powder. IR (neat) ν (cm^{-1}) 2951, 1600, 1494, 1446, 1246, 1182, 1115, 1089, 1065, 1027, 964, 857, 826, 771, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 - 7.11 (m, 3H), 7.07 - 7.03 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 2H), 3.70 (d, *J* = 10.8 Hz, 3H), 3.67 (d, *J* = 10.8 Hz, 3H), 2.96 (ddd, *J* = 16.0, 9.0, and 6.5 Hz, 1H), 2.07 (ddd, J = 17.0, 9.0, and 5.0 Hz, 1H), 1.68 (ddd, *J* = 12.0, 6.0, and 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.8 (d, J_{CP} = 2.9 Hz), 133.3 (d, J_{CP} = 2.0 Hz), 132.3 (d, J_{CP} = 4.4 Hz), 129.4, 128.2 (d, J_{CP} = 2.6 Hz), 128.0 (two aromatic signals overlapping), 127.6 (d, J_{CP} = 3.0 Hz), 53.6 (d, J_{CP} = 6.8 Hz), 53.5 (d, J_{CP} = 6.8 Hz), 29.8 (d, J_{CP} = 185.9 Hz), 26.6 (d, J_{CP} = 1.9 Hz), 17.0 (d, J_{CP} = 3.5 Hz); ^{31}P NMR (200 MHz, $CDCl_3$) δ 29.31; LC-MS: *m/z* calcd for $C_{17}H_{19}ClO_3P$ ($M+H^+$): 337.0, found: 337.0; HRMS (ESI): *m/z* calcd for $C_{17}H_{19}ClO_3P$ ($M+H^+$): 337.0760, found: 337.0752; HPLC analysis: 97% ee (OJ column, 5% 2-propanol in hexanes, 1.0 mL/min, 230 nm, t_R = 13.82 (minor) and 16.66 (major) min).

Dimethyl (2-(4-chlorophenyl)-1-phenylcyclopropyl)phosphonate (11g')



Synthesis of the racemic compound of **11g'** was carried out using $Rh_2(OAc)_4$ (1% mol) as catalyst in the same reaction conditions as described above to obtain 61% yield. NMR spectroscopic data is same as **11g**.

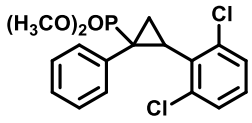
Dimethyl ((*1S,2R*)-2-(2,6-dichlorophenyl)-1-phenylcyclopropyl)phosphonate (11h)



Dimethyl ((*1S,2R*)-2-(2,6-dichlorophenyl)-1-phenylcyclopropyl)phosphonate (**11h**) was prepared by known method.[18] A stirred mixture of 2,6-dichlorostyrene (**10h**, 204.2 mg, 1.18 mmol, 5.9 eq.) and Rh_2(*S*-PTAD)$_4$ (3.1 mg, 1 mol %, 0.002 eq.) in pentane (5 mL) was heated under reflux under an argon atmosphere. To this solution was added the dimethyl (diazo(phenyl)methyl)phosphonate (**9**) (45.2 mg, 0.2 mmol, 1.0 eq.) in pentane (15 mL) via syringe pump over 8 h, and the mixture was then stirred for an additional 4 h. The mixture was then concentrated *in vacuo*, and the residue was purified on silica (SiO_2, EA 100%) to obtain 76% yield (95% ee) as a white powder. IR (neat) ν (cm^{-1}) 3052, 2954, 2487, 1713, 1494, 1449, 1247, 1041, 974, 865, 821, 788, 753, 707, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.29 (m, 2H), 7.11 - 7.07 (m, 5H), 6.90 (ddd, *J* = 8.0, 8.0, and 0.4 Hz, 1H), 3.79 (d, *J* = 10.4 Hz, 3H), 3.69 (d, *J* = 10.4 Hz, 3H), 3.11 (ddd, *J* = 16.8, 9.6, and 7.6 Hz, 1H), 2.91 (ddd, *J* = 13.2, 7.2, and 5.6 Hz, 1H), 2.20 (ddd, *J* = 17.6, 9.6, and 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7 (d, J_{CP} = 2.9 Hz), 131.4 (d, J_{CP} = 2.5 Hz), 131.0 (d, J_{CP} = 4.5 Hz), 130.5 (d, J_{CP} = 4.0 Hz), 128.5, 128.3, 128.0 (d, J_{CP} = 1.8 Hz), 127.4 (d, J_{CP} = 2.3 Hz), 53.7 (d, J_{CP} = 6.8 Hz), 53.5 (d, J_{CP} = 6.5 Hz), 27.9 (d, J_{CP} = 189.6 Hz), 27.7, 18.5 (d, J_{CP} = 3.8 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 30.03; LC-MS: *m/z* calcd for $C_{17}H_{18}Cl_2O_3P$ ($M+H^+$): 371.0, found: 371.0; HRMS (ESI): *m/z* calcd for $C_{17}H_{18}Cl_2O_3P$ ($M+H^+$): 371.0371, found: 371.0368; HPLC analysis: 95%

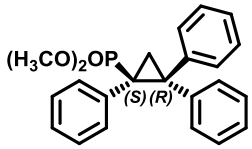
ee (OJ column, 1% 2-propanol in hexanes, 1.0 mL/min, 230 nm, t_R = 25.02 (minor) and 29.97 (major) min).

Dimethyl (2-(2,6-dichlorophenyl)-1-phenylcyclopropyl)phosphonate (11h')



Synthesis of the racemic compound of **11h'** was carried out using $Rh_2(OAc)_4$ (1% mol) as catalyst in the same reaction conditions as described above to obtain 24% yield. NMR spectroscopic data is same as **11h**.

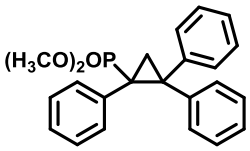
Dimethyl (*R*)-(1,2,2-triphenylcyclopropyl)phosphonate (11i)



Dimethyl (*R*)-(1,2,2-triphenylcyclopropyl)phosphonate (**11i**) was prepared by known method.[18] A stirred mixture of 1,1-diphenylethylene (**10i**, 212.7 mg, 1.18 mmol, 5.9 eq.) and Rh_2(*S*-PTAD)$_4$ (3.1 mg, 1 mol %, 0.002 eq.) in pentane (5 mL) was heated under reflux under an argon atmosphere. To this solution was added the dimethyl (diazo(phenyl)methyl)phosphonate (**9**) (45.2 mg, 0.2 mmol, 1.0 eq.) in pentane (15 mL) via syringe pump over 8 h, and the mixture was then stirred for an additional 4 h. The mixture was then concentrated *in vacuo*, and the residue was purified on silica (SiO_2, EA 100%) to obtain 87% yield (99% ee) as a white powder. IR (neat) ν (cm^{-1}) 2954, 2852,

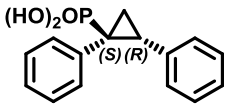
1714, 1560, 1493, 1435, 1248, 1178, 1031, 832, 777, 713, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.36 (t, 3H), 7.23 - 7.05 (m, 8H), 6.97 (t, 2H), 6.89 (t, 1H), 3.30 (d, *J* = 10.8 Hz, 3H), 3.03 (d, *J* = 10.8 Hz, 3H), 2.45 (dd, *J* = 10.4, and 5.2 Hz,1H), 2.40 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 140.5 (d, J_{CP} = 3.2 Hz), 134.7 (d, J_{CP} = 3.4 Hz), 130.5, 129.3 (d, J_{CP} = 1.3 Hz), 128.3, 128.0 (d, J_{CP} = 1.6 Hz), 127.8 (two aromatic signals overlapping), 127.2 (d, J_{CP} = 2.4 Hz), 126.9, 126.3, 53.3 (d, J_{CP} = 7.0 Hz), 52.4 (d, J_{CP} = 6.7 Hz), 43.1 (d, J_{CP} = 1.9 Hz), 35.7 (d, J_{CP} = 185.6 Hz), 21.3 (d, J_{CP} = 4.8 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 26.47; LC-MS: *m/z* calcd for $C_{23}H_{24}O_3P$ ($M+H^+$): 378.0, found: 378.0; HRMS (ESI): *m/z* calcd for $C_{23}H_{24}O_3P$ ($M+H^+$): 379.1463, found: 379.1460; HPLC analysis: 99% ee (OD column, 1% 2-propanol in hexanes, 1.0 mL/min, 230 nm, t_R = 23.83 (major) and 28.59 (minor) min).

Dimethyl-(1,2,2-triphenylcyclopropyl)phosphonate (11i')



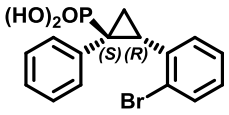
Synthesis of the racemic compound of **11i'** was carried out using $Rh_2(OAc)_4$ (1% mol) as catalyst in the same reaction conditions as described above to obtain 65% yield. NMR spectroscopic data is same as **11i**.

((*1S,2R*)-1,2-Diphenylcyclopropyl)phosphoric acid (12a)



((*1S,2R*)-1,2-Diphenylcyclopropyl)phosphoric acid (**12a**) was prepared by known method.[30] To a solution of dimethyl ((*1S,2R*)-1,2-diphenylcyclopropyl)phosphonate (**11a**) (108.1 mg, 0.36 mmol, 1.0 eq.) and NaI (161.9 mg, 1.08 mmol, 3.0 eq.) in acetonitrile (25 mL), chlorotrimethylsilane (117.3 mg, 1.08 mmol, 3.0 eq.) was added with continuous good stirring. The reaction mixture was then heated under reflux for 1 day. The reaction mixture was cooled to RT, and the product was filtered and evaporated to remove solvent to obtain **12a**. $[\alpha]_D^{20}$ = - 10.3 ^{o} (C 0.32, $CHCl_3$); IR (neat) ν (cm^{-1}) 3431, 2927, 2314, 1734, 1621, 1494, 1373, 1240, 1095, 1029, 988, 938, 834, 771, 700; ^{1}H NMR (600 MHz, CD_3OD) δ 7.14 - 7.04 (m, 8H), 6.80 - 6.78 (m, 2H), 2.92 (ddd, *J* = 16.4, 8.8, and 6.4 Hz, 1H), 1.90 (ddd, *J* = 17.6, 8.8, and 5.2 Hz, 1H), 1.76 (ddd, *J* = 11.6, 6.4, and 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7 (d, J_{CP} = 2.3 Hz), 136.9 (d, J_{CP} = 2.0 Hz), 134.0 (d, J_{CP} = 3.9 Hz), 129.3, 128.7, 128.6 (d, J_{CP} = 2.3 Hz), 127.6 (d, J_{CP} = 2.6 Hz), 127.0, 33.3 (d, J_{CP} = 179.6 Hz), 28.5, 17.3 (d, J_{CP} = 3.0 Hz); ^{31}P NMR (240 MHz, CD_3OD) δ 24.65; HRMS (ESI): *m/z* calcd for $C_{15}H_{16}O_3P$ ($M+H^+$): 275.0837, found: 275.0832.

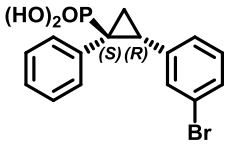
((*1S,2R*)-2-(2-Bromophenyl)-1-phenylcyclopropyl)phosphoric acid (12b)



((*1S,2R*)-2-(2-Bromophenyl)-1-phenylcyclopropyl)phosphoric acid (**12b**) was prepared by known method.[30] To a solution of dimethyl ((*1S,2R*)-2-(2-bromophenyl)-1-phenylcyclopropyl)phosphonate (**11b**) (58.2 mg, 0.15 mmol, 1.0 eq.) and NaI (67.5 mg, 0.45 mmol, 3.0 eq.) in acetonitrile (11 mL), chlorotrimethylsilane (48.9 mg, 0.45 mmol,

3.0 eq.) was added with continuous good stirring. The reaction mixture was then heated under reflux for 1 day. The reaction mixture was cooled to RT, and the product was filtered and evaporated to remove solvent to obtain **12b**. $[\alpha]_D^{20}$ = - 141.0 ^{o} (C 0.30, $CHCl_3$); IR (neat) ν (cm^{-1}) 2981, 1732, 1493, 1444, 1374, 1259, 1043, 943, 751, 722, 700; ^{1}H NMR (600 MHz, CD_3OD) δ 7.51 (dd, *J* = 7.6, and 1.2 Hz, 1H), 7.22 (d, *J* = 2.0 Hz, 2H), 7.05 - 7.01 (m, 3H), 6.93 (ddd, *J* = 7.2, 7.2, and 1.6 Hz, 1H), 6.87 (ddd, *J* = 7.6, 7.6, and 1.6 Hz, 1H), 6.48 (dd, *J* = 7.6, and 1.6 Hz, 1H), 3.21 (ddd, *J* = 15.6, 8.0, and 7.6 Hz, 1H), 1.95 - 1.83 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7 (d, J_{CP} = 2.1 Hz), 137.9 (d, J_{CP} = 2.4 Hz), 133.6 (d, J_{CP} = 3.9 Hz), 133.5, 129.3 (d, J_{CP} = 1.5 Hz), 128.5, 128.4 (d, J_{CP} = 2.0 Hz), 128.0, 127.7, 127.3 (d, J_{CP} = 2.6 Hz), 33.7 (d, J_{CP} = 178.2 Hz), 29.6 (d, J_{CP} = 1.4 Hz), 16.0 (d, J_{CP} = 2.9 Hz); ^{31}P NMR (240 MHz, CD_3OD) δ 24.31; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}BrO_3P$ ($M+H^+$): 352.9942, found: 352.9939.

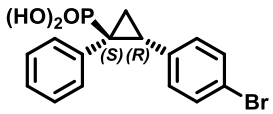
((*1S,2R*)-2-(3-Bromophenyl)-1-phenylcyclopropyl)phosphoric acid (12c)



((*1S,2R*)-2-(3-Bromophenyl)-1-phenylcyclopropyl)phosphoric acid (**12c**) was prepared by known method.[30] To a solution of dimethyl ((*1S,2R*)-2-(3-bromophenyl)-1-phenylcyclopropyl)phosphonate (**11c**) (83.6 mg, 0.22 mmol, 1.0 eq.) and NaI (71.7 mg, 0.66 mmol, 3.0 eq.) in acetonitrile (16 mL), chlorotrimethylsilane (98.9 mg, 0.66 mmol, 3.0 eq.) was added with continuous good stirring. The reaction mixture was then heated under reflux for 1 day. The reaction mixture was cooled to RT, and the product was

filtered and evaporated to remove solvent to obtain **12c**. $[\alpha]_D^{20}$ = - 33.4 ^{o} (C 0.42, $CHCl_3$); IR (neat) ν (cm^{-1}) 3436, 2981, 1711, 1623, 1596, 1565, 1478, 1374, 1261, 1043, 995, 930, 699; ^{1}H NMR (600 MHz, CD_3OD) δ 7.18 - 7.13 (m, 6H), 6.96 - 6.92 (m, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 2.89 (ddd, *J* = 15.6, 8.8, and 6.4 Hz, 1H), 1.93 (ddd, *J* = 17.2, 8.8, and 5.2 Hz, 1H), 1.77 (ddd, *J* = 12.0, 5.6, and 4.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.1 (d, J_{CP} = 2.3 Hz), 137.1 (d, J_{CP} = 1.7 Hz), 133.8 (d, J_{CP} = 3.8 Hz), 132.3, 130.2, 129.8, 128.7 (d, J_{CP} = 5.6 Hz), 128.0, 127.7 (d, J_{CP} = 2.4 Hz), 122.7, 34.2 (d, J_{CP} = 177.3 Hz), 28.0, 17.7 (d, J_{CP} = 2.9 Hz); ^{31}P NMR (240 MHz, CD_3OD) δ 25.01; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}BrO_3NaP$ ($M+Na^+$): 374.9762, found: 374.9758.

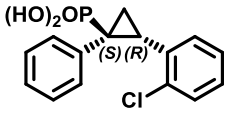
((*1S,2R*)-2-(4-Bromophenyl)-1-phenylcyclopropyl)phosphoric acid (12d)



((*1S,2R*)-2-(4-Bromophenyl)-1-phenylcyclopropyl)phosphoric acid (**12d**) was prepared by known method.[30] To a solution of dimethyl ((*1S,2R*)-2-(4-bromophenyl)-1-phenylcyclopropyl)phosphonate (**11d**) (65.5 mg, 0.17 mmol, 1.0 eq.) and NaI (76.4 mg, 0.51 mmol, 3.0 eq.) in acetonitrile (12 mL), chlorotrimethylsilane (55.4 mg, 0.51 mmol, 3.0 eq.) was added with continuous good stirring. The reaction mixture was then heated under reflux for 1 day. The reaction mixture was cooled to RT, and the product was filtered and evaporated to remove solvent to obtain **12d**. $[\alpha]_D^{20}$ = - 19.8 ^{o} (C 0.35, $CHCl_3$); IR (neat) ν (cm^{-1}) 3428, 2979, 2360, 1712, 1490, 1259, 1073, 1008, 928, 841, 715, 699; ^{1}H NMR (600 MHz, CD_3OD) δ 6.72 (d, *J* = 8.4 Hz, 2H), 7.18 - 7.12 (m, 5H),

6.72 (d, *J* = 8.4 Hz, 2H), 2.89 (ddd, *J* = 15.6, 8.8, and 6.4 Hz, 1H), 1.92 (ddd, *J* = 17.2, 8.8, and 5.2 Hz, 1H), 1.75 (ddd, *J* = 12.0, 6.4, and 5.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.5 (d, J_{CP} = 2.4 Hz), 136.9 (d, J_{CP} = 2.0 Hz), 133.9 (d, J_{CP} = 3.8 Hz), 131.7, 131.1, 128.8 (d, J_{CP} = 2.1 Hz), 127.8 (d, J_{CP} = 2.6 Hz), 120.7, 33.7 (d, J_{CP} = 178.7 Hz), 28.0, 17.5 (d, J_{CP} = 2.9 Hz); ^{31}P NMR (240 MHz, CD_3OD) δ 24.83; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}BrO_3NaP$ ($M+Na^+$): 374.9762, found: 374.9759.

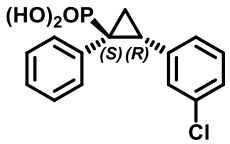
((*1S,2R*)-2-(2-Chlorophenyl)-1-phenylcyclopropyl)phosphoric acid (12e)



((*1S,2R*)-2-(2-Chlorophenyl)-1-phenylcyclopropyl)phosphoric acid (**12e**) was prepared by known method.[30] To a solution of dimethyl ((*1S,2R*)-2-(2-chlorophenyl)-1-phenylcyclopropyl)phosphonate (**11e**) (54.6 mg, 0.16 mmol, 1.0 eq.) and NaI (71.9 mg, 0.48 mmol, 3.0 eq.) in acetonitrile (12 mL), chlorotrimethylsilane (52.1 mg, 0.48 mmol, 3.0 eq.) was added with continuous good stirring. The reaction mixture was then heated under reflux for 1 day. The reaction mixture was cooled to RT, and the product was filtered and evaporated to remove solvent to obtain **12e**. $[\alpha]_D^{20}$ = - 121.9 ^{o} (C 0.43, $CHCl_3$); IR (neat) ν (cm^{-1}) 3446, 2981, 2360, 1731, 1623, 1480, 1374, 1258, 1048, 998, 931, 752, 699; ^{1}H NMR (600 MHz, CD_3OD) δ 7.34 (dd, *J* = 8.0, and 1.2 Hz, 1H), 7.23 - 7.20 (m, 2H), 7.06 - 6.99 (m, 4H), 6.86 (ddd, *J* = 7.6, 7.6, and 1.2 Hz, 1H), 6.51 (dd, *J* = 8.0, and 1.2 Hz, 1H), 3.23 (ddd, *J* = 15.2, 8.4, and 6.4 Hz, 1H), 1.92 (dd, *J* = 11.6, and 5.6 Hz, 1H), 1.87 (ddd, *J* = 10.8, 8.0, and 2.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.0

(d, J_{CP} = 3.0 Hz), 137.3, 137.1 (d, J_{CP} = 2.7 Hz), 133.5 (d, J_{CP} = 4.2 Hz), 130.0, 129.2 (d, J_{CP} = 1.8 Hz), 128.5 (d, J_{CP} = 2.6 Hz), 128.3, 127.3 (d, J_{CP} = 2.9 Hz), 127.1, 33.7 (d, J_{CP} = 178.1 Hz), 26.8 (d, J_{CP} = 1.8 Hz), 15.6 (d, J_{CP} = 3.5 Hz); ^{31}P NMR (240 MHz, CD_3OD) δ 24.58; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}ClO_3NaP$ ($M+Na^+$): 331.0267, found: 331.0264.

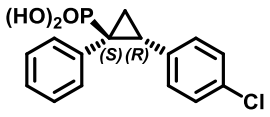
((*1S,2R*)-2-(3-Chlorophenyl)-1-phenylcyclopropyl)phosphoric acid (12f)



((*1S,2R*)-2-(3-Chlorophenyl)-1-phenylcyclopropyl)phosphoric acid (**12f**) was prepared by known method.[30] To a solution of dimethyl ((*1S,2R*)-2-(3-chlorophenyl)-1-phenylcyclopropyl)phosphonate (**11f**) (63.9 mg, 0.19 mmol, 1.0 eq.) and NaI (85.4 mg, 0.57 mmol, 3.0 eq.) in acetonitrile (14 mL), chlorotrimethylsilane (61.9 mg, 0.57 mmol, 3.0 eq.) was added with continuous good stirring. The reaction mixture was then heated under reflux for 1 day. The reaction mixture was cooled to RT, and the product was filtered and evaporated to remove solvent to obtain **12f**. $[\alpha]_D^{20}$ = - 31.8 ^{o} (C 0.57, $CHCl_3$); IR (neat) ν (cm^{-1}) 3460, 3023, 1717, 1598, 1572, 1492, 1446, 1374, 931, 835, 781, 700; ^{1}H NMR (600 MHz, CD_3OD) δ 7.17 - 7.10 (m, 5H), 7.00 - 6.97 (m, 2H), 6.80 - 6.79 (m, 1H), 6.72 - 6.69 (m, 1H), 2.89 (ddd, *J* = 16.0, 8.8, and 6.4 Hz, 1H), 1.94 (ddd, *J* = 17.2, 8.8, and 5.2 Hz, 1H), 1.71 (ddd, *J* = 12.0, 6.4, and 5.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.0 (d, J_{CP} = 2.3 Hz), 137.3 (d, J_{CP} = 1.2 Hz), 134.6, 133.9 (d, J_{CP} = 3.8 Hz), 130.0, 129.3, 128.7 (d, J_{CP} = 1.8 Hz), 127.6, 127.6, 126.8, 34.3 (d, J_{CP} = 176.7 Hz), 28.1,

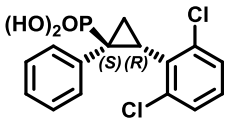
17.7 (d, J_{CP} = 2.9 Hz); ^{31}P NMR (240 MHz, CD_3OD) δ 24.00; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}ClO_3NaP$ ($M+Na^+$): 331.0267, found: 331.0264.

((*1S,2R*)-2-(4-Chlorophenyl)-1-phenylcyclopropyl)phosphoric acid (12g)



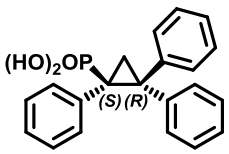
((*1S,2R*)-2-(4-Chlorophenyl)-1-phenylcyclopropyl)phosphoric acid (**12g**) was prepared by known method.[30] To a solution of dimethyl ((*1S,2R*)-2-(4-chlorophenyl)-1-phenylcyclopropyl)phosphonate (**11g**) (71.6 mg, 0.21 mmol, 1.0 eq.) and NaI (94.4 mg, 0.63 mmol, 3.0 eq.) in acetonitrile (15 mL), chlorotrimethylsilane (68.4 mg, 0.63 mmol, 3.0 eq.) was added with continuous good stirring. The reaction mixture was then heated under reflux for 1 day. The reaction mixture was cooled to RT, and the product was filtered and evaporated to remove solvent to obtain **12g**. $[\alpha]_D^{20}$ = - 5.7 ^{o} (C 0.40, $CHCl_3$); IR (neat) ν (cm^{-1}) 3433, 2982, 1735, 1623, 1495, 1446, 1374, 1241, 1114, 1013, 997, 939, 844, 699; ^{1}H NMR (600 MHz, CD_3OD) δ 7.15 - 7.10 (m, 5H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 2.90 (ddd, *J* = 15.6, 8.8, and 6.4 Hz, 1H), 1.96 (ddd, *J* = 17.2, 8.4, and 5.2 Hz, 1H), 1.76 (ddd, *J* = 11.6, 6.0, and 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8 (d, J_{CP} = 2.6 Hz), 136.7 (d, J_{CP} = 2.0 Hz), 133.9 (d, J_{CP} = 3.8 Hz), 132.8, 130.8, 128.8 (d, J_{CP} = 2.1 Hz), 128.7, 127.8 (d, J_{CP} = 2.6 Hz), 33.5 (d, J_{CP} = 179.4 Hz), 27.9, 17.5 (d, J_{CP} = 3.0 Hz); ^{31}P NMR (240 MHz, CD_3OD) δ 24.95; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}ClO_3NaP$ ($M+Na^+$): 331.0267, found: 331.0263.

((*1S,2R*)-2-(2,6-Dichlorophenyl)-1-phenylcyclopropyl)phosphoric acid (12h)



((*1S,2R*)-2-(2,6-Dichlorophenyl)-1-phenylcyclopropyl)phosphoric acid (**12h**) was prepared by known method.[30] To a solution of dimethyl ((*1S,2R*)-2-(2,6-dichlorophenyl)-1-phenylcyclopropyl)phosphonate (**11h**) (57.5 mg, 0.15 mmol, 1.0 eq.) and NaI (67.5 mg, 0.45 mmol, 3.0 eq.) in acetonitrile (12 mL), chlorotrimethylsilane (48.9 mg, 0.45 mmol, 3.0 eq.) was added with continuous good stirring. The reaction mixture was then heated under reflux for 1 day. The reaction mixture was cooled to RT, and the product was filtered and evaporated to remove solvent to obtain **12h**. $[\alpha]_D^{20}$ = - 34.0 ^{o} (C 0.29, $CHCl_3$); IR (neat) ν (cm^{-1}) 2981, 1713, 1558, 1493, 1443, 1429, 1374, 1260, 1044, 936, 778, 699; ^{1}H NMR (600 MHz, CD_3OD) δ 7.39 (ddd, *J* = 5.6, 4.4, and 2.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.08 - 7.04 (m, 4H), 7.00 (t, 1H), 3.05 (ddd, *J* = 16.4, 9.2, and 7.2 Hz, 1H), 2.86 (ddd, *J* = 12.8, 6.8, and 6.0 Hz, 1H), 2.02 (ddd, *J* = 17.2, 9.2, and 5.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.4 (d, J_{CP} = 3.0 Hz), 134.1 (d, J_{CP} = 2.0 Hz), 132.5 (d, J_{CP} = 4.2 Hz), 132.0 (d, J_{CP} = 3.6 Hz), 130.0, 129.2, 128.5, 127.6 (d, J_{CP} = 1.5 Hz), 31.3 (d, J_{CP} = 183.6 Hz), 29.4, 19.2 (d, J_{CP} = 3.0 Hz); ^{31}P NMR (240 MHz, CD_3OD) δ 25.08; HRMS (ESI): *m/z* calcd for $C_{15}H_{13}Cl_2O_3NaP$ ($M+Na^+$): 364.9877, found: 364.9874.

(*R*)-(1,2,2-Triphenylcyclopropyl)phosphoric acid (12i)



(*R*)-(1,2,2-Triphenylcyclopropyl)phosphoric acid (**12i**) was prepared by known method.[30] To a solution of dimethyl (*R*)-(1,2,2-triphenylcyclopropyl)phosphonate (**11i**) (136.2 mg, 0.36 mmol, 1.0 eq.) and NaI (161.9 mg, 1.08 mmol, 3.0 eq.) in acetonitrile (25 mL), chlorotrimethylsilane (117.3 mg, 1.08 mmol, 3.0 eq.) was added with continuous good stirring. The reaction mixture was then heated under reflux for 1 day. The reaction mixture was cooled to RT, and the product was filtered and evaporated to remove solvent to obtain **12i**. $[\alpha]_D^{20}$ = - 15.2 ^{o} (C 0.67, $CHCl_3$); IR (neat) ν (cm^{-1}) 3431, 2927, 1734, 1621, 1494, 1445, 1373, 1240, 1029, 988, 938, 834, 771, 699; ^{1}H NMR (600 MHz, CD_3OD) δ 7.74 (dd, *J* = 8.4, and 1.2 Hz, 2H), 7.28 (t, 3H), 7.19 - 7.05 (m, 6H), 6.99 (dd, *J* = 7.2, and 1.2 Hz, 1H), 6.91 (t, 2H), 6.83 (t, 1H), 2.50 (dd, *J* = 9.6, and 5.2 Hz, 1H), 2.30 (dd, *J* = 18.4, and 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.8 (d, J_{CP} = 5.0 Hz), 142.9 (d, J_{CP} = 2.4 Hz), 138.2 (d, J_{CP} = 2.7 Hz), 133.4, 131.7, 130.5, 129.1, 128.6 (two aromatic signals overlapping), 127.5, 127.4 (d, J_{CP} = 2.3 Hz), 126.8, 44.6 (d, J_{CP} = 1.8 Hz), 37.8 (d, J_{CP} = 180.0 Hz), 22.1 (d, J_{CP} = 3.5 Hz); ^{31}P NMR (240 MHz, CD_3OD) δ 25.31; HRMS (ESI): *m/z* calcd for $C_{21}H_{19}O_3NaP$ ($M+Na^+$): 373.0970, found: 373.0967.

General procedure A: the synthesis of C-H insertion of indoles with $Rh_2(OAc)_4$

To a flame-dried 50 mL flask containing $Rh_2(OAc)_4$ (1 mol%, 0.01 eq.), indoles (6.0 equiv.), and phosphoric acid catalyst **12a** (5 mol%, 0.05 eq.) in 8 mL dried toluene under argon atmosphere was added a solution of methyl 2-diazo-2-phenylacetate (1.0 eq.) in 8 mL dried toluene by syringe pump over 3 h at 0 °C. The solution was stirred at 0 °C overnight and warmed up to room temperature over 2 h. The mixture was concentrated

under reduced pressure and purified by Isolera chromatography in silica gel (Hexane: ether = 4:1) to provide the corresponding products.

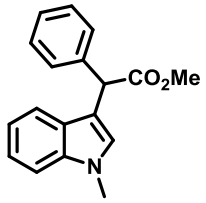
General procedure B: the synthesis of C-H insertion of indoles with $Rh_2(Oct)_4$

To a flame-dried 50 mL flask containing $Rh_2(Oct)_4$ (1 mol%, 0.01 eq.), indoles (6.0 eq.), and phosphoric acid catalyst **12a** (5 mol%, 0.05 eq.) in 8 mL dried THF under argon atmosphere was added a solution of methyl 2-diazo-2-phenylacetate (1.0 eq.) in 8 mL dried THF by syringe pump over 3 h at -41 °C. The solution was stirred at -41 °C overnight and warmed up to room temperature over 2 h. The mixture was concentrated under reduced pressure and purified by Isolera chromatography in silica gel (Hexane: ether = 4:1) to provide the corresponding products.

General procedure C: the synthesis of C-H insertion of indoles with Rh_2(*S*-DOSP)$_4$

To a flame-dried 50 mL flask containing Rh_2(*S*-DOSP)$_4$ (1 mol%, 0.01 eq.), indoles (6.0 eq.), and phosphoric acid catalyst **12a** (5 mol%, 0.05 eq.) in 8 mL dried THF under argon atmosphere was added a solution of methyl 2-diazo-2-phenylacetate (1.0 eq.) in 8 mL dried THF by syringe pump over 3 h at -41 °C. The solution was stirred at -41 °C overnight and warmed up to room temperature over 2 h. The mixture was concentrated under reduced pressure and purified by Isolera chromatography in silica gel (Hexane: ether = 4:1) to provide the corresponding products.

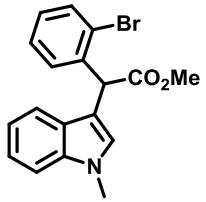
Methyl 2-(1-methyl-1*H*-indol-3-yl)-2-phenylacetate (15)



Title compound was prepared by general procedure A or B and obtained as a white solid: procedure A with **12a**: 40% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 0.7 mL/min, 30 min, 254 nm, runtime 70 min) retention times of 36.10 min (minor) and 56.43 min (major), 9% ee; procedure B and toluene with **12a**: 64% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 0.7 mL/min, 30 min, 254 nm, runtime 70 min) retention times of 36.04 min (minor) and 56.22 min (major), 11% ee; procedure B and DCM with **12a**: 66% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 0.7 mL/min, 30 min, 254 nm, runtime 70 min) retention times of 36.05 min (minor) and 56.41 min (major), 11% ee; procedure B and TFT with **12a**: 60% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 0.7 mL/min, 30 min, 254 nm, runtime 70 min) retention times of 35.92 min (minor) and 56.14 min (major), 11% ee; procedure B and hexane with **12a**: 69% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 0.7 mL/min, 30 min, 254 nm, runtime 70 min) retention times of 35.77 min (minor) and 55.94 min (major), 5% ee; procedure B and $CHCl_3$ with **12a**: 18% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 0.7 mL/min, 30 min, 254 nm, runtime 70 min) retention times of 36.56 min (minor) and 58.21 min (major), 2% ee; procedure B and THF with **12a**: 95% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 0.7 mL/min, 30 min, 254 nm, runtime 70 min) retention times of 36.06 min (minor) and 56.32 min (major), 18% ee; procedure B

and THF with **12b**: 96% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 1 mL/min, 30 min, 230 nm, runtime 60 min) retention times of 27.71 min (minor) and 40.44 min (major), 31% ee; procedure B and THF with **12d**: 93% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 1 mL/min, 30 min, 230 nm, runtime 60 min) retention times of 27.71 min (minor) and 40.18 min (major), 29% ee; procedure B and THF with **12e**: 99% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 1 mL/min, 30 min, 230 nm, runtime 60 min) retention times of 26.89 min (minor) and 40.87 min (major), 24% ee; procedure B and THF with **12h**: 96% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 1 mL/min, - (major), 13% ee; procedure B and THF with **12i**: 97% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 1 mL/min, 30 min, 230 nm, runtime 60 min) retention times of 27.82 min (minor) and 40.47 min (major), 17% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, 3H), 7.35 - 7.28 (m, 4H), 7.22 (t, 1H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.05 (s, 1H), 5.28 (s, 1H), 3.76 (s, 6H); LC-MS: *m/z* calcd for $C_{18}H_{18}NO_2$ ($M+H^+$): 280.0, found: 279.9. The spectroscopic data matches what was previously reported in the literature.[31]

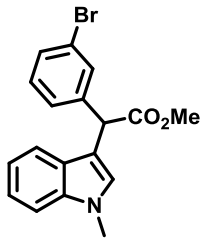
Methyl 2-(2-bromophenyl)-2-(1-methyl-*1H*-indol-3-yl)acetate (19)



Title compound was prepared by general procedure B and obtained as a white solid: 90% yield; HPLC: (Chiralcel ASH, 1% *i*-PrOH in hexane, 0.7 mL/min, 30 min, 254 nm) retention times of 9.89 min (minor) and 11.98 min (major), 6% ee; ^{1}H NMR

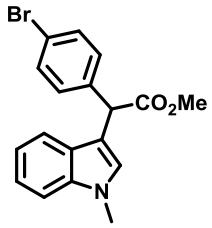
(400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.0, and 1.6 Hz, 1H), 7.48 (tt, 1H), 7.36 (dd, *J* = 7.6, and 1.6 Hz, 1H), 7.32 (tt, 1H), 7.23 (ddd, *J* = 7.2, 6.8, and 0.8 Hz, 2H), 7.19 (ddd, *J* = 5.6, 5.2, and 0.8 Hz, 1H), 7.13 - 7.06 (m, 3H), 7.04 (s, 1H), 5.71 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H); LC-MS: *m/z* calcd for $C_{18}H_{17}BrNO_2$ ($M+H^+$): 359.0, found: 358.8. The spectroscopic data matches what was previously reported in the literature.[15, 32]

Methyl 2-(3-bromophenyl)-2-(1-methyl-*1H*-indol-3-yl)acetate (20)



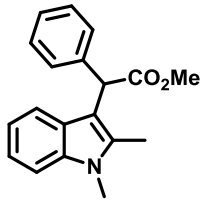
Title compound was prepared by general procedure B and obtained as a white solid: 84% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 0.7 mL/min, 30 min, 254 nm, runtime 120 min) retention times of 39.81 min (minor) and 80.29 min (major), 15% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (t, 1H), 7.45 - 7.31 (m, 5H), 7.24 - 7.17 (m, 3H), 7.10 (t, 2H), 5.24 (s, 1H), 3.78 (s, 3H), 3.77 (s, 3H); LC-MS: *m/z* calcd for $C_{18}H_{17}BrNO_2$ ($M+H^+$): 359.0, found: 358.8. The spectroscopic data matches what was previously reported in the literature.[15, 32]

Methyl 2-(4-bromophenyl)-2-(1-methyl-*1H*-indol-3-yl)acetate (21)



Title compound was prepared by general procedure B in THF and obtained as a white solid. **12a**: 82% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 0.7 mL/min, 30 min, 254 nm, runtime 80 min) retention times of 36.94 min (minor) and 62,49 min (major), 19% ee; **12b**: 85% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 1 mL/min, 30 min, 230 nm, runtime 60 min) retention times of 30.10 min (minor) and 46.24 min (major), 26% ee; **12d**: 85% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 1 mL/min, 30 min, 230 nm, runtime 60 min) retention times of 29.92 min (minor) and 46.50 min (major), 18% ee; **12e**: 91% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 1 mL/min, 30 min, 230 nm, runtime 60 min) retention times of 29.90 min (minor) and 47.18 min (major), 20% ee; **12h**: 89% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 1 mL/min, 30 min, 230 nm, runtime 60 min) retention times of 29.96 min (minor) and 47.09 min (major), 13% ee; **12i**: 90% yield; HPLC: (Chiralcel ODH, 1% *i*-PrOH in hexane, 1 mL/min, 30 min, 230 nm, runtime 60 min) retention times of 30.05 min (minor) and 46.63 min (major), 18% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.41 (m, 3H), 7.32 (t, 1H), 7.31 - 7.29 (m, 2H), 7.26 - 7.22 (m, 1H), 7.10 (t, 1H), 7.07 (s, 1H), 5.23 (s, 1H), 3.77 (s, 3H), 3.76 (s, 3H); LC-MS: *m/z* calcd for $C_{18}H_{17}BrNO_2$ ($M+H^+$): 359.0, found: 358.8. The spectroscopic data matches what was previously reported in the literature.[15, 32]

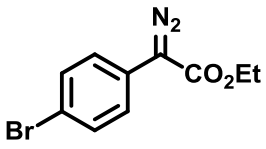
Methyl 2-(1,2-dimethyl-*1H*-indol-3-yl)-2-phenylacetate (23)



Title compound was prepared by general procedure B or C and obtained as a white solid: procedure B with **12a**: 80% yield; HPLC: (Chiralcel OD-R, 1% *i*-PrOH in hexane, 1.0 mL/min, 30 min) retention times of 18.34 min (major) and 20.39 min (minor), 17% ee; procedure B with **12b**: 91% yield; HPLC: (Chiralcel OD-R, 2% *i*-PrOH in hexane, 1.0 mL/min, 30 min) retention times of 15.63 min (major) and 18.01 min (minor), 30% ee; procedure B with **12d**: 88% yield; HPLC: (Chiralcel OD-R, 2% *i*-PrOH in hexane, 1.0 mL/min, 30 min) retention times of 14.79 min (major) and 16.90 min (minor), 21% ee; procedure B with **12e**: 83% yield; HPLC: (Chiralcel OD-R, 2% *i*-PrOH in hexane, 1.0 mL/min, 30 min) retention times of 14.96 min (major) and 17.10 min (minor), 19% ee; procedure B with **12h**: 63% yield; HPLC: (Chiralcel OD-R, 2% *i*-PrOH in hexane, 1.0 mL/min, 30 min) retention times of 14.75 min (major) and 16.82 min (minor), 28% ee; procedure B with **12i**: 99% yield; HPLC: (Chiralcel OD-R, 2% *i*-PrOH in hexane, 1.0 mL/min, 30 min) retention times of 14.80 min (major) and 16.97 min (minor), 19% ee; procedure C with **12a**: 60% yield; HPLC: (Chiralcel OD-R, 1% *i*-PrOH in hexane, 1.0 mL/min, 30 min) retention times of 18.77 min (major) and 20.68 min (minor), 21% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 1H), 7.30 - 7.23 (m, 6H), 7.16 (ddd, *J* = 8.0, 6.8, and 1.2 Hz, 1H), 7.04 (ddd, *J* = 8.0, 7.2, and 1.2 Hz, 1H), 5.32 (s, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 2.36 (s, 3H); LC-MS: *m/z* calcd for $C_{19}H_{20}NO_2$ ($M+H^+$):

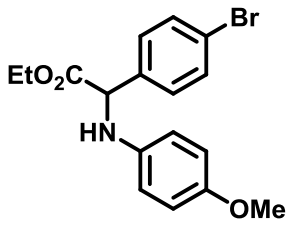
294.1, found: 294.1. The spectroscopic data matches what was previously reported in the literature.[31]

Ethyl 2-(4-bromophenyl)-2-diazoacetate (24)



Ethyl 2-(4-bromophenyl)-2-diazoacetate (**24**) was prepared by known method.[29] Ethyl 2-(4-bromophenyl)acetate (**24a**) (7.3 g, 30.0 mmol) and *p*-acetamidobenzene-sulfonyl azide (*p*-ABSA) (10.8 g, 45.0 mmol) were dissolved in acetonitrile (35 mL) and cooled to 0 ^{o}C. 1,8-Diazabicyclo-[*5,4,0*]-undec-7-ene (DBU) (8.3 g, 54.6 mmol) was added dropwise at 0 ^{o}C, and the reaction was stirred at RT overnight. The reaction mixture was poured into saturated ammonium chloride solution and extracted with diethyl ether (2 x 100 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The product was purified by flash chromatography (silica gel, 3:1 hexanes:diethyl ether) to obtain an orange solid (5.5 g, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 9.2 Hz, 2H), 7.37 (d, *J* = 9.2 Hz, 2H), 4.34 (dd, *J* = 14.4, and 7.2 Hz, 2H), 1.34 (t, 3H). The spectroscopic data matches what was previously reported in the literature.[33]

Ethyl 2-(4-bromophenyl)-2-((4-methoxyphenyl)amino)acetate (26)



To a flame-dried 10 mL flask, ethyl 2-(4-bromophenyl)-2-diazoacetate (**24**) (53.8 mg, 0.2 mmol, 1.0 eq.), *p*-anisidine (**25**) (73.9 mg, 0.6 mmol, 3.0 eq.), and phosphoric acid catalyst (5 mol%, 0.05 eq.) without/with $Rh_2(OAc)_4$ (0.9 mg, 0.002 mmol, 1 mol%, 0.01 eq.) were dissolved in DCM (5 mL) added under air atmosphere. The solution was stirred at RT overnight in the presence of blue LED. The mixture was concentrated under reduced pressure and purified by Isolera chromatography in silica gel (Hexane: ether = 4:1) to provide the corresponding product, ethyl 2-(4-bromophenyl)-2-((4-methoxyphenyl) -amino)acetate (**26**). **Catalyst 4** (7.5 mg, 0.01 mmol, 0.05 eq.) without $Rh_2(OAc)_4$: 73% yield; HPLC: (Chiralcel OD-R, 0.5% *i*-PrOH in hexane, 1.0 mL/min, 30 min, 230 nm, runtime 60 min) retention times of 39.07 min (major) and 49.44 min (minor), 7% ee; **Catalyst 4** (7.5 mg, 0.01 mmol, 0.05 eq.) with $Rh_2(OAc)_4$: 76% yield; HPLC: (Chiralcel OD-H, 0.5% *i*-PrOH in hexane, 1.0 mL/min, 60 min, 230 nm) retention times of 28.28 min (minor) and 32.43 min (major), 1% ee; **Catalyst 5** (6.0 mg, 0.01 mmol, 0.05 eq.) without $Rh_2(OAc)_4$: 81% yield; HPLC: (Chiralcel OD-R, 0.5% *i*-PrOH in hexane, 1.0 mL/min, 30 min, 230 nm, runtime 60 min) retention times of 36.50 min (major) and 41.23 min (minor), 8% ee; **Catalyst 5** (6.0 mg, 0.01 mmol, 0.05 eq.) with $Rh_2(OAc)_4$: 78 % yield; HPLC: (Chiralcel OD-H, 0.5% *i*-PrOH in hexane, 1.0 mL/min, 60 min, 230 nm) retention times of 28.43 min (major) and 32.67 min (minor), 1% ee; **12b** (3.6 mg, 0.01

mmol, 0.05 eq.) without $Rh_2(OAc)_4$: 77% yield; HPLC: (Chiralcel OD-R, 0.5% *i*-PrOH in hexane, 1.0 mL/min, 30 min, 230 nm, runtime 60 min) retention times of 35.72 min (major) and 44.87 min (minor), 5% ee; **12b** (3.6 mg, 0.01 mmol, 0.05 eq.) with $Rh_2(OAc)_4$: 76% yield; HPLC: (Chiralcel OD-H, 0.5% *i*-PrOH in hexane, 1.0 mL/min, 60 min, 230 nm) retention times of 29.18 min (minor) and 33.64 min (major), 2% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.50 (d, *J* = 8.8 Hz, 2H), 4.95 (s, 1H), 4.20 - 4.16 (m, 2H), 3.71 (s, 3H), 1.21 (ddd, *J* = 7.2, 6.8, and 0.4 Hz, 3H). The spectroscopic data matches what was previously reported in the literature.[33]

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Chapter 3: Development of Diverse Enantioselective Cyclopropyl Amine Derivatives for Inhibition of EBOV

3.1. INTRODUCTION

3.1.1. Ebola Virus (EBOV)

Ebola virus (EBOV), a member of the family *Filoviridae*, is an enveloped, single-stranded, negative-sense ribonucleic acid (RNA) linear genome and causes a severe and often fatal Ebola hemorrhagic fever (EHF), which are highly lethal zoonosis that affect both humans and nonhuman primates.[1] EBOV genome is about 18-19 kb in length and encodes seven specific genes: NP (nucleoprotein), VP35 (polymerase cofactor), VP40 (viral matrix protein), GP (surface glycoprotein that forms spikes on virions), VP30 (transcription activator), VP24 (minor viral matrix protein), and L (RNA-dependent RNA polymerase).[2-5] The matrix protein VP40 causes the formation of virus-like particles (VLP) onto the host cell because of GP exposed on VP40 surfaces.[6, 7] The subsequent virus fusion and entry occur through a complex cascade of micropinocytosis-endocytosis, endosome trafficking and proteolytic activation steps, resulting in internalized virions and the replicated viral genome.[8-13] The virus infection is characterized by massive production of proinflammatory cytokines, severe host immunosuppression and rapid viremia, and often manifests in the form of a fulminant hemorrhagic fever.[14, 15]

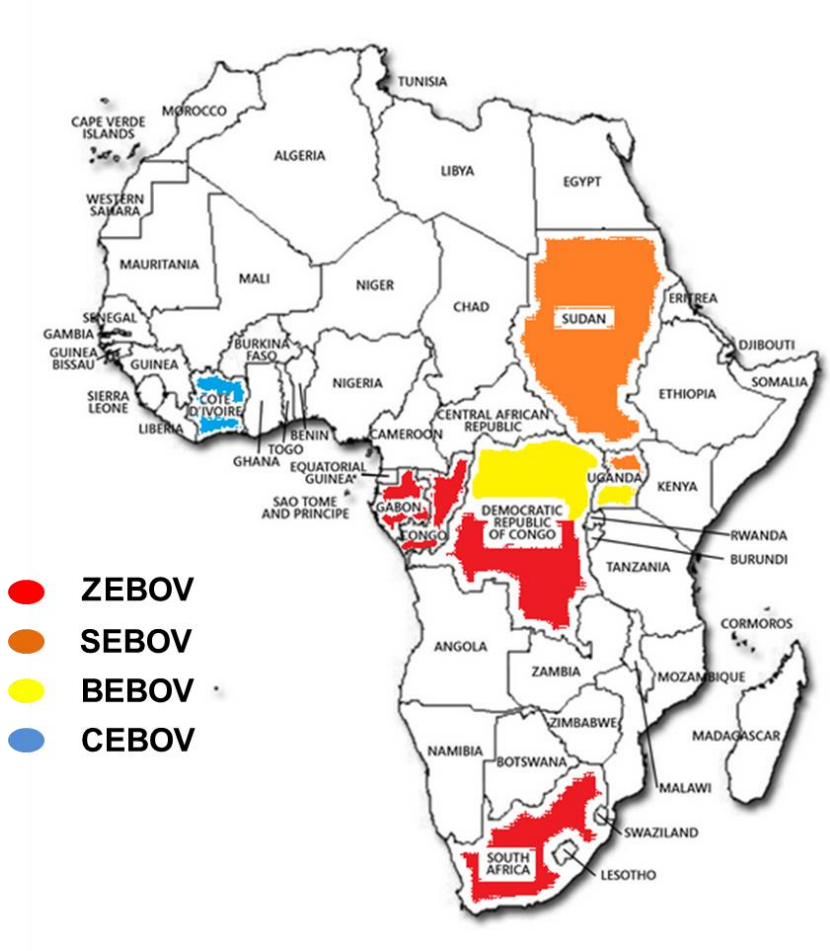


Figure 3.1. EBOV outbreaks in Africa since discovery in 1976

Five EBOV species with the genus EBOV have been known such as Zaire Ebola virus (ZEBOV), Sudan Ebola virus (SEBOV), Cote d'Ivpore Ebola virus (CEBOV), Bundibugyo Ebola virus (BEBOV), and Reston Ebola virus (REVOB), are different in the sequence, number and location of gene overlaps (**Figure 3.1**).[16] Among them, REBOV species is showed to cause disease only in nonhuman primates, but ZEBOV, SEBOV, and BEBOV are responsible for Ebola virus disease (EVD), particularly EHF.[17] Especially, ZEBOV is the largest outbreak of EHF in history in West Africa. It is the main cause of EHF in human and nonhuman primates with high mortality rate up to 90%.

The natural reservoir is believed to be bats, particularly fruit bats, and it is primarily transmitted from animals to humans, or from humans to humans through blood, body fluids, skin of EVD patients or persons who have died of EVD (**Figure 3.2**).[18] Because of its high mortality rate, EBOV is listed as a select agent, World Health Organization Risk Group 4 Pathogen (Biosafety Level 4).[19] So far, there are no approved antiviral drugs or vaccines against EBOV as the development of EBOV vaccine is difficult due to its dangerous nature and lack of accessibility. The prevention of EHF requires improving our understanding of the epidemiology.

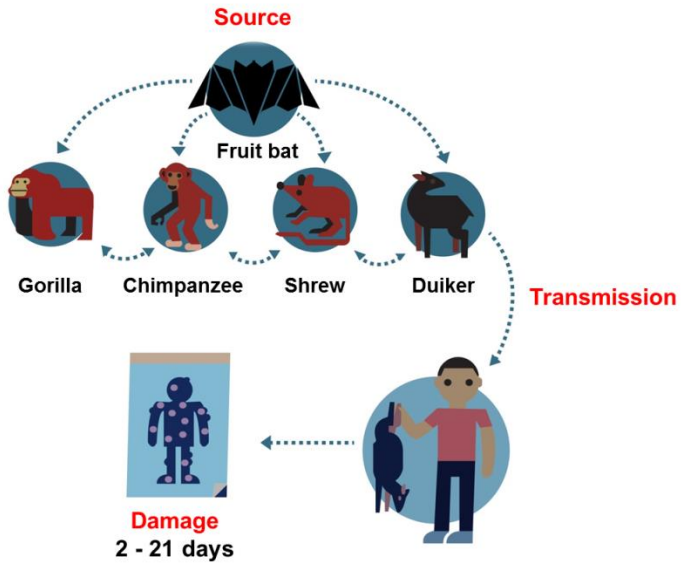


Figure 3.2. The route of the epidemic of EBOV (Source - In Africa, particular species of fruit bats are considered possible natural hosts of EBOV; Transmission - Infected bats are thought to transmit the disease to humans, or indirectly through other animals which are hunted for their meat; Damage - Incubation period from 2 to 21 days. Death from the disease is often caused by multiple organ failure and tissue death) (adapted from https://www.shutterstock.com/image-vector/ebola-virus-disease-infographics-212896825)

As EBOV was first identified in 1976, intermittent outbreaks of EVD have been reported in Africa area with high mortality.[20] Zaire species was first introduced in diverse regions with high mortality rate up to 88%. Sudan virus has discovered in Sudan in the 1970s and 2000s, and Uganda in 2000 with approximately 50% case-fatality rate.[21] And also, Ivory Coast virus case for human has only been known in dead chimpanzee in the Tai Forest where the population of apes was decreased.[17] The Bundibugyo virus with 30% case-fatality rate was monitored in Uganda in 2007 and is closely related to the Ivory Coast agent.[22, 23] Reston virus is found in the Philippines, not in Africa, and this was discovered first because it caused infection in macaques imported into the United States in 1989.[24] Although the World Health Organization (WHO) in the late 2013 has confirmed that EBOV outbreak started in the West Africa in Guinea, Central Africa is the most common outbreak region because the disease has spread from West Africa to Liberia, Sierra Leone, Nigeria, and Mali.[25] Ebola patients in Sierra Leone showed that the epidemic was originated from sustained person-to-person transmission without additional introductions from animal reservoirs with 70% case-fatality.[26] A few cases have also been reported in countries outside of West Africa, all related to healthcare workers caring for patients suffering from EBOV disease as well as international travelers who were exposed in the most affected regions and later showed symptoms of Ebola fever after reaching their destinations.[26, 27]

3.1.2. Overview of Current Approaches of EBOV Vaccines and Therapeutics

Since the initial symptoms of EVD are nonspecific and similar to other common diseases such as malaria and typhoid with a high fever, hematemesis, diarrhea with blood,

and retrosternal abdominal pain, it is difficult to diagnose EBOV in advance from infected person.[16, 18] Seroconversion of EVD in blood can be detected after symptoms appear with high levels of circulating virus within the patient and three days are needed to reach for viral detectable levels of EVD. Laboratory tests conducted in diagnosis such as antigen-capture enzyme-linked immunosorbent assay (ELISA), IgM ELISA, and polymerase chain reaction (PCR) using specific primers are used within a few days after symptoms begin. Deceased patients could be tested for EBOV by immunohistochemistry testing, PCR, and virus isolation (**Figure 3.3**).[28]

Timeline of EBOV Infection	Diagnostic Tests Available
Within a few days after symptoms begins	ELISA IgM ELISA PCR Virus isolation
Later in disease course or after recovery	IgM and IgG antibodies
Retrospectively in deceased patients	Immunohistochemistry testing PCR Virus isolation

Figure 3.3. Current diagnosis of EBOV

Although EBOV pathogenesis has been well characterized in animal disease models (the mouse, rodent, guinea pig, and macaque models) and the limited data is available from human cases as well as diverse national departments of drug have researched useful treatments and vaccines, there is still no licensed vaccine or treatment available by Food and Drug Administration (FDA) for human use.[18] EBOV is a category A pathogen and can only be handled in maximum containment laboratories.[16] Therefore, the development of vaccines and treatment for EBOV has been a priority of research

laboratories, and a few pharmaceutical companies and many candidates have been developed in the past decade. A DNA vaccine has been shown to be safe and immunogenic in a phase I clinical trial, as well as DNA vaccine synthesizing immune-related genes such as NP, GP in plasmid vector showed significant efficacy to guinea pig and mouse model against various infectious diseases, but DNA vaccine showed less effect on nonhuman primate and human models. The animal which is challenged by lethal viral dose, however, indicated complete protection, displaying the way to prevent EBOV on primates against infection. In recent days, vesicular stomatitis virus and chimpanzee adenovirus are being studied as a potential vaccine for EVD.[29] Especially, the recombinant vesicular stomatitis virus (rVSV) vaccine has been found to be effective in primates.[30] Since VSV is not critical to human, its biosafety and immune response are being estimated in clinical human trials (phase I).[28]

Furthermore, the development of RNA-based drugs and small antiviral therapeutic drugs are being performed. ZMapp, one of the powerful therapeutics, is an experimental biopharmaceutical drug with three chimeric monoclonal antibodies as a treatment for EVD.[31] The drug was first tested in humans during the 2014 West Africa Ebola virus outbreak, but has not been subjected to a randomized controlled trial to determine whether it works, and whether it is safe enough to allow on the market. Therefore, more study for producing ZMapp is needed.

In addition, favipiravir (T-705) is investigated as an experimental antiviral drug against diverse RNA viruses, especially influenza viruses as phase III clinical trials for the treatment of influenza with minimal cytotoxicity.[32] It is a pyrazinecarboxamide derivative, and the mechanism is related to the selective inhibition of viral RNA-

dependent RNA polymerase via an active metabolite and to induce a high rate of lethal RNA mutation, as well as this favipiravir has been shown to be effective to inhibit EBOV replication *in vitro* without any cytotoxicity under the experimental conditions (**Figure 3.4**).[33-37] Another small molecule, BCX4430, is an adenosine analog, active *in vitro* against EBOV and multiple negative-sense RNA viruses, and did not show any significant mutagenicity (**Figure 3.4**). Further research evaluating the EBOV protection by BCX4430 in nonhuman primates is ongoing.[38] Finally, chloroquine was developed as one of the best *in vitro* EBOV inhibitors, and also was the only tested drug able to reduce mortality significantly through *in vivo* studies (**Figure 3.4**). Chloroquine has been shown to apply multiple biological actions in cells, notably endosomal trafficking interference, all likely to contribute to its observed antiviral effect.[39]

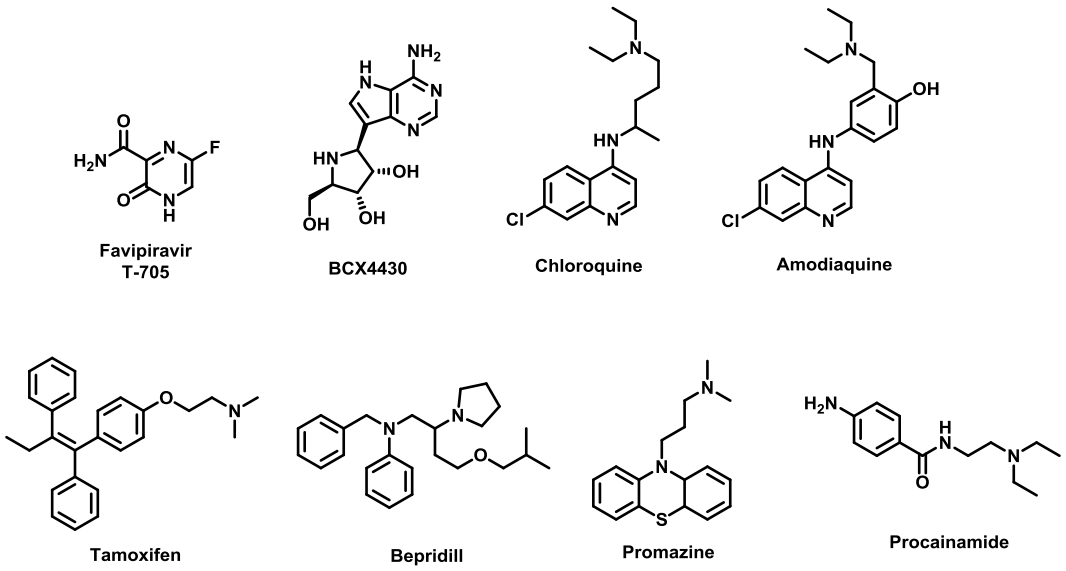


Figure 3.4. Small molecule inhibitors with reported anti EBOV activity[40]

3.1.3. Design of Diverse Enantioselective Cyclopropanes for Inhibition of EBOV

Even though EBOV is of great current public interest, there are still no specific therapeutic agents specifically designed for treatment of EBOV infection. Extensive studies to determine the natural reservoir of EBOV have identified a common species of fruit bat as the most likely candidate. In addition, promising clinical results have been obtained from existing experimental antiviral agents or approved medications.[41] An effective antiviral treatment could assist the natural immune system to fight against EBOV.[42]

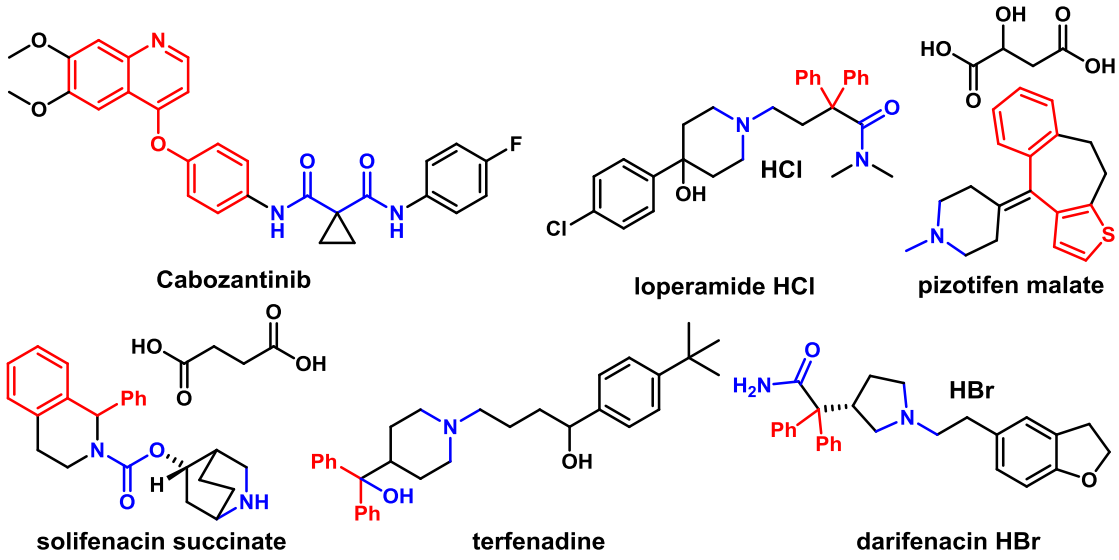


Figure 3.5. Identified commercial drugs which showed anti-EBOV activity (red: a diaryl system; blue: a Lewis basic feature).

One of the main reasons to develop new synthetic methods is to generate new synthetic strategies that could be applied to drug discovery. Recently, Davies lab has

started collaboration with Dr. Greg Melikian toward the development of medications for the treatment of EBOV. The Melikian laboratory performed a screen of commercially available FDA-approved drugs looking for influenza A (for proof of selective activity), infectivity assay (EBOV infected cells), and cell viability assay (uninfected cells). From the original screening data, a set of leads was generated having activity, selectivity, and low to no toxicity. In looking for similarities among the active compounds, two structural features were identified in many of the hits, a diaryl subunit and a basic amine or amide located off of the diaryl unit (**Figure 3.5**).

Previously, the Davies laboratory has studied and synthesized in enantiomerically pure form various cyclopropane derivatives with mono- and diaryl amines and amides for the goal of studying SERT (serotonin transporter) inhibitors and $5HT_{2A}$ (serotonin) antagonists. These types of compounds are readily derived from an enabling methodology developed by the Davies group, stereoselective cyclopropanation with donor-acceptor carbene.[43] Since a wide variety of diarylcycloprpylamines were available in the Davies group, a collection of 34 derivatives were selected and supplied to the Melikian group for biological evaluation (**Figure 3.6**). These compounds were screened for percent cell viability compared to no compound in the infectivity assay and cell viability assay with the negative control in DMSO, and positive controls of cabozantinib and NH_4Cl. Red squares (12 compounds) shown in **Figure 3.6** are the structures of the compounds found to have inhibitory activity against EBOV fusion of 1% - 28% at 20 μM. The results showed that the active compounds have all diaryl cyclopropanes with most having an attached amine unit. In general, the compounds showing cytotoxicity were the most active and also we would need to determine if there was a therapeutic window in

which they are useful or may be useful starting points for SAR (structure-activity relationship). The high hit rate in the relatively small family of compounds, added support to the concept that a diaryl group next to an amine is a promising pharmacophore, and further evaluation of diarylcyclopropylamine would be worthwhile.

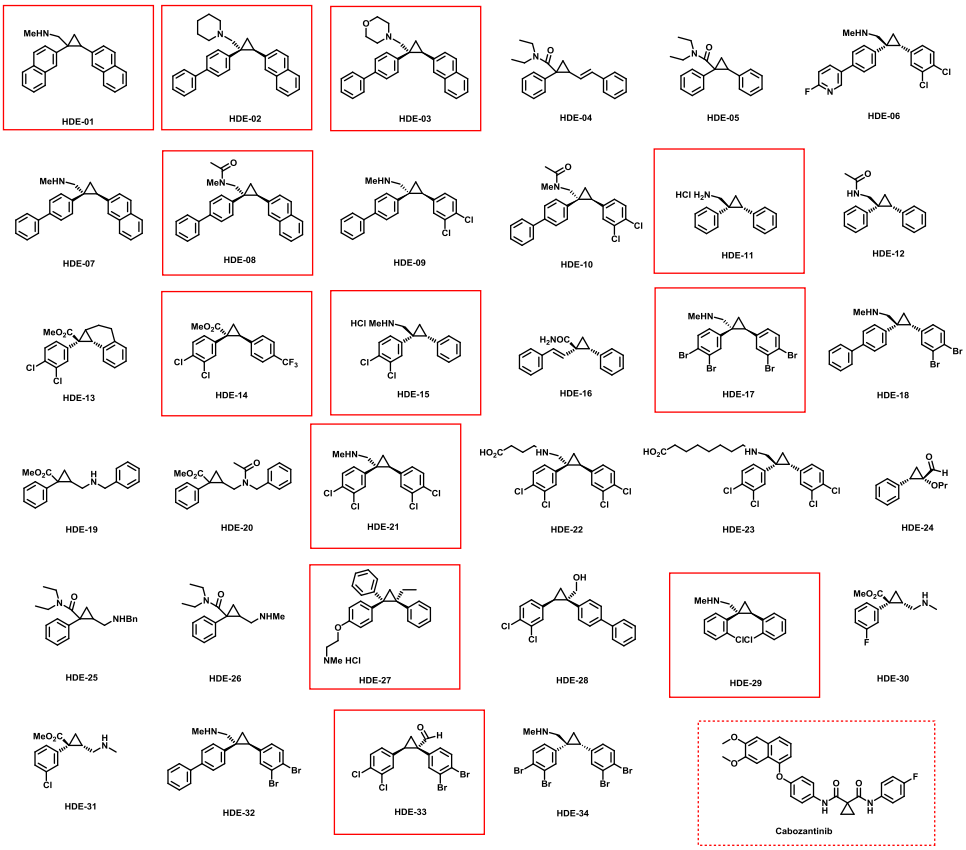


Figure 3.6. A set of the tested cyclopropanes (red square: the structures of the compounds with inhibitory activity against EBOV; red dash square: Cabozantinib for control standard).

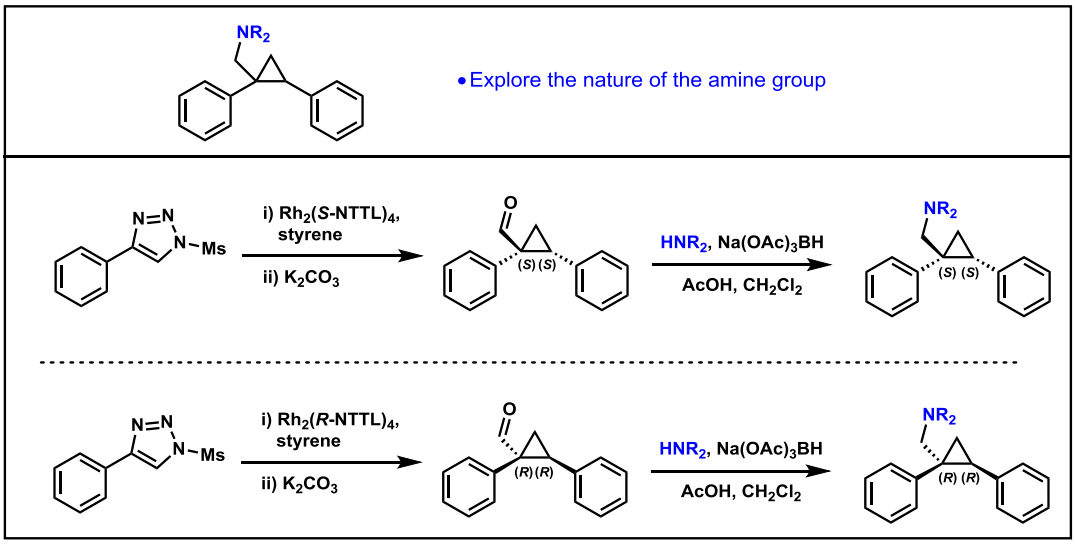


Figure 3.7. Synthetic strategy towards enantioselective cyclopropylamines

Based on the initial results, the diarylcyclopropylamine **HDE-11** was chosen as the starting point in order to better understand the anti-EBOV activity and potential safety of the identified cyclopropanes because it was found to be most consistently active against EBOV in the initial screen.[43] In addition, the original screen was mostly limited to simple cyclic amines and methyl amines, thus, the expansion of the types of diverse amine derivatives would be requested to investigate the EBOV inhibition activities and cytotoxicity through amine heterocycles of various sizes containing extra heteroatoms, acyclic amines, and amines containing a second hydrogen bond donor or acceptor. Furthermore, after exploring the amine derivatives, diverse aromatic rings such as biphenyls, hetero aromatics, and halogenated aromatics will be examined. For this issue, the synthesis of asymmetric cyclopropane compounds with methylamine derivatives would be focused and designed based on **HDE-11** because these designed compounds are simple and easy to synthesize via cyclopropanation with Rh(II) catalysts (Rh_2(*S*-NTTL)$_4$

or Rh_2(*R*-NTTL)$_4$) with *N*-sulfonyltriazole chemistry, and reductive amination step (**Figure 3.7**). Finally, synthesis of structurally unique enantiomers would be performed through utilizing Rh(II) catalytic asymmetric intermolecular cyclopropanation because the structurally unique chiral cyclopropane scaffolds could be potential pharmaceutical agents in drug discovery based on the data between **HDE-17** and **HDE-34** in **Figure 3.6**.

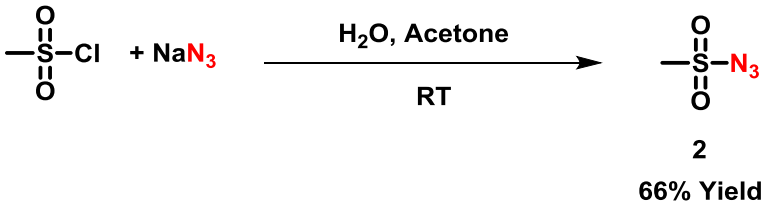
3.2. RESULTS AND DISCUSSION

3.2.1. Chemistry

The main goal of this project is to synthesize novel anti-virus compounds based on cyclopropane with amine analogues. For the new and diverse enantioselective cyclopropanes for inhibition of EBOV, the main steps are cyclopropanation with donor-acceptor 1,2,3-triazoles, various styrene derivatives, and dirhodium catalysts (Rh_2(*S*-NTTL)$_4$ or Rh_2(*R*-NTTL)$_4$),[44-47] as well as synthesis of the reductive amination between enantioselective diaryl cyclopropyl aldehydes and varied amine derivatives such as primary or secondary amines.[48,49]

3.2.1.1. Synthesis of Methanesulfonyl Azide

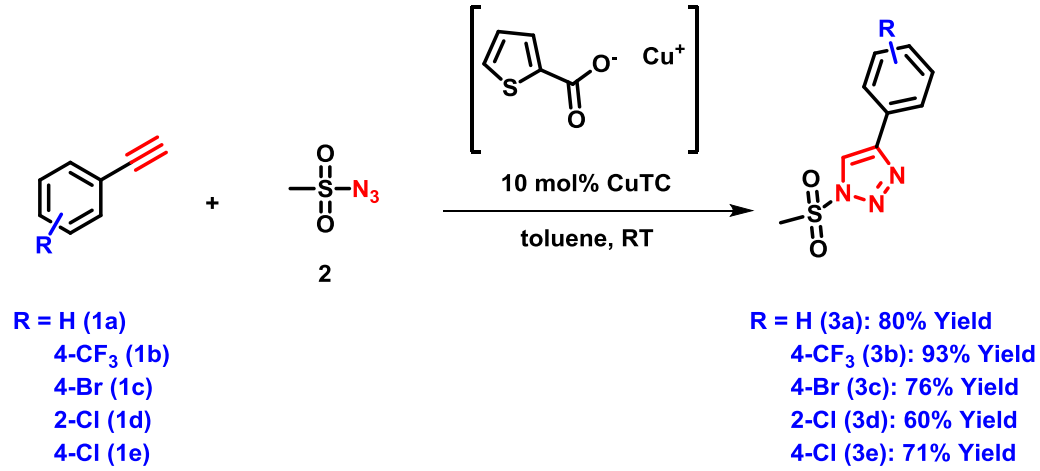
First, methanesulfonyl azide (**2**) was synthesized via nucleophilic substitution between methanesulfonyl chloride and sodium azide in aqueous solution condition such as H_2O and acetone at RT (**Scheme 3.1**). This azide compound was prepared to synthesize triazole derivatives for cyclopropanation.



Scheme 3.1. Synthesis of methanesulfonyl azide (**2**)

3.2.1.2. Synthesis of *N*-Sulfonyl-1,2,3-triazole Derivatives

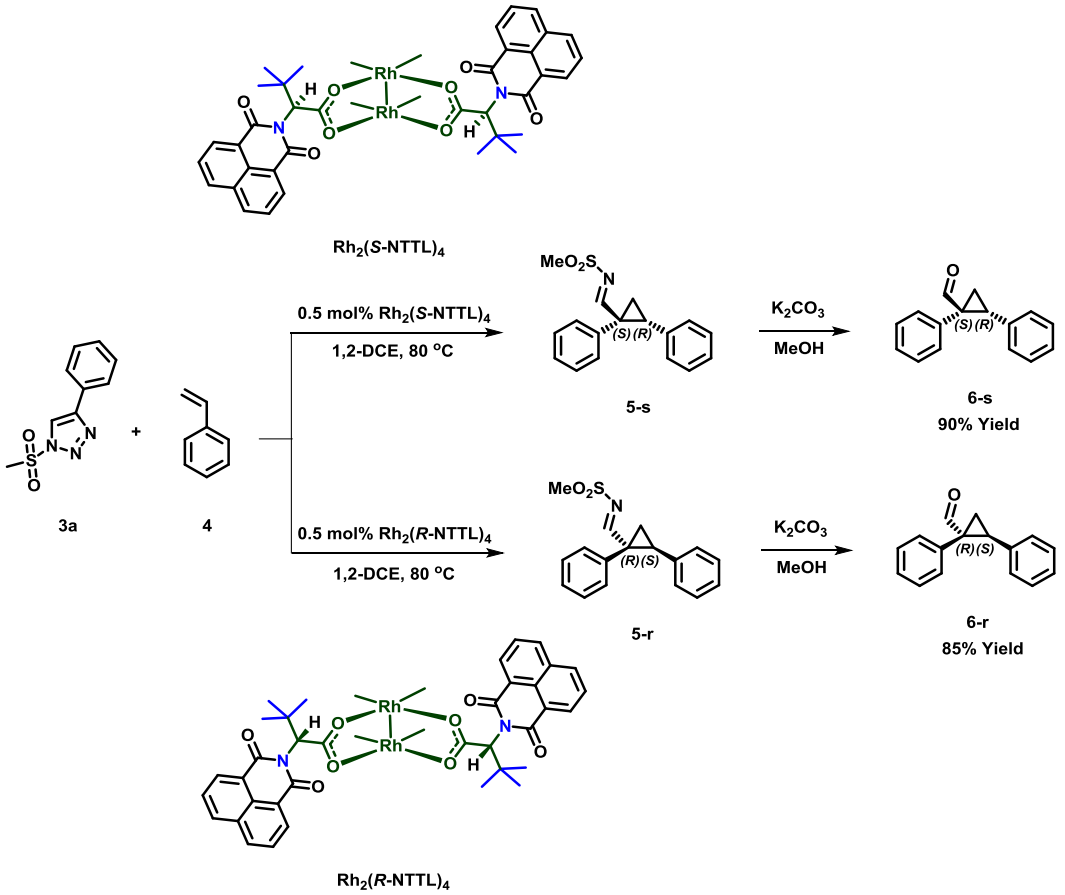
Next, *N*-sulfonyl-1,2,3-triazole derivatives (**3a**, **3b**, **3c**, **3d**, and **3e**) were synthesized via the copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC) with phenylacetylene substrates (**1a**, **1b**, **1c**, **1d**, and **1e**), methanesulfonyl azide (**2**), and copper (I) thiphene-2-carboxylate (CuTC) as a catalyst in toluene (**Scheme 3.2**).[44, 50] This time, diverse phenylacetylene derivatives (**1a**: phenylacetylene; **1b**: 4-ethynyl-a,a,a,-trifluorotoluene; **1c**: 1-bromo-4-ethynylbenzene; **1d**: 2-chlorophenyl acetylene; **1e**: 4-chlorophenyl acetylene) were used as starting materials with **2** for CuAAC to synthesize triazole intermediates, and completely synthesized as good yields (**3a**: 80%; **3b**: 93%; **3c**: 76%; **3d**: 60%; **3e**: 76%). In addition, these triazole intermediates were obtained to check the effectivity of novel cyclopropane compounds with amine derivative and modified aromatic rings (**3a**: H; **3b**: 4-CF_3; **3c**: 4-Br; **3d**: 2-Cl; **3e**: 4-Cl).



Scheme 3.2. Synthesis of 1-*N*-sulfonyl-1,2,3-triazole derivatives

3.2.1.3. Enantioselective Synthesis of Cyclopropyl Aldehyde Intermediates

A series of cyclopropyl aldehydes were synthesized by using the highly diastereo- and enantioselective Rh(II)-catalyzed cyclopropanation from **3a**. This is because Rh-catalyzed transannulation of *N*-sulfonyl 1,2,3-triazoles has proven that Rh(II) catalysis with 1,2,3-triazoles could target enantioselective transformations and could be easily available, reasonably stable, and seemingly unreactive. Accordingly, using cyclopropanation of styrene **4** with **3a** in the presence of diverse chiral Rh(II) complexes, especially Rh_2(*S*-NTTL)$_4$ or Rh_2(*R*-NTTL)$_4$, in 1,2-dichloroethane at 80 °C, these desired enantioselective intermediates **5-s** or **5-r** were obtained.[44] The resulting sulfonyl imines **5-s** or **5-r** were gently converted into the desired enantioenriched cyclopropyl aldehydes **6-s** or **6-r** by treatment with K_2CO_3 in wet methanol with excellent enantioselectivity (96% ee) and high yield (**Scheme 3.3**).[51-54]

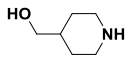
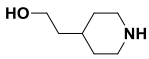
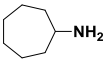
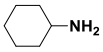
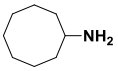
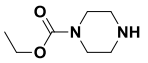
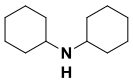
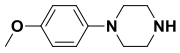
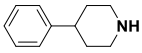
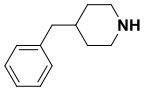
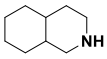
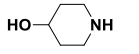


Scheme 3.3. Enantioselective synthesis of cyclopropyl aldehyde intermediates via Rh_2(*S*-NTTL)$_4$ or Rh_2(*R*-NTTL)$_4$

3.2.1.4. Enantioselective Synthesis of Various Cyclopropylamines

For the purpose of enantioselective synthesis of cyclopropylamines including secondary or tertiary amine compounds and organization of the small library of cyclopropylamines, reductive amination between those enantioselective cyclopropyl aldehydes (**6-s** or **6-r**) and various primary or secondary amines was performed (**Scheme 3.4**). For the optimal reductive amination with high yield, $Na(OAc)_3BH$ was used as a

reducing agent because $Na(OAc)_3BH$ is a mild reducing agent and can react selectively with imine and give desired diverse primary or secondary amine products in good yield.[49] Therefore, the aldehyde could be readily converted to various cyclopropylamines through the reductive amination using $Na(OAc)_3BH$ and an appropriately chosen amine to quickly probe the amine functionality.

Entry (HDE-xx)	Amine	Yield (%)	Entry (HDE-xx)	Amine	Yield (%)	Entry (HDE-xx)	Amine	Yield (%)
35 / 39		60 / 38	71 / 45		88 / 89	83 / 55		33 / 36
36 / 40		29 / 35	72 / 46		79 / 75	84 / 56		32 / 47
37 / 41		74 / 55	73 / 47		24 / 25	85 / 86		77 / 63
38 / 42		63 / 58	74 / 48		12 / 39	87 / 88		60 / 58
57 / 58		69 / 60	75 / 51		60 / 61	50 / 49		56 / 77
59 / 60		85 / 76	76 / 52		65 / 71	89 / 90		14 / 10
61 / 43		58 / 43	77 / 53		83 / 76	91 / 92		70 / 30
62 / 63		25 / 18	78 / 79		20 / 28	93 / 94		14 / 19
64 / 65		94 / 57	80 / 81		40 / 27	95 / 96		59 / 46
66 / 67		70 / 63	82 / 54		17 / 17			
68 / 69		82 / 77						
70 / 44		92 / 83						

Scheme 3.4. Enantioselective synthesis of various cyclopropylamines (Entry: **blue color**: (*S*, *R*) cyclopropylamine enantiomers synthesized from (*S*, *R*) cyclopropyl aldehyde enantiomer **6-s** ; **green color**: (*R*, *S*) cyclopropylamine enantiomers synthesized from (*R*, *S*) cyclopropyl aldehyde enantiomer **6-r**)

In order to better understand how these compounds target EBOV and how these compounds have different activities depending on amine derivatives, a broad range of amine analogues were prepared, including secondary or tertiary amine compounds by reductive amination (**Scheme 3.4**). First, enatioselective cyclopropanes with secondary or tertiary amine were synthesized using methyl amine (**HDE-35** or **HDE-39**), dimethyl amine (**HDE-36** or **HDE-40**), ethyl amine (**HDE-61** or **HDE-43**) or diethyl amine (**HDE-62** or **HDE-63**) to compare biological activities depending on methyl or ethylamine derivatives. And also, the reductive amination with piperidine or cyclohexylamine gave the desired piperidine (**HDE-37** or **HDE-41**) or secondary cyclohexylamine compounds (**HDE-38** or **HDE-42**). Furthermore, diverse saturated heterocyclic organic compounds containing several kinds of carbon atoms and one nitrogen atom were designed and synthesized as tertiary amine compounds to determine which carbon cyclic compound would be the best for EBOV activities (azetidine: **HDE-57** or **HDE-58**; pyrrolodine: **HDE-59** or **HDE-60**; piperidine: **HDE-37** or **HDE-41**; azepane: **HDE-66** or **HDE-67**; heptamethyleneimine: **HDE-68** or **HDE-69**). Saturated cyclic secondary amine compounds were also designed and obtained via reductive amination (cyclopropylamine: **HDE-70** or **HDE-44**; cyclobutylamine: **HDE-71** or **HDE-45**; cyclopentylamine: **HDE-72** or **HDE-46**; cyclohexylamine: **HDE-38** or **HDE-42**; cycloheptylamine: **HDE-73** or **HDE-47**; cyclootylamine: **HDE-74** or **HDE-48**). In addition, another saturated heterocyclic small molecules such as morpholine (**HDE-64** or **HDE-65**), piperazine derivatives (1-methylpiperazine: **HDE-75** or **HDE-51**; 1-ethylpiperazine-1-carboxylate: **HDE-76** or **HDE-52**; 1-(4-methoxyphenyl)piperazine: **HDE-77** or **HDE-53**), or thiomorpholine (**HDE-85** or **HDE-86**) were investigated to

compared to the EBOV inhibition activities based on **HDE-37** or **HDE-41**. Finally, enantioselective cyclopropyl piperidine derivatives series such as 4-phenylpiperidine (**HDE-78** or **HDE-79**), 4-benzylpiperidine (**HDE-80** or **HDE-81**), 4-hydroxypiperidine (**HDE-82** or **HDE-54**), 4-piperidinemethaonl (**HDE-83** or **HDE-55**), or 4-piperidineethanol (**HDE-84** or **HDE-56**) were synthesized, as well as various substitutions of the secondary or tertiary amine compounds were also produced as the potential EBOV treatment drugs (1,2,3,6-tetrahydropyridine: **HDE-87** or **HDE-88**; 3-dimethylaminopropylamine: **HDE-50** or **HDE-49**; dicyclohexylamine: **HDE-89** or **HDE-90**; decahydroquinoline: **HDE-91** or **HDE-92**; *trans*-decahydroquinoline: **HDE-93** or **HDE-94**; perhydroisoquinoline: **HDE-95** or **HDE-96**).

3.2.2. Biological Analysis

3.2.2.1. Preliminary Test of Cyclopropane Scaffolds against EBOV

As mentioned before, the Davies lab has studied and synthesized various diarylcyclopropylamines.[43] In the initial evaluation, 34 of these compounds were sent to Dr. Melikian's laboratory for *in vitro* testing for EBOV infection activity and cell viability as preliminary test of cyclopropane scaffolds for EBOV (**Figure 3.6**). All *in vitro* studies were performed in Dr. Melikian's laboratory at Emory Children's Center. These compounds were screened for cell viability and infectivity against EBOV by using Luciferase (Luc) assay using EBOV pseudoparticles (EBOVpp) including β-lactamase-Vpr (BlaM-Vpr), cyclopropane compounds were used at 20 uM and experiments in triplicates. TZM-bl cells was used as the cell line, which were grown in Dulbecco modified Eagle medium (DMEM) supplemented with 10% heat inactivated fetal bovine

serum (FBS) and penicillin-streptomycin. For cell viability experiment, TZM-bl cells were seeded in costar black 96 well clear bottom plate the day before the experiment. The plate was briefly chilled on ice and BlaM-containing VLPs or pseudoparticles were added to cells and centrifuged for 30 min at 4 ^{o}C. Cells were washed and inhibitors were added at the indicated concentration prior incubation the cells for 90 min at 37 ^{o}C in 5% CO_2. The fusion reaction was stopped by briefly chilling the plates on ice, and cells were loaded with the CCF4 acetoxymethyl ester (CCF4-AM) substrate. Cells were incubated overnight at 12 °C, and the fluorescence changes in substrate were measured by using a SpectraMax i3 plate reader. The fusion activity was derived from the ratio of the blue and green emissions. Cell viability was measured after addition of the fluorescent CellTiter-Bluereagent and incubation for 30 min at 37 ^{o}C, 5% CO_2, by reading the fluorescence at 560/590 nm. For infectivity assay, TZM-bl cells, which seeded the day before the experiment in a costar black 96 well clear bottom plate with DMEM, were exposed to HIV-1 derived particles pseudo-typed with EBOV-GP on ice and centrifuged for 30 min at 4 ^{o}C. Cells were washed and medium containing inhibitors was added. Cells were then incubated for 48 h at 37 ^{o}C, 5% CO_2, and the resulting luciferase signal was read using a TopCount NXT plate reader, after adding the BrightGloTM luciferase substrate. **Table 3.1** and **Figure 3.8** are shown that twelve compounds (yellow squares: **HDE-01**, **HDE-02**, **HDE-03**, **HDE-08**, **HDE-11**, **HDE-14**, **HDE-15**, **HDE-17**, **HDE-21**, **HDE-27**, **HDE-29** and **HDE-33**) had not only inhibitory activity against EBOV fusion of 1% - 28% at 20 μM, but also the significant cell viability. However, five compounds (red squares: **HDE-06**, **HDE-07**, **HDE-09**, **HDE-18**, and **HDE-32**) had a significant effect on infectivity but poor cell viability (less than 40% cell survival). This result showed that the active

compounds have all diaryl cyclopropanes with secondary or tertiary amine moiety, but amide moiety was not effective. In addition, this data indicated that the specific enantiomer was better effect than others because (*R, S*) enantiomer **HDE-17** was relatively more efficient than (*S, R*) enantiomer **HDE-34** in this initial data.

	Infectivity (% of control)		Cell viability (% of control)	
	EBOVpp	STD	EBOVpp	STD
No Inh	100.00	17.76	100.00	1.29
HDE-01	3.35	0.37	90.43	10.49
HDE-02	4.93	0.74	90.11	5.26
HDE-03	28.56	4.06	89.99	0.69
HDE-04	57.01	11.06	87.14	8.02
HDE-05	72.51	14.01	84.14	3.93
HDE-06	1.60	1.01	40.52	24.50
HDE-07	1.64	0.45	32.28	26.60
HDE-08	20.76	6.68	84.56	1.71
HDE-09	1.60	0.53	38.05	18.68
HDE-11	7.89	2.48	98.51	1.70
HDE-12	95.44	6.80	98.84	1.35
HDE-13	50.72	4.92	91.82	5.65
HDE-14	22.74	6.34	86.56	10.35
HDE-15	3.53	0.27	87.54	10.00
HDE-16	72.93	19.18	90.33	8.52
HDE-17	4.11	0.68	78.74	7.09
HDE-18	1.12	0.86	12.42	8.30
HDE-19	60.72	17.28	92.21	4.37
HDE-20	136.70	31.23	94.39	4.13
HDE-21	2.96	0.43	73.06	3.48
HDE-22	56.68	13.94	92.23	0.87
HDE-23	41.12	4.74	86.07	7.17
HDE-24	117.89	28.64	96.74	14.05
HDE-25	51.82	65.75	93.74	14.72
HDE-26	73.42	21.23	92.56	8.63
HDE-27	3.39	0.25	98.25	12.39
HDE-28	56.72	72.19	95.78	9.03
HDE-29	4.07	0.69	94.20	9.92
HDE-30	152.63	16.82	94.80	11.00
HDE-31	128.60	11.12	109.03	1.08
HDE-32	1.02	0.97	8.10	2.59
HDE-33	14.21	2.59	102.01	1.63
HDE-34	75.85	63.09	92.52	19.98
Cabozantinib	20.31	10.85	98.63	6.74
DMSO	127.49	7.56	98.69	3.85
NH_4Cl	3.66	0.58	93.37	12.32
No Virus	3.56	0.48		

Table 3.1. Data of selected diverse cyclopropylamine compounds for infectivity and cell viability against EBOV (Carbozantinib: Control) prepared by Dr. Mariana Marin

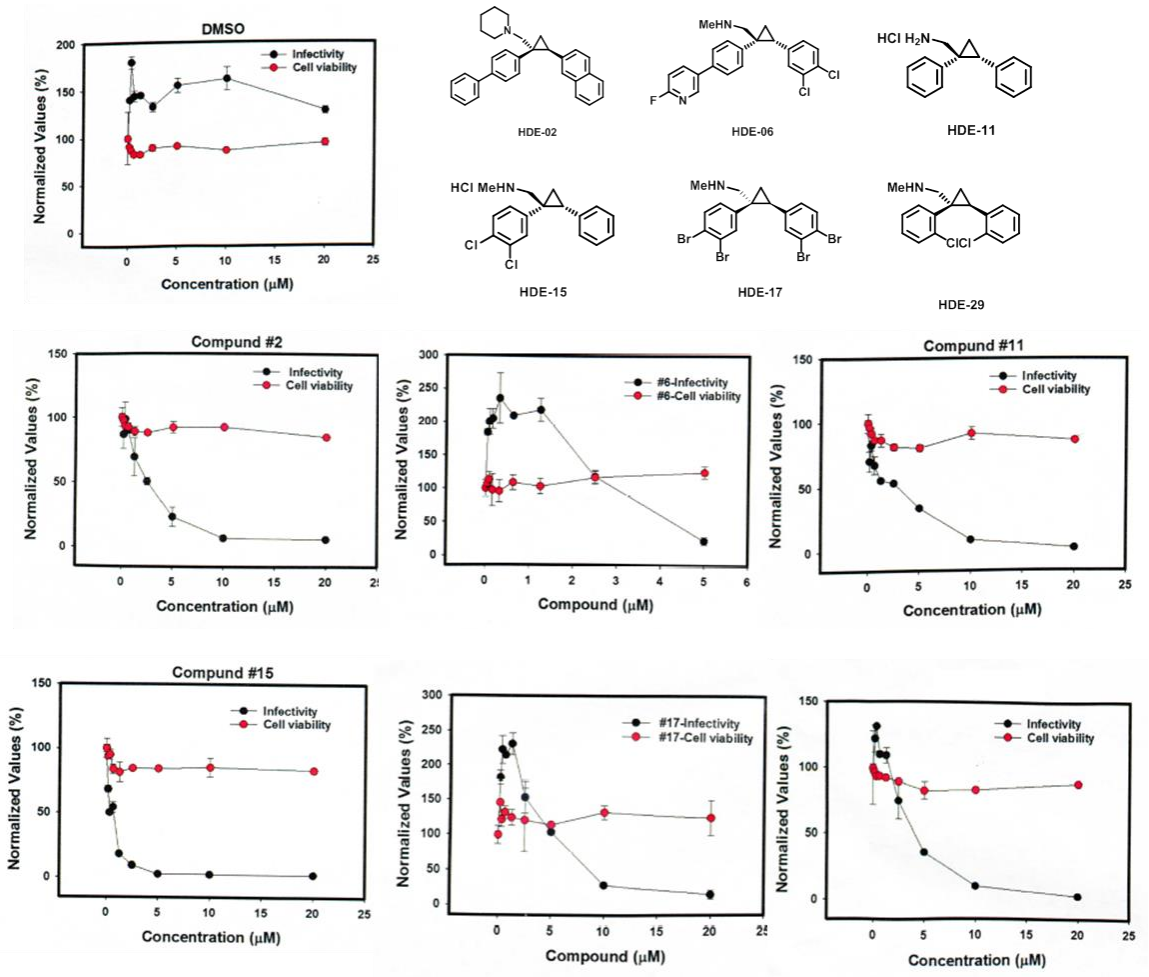


Figure 3.8. Graph of selected diverse cyclopropylamine compounds for infectivity and cell viability against EBOV (Carbozantinib: Control).

3.2.2.2. *In Vitro* Test of (*S*,*R*) or (*R*,*S*) Cyclopropane Enantiomers with Secondary or Tertiary Amine Derivatives for EBOV Infection Activity and Cell Viability

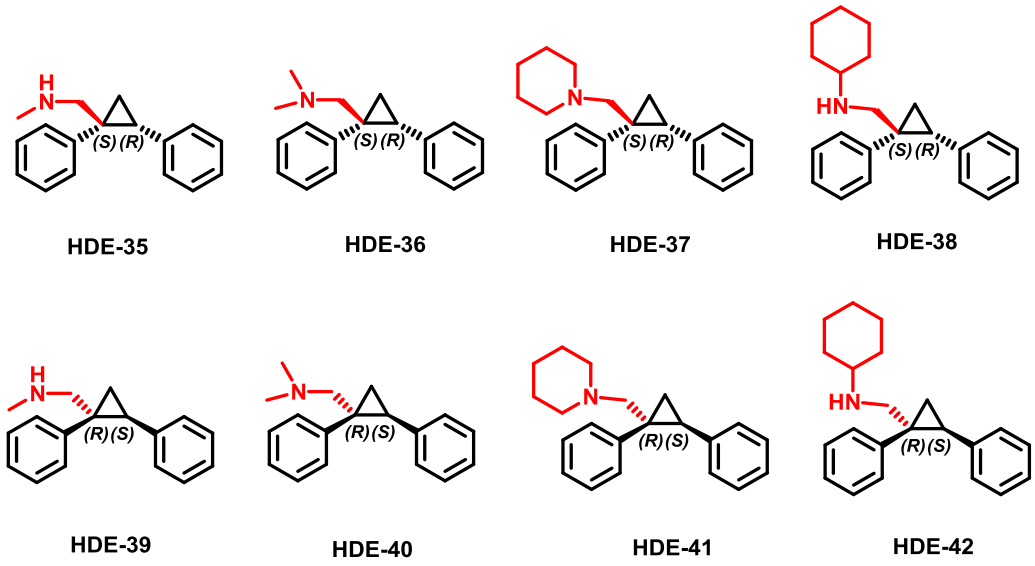


Figure 3.9. Selected diverse cyclopropylamine compounds: (*S*,*R*) or (*R*,*S*) cyclopropane enantiomers with secondary or tertiary amine derivatives for biological test against EBOV

Considering the clinical importance of this study, eight cyclopropylamine compounds as the highest priority samples for EBOV inhibition were selected, and they would tell what structural features are most important and whether the two enantiomers have different properties (**Figure 3.9**). Based on this, eight compounds (**HDE-35**, **HDE-36**, **HDE-37**, **HDE-38**, **HDE-39**, **HDE-40**, **HDE-41**, and **HDE-42**) were sent to Dr. Melikian's laboratory for *in vitro* testing for EBOV infection activity and cell viability. Two independent experiments for **HDE-35**, **HDE-36**, **HDE-37**, **HDE-38**, **HDE-39**, **HDE-40**, **HDE-41**, and **HDE-42** were performed. First experiment was the potency for inhibiting EBOV infection, and second experiment was the effect on the cell viability of

the target cells in DMSO at 20 mM which is the best concentration. The results showed that **HDE-39** and **HDE-42** are the most potent to inhibit the EBOV infection by using 20 uM of the compounds and these compounds were compared with NH_4Cl and cabozantinib as control for inhibition of EBOV (**Figure 3.10**). In other words, **HDE-39** and **HDE-42** are the best for inhibiting EBOV infection without having a significant effect on the cell viability. Interestingly, enantioenriched cyclopropylamines with (*R*, *S*) configuration shows much better EBOV inhibition effect than the corresponding (*S*, *R*) enentiomers. Also, the secondary amine compounds had a greater effect than tertiary amine compounds. At this point, these results gave us an indication which one is the most potent without doing a full dose-response curve. This data showed that **HDE-39** and **HDE-42** were the most promising as potential EBOV inhibitors. Further studies are needed to determine the efficacy of these compounds at lower concentrations, but these studies have not yet been carried out.

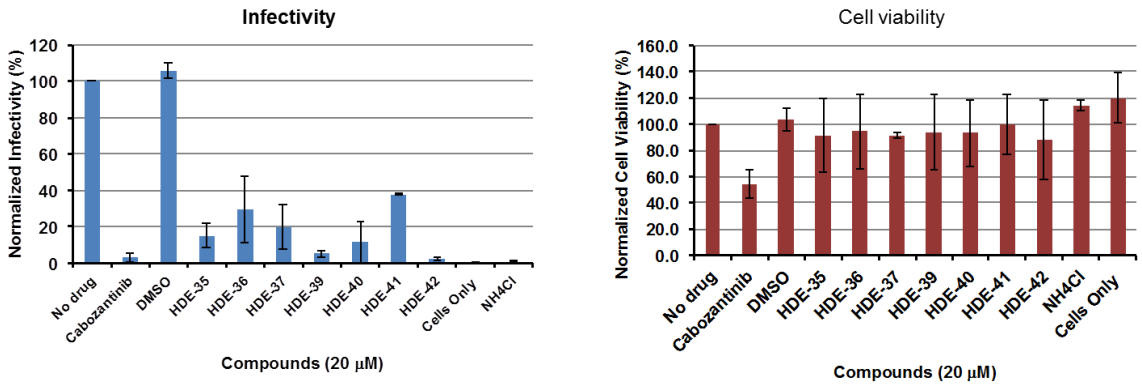


Figure 3.10. Data of EBOV infectivity and cell viability activity of (*S*,*R*) or (*R*,*S*) cyclopropane enantiomers with secondary or tertiary amine derivatives prepared by Dr. Mariana Marin

3.2.2.3. *In Vitro* Test of (*R*,*S*) Cyclopropane Enantiomers with Secondary Amine Derivatives for EBOV Infection Activity and Cell Viability

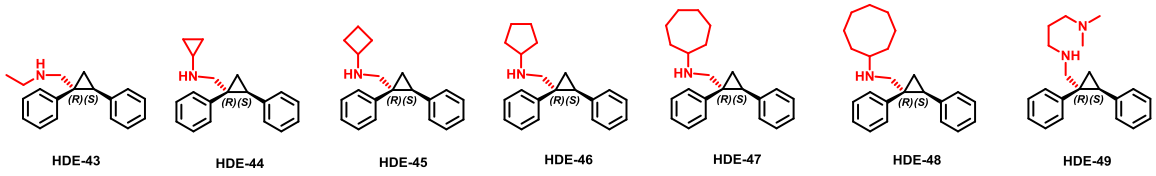


Figure 3.11. Selected diverse cyclopropylamine compounds: (*R*,*S*) cyclopropane enantiomers with secondary amine derivatives for biological test against EBOV

Based on the data described in **Figure 3.10**, the (*R*,*S*) enantiomeric series were shown to be more potent than (*S*,*R*) enantiomers, and secondary amine compounds had a greater effect than tertiary amine compounds. Therefore, among (*R*,*S*)-cyclopropane enantiomers and secondary amine derivatives, seven new compounds with changes at the amino group (**HDE-43**, **HDE-44**, **HDE-45**, **HDE-46**, **HDE-47**, **HDE-48**, and **HDE-49**) were selected and used to determine EBOV activity based on **HDE-42**, which is the best for inhibiting EBOV infection without having a significant effect on the cell viability (**Figure 3.11**). The main goal was to find the best compounds against EBOV in these cyclopropylamine series, then, we can perform further *in vivo* test against EBOV. Two independent experiments for **HDE-43**, **HDE-44**, **HDE-45**, **HDE-46**, **HDE-47**, **HDE-48**, and **HDE-49** were performed individually. The first experiment determined the potency for inhibiting EBOV infection, and second experiment evaluated the effect of the compounds on the cell viability of the target cells. The results showed that **HDE-49** is the most potent to inhibit the EBOV infection even 5 uM of **HDE-49**, and **HDE-49** was

compared with NH_4Cl and cabozantinib as control for inhibition of EBOV, as well as greater effects than control material (**Figure 3.12**). Structural features, including different secondary amine moieties with or without a dimethylamino group, were considered to exploit potential activity in these compounds, and (*R*, *S*) cyclopropyl enantiomer with dimethylaminopropylamine **HDE-49** was the most potent compound. In other words, enantioselective **HDE-49** is the best for inhibiting EBOV infection without having a significant effect on the cell viability (**Figure 3.13**).

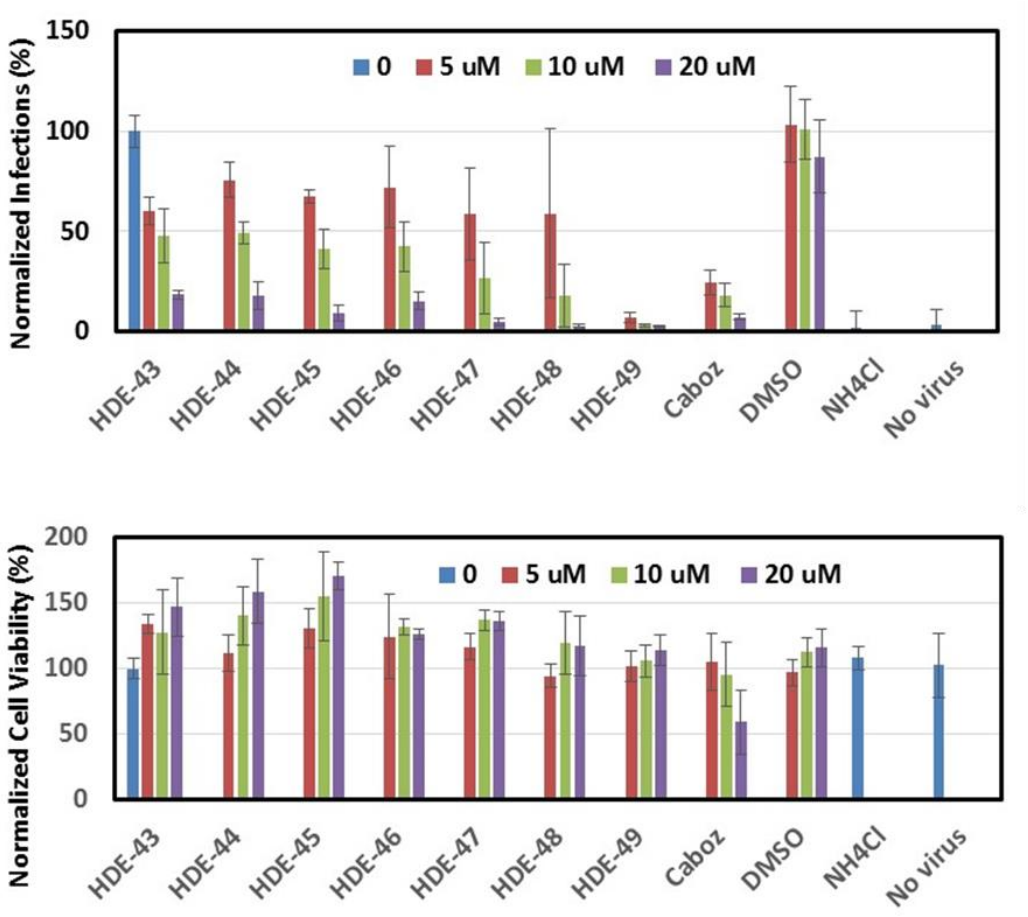


Figure 3.12. Data of EBOV infectivity and cell viability activity of (*R*,*S*) cyclopropane enantiomers with secondary amine derivatives prepared by Dr. Mariana Marin

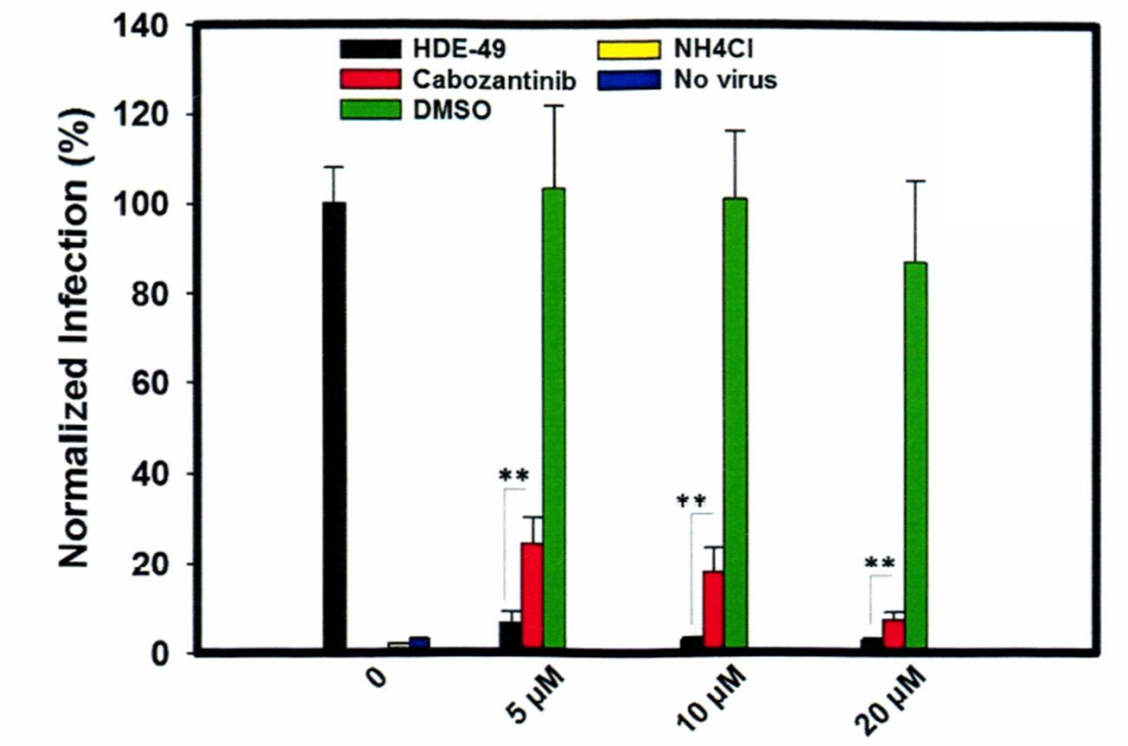


Figure 3.13. Data of EBOV infectivity and cell viability activity of (*R*,*S*) cyclopropane enantiomer with secondary amine derivative (**HDE-49**) prepared by Dr. Mariana Marin

3.3. CONCLUSIONS

In summary, novel enantioselective cyclopropylamines for inhibition of EBOV were designed and synthesized based on cyclopropyl primary amine analogue (**HDE-11**) that could be potential EBOV inhibitors. These novel enantioenriched cyclopropylamines were synthesized by utilizing the enantioselective cyclopropanation with donor-acceptor 1,2,3-triazoles, various styrene derivatives in the presence of dirhodium catalysts (Rh_2(*S*-NTTL)$_4$ or Rh_2(*R*-NTTL)$_4$), as well as synthesis of the reductive amination between enantioselective diaryl cyclopropyl aldehydes and varied amine derivatives such as primary or secondary amines.

Biological studies (infectivity and cell viability activity) of **HDE-35**, **HDE-36**, **HDE-37**, **HDE-38**, **HDE-39**, **HDE-40**, **HDE-41**, and **HDE-42** from Dr. Melikian's laboratory at Emory Children's Center were performed to determine the ability of EBOV inhibition. And the initial data showed that **HDE-39** and **HDE-42** have the potential EBOV inhibition ability. The (*R,S*) enantiomeric series were more potent than the (*S,R*) series, and secondary amines had a greater effect than tertiary amines.

Finally, based on (*R,S*)-cyclopropane enantiomers and secondary amine derivatives, seven new compounds (**HDE-43**, **HDE-44**, **HDE-45**, **HDE-46**, **HDE-47**, **HDE-48**, and **HDE-49**) were evaluated to determine the ability of EBOV inhibition to find the best compounds against EBOV in these cyclopropylamine series. The data showed that **HDE-49** are the most potent to inhibit the EBOV infection even 5 uM of **HDE-49**. In other words, **HDE-49** is the best for inhibiting EBOV infection without having a significant effect on the cell viability.

To advance the further medicinal chemistry for EBOV, **HDE-49**, which has effective structural moieties including (*R, S*) cyclopropyl enantiomer with dimethylaminopropyl amine, would be beneficial to obtain suitable structural scaffolds and purpose further synthetic modifications for EBOV.

3.4. EXPERIMENTAL SECTION

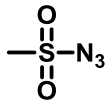
General Methods

All experiments were performed under anhydrous conditions in an atmosphere of argon except where stated, using oven-dried glassware. Hexane, pentane, THF, toluene, acetonitrile, and methylenechloride were dried by a solvent purification system. Unless

otherwise noted, all other reagents were obtained from commercial sources and used as received. ^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded at 400 MHz, 500 MHz, or 600 MHz on an INOVA-400, Varian-400, INOVA-500, or BRUKER-600. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ H 7.26 for the residual protons in $CDCl_3$, 3.31 in CD_3OD, or 2.50 in DMSO), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, etc), coupling constant (J/Hz), integration. Coupling constants were taken directly from the spectra and are uncorrected. ^{13}C NMR spectra were recorded at 100 MHz, 125 MHz, or 150 MHz, and all chemical shift values are reported in ppm on the δ scale, with an internal reference of δ C 77.16 for $CDCl_3$, 49.00 for CD_3OD, or 39.52 for DMSO. Melting points were measured with electrothermal melting point apparatus model 1001D and by Barnstead International (Volts: 120, AMPs: 1.6, Watts: 200, Hz: 50/60, Phase: 1) and were uncorrected. Optical rotations were measured on a PerkinElmer Model 341 Polarimeter. Infrared (IR) spectra were collected on a Nicolet iS10 FT-IR spectrometer. High Resolution Mass spectra (HRMS) were taken on a Thermo Finnigan LTQ-FTMS spectrometer with APCI, ESI or NSI, and Liquid Chromatography Mass spectra (LC-MS) was measured on Agilent Technologies 6120 Quadrupole LC/MS spectrometer. Thin layer chromatographic analysis was performed with silica gel plates, visualizing with UV light. Flash column chromatography was performed on silica gel 60 Å (230-400 mesh), or Isolera. Analytical enantioselective chromatographies were measured on Varian Prostar instrument and used isopropanol/hexane as gradient. Sulfonyl azide was prepared using standard procedure,[55, 56] and CuTC was prepared according to the literature

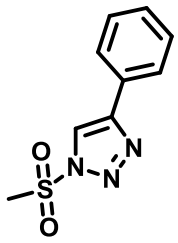
procedure.[57] All other reagents were purchased from Aldrich, Acros Organics, Fisher, Alfa Aesar, or Oakwood and used as received.

Methanesulfonyl azide (2)



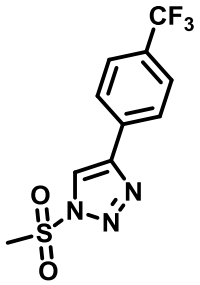
Methanesulfonyl azide (**2**) was prepared by known method.[58] To a flask of 100 mL, a solution of sodium azide (8.3 g, 128 mmol) in DI water (50 mL) and acetone (80 mL) at 0 °C was added dropwise methanesulfonyl chloride (6.6 mL, 85 mmol). After stirring at room temperature for 15 h, acetone was evaporated under reduced pressure (35 °C), the residue was extracted with DCM (3 x 40 mL), washed with water (2 x 35 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give **2** as a colorless oil (6.7 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1; The spectroscopic data matches what was previously reported in the literature.[58]

1-(Methylsulfonyl)-4-phenyl-*1H*-1,2,3-triazole (3a)



1-(Methylsulfonyl)-4-phenyl-*1H*-1,2,3-triazole (**3a**) was prepared by known method.[44] To a stirred solution of phenylacetylene (1.02 g, 10.0 mmol) in toluene (45 mL), CuTC (190.0 mg, 1.0 mmol) was added at RT. After stirring for 5 min, a solution of methanesulfonyl azide (2.12 g, 10.0 mmol) in toluene (5 mL) was added dropwise to the resulting suspension. The reaction mixture was stirred at RT for 12 hrs, then concentrated under reduce pressure, and filtered through a short silica (SiO_2, EA: Hex = 1:1) to obtain 80% yield as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.88 (t, 1H), 7.86 (t, 1H), 7.50 - 7.40 (m, 3H), 3.58 (s, 3H); LC-MS: *m/z* calcd for $C_9H_{10}N_3O_2S$ ($M+H^+$): 224.1, found: 224.1. The spectroscopic data matches what was previously reported in the literature.[44]

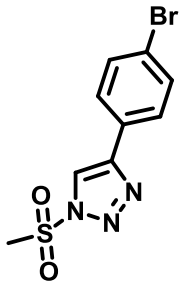
1-(Methylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3b)



1-(Methylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole (**3b**) was prepared by known method.[44] To a stirred solution of 4-ethynyl-a,a,a,-trifluorotoluene (850.7 mg, 5.0 mmol) in toluene (22 mL), CuTC (95.3 mg, 0.5 mmol) was added at RT. After stirring for 5 min, a solution of methanesulfonyl azide (605.6 mg, 5.0 mmol) in toluene (3 mL) was added dropwise to the resulting suspension. The reaction mixture was stirred at RT for 12 hrs, then concentrated under reduce pressure, and filtered through a

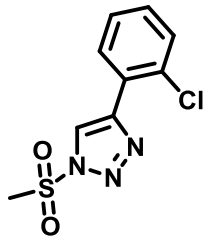
short silica (SiO_2, EA: Hex = 1:1) to obtain 93% yield as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 3.60 (s, 3H); LC-MS: *m/z* calcd for $C_{10}H_9F_3N_3O_2S$ ($M+H^+$): 292.0, found: 292.0. The spectroscopic data matches what was previously reported in the literature.[44]

4-(4-Bromophenyl)-1-(methylsulfonyl)-*1H*-1,2,3-triazole (3c)



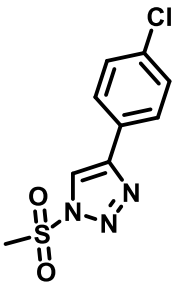
4-(4-Bromophenyl)-1-(methylsulfonyl)-*1H*-1,2,3-triazole (**3c**) was prepared by known method.[44] To a stirred solution of 1-bromo-4-ethynylbenzene (905.2 mg, 5.0 mmol) in toluene (22 mL), CuTC (95.3 mg, 0.5 mmol) was added at RT. After stirring for 5 min, a solution of methanesulfonyl azide (605.6 mg, 5.0 mmol) in toluene (3 mL) was added dropwise to the resulting suspension. The reaction mixture was stirred at RT for 12 hrs, then concentrated under reduce pressure, and filtered through a short silica (SiO_2, EA: Hex = 1:1) to obtain 76% yield as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 3.58 (s, 3H); LC-MS: *m/z* calcd for $C_9H_9BrN_3O_2S$ ($M+H^+$): 302.0, found: 302.0. The spectroscopic data matches what was previously reported in the literature.[44]

4-(2-Chlorophenyl)-1-(methylsulfonyl)-*1H*-1,2,3-triazole (3d)



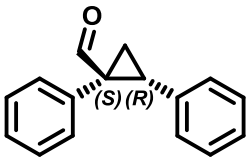
4-(2-Chlorophenyl)-1-(methylsulfonyl)-*1H*-1,2,3-triazole (**3d**) was prepared by known method.[44] To a stirred solution of 1-chloro-2-ethynylbenzene (682.9 mg, 5.0 mmol) in toluene (22 mL), CuTC (95.3 mg, 0.5 mmol) was added at RT. After stirring for 5 min, a solution of methanesulfonyl azide (605.6 mg, 5.0 mmol) in toluene (3 mL) was added dropwise to the resulting suspension. The reaction mixture was stirred at RT for 12 hrs, then concentrated under reduce pressure, and filtered through a short silica (SiO_2, EA: Hex = 1:3) to obtain 60% yield as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.19 (dd, *J* = 7.6, and 2.0 Hz, 1H), 7.44 (dd, *J* = 7.6, and 0.8 Hz, 1H), 7.40 - 7.30 (m, 2H), 3.59 (s, 3H); LC-MS: *m/z* calcd for $C_9H_9ClN_3O_2S$ ($M+H^+$): 258.0, found: 258.0. The spectroscopic data matches what was previously reported in the literature.[44]

4-(4-Chlorophenyl)-1-(methylsulfonyl)-*1H*-1,2,3-triazole (3e)



4-(4-Chlorophenyl)-1-(methylsulfonyl)-*1H*-1,2,3-triazole (**3e**) was prepared by known method.[44] To a stirred solution of 4-chlorophenyl acetylene (682.9 mg, 5.0 mmol) in toluene (22 mL), CuTC (95.3 mg, 0.5 mmol) was added at RT. After stirring for 5 min, a solution of methanesulfonyl azide (605.6 mg, 5.0 mmol) in toluene (3 mL) was added dropwise to the resulting suspension. The reaction mixture was stirred at RT for 12 hrs, then concentrated under reduce pressure, and filtered through a short silica (SiO_2, EA: Hex = 1:1) to obtain 71% yield as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 3.58 (s, 3H); LC-MS: *m/z* calcd for $C_9H_9ClN_3O_2S$ ($M+H^+$): 258.0, found: 258.0. The spectroscopic data matches what was previously reported in the literature.[44]

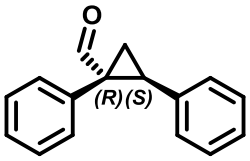
(*1S,2R*)-1,2-Diphenylcyclopropane-1-carbaldehyde (6-s)



(*1S,2R*)-1,2-diphenylcyclopropane-1-carbaldehyde (**6-s**) was prepared by known method.[44] Triazole **3** (446.6 mg, 2.0 mmol, 1.0 eq.) and Rh_2(*S*-NTTL)$_4$ (7.2 mg, 0.5 mol %, 0.005 eq.) were added under ambient atmosphere, followed by dry 1,2-dichloroethane (10 mL) and styrene (250.1 mg, 2.4 mmol, 1.2 eq.). The reaction mixture was stirred at 65 °C for 4-5 hrs until triazole **3** completely consumed. An equal volume of methanol, few drops of water and anhydrous potassium carbonate (552.0 mg, 4.0 mmol, 2.0 eq.) were added to the reaction mixture, and the obtained suspension was vigorously stirred for 1 hr until hydrolysis of imine was complete. Solvents were removed in vacuum, and

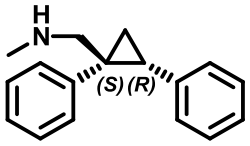
the residue was re-suspended in dichloromethane, dried over anhydrous sodium sulfate. After that, the mixture was then concentrated *in vacuo*, and the residue was purified on silica to obtain 90% yield as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.25 - 7.22 (m, 3H), 7.10 - 7.07 (m, 5H), 6.81 (dd, *J* = 7.6, and 3.2 Hz, 2H), 3.01 (dd, *J* = 9.2, and 7.5 Hz, 1H), 2.21 (dd, *J* = 9.2, and 5.1 Hz, 1H), 2.10 (dd, *J* = 7.4, and 5.1 Hz, 1H). The enantiomeric excess was determined by HPLC using the published procedure and the spectroscopic data matches what was previously reported in the literature.[44]

(*1R,2S*)-1,2-Diphenylcyclopropane-1-carbaldehyde (6-r)



Synthesis of the enantiomer of **6-r** was carried out using Rh_2(*R*-NTTL)$_4$ (0.5% mol) as catalyst in the same reaction conditions as described above to obtain 85% yield. NMR spectroscopic data is same as **6-s**.

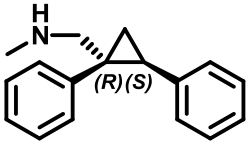
1-((*1S,2R*)-1,2-Diphenylcyclopropyl)-*N*-methylmethanamine (HDE-35)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with methylamine

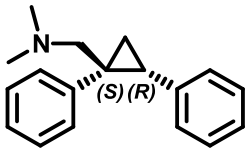
hydrochloride (45.6 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 60% yield (63.1 mg). $[\alpha]_D^{20}$ = - 34.0 ^{o} (C 0.30, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2930, 2788, 1602, 1497, 1445, 1381, 1074, 1031, 775, 745, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 - 6.99 (m, 8H), 6.73 (dd, *J* = 8.4, and 2.0 Hz, 2H), 3.12 (dd, *J* = 12.4, and 1.2 Hz, 1H), 2.60 (d, *J* = 12.4 Hz, 1H), 2.42 (s, 3H), 2.30 - 2.26 (m, 1H), 1.53 (ddd, *J* = 6.4, 5.6, and 1.2 Hz, 1H), 1.42 (dd, *J* = 8.8, and 5.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 139.0, 130.7, 128.0, 127.8, 127.7, 126.4, 125.5, 71.0, 46.2, 34.2, 28.6, 18.1; LC-MS: *m/z* calcd for $C_{17}H_{20}N$ ($M+H^+$): 238.2, found: 238.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{20}N$ ($M+H^+$): 238.1596, found: 238.1590.

1-((*1R,2S*)-1,2-Diphenylcyclopropyl)-*N*-methylmethanamine (HDE-39)



Synthesis of the enantiomer of **HDE-39** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 38% yield of product. NMR spectroscopic data is same as **HDE-35**.

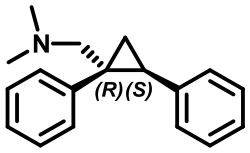
1-((*1S,2R*)-1,2-Diphenylcyclopropyl)-*N,N*-dimethylmethanamine (HDE-36)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with dimethylamine hydrochloride (55.0 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 29% yield (32.0 mg). $[\alpha]_D^{20}$ = - 20.0 ^{o} (C 0.18, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2939, 2812, 2767, 1677, 1602, 1498, 1454, 1364, 1264, 1095, 1036, 776, 745, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 - 6.98 (m, 8H), 6.71 (dd, *J* = 8.0, and 1.6 Hz, 2H), 2.99 (d, *J* = 12.4 Hz, 1H), 2.28 (d, *J* = 12.4 Hz, 1H), 2.25 (s, 3H), 2.16 (dd, *J* = 8.8, and 6.0 Hz, 1H), 1.61 (dd, *J* = 6.0, and 5.2 Hz, 1H), 1.36 (dd, *J* = 8.8, and 5.2 Hz, 1H); ^{13}C NMR (125

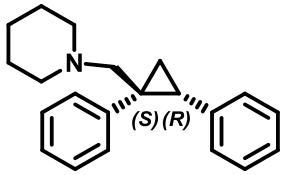
MHz, $CDCl_3$) δ 139.5, 138.7, 130.5, 127.8, 127.6, 127.5, 126.2, 125.3, 70.7, 45.9, 33.9, 28.5, 17.9; LC-MS: *m/z* calcd for $C_{18}H_{22}N$ ($M+H^+$): 252.2, found: 252.2; HRMS (ESI): *m/z* calcd for $C_{18}H_{22}N$ ($M+H^+$): 252.1752, found: 252.1747.

1-((*1S,2R*)-1,2-Diphenylcyclopropyl)-*N,N*-dimethylmethanamine (HDE-40)



Synthesis of the enantiomer of **HDE-40** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 35% yield of product. NMR spectroscopic data is same as **HDE-36**.

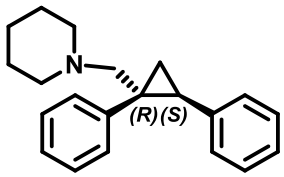
1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)piperidine (HDE-37)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with piperidine (57.5 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^oC, and then stirred at 0 ^oC for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^oC, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted

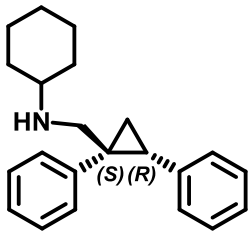
with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 74% yield (96.7 mg). $[\alpha]_D^{20}$ = - 12.4 ^{o} (C 0.78, $CHCl_3$); IR (neat) ν (cm^{-1}) 3024, 2932, 2851, 2753, 1675, 1602, 1497, 1444, 1155, 1114, 1031, 998, 774, 695; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 - 6.98 (m, 8H), 6.70 (dd, *J* = 8.0, and 1.6 Hz, 2H), 2.81 (d, *J* = 14.0 Hz, 1H), 2.53 (d, *J* = 14.8 Hz, 1H), 2.44 (s, 3H), 2.20 (dd, *J* = 8.8, and 6.0 Hz, 1H), 1.64 - 1.58 (brm, 1H), 1.54 - 1.47 (m, 5H), 1.39 - 1.34 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.0, 138.9, 130.8, 127.7, 127.6, 127.5, 126.1, 125.3, 69.3, 54.9, 33.3, 28.9, 25.4, 24.0, 17.5; LC-MS: *m/z* calcd for $C_{21}H_{26}N$ ($M+H^+$): 292.2, found: 292.2; HRMS (ESI): *m/z* calcd for $C_{21}H_{26}N$ ($M+H^+$): 292.2065, found: 292.2060.

1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)piperidine (HDE-41)



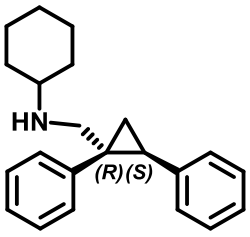
Synthesis of the enantiomer of **HDE-41** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 55% yield of product. NMR spectroscopic data is same as **HDE-37**.

***N*-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)cyclohexanamine (HDE-38)**



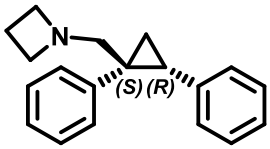
In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with cyclohexylamine (66.9 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a white powder in 63% yield (86.5 mg). $[\alpha]_D^{20}$ = - 7.9 ^{o} (C 0.75, $CHCl_3$); IR (neat) ν (cm^{-1}) 3024, 2923, 2850, 1602, 1497, 1445, 1126, 1028, 889, 773, 695; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 - 7.00 (m, 8H), 6.74 (dd, *J* = 8.4, and 2.0 Hz, 2H), 3.22 (d, *J* = 11.6 Hz, 1H), 2.77 (d, *J* = 15.2 Hz, 1H), 2.56 - 2.47 (m, 1H), 2.32 (dd, *J* = 9.6, and 7.2 Hz, 1H), 1.54 - 1.40 (m, 6H), 1.17 - 1.10 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.2, 139.0, 130.9, 128.0, 127.6, 127.5, 126.4, 125.2, 57.5, 56.1, 35.9, 33.3, 28.4, 26.2, 25.1, 17.9; LC-MS: *m/z* calcd for $C_{22}H_{28}N$ ($M+H^+$): 306.2, found: 306.3; HRMS (ESI): *m/z* calcd for $C_{22}H_{28}N$ ($M+H^+$): 306.2222, found: 306.2217.

***N*-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)cyclohexanamine (HDE-42)**



Synthesis of the enantiomer of **HDE-42** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 58% yield of product. NMR spectroscopic data is same as **HDE-38**.

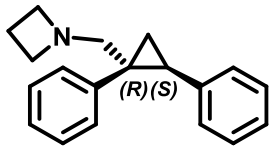
1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)azetidine (HDE-57)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with azetidine hydrochloride (63.2 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was

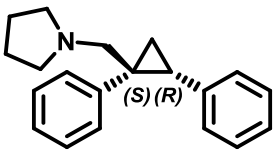
then filtered and concentrated under reduced pressure to give a white powder in 69% yield (81.7 mg). $[\alpha]_D^{20}$ = - 12.3 ^{o} (C 0.91, $CHCl_3$); IR (neat) ν (cm^{-1}) 3024, 2996, 2955, 2812, 1602, 1497, 1444, 1361, 1300, 1189, 1073, 1029, 772, 694; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 - 6.97 (m, 8H), 6.71 (dd, *J* = 8.0, and 1.6 Hz, 2H), 3.12 - 3.05 (m, 4H), 2.95 (d, *J* = 11.6 Hz, 1H), 2.47 (d, *J* = 12.4 Hz, 1H), 2.23 (dd, *J* = 8.8, and 6.0 Hz, 1H), 2.01 (ddd, *J* = 14.0, 7.2, and 6.8 Hz, 2H), 1.49 (dd, *J* = 6.0, and 5.2 Hz, 1H), 1.38 (dd, *J* = 8.4, and 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.6, 139.1, 131.0, 127.7, 127.6, 127.4, 126.2, 125.2, 71.2, 56.4, 35.3, 28.0, 18.3, 17.3; LC-MS: *m/z* calcd for $C_{19}H_{22}N$ ($M+H^+$): 264.2, found: 264.2; HRMS (ESI): *m/z* calcd for $C_{19}H_{22}N$ ($M+H^+$): 264.1752, found: 264.1747.

1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)azetidine (HDE-58)



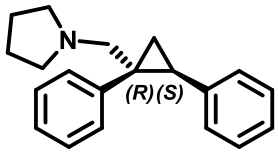
Synthesis of the enantiomer of **HDE-58** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 60% yield of product. NMR spectroscopic data is same as **HDE-57**.

1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)pyrrolidine (HDE-59)



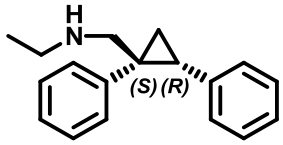
In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with pyrrolidine (48.0 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a white powder in 85% yield (105.2 mg). $[\alpha]_D^{20}$ = - 15.5 ^{o} (C 0.80, $CHCl_3$); IR (neat) ν (cm^{-1}) 3024, 2962, 2780, 1681, 1602, 1497, 1457, 1345, 1128, 1029, 775, 695; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 - 6.97 (m, 8H), 6.71 (dd, *J* = 8.0, and 1.6 Hz, 2H), 3.03 - 2.96 (brm, 1H), 2.58 - 2.45 (brm, 5H), 2.25 - 2.20 (brm, 1H), 1.75 - 1.68 (brm, 5H), 1.26 - 1.23 (brm, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.6, 138.7, 130.8, 127.8, 127.6, 127.5, 126.3, 125.3, 67.6, 54.8, 34.6, 29.2, 23.4, 17.7; LC-MS: *m/z* calcd for $C_{20}H_{24}N$ ($M+H^+$): 278.2, found: 278.2; HRMS (ESI): *m/z* calcd for $C_{20}H_{24}N$ ($M+H^+$): 278.1909, found: 278.1903.

1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)pyrrolidine (HDE-60)



Synthesis of the enantiomer of **HDE-60** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 76% yield of product. NMR spectroscopic data is same as **HDE-59**.

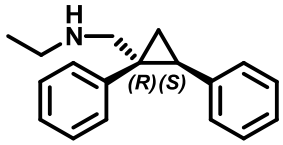
***N*-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)ethanamine (HDE-61)**



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with ethanamine hydrochloride (55.0 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a white powder in 58% yield (65.0 mg). $[\alpha]_D^{20}$ = - 36.6 ^{o} (C 0.49, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2964, 1602, 1497, 1444, 1378, 1113, 1074, 1031, 774, 696; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 - 6.99 (m, 8H), 6.73 (dd, *J* = 8.4, and 2.0 Hz, 2H), 3.15 (dd, *J* = 12.4, and 1.2 Hz, 1H), 2.72 - 2.62 (m, 3H), 2.27 (dd, *J* = 8.8, and 6.0 Hz, 1H), 1.52 (ddd, *J* = 6.4, 5.2, and 1.2 Hz, 1H), 1.42 (dd, *J* = 8.8, and 5.6 Hz, 1H), 1.04 (t, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ

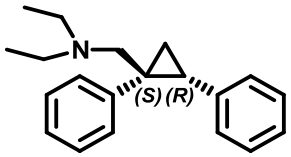
139.2, 139.1, 131.1, 128.3, 127.8, 127.7, 126.7, 125.5, 60.7, 43.9, 35.9, 28.5, 18.1, 15.3; LC-MS: *m/z* calcd for $C_{18}H_{22}N$ ($M+H^+$): 252.2, found: 252.2; HRMS (ESI): *m/z* calcd for $C_{18}H_{22}N$ ($M+H^+$): 252.1752, found: 252.1747.

***N*-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)ethanamine (HDE-43)**



Synthesis of the enantiomer of **HDE-43** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 43% yield of product. NMR spectroscopic data is same as **HDE-61**.

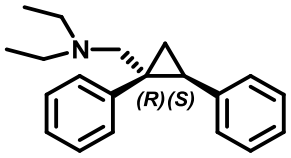
***N*-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)-*N*-ethylethanamine (HDE-62)**



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with diethylamine (49.4 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^oC, and then stirred at 0 ^oC for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^oC, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was

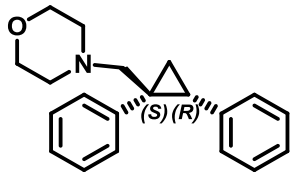
extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 25% yield (30.7 mg). $[\alpha]_D^{20}$ = - 25.0 ^{o} (C 0.30, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2967, 2930, 2799, 1602, 1497, 1445, 1382, 1205, 1174, 1072, 1029, 774, 696; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 - 6.98 (m, 8H), 6.73 (dd, *J* = 8.0, and 1.2 Hz, 2H), 2.97 (d, *J* = 13.6 Hz, 1H), 2.60 - 2.48 (m, 4H), 2.27 (dd, *J* = 8.8, and 6.4 Hz, 1H), 1.50 (dd, *J* = 6.4, and 4.8 Hz, 1H), 1.39 (dd, *J* = 8.4, and 4.8 Hz, 1H), 1.03 - 0.96 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 131.4, 131.1, 128.4, 128.0, 127.8, 127.7, 126.3, 125.4, 72.2, 63.2, 47.5, 29.9, 27.6, 17.2; LC-MS: *m/z* calcd for $C_{20}H_{26}N$ ($M+H^+$): 280.2, found: 280.2; HRMS (ESI): *m/z* calcd for $C_{20}H_{26}N$ ($M+H^+$): 280.2065, found: 280.2060.

_N_-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)-_N_-ethylethanamine (HDE-63)



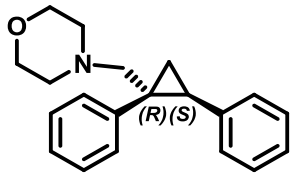
Synthesis of the enantiomer of **HDE-63** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 18% yield of product. NMR spectroscopic data is same as **HDE-62**.

4-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)morpholine (HDE-64)



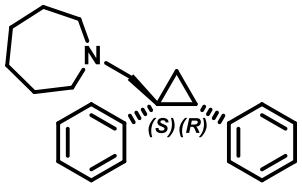
In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with morpholine (58.8 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 94% yield (123.3 mg). $[\alpha]_D^{20}$ = - 16.6 ^{o} (C 0.95, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2854, 2805, 1663, 1601, 1497, 1445, 1115, 1070, 1033, 1009, 909, 864, 776, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 - 6.99 (m, 8H), 6.70 (dd, *J* = 8.0, and 2.0 Hz, 2H), 3.73 - 3.59 (m, 4H), 2.84 (d, *J* = 11.2 Hz, 1H), 2.55 - 2.45 (m, 5H), 2.20 (dd, *J* = 8.5, and 6.0 Hz, 1H), 1.58 (dd, *J* = 6.0, and 5.0 Hz, 1H), 1.38 (dd, *J* = 8.5, and 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 139.0, 131.0, 127.8, 127.7, 127.6, 126.3, 125.5, 69.9, 66.9, 54.3, 33.6, 28.8, 17.9; LC-MS: *m/z* calcd for $C_{20}H_{24}NO$ ($M+H^+$): 294.2, found: 294.2; HRMS (ESI): *m/z* calcd for $C_{20}H_{24}NO$ ($M+H^+$): 294.1858, found: 294.1853.

4-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)morpholine (HDE-65)



Synthesis of the enantiomer of **HDE-65** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 57% yield of product. NMR spectroscopic data is same as **HDE-64**.

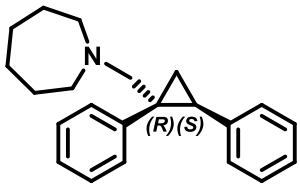
1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)azepane (HDE-66)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with azepane (67.0 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 70% yield (95.9 mg).

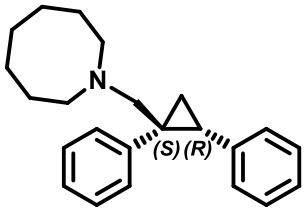
$[\alpha]_D^{20}$ = - 12.1 ^{o} (C 0.68, $CHCl_3$); IR (neat) ν (cm^{-1}) 3024, 2922, 2851, 1674, 1602, 1497, 1445, 1357, 1075, 1029, 773, 696; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 - 6.98 (m, 8H), 6.71 (dd, *J* = 8.4, and 1.6 Hz, 2H), 3.01 (d, *J* = 13.2 Hz, 1H), 2.75 (d, *J* = 13.6 Hz, 1H), 2.70 - 2.69 (m, 4H), 2.22 (dd, *J* = 8.8, and 6.4 Hz, 1H), 1.64 - 1.45 (m, 9H), 1.36 (dd, *J* = 8.8, and 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.3, 139.4, 131.0, 127.6 (two aromatic signals overlapping), 127.4, 125.9, 125.1, 68.4, 56.0, 35.0, 28.1, 27.9, 27.1, 17.3; LC-MS: *m/z* calcd for $C_{22}H_{28}N$ ($M+H^+$): 306.2, found: 306.2; HRMS (ESI): *m/z* calcd for $C_{22}H_{28}N$ ($M+H^+$): 306.2222, found: 306.2217.

1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)azepane (HDE-67)



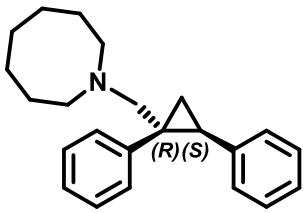
Synthesis of the enantiomer of **HDE-67** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 63% yield of product. NMR spectroscopic data is same as **HDE-66**.

1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)azocane (HDE-68)



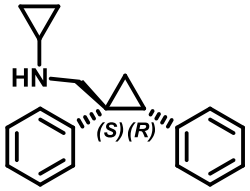
In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with heptamthyleneimine (76.4 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 82% yield (116.9 mg). $[\alpha]_D^{20}$ = - 16.8 ^{o} (C 0.85, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2914, 2847, 1602, 1497, 1444, 1354, 1096, 1028, 773, 694; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 - 6.98 (m, 8H), 6.74 (dd, *J* = 8.4, and 1.6 Hz, 2H), 3.14 (d, *J* = 13.6 Hz, 1H), 2.65 - 2.59 (m, 2H), 2.56 (s, 1H), 2.51 - 2.45 (m, 2H), 2.16 (dd, *J* = 8.4, and 6.8 Hz, 1H), 1.47 - 1.43 (brm, 4H), 1.39 - 1.33 (brm, 7H), 1.27 - 1.25 (brm, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.5, 139.7, 131.1, 127.8, 127.7, 127.6, 126.0, 125.3, 70.1, 54.4, 35.4, 28.1, 27.8, 27.3, 26.3, 18.1; LC-MS: *m/z* calcd for $C_{23}H_{30}N$ ($M+H^+$): 320.2, found: 320.3; HRMS (ESI): *m/z* calcd for $C_{23}H_{30}N$ ($M+H^+$): 320.2378, found: 320.2373.

1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)azocane (HDE-69)



Synthesis of the enantiomer of **HDE-69** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 77% yield of product. NMR spectroscopic data is same as **HDE-68**.

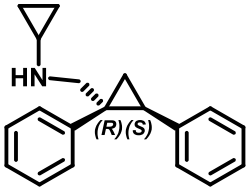
***N*-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)cyclopropanamine (HDE-70)**



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with cyclopropylamine (38.5 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 92% yield (109.0 mg). $[\alpha]_D^{20}$ = - 33.8 ^{o} (C 0.46, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2920, 1655, 1601, 1497, 1445, 1370, 1028, 775, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 - 6.99 (m, 8H), 6.72 (dd, *J* = 8.4, and 1.6 Hz, 2H), 3.23 (d, *J* = 12.8 Hz, 1H), 2.70 (d, *J* = 12.8 Hz, 1H), 2.29 - 2.24 (m, 2H), 1.53 (ddd, *J* = 6.4, 5.6, and 0.8 Hz, 1H), 1.42 (dd, *J* = 8.8, and 5.6 Hz,

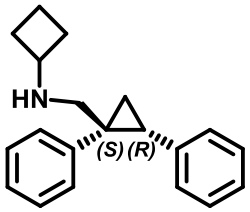
1H), 0.46 - 0.42 (m, 2H), 0.36 - 0.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 131.0, 128.4, 128.3, 127.8, 127.7, 126.6, 125.4, 60.5, 29.9, 28.5, 18.1, 6.9, 6.6; LC-MS: *m/z* calcd for $C_{19}H_{22}N$ ($M+H^+$): 264.2, found: 264.2; HRMS (ESI): *m/z* calcd for $C_{19}H_{22}N$ ($M+H^+$): 264.1752, found: 264.1747.

_N_-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)cyclopropanamine (HDE-44)



Synthesis of the enantiomer of **HDE-70** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 83% yield of product. NMR spectroscopic data is same as **HDE-44**.

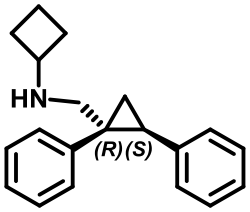
_N_-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)cyclobutanamine (HDE-71)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with cyclobutylamine (48.0 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min.

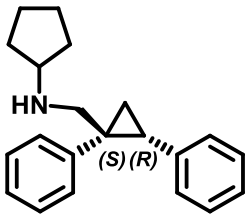
$Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^oC, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 88% yield (109.1 mg). $[\alpha]_D^{20}$ = - 31.8 ^{o} (C 0.70, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2972, 1676, 1601, 1497, 1444, 1159, 1028, 773, 695; ^1H NMR (600 MHz, $CDCl_3$) δ 7.17 - 6.98 (m, 8H), 6.71 (dd, *J* = 8.4, and 2.0 Hz, 2H), 3.26 (ddd, *J* = 15.2, 8.4, and 6.8 Hz, 1H), 3.16 (dd, *J* = 12.0, and 1.2 Hz, 1H), 2.50 (d, *J* = 12.0 Hz, 1H), 2.26 (dd, *J* = 8.8, and 6.0 Hz, 1H), 2.18 - 2.11 (m, 2H), 1.66 - 1.62 (m, 3H), 1.54 (ddd, *J* = 5.6, 5.2, and 1.2 Hz, 2H), 1.41 (dd, *J* = 8.8, and 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.2, 131.1, 128.3, 127.8, 127.7, 126.7, 125.4, 121.4, 57.9, 54.0, 36.0, 30.9, 28.7, 18.0, 14.9; LC-MS: *m/z* calcd for $C_{20}H_{24}N$ ($M+H^+$): 278.2, found: 278.2; HRMS (ESI): *m/z* calcd for $C_{20}H_{24}N$ ($M+H^+$): 278.1909, found: 278.1904.

_N_-(((_1R,2S_)-1,2-Diphenylcyclopropyl)methyl)cyclobutanamine (HDE-45)



Synthesis of the enantiomer of **HDE-45** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 89% yield of product. NMR spectroscopic data is same as **HDE-71**.

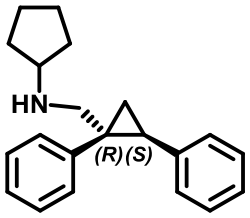
***N*-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)cyclopentanamine (HDE-72)**



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with cyclopentylamine (57.5 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 79% yield (103.1 mg). $[\alpha]_D^{20}$ = - 22.4 ^{o} (C 0.37, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2949, 2865, 1602, 1497, 1445, 1336, 1119, 1075, 1028, 773, 695; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 - 6.98 (m, 8H), 6.71 (dd, *J* = 8.0, and 1.6 Hz, 2H), 3.16 (dd, *J* = 12.4, and 1.6 Hz, 1H), 3.11 (t, 1H), 2.59 (d, *J* = 12.4 Hz, 1H), 2.26 (dd, *J* = 8.4, and 6.0 Hz, 1H), 1.81 - 1.73 (m, 2H),

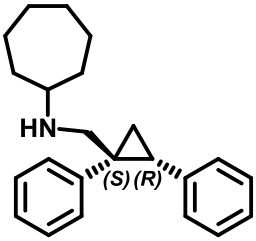
1.66 - 1.60 (m, 2H), 1.51 - 1.48 (m, 2H), 1.43 (dd, *J* = 8.8, and 5.2 Hz, 1H), 1.26 - 1.20 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.3, 139.2, 131.1, 128.2, 127.8, 127.7, 126.6, 125.4, 59.5, 59.2, 36.1, 33.2, 28.6, 24.3, 18.1; LC-MS: *m/z* calcd for $C_{21}H_{26}N$ ($M+H^+$): 292.2, found: 292.2; HRMS (ESI): *m/z* calcd for $C_{21}H_{26}N$ ($M+H^+$): 292.2065, found: 292.2060.

_N_-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)cyclopentanamine (HDE-46)



Synthesis of the enantiomer of **HDE-46** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 75% yield of product. NMR spectroscopic data is same as **HDE-72**.

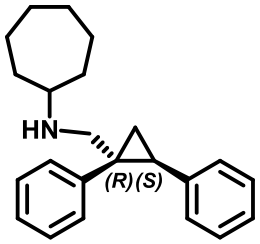
_N_-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)cycloheptanamine (HDE-73)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with

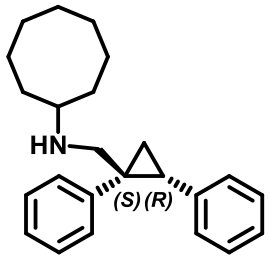
cycloheptylamine (76.4 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 24% yield (33.2 mg). $[\alpha]_D^{20}$ = - 10.2 ^{o} (C 0.40, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2922, 2852, 1602, 1497, 1457, 1445, 1114, 1074, 1029, 774, 696; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 - 6.99 (m, 8H), 6.73 (dd, *J* = 8.0, and 1.6 Hz, 2H), 3.14 (d, *J* = 12.8 Hz, 1H), 2.71 (d, *J* = 12.4 Hz, 2H), 2.28 (dd, *J* = 9.2, and 6.0 Hz, 1H), 1.78 - 1.67 (brm, 4H), 1.54 - 1.46 (brm, 7H), 1.36 - 1.33 (brm, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.3, 139.1, 131.1, 128.3, 127.8, 127.7, 126.7, 125.4, 58.4, 58.1, 44.1 (impurity), 36.0, 34.8, 30.7 (impurity), 28.6, 28.3, 24.8, 18.1; LC-MS: *m/z* calcd for $C_{23}H_{30}N$ ($M+H^+$): 320.2, found: 320.2; HRMS (ESI): *m/z* calcd for $C_{23}H_{30}N$ ($M+H^+$): 320.2378, found: 320.2374.

_N_-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)cycloheptanamine (HDE-47)



Synthesis of the enantiomer of **HDE-47** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 25% yield of product. NMR spectroscopic data is same as **HDE-73**.

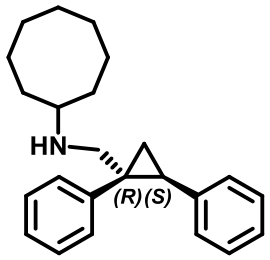
***N*-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)cyclooctanamine (HDE-74)**



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with cyclooctylamine (85.9 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 12% yield (17.7 mg). $[\alpha]_D^{20}$ = - 13.0 ^{o} (C 0.15, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2921, 2852, 1664, 1602, 1497, 1446, 1378, 1029, 773, 697; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 - 6.99 (m, 8H), 6.72 (dd, *J* = 8.0, and 1.6 Hz, 2H), 3.14 (dd, *J* = 12.4, and 0.8 Hz, 1H), 2.70 - 2.68

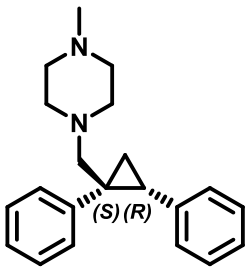
(m, 1H), 2.66 (d, *J* = 12.8 Hz, 1H), 2.26 (dd, *J* = 8.8, and 6.0 Hz, 1H), 1.65 - 1.61 (m, 3H), 1.55 - 1.53 (m, 4H), 1.43 - 1.39 (m, 6H), 1.29 - 1.25 (m, 2H), 0.90 - 0.88 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7, 138.3, 131.1, 128.6, 127.8, 127.7, 127.1, 125.7, 57.5, 57.1, 29.9, 28.9, 26.9, 26.0, 24.5, 24.3, 18.1; LC-MS: *m/z* calcd for $C_{24}H_{32}N$ ($M+H^+$): 334.2, found: 334.3; HRMS (ESI): *m/z* calcd for $C_{24}H_{32}N$ ($M+H^+$): 334.2535, found: 334.2530.

_N_-(((_1R,2S_)-1,2-Diphenylcyclopropyl)methyl)cyclooctanamine (HDE-48)



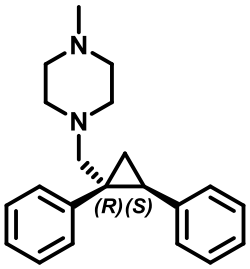
Synthesis of the enantiomer of **HDE-48** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 39% yield of product. NMR spectroscopic data is same as **HDE-74**.

1-(((_1S,2R_)-1,2-Diphenylcyclopropyl)methyl)-4-methylpiperazine (HDE-75)



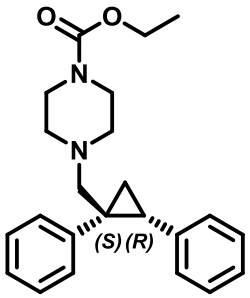
In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with 1-methylpiperazine (67.6 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 60% yield (82.7 mg). $[\alpha]_D^{20}$ = - 12.3 ^{o} (C 0.71, $CHCl_3$); IR (neat) ν (cm^{-1}) 3024, 2934, 2792, 1602, 1497, 1455, 1355, 1290, 1165, 1145, 1012, 816, 775, 695; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 - 6.98 (m, 8H), 6.69 (dd, *J* = 7.6, and 2.0 Hz, 2H), 2.82 (d, *J* = 12.8 Hz, 1H), 2.57 - 2.48 (brm, 4H), 2.40 - 2.30 (brm, 4H), 2.24 (s, 3H), 2.19 (dd, *J* = 8.8, and 6.0 Hz, 2H), 1.53 (dd, *J* = 6.0, and 5.2 Hz, 1H), 1.34 (dd, *J* = 8.8, and 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.1, 139.3, 131.1, 127.8, 127.7, 127.6, 126.2, 125.4, 69.3, 55.2, 53.7, 46.2, 33.9, 28.8, 17.9; LC-MS: *m/z* calcd for $C_{21}H_{27}N_2$ ($M+H^+$): 307.2, found: 307.3; HRMS (ESI): *m/z* calcd for $C_{21}H_{27}N_2$ ($M+H^+$): 307.2174, found: 307.2170.

1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)-4-methylpiperazine (HDE-51)



Synthesis of the enantiomer of **HDE-51** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 61% yield of product. NMR spectroscopic data is same as **HDE-75**.

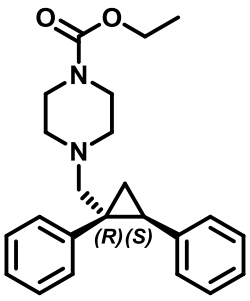
Ethyl 4-(((*1S,2R*)-1,2-diphenylcyclopropyl)methyl)piperazine-1-carboxylate (HDE-76)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with 1-ethylpiperazine-1-carboxylate (106.8 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the

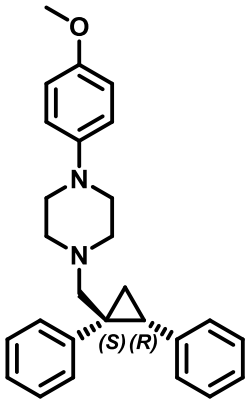
reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 65% yield (106.6 mg). $[\alpha]_D^{20}$ = - 1.0 ^{o} (C 0.90, $CHCl_3$); IR (neat) ν (cm^{-1}) 2980, 2806, 1695, 1429, 1378, 1355, 1285, 1236, 1124, 1095, 1032, 1005, 765, 696; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 - 6.99 (m, 8H), 6.69 (dd, *J* = 8.0, and 2.0 Hz, 2H), 3.44 (t, 1H), 3.37 (m, 4H), 2.86 - 2.81 (m, 2H), 2.52 (d, *J* = 12.8 Hz, 1H), 2.47 - 2.43 (brm, 3H), 2.17 (dd, *J* = 8.8, and 6.0 Hz, 1H), 1.57 (s, 1H), 1.54 (ddd, *J* = 6.0, 5.2, and 0.8 Hz, 1H), 1.32 (dd, *J* = 8.8, and 5.2 Hz, 1H), 1.24 (t, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.8, 139.8, 139.0, 131.0, 127.9, 127.7 (two aromatic signals overlapping), 126.3, 125.6, 69.5, 61.5, 53.5, 43.7, 33.8, 28.8, 17.9, 14.9; LC-MS: *m/z* calcd for $C_{23}H_{29}N_2O_2$ ($M+H^+$): 365.2, found: 365.2; HRMS (ESI): *m/z* calcd for $C_{23}H_{29}N_2O_2$ ($M+H^+$): 365.2229, found: 365.2224.

Ethyl 4-(((*1R,2S*)-1,2-diphenylcyclopropyl)methyl)piperazine-1-carboxylate (HDE-52)



Synthesis of the enantiomer of **HDE-52** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 71% yield of product. NMR spectroscopic data is same as **HDE-76**.

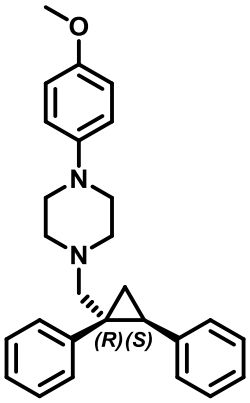
1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)-4-(4-methoxyphenyl)piperazine (HDE-77)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with 1-(4-methoxyphenyl)piperazine (129.8 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 83% yield (148.8 mg). $[\alpha]_D^{20}$ = - 3.7 ^{o} (C 0.63, $CHCl_3$); IR (neat) ν (cm^{-1}) 3030, 2936,

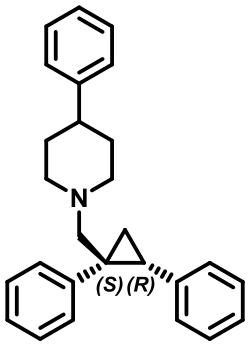
2813, 1601, 1509, 1453, 1293, 1240, 1181, 1145, 1034, 1013, 924, 822, 776, 697; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 - 7.01 (m, 7H), 6.90 - 6.80 (m, 5H), 6.69 (dd, *J* = 8.4, and 2.0 Hz, 2H), 3.76 (s, 3H), 3.16 - 3.09 (m, 1H), 3.04 - 3.01 (m, 4H), 2.87 (d, *J* = 12.8 Hz, 1H), 2.69 - 2.66 (m, 3H), 2.58 (d, *J* = 12.8 Hz, 1H), 2.23 (dd, *J* = 8.8, and 6.0 Hz, 1H), 1.58 (dd, *J* = 6.0, and 5.2 Hz, 1H), 1.38 (dd, *J* = 8.8, and 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.7, 145.9, 139.8, 139.0, 130.9, 127.5, 126.1, 125.3, 118.8, 118.1, 114.5, 114.4, 69.2, 55.6, 53.8, 50.5, 33.8, 28.7, 17.7; LC-MS: *m/z* calcd for $C_{27}H_{31}N_2O$ ($M+H^+$): 399.2, found: 399.2; HRMS (ESI): *m/z* calcd for $C_{27}H_{31}N_2O$ ($M+H^+$): 399.2436, found: 399.2431.

1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)-4-(4-methoxyphenyl)piperazine (HDE-53)



Synthesis of the enantiomer of **HDE-53** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 76% yield of product. NMR spectroscopic data is same as **HDE-77**.

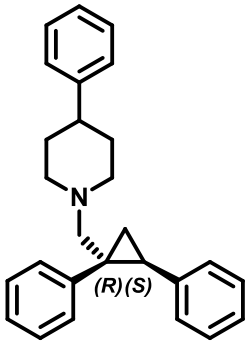
1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)-4-phenylpiperidine (HDE-78)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with 4-phenylpiperidine (108.8 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 20% yield (33.0 mg). $[\alpha]_D^{20}$ = - 3.6 ^{o} (C 0.56, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2931, 2753, 1602, 1496, 1451, 1363, 1127, 1028, 995, 774, 695; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 - 7.24 (m, 2H), 7.19 - 6.97 (m, 11H), 6.71 (dd, *J* = 8.0, and 1.6 Hz, 2H), 3.07 (dd, *J* = 11.2, and 3.2 Hz, 2H), 2.88 (d, *J* = 12.8 Hz, 1H), 2.55 (d, *J* = 13.2 Hz, 1H), 2.46 - 2.38 (m, 1H), 2.21 (dd, *J* = 8.8, and 6.0 Hz, 1H), 2.14 (ddd, *J* = 11.6, 11.2, and 3.2 Hz, 1H), 2.07 (ddd, *J* = 11.6, 11.2, and 2.8 Hz, 1H), 1.76 - 1.66 (m, 4H), 1.55 (dd, *J* = 5.6, and 5.2 Hz, 1H),

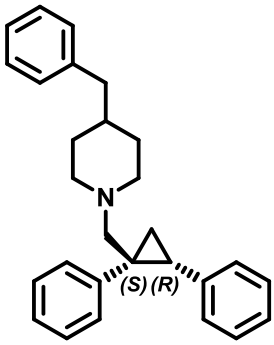
1.37 (dd, *J* = 8.8, and 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.8, 140.3, 139.4, 131.4, 131.1, 128.5, 127.8, 127.7, 127.6, 127.1, 126.2, 125.4, 72.2, 69.5, 55.1, 42.7, 33.5, 28.7, 17.9; LC-MS: *m/z* calcd for $C_{27}H_{30}N$ ($M+H^+$): 368.2, found: 368.2; HRMS (ESI): *m/z* calcd for $C_{27}H_{30}N$ ($M+H^+$): 368.2378, found: 368.2373.

1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)-4-phenylpiperidine (HDE-79)



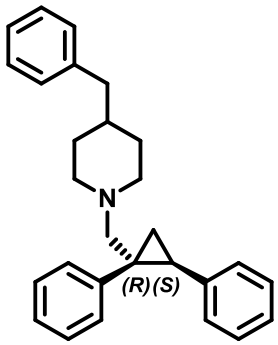
Synthesis of the enantiomer of **HDE-79** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 18% yield of product. NMR spectroscopic data is same as **HDE-78**.

1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)-4-benzylpiperidine (HDE-80)



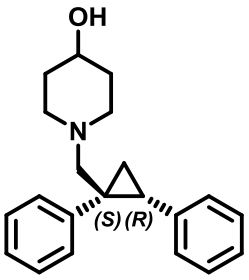
In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with 4-benzylpiperidine (118.3 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 40% yield (68.8 mg). $[\alpha]_D^{20}$ = - 1.2 ^{o} (C 0.65, $CHCl_3$); IR (neat) ν (cm^{-1}) 3024, 2916, 2750, 1602, 1496, 1453, 1365, 1129, 1075, 1029, 975, 774, 744, 695; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (t, 2H), 7.20 - 7.16 (m, 1H), 7.12 - 6.98 (m, 10H), 6.68 (dd, *J* = 8.4, and 2.0 Hz, 2H), 2.92 (dd, *J* = 14.8, and 11.6 Hz, 2H), 2.78 (d, *J* = 13.2 Hz, 1H), 2.53 - 2.46 (m, 4H), 2.17 (dd, *J* = 8.8, and 6.4 Hz, 1H), 1.94 (ddd, *J* = 11.6, 11.6, and 2.4 Hz, 1H), 1.89 (ddd, *J* = 11.6, 5.6, and 2.4 Hz, 1H), 1.46 - 1.43 (m, 1H), 1.30 (dd, *J* = 8.8, and 5.2 Hz, 1H), 1.24 - 1.15 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.1, 140.4, 139.4, 131.1, 129.3, 128.3, 127.8, 127.7, 127.6, 126.3, 125.9, 125.4, 69.5, 54.7, 43.3, 38.1, 34.1, 32.4, 28.9, 17.8; LC-MS: *m/z* calcd for $C_{28}H_{32}N$ ($M+H^+$): 382.2, found: 382.2; HRMS (ESI): *m/z* calcd for $C_{28}H_{32}N$ ($M+H^+$): 382.2535, found: 382.2530.

1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)-4-benzylpiperidine (HDE-81)



Synthesis of the enantiomer of **HDE-81** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 27% yield of product. NMR spectroscopic data is same as **HDE-80**.

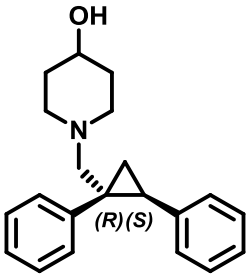
1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)-4-hydroxylpiperidine (HDE-82)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with 4-hydroxylpiperidine (68.3 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was

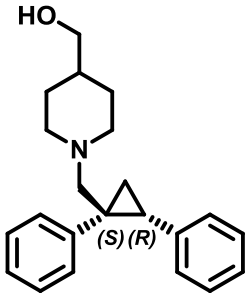
extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 17% yield (23.2 mg). $[\alpha]_D^{20}$ = - 15.7 ^{o} (C 0.94, $CHCl_3$); IR (neat) ν (cm^{-1}) 3351, 3025, 2937, 1602, 1497, 1445, 1361, 1114, 1065, 775, 743, 696; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 - 6.98 (m, 8H), 6.71 (dd, *J* = 8.4, and 2.0 Hz, 2H), 3.65 - 3.59 (m, 1H), 2.80 (d, *J* = 12.8 Hz, 3H), 2.53 (d, *J* = 12.8 Hz, 1H), 2.23 - 2.14 (m, 3H), 1.81 - 1.79 (m, 2H), 1.54 - 1.45 (m, 3H), 1.33 (dd, *J* = 8.8, and 5.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 131.4, 131.1, 128.4, 127.8, 127.7, 127.0, 126.3, 125.5, 72.2, 69.0, 51.7, 34.6, 28.8, 27.6, 17.8; LC-MS: *m/z* calcd for $C_{21}H_{26}NO$ ($M+H^+$): 308.2, found: 308.2; HRMS (ESI): *m/z* calcd for $C_{21}H_{26}NO$ ($M+H^+$): 308.2014, found: 308.2009.

1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)-4-hydroxylpiperidine (HDE-54)



Synthesis of the enantiomer of **HDE-54** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 17% yield of product. NMR spectroscopic data is same as **HDE-82**.

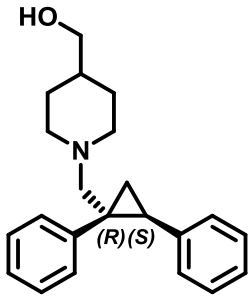
(1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)piperidin-4-yl)methanol (HDE-83)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with 4-peperidinemethanol (77.7 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 33% yield (47.7 mg). $[\alpha]_D^{20}$ = - 12.0 ^{o} (C 0.25, $CHCl_3$); IR (neat) ν (cm^{-1}) 3342, 3025, 2917, 2801, 1602, 1497, 1445, 1363, 1119, 1033, 1009, 909, 775, 731, 696; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 - 6.98 (m, 8H), 6.70 (dd, *J* = 7.2, and 1.2 Hz, 2H), 3.42 (d, *J* = 6.4 Hz, 2H), 2.97 (d, *J* = 11.2 Hz, 2H), 2.88 (d, *J* = 12.8 Hz, 1H), 2.52 (d, *J* = 12.8 Hz, 1H), 2.17 (dd, *J* = 8.8, and 6.0 Hz, 1H), 2.03 (ddd, *J* = 12.0, 11.6, and 2.0 Hz, 1H), 1.96 (ddd, *J* = 11.6, 11.6, and 2.0 Hz, 1H), 1.61 (dd, *J* = 11.8, and 2.0 Hz, 2H), 1.53 (dd, *J* = 6.0, and 5.2 Hz, 1H), 1.45 - 1.42 (m, 1H), 1.33 (dd, *J* = 8.8, and 5.2 Hz, 1H), 1.22 - 1.15 (m, 2H); ^{13}C

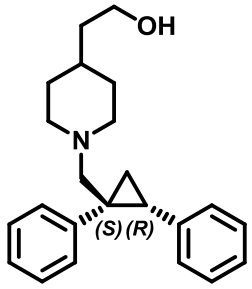
NMR (150 MHz, $CDCl_3$) δ 140.3, 139.4, 131.1, 127.8, 127.7, 127.6, 126.2, 125.4, 69.4, 68.2, 54.2, 54.0, 38.7, 34.0, 28.8, 17.9; LC-MS: *m/z* calcd for $C_{22}H_{28}NO$ ($M+H^+$): 322.2, found: 322.2; HRMS (ESI): *m/z* calcd for $C_{22}H_{28}NO$ ($M+H^+$): 322.2171, found: 322.2166.

(1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)piperidin-4-yl)methanol (HDE-55)



Synthesis of the enantiomer of **HDE-55** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 17% yield of product. NMR spectroscopic data is same as **HDE-83**.

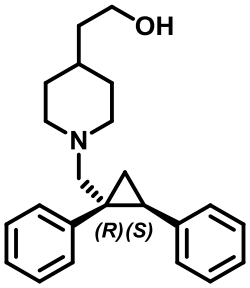
2-(1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)piperidin-4-yl)ethan-1-ol (HDE-84)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with 4-peperidineethanol (87.2 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5

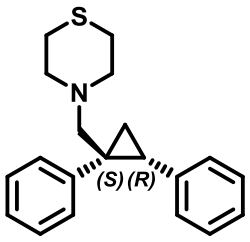
eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 32% yield (47.6 mg). $[\alpha]_D^{20}$ = - 10.0 ^{o} (C 0.29, $CHCl_3$); IR (neat) ν (cm^{-1}) 3334, 3025, 2921, 1602, 1497, 1444, 1365, 1086, 1029, 984, 775, 732, 695; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 - 6.99 (m, 8H), 6.69 (dd, *J* = 8.0, and 1.6 Hz, 2H), 3.65 (t, 2H), 2.96 - 2.92 (m, 3H), 2.81 (d, *J* = 12.8 Hz, 1H), 2.52 (d, *J* = 12.8 Hz, 1H), 2.18 (dd, *J* = 8.8, and 6.0 Hz, 1H), 2.00 (ddd, *J* = 12.0, 11.6, and 2.0 Hz, 1H), 1.94 (ddd, *J* = 11.6, 11.6, and 2.4 Hz, 1H), 1.65 - 1.60 (m, 2H), 1.53 (dd, *J* = 6.0, and 5.2 Hz, 1H), 1.44 (dd, *J* = 13.2, and 6.8 Hz, 2H), 1.32 (dd, *J* = 8.8, and 5.2 Hz, 2H), 1.23 - 1.19 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.4, 139.4, 131.1, 127.8, 127.8, 127.6, 126.2, 125.4, 69.5, 60.8, 54.6, 54.5, 39.6, 34.1, 32.5, 28.8, 17.9; LC-MS: *m/z* calcd for $C_{23}H_{30}NO$ ($M+H^+$): 336.2, found: 336.2; HRMS (ESI): *m/z* calcd for $C_{23}H_{30}NO$ ($M+H^+$): 336.2327, found: 336.2322.

2-(1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)piperidin-4-yl)ethan-1-ol (HDE-56)



Synthesis of the enantiomer of **HDE-56** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 47% yield of product. NMR spectroscopic data is same as **HDE-84**.

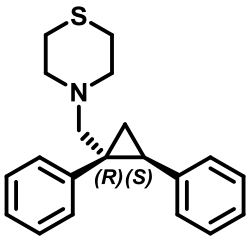
4-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)thiomorpholine (HDE-85)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with thiomorhholine (69.6 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 77% yield (107.2 mg). $[\alpha]_D^{20}$ = - 14.4 ^{o} (C 0.89, $CHCl_3$); IR (neat) ν (cm^{-1}) 3024, 2907, 2802, 1676, 1602, 1497, 1455, 1416, 1362, 1283, 1207, 1118, 1028, 960, 774, 743, 695; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 - 6.99 (m, 8H), 6.69 (dd, *J* = 9.2, and 1.6 Hz, 2H), 2.85 (d, *J* = 13.2 Hz, 1H), 2.78 - 2.74 (m, 5H), 2.58 - 2.54 (m, 4H), 2.18 (dd, *J* = 8.4, and 5.6 Hz, 1H),

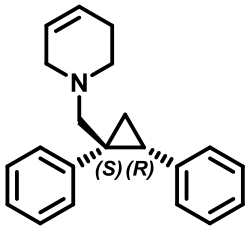
1.52 (d, *J* = 5.6 Hz, 1H), 1.33 (dd, *J* = 8.8, and 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.0, 139.2, 131.1, 127.9, 127.8, 127.7, 126.3, 125.5, 69.7, 55.6, 33.9, 28.5, 28.0, 17.7; LC-MS: *m/z* calcd for $C_{20}H_{24}NS$ ($M+H^+$): 310.2, found: 310.1; HRMS (ESI): *m/z* calcd for $C_{20}H_{24}NS$ ($M+H^+$): 310.1629, found: 310.1625.

4-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)thiomorpholine (HDE-86)



Synthesis of the enantiomer of **HDE-86** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 63% yield of product. NMR spectroscopic data is same as **HDE-85**.

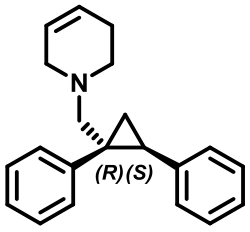
1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)-1,2,3,6-tetrahydropyridine (HDE-87)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with 1,2,3,6-tetrahydropyridine (56.1 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5

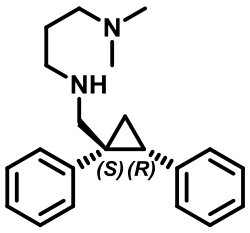
eq). The reaction mixture was cooled to 0 ^{o}C, and then stirred at 0 ^{o}C for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^{o}C, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 60% yield (78.1 mg). $[\alpha]_D^{20}$ = - 30.3 ^{o} (C 0.66, $CHCl_3$); IR (neat) ν (cm^{-1}) 3026, 2917, 1660, 1602, 1497, 1445, 1360, 1030, 909, 776, 732, 696; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 - 6.98 (m, 8H), 6.70 (dd, *J* = 8.4, and 2.0 Hz, 2H), 5.70 - 5.58 (m, 2H), 3.01 (s, 1H), 2.94 (d, *J* = 12.4 Hz, 1H), 2.62 - 2.58 (m, 3H), 2.24 (dd, *J* = 8.8, and 6.4 Hz, 1H), 2.09 - 2.05 (m, 2H), 1.56 (dd, *J* = 6.4, and 4.8 Hz, 2H), 1.40 (dd, *J* = 8.8, and 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.2, 139.3, 131.1, 127.9, 127.8, 127.7, 126.3, 125.6, 125.4, 125.3, 69.1, 53.5, 50.4, 34.1, 28.8, 26.1, 17.9; LC-MS: *m/z* calcd for $C_{21}H_{24}N$ ($M+H^+$): 290.2, found: 290.2; HRMS (ESI): *m/z* calcd for $C_{21}H_{24}N$ ($M+H^+$): 290.1909, found: 290.1904.

1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)-1,2,3,6-tetrahydropyridine (HDE-88)



Synthesis of the enantiomer of **HDE-88** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 58% yield of product. NMR spectroscopic data is same as **HDE-87**.

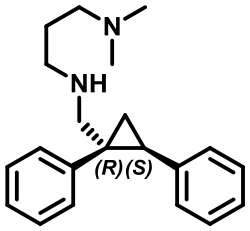
N^1-(((*1S,2R*)-1,2-Diphenylcyclopropyl)methyl)-N^3,N^3-dimethylpropane-1,3-diamine (HDE-50)



In a 10 mL round bottom flask equipped with a magnetic stir bar, **6-s** (100.0 mg, 0.45 mmol, 1 eq.) was dissolved in DCM (3 mL). This solution was treated with 3-dimethylaminopropylamine (69.0 mg, 0.675 mmol, 1.5 eq.) and AcOH (40.5 mg, 0.675 mmol, 1.5 eq). The reaction mixture was cooled to 0 ^oC, and then stirred at 0 ^oC for 20 min. $Na(OAc)_3BH$ (286.1 mg, 1.35 mmol, 3.0 eq.) was added dropwise at 0 ^oC, and then the reaction was stirred at RT overnight. After the allotted time had passed, the reaction was extracted with 1M HCl (10 mL x 3) and ether (10 mL). 2M KOH solution was added into the collected aqueous 1M HCl solution until basic (pH 14), and the product was extracted with DCM. The extracted organic solution was dried over $MgSO_4$, the organic phase was then filtered and concentrated under reduced pressure to give a colorless oil in 56% yield (77.7 mg). $[\alpha]_D^{20}$ = - 28.1 ^{o} (C 0.80, $CHCl_3$); IR (neat) ν (cm^{-1}) 3025, 2941, 2779, 1655, 1601, 1497, 1445, 1033, 775, 696; ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 - 6.99 (m, 8H), 6.73 (dd, *J* = 8.4, and 1.6 Hz, 2H), 3.12 (d, *J* = 12.4 Hz, 1H), 2.72 - 2.62 (m, 3H),

2.27 (dd, *J* = 8.5, and 6.0 Hz, 1H), 2.25 - 2.20 (m, 2H), 2.11 (s, 6H), 1.62 (ddd, *J* = 7.0, 7.0, and 1.5 Hz, 1H), 1.58 (ddd, *J* = 7.5, 7.0, and 1.5 Hz, 1H), 1.51 (dd, *J* = 6.0, and 5.5 Hz, 1H), 1.43 (dd, *J* = 8.5, and 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 138.8, 131.0, 128.2, 127.7, 127.6, 126.7, 125.4, 60.7, 58.2, 48.4, 45.5, 35.6, 28.4, 27.3, 18.1; LC-MS: *m/z* calcd for $C_{21}H_{29}N_2$ ($M+H^+$): 309.2, found: 309.3; HRMS (ESI): *m/z* calcd for $C_{21}H_{29}N_2$ ($M+H^+$): 309.2331, found: 309.2326.

N^1-(((*1R,2S*)-1,2-Diphenylcyclopropyl)methyl)-N^3,N^3-dimethylpropane-1,3-diamine (HDE-49)



Synthesis of the enantiomer of **HDE-49** was carried out using **6-r** as starting material in the same reaction conditions as described above to obtain in 77% yield of product. NMR spectroscopic data is same as **HDE-50**.

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